Scientific Committee on Consumer Safety

SCCS

OPINION ON

new coating for Titanium Dioxide (nano form)

The SCCS adopted this document
at its plenary meeting on 20 May 2024

ACKNOWLEDGMENTS

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1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided, does the SCCS consider safe the use of Titanium Dioxide (nano) coated with a combination of w/w 6% Aluminium Hydroxide, 14% Sodium Myristoyl Sarcosinate and 10% Dimethicone, for use as UV filter in dermally applied cosmetic products?

   Considering all the provided information, the SCCS is of the view that there are a number of uncertainties and data gaps that do not allow a conclusion on the safety of titanium dioxide (nano) coated with a combination of w/w 6% aluminium hydroxide, 14% sodium myristoyl sarcosinate and 10% dimethicone (Eclipse 70) - either on the basis of a similarity to the TiO_2 nanomaterials previously assessed by the SCCS, or on the basis of the additional information provided in the current submission.

2. Does the SCCS have any further scientific concerns regarding the use of Titanium Dioxide (nano) coated with the above-mentioned materials when used as UV-filter in dermally applied cosmetic products?

   The provided information has not demonstrated a similarity of the titanium dioxide with the above-mentioned composite coating (Eclipse 70) to other TiO_2 nanomaterials assessed in the previous SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014) in terms of physicochemical characteristics, stability of the coating, and the lack of dermal absorption of the nanoparticles. If these aspects cannot be addressed, additional data on physicochemical, toxicological and exposure aspects specifically relating to the nanomaterial under evaluation (Eclipse 70) will be needed to conclude on the safety of its use in cosmetic products.

Keywords: SCCS, scientific opinion, TiO_2, coatings, nano, CAS/EC numbers 13463-67-7/236-675-5, 1317-70-0/215-280-1, 1317-80-2/215-282-2, Regulation 1223/2009

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Titanium Dioxide, TiO_2, (CAS/EC numbers 13463-67-7/236-675-5, 1317-70-0/215-280-1, 1317-80-2/215-282-2) is authorized both as colorant under entry 143 of Annex IV, as UV-filter under entry 27 of Annex VI, and in powder form in entry 321 of Annex III to Regulation (EC) No 1223/2009.

In July 2013[1], the Scientific Committee on Consumer Safety (SCCS) issued the safety evaluation on Titanium Dioxide (nano) concluding that the use of Titanium Dioxide (nano) as UV-filter, at concentrations up to 25 % and with the characteristics indicated in the opinion, 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 that opinion, the SCCS indicated the substances considered safe for use as coating for TiO_2 (nano). Regarding 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 need 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 August 2023, the Commission' services received a dossier related to a new nano-form of TiO_2 material (i.e., Eclipse 70) coated with 'Aluminium Hydroxide', 'Sodium Myristoyl Sarcosinate' and 'Dimethicone'. 'Aluminium Hydroxide' and 'Dimethicone' coatings were already assessed by SCCS in 2014, while 'Sodium Myristoyl Sarcosinate' coating has not yet been assessed.

The Commission requests the SCCS to carry out a safety assessment on 'Sodium Myristoyl Sarcosinate' (CAS No. 30364-51-3/ EC No. 250-151-3) as a coating of Titanium Dioxide (nano) in view of the information provided.

[1] SCCS (Scientific Committee on Consumer Safety), Opinion on 56 titanium dioxide (nano form), 22 July 2013, revision of 22 April 2014

Terms of reference

1. In light of the data provided, does the SCCS consider safe the use of Titanium Dioxide (nano) coated with a combination of w/w 6% Aluminium Hydroxide, 14% Sodium Myristoyl Sarcosinate and 10% Dimethicone, for use as UV filter in dermally applied cosmetic products?

2. Does the SCCS have any further scientific concerns regarding the use of Titanium Dioxide (nano) coated with the above-mentioned materials when used as UV-filter in dermally applied cosmetic products?

3. OPINION

Preamble

As indicated in section 2 (Background), the SCCS can consider the use of a new coating on TiO_2 nanomaterials safe, if the properties/behaviour of the particles with the new coating are demonstrated to be not significantly different compared to those already covered in the SCCS opinion (SCCS/1516/13). For this, data need to demonstrate that a TiO_2 nanomaterial with the new coating has a comparable profile in terms of physicochemical properties (in line with those provided in Tables 1-3 of the previous Opinion SCCS/1516/13-Revision of 22 April 2014), the new coating is stable, and that dermal penetration has not changed as a result of the new coating.

The submission under current evaluation relates to a TiO_2 nanomaterial (Eclipse 70-D13-NT-77891, abbreviated as Eclipse 70) that has a composite surface coating made of 3 substances – an inner layer of aluminium hydroxide on to the surface of TiO_2 nanoparticles; followed by sequential layers of sodium myristoyl sarcosinate and dimethicone.

During the process of evaluation, the SCCS raised a request for further information on a number of aspects relating to the submission. The replies received from the Applicant in response to the SCCS request have also been taken into consideration in this Opinion.

The Tables and Figures included in this Opinion have been renumbered by the SCCS to follow a sequence.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Provided by the Applicant:

Chemical identity of ECLIPSE 70

Description: Amino acid-treated nano titanium dioxide with dimethicone

Core material: TITANIUM DIOXIDE (nano form)
Coating materials: ALUMINUM HYDROXIDE (and) SODIUM MYRISTOYL SARCOSINATE (and) DIMETHICONE

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.1.2 Chemical names

Provided by the Applicant:

Core material: Titanium dioxide (nano form); Titanium (IV) oxide
Coating materials: Aluminium hydroxide
Sodium myristoyl sarcosinate: sodium;2-[methyl(tetradecanoyl)amino] acetate
Dimethicone: dimethyl-bis(trimethylsilyloxy)silane

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.1.3 Trade names and abbreviations

Provided by the Applicant:

ECLIPSE70-D13-NT-77891 (abbreviated as 'Eclipse 70')

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.1.4 CAS / EC number

Provided by the Applicant:

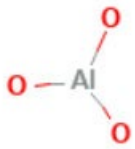
Core material: Titanium dioxide (nano form) - CAS No. 13463-67-7; EC No. 236-675-5
Coating materials: Aluminium hydroxide - CAS No. 21645-51-2; EC No. 244-492-7
Sodium myristoyl sarcosinate - CAS No. 30364-51-3; EC No. 250-151-3
Dimethicone - CAS No. 63148-62-9; EC No. not available

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

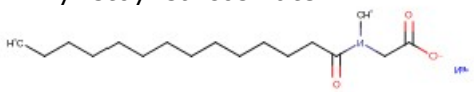
3.1.1.5 Structural formula

Provided by the Applicant:

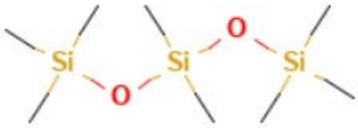
Core material: Titanium dioxide
Coating materials: Aluminium hydroxide:



Sodium myristoyl sarcosinate:



Dimethicone



ECLIPSE70-D13-NT-77891, abbreviated as 'Eclipse 70' consists of an amino-acid treated nano titanium dioxide core (TiO_2; up to 70% w/w) coated with the following materials: 1) aluminium hydroxide (up to 6% w/w), 2) sodium myristoyl sarcosinate (up to 14% w/w), and 3) dimethicone (up to 10% w/w).

The structure is shown in **Figure 1**:

- Aluminium hydroxide (in blue) forms a layer around the central titanium dioxide particles. The original composite alumina coating is characterized by a dense portion and a hydrated portion (boehmite).
- The green filaments represent the sodium myristoyl sarcosinate moieties, chemically bound to the titanium dioxide particles via the aluminium hydroxide.
- The yellow planes correspond to the dimethicone coating, which is bound to the particle via amino acid chains.

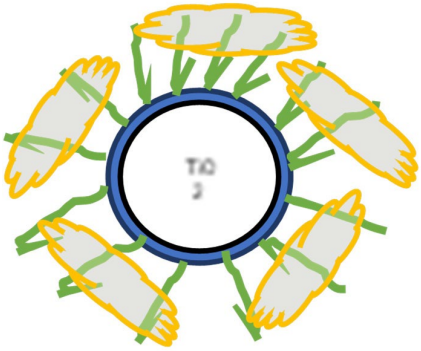


Figure 1: Schematic representation of Eclipse 70

From Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment

In the submission, CAS number 63148-62-9 has been quoted for one of the coating materials (dimethicone), with the assertion that it has already been assessed as a coating material in a previous SCCS Opinion. The SCCS however noted that dimethicone (dimethylpolysiloxane) is a silicone polymer that as such does not have an assigned discrete chemical formula/structure, and the chemical formula/structure and molecular weight quoted in the submission all belong to another discrete compound 'dimeticone' (octamethyltrisiloxane; CAS Number: 28349-86-2).

In response to the SCCS request for further information, the Applicant confirmed that it was dimethicone that was used as one of the components of the coating. This means that the information provided in the submission relating to chemical formula, structure, molecular weight needs to be corrected.

3.1.1.6 Empirical formula

Provided by the Applicant

Core material: Titanium dioxide
Coating materials: Aluminium hydroxide – AlH3O3/ Al(OH)3
Sodium myristoyl sarcosinate – C17H32NNaO3
Dimethicone – C8H24O2Si3

From Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.2 Physical form

Provided by the Applicant

Manufacturing process description:

The manufacturing process involves several steps:

- *Mixing:* the substrate (titanium dioxide) and the first surface treatment (sodium myristoyl sarcosinate) are placed in a tank and mixed for a given amount of time. pH and

temperature are controlled at mixing. The second and third treatments, dimethicone and aluminium hydroxide, are added subsequently, with pH and temperature checked at the end of each mix.

- *Pressing:* the product in the tank is transferred into a filter press, and pressed until it reaches the correct parameters.
- *Heating:* the material is transferred into drying trays and left until the oven cycle is completed. Hydrophobicity and LOD are checked to ensure the quality of the manufacturing process.
- *Packaging*

The process is conducted under optimum conditions and controlled at each step to ensure the adequacy with expected results, and the repeatability and stability of the end material. Any deviation to the process or check results is reported and solved.

General appearance:
Eclipse 70 is presented as a white powder. The morphological observation by scanning electron microscopy (SEM) reveals the presence of particles with a needle-like morphology, as illustrated in **Figure 2**.

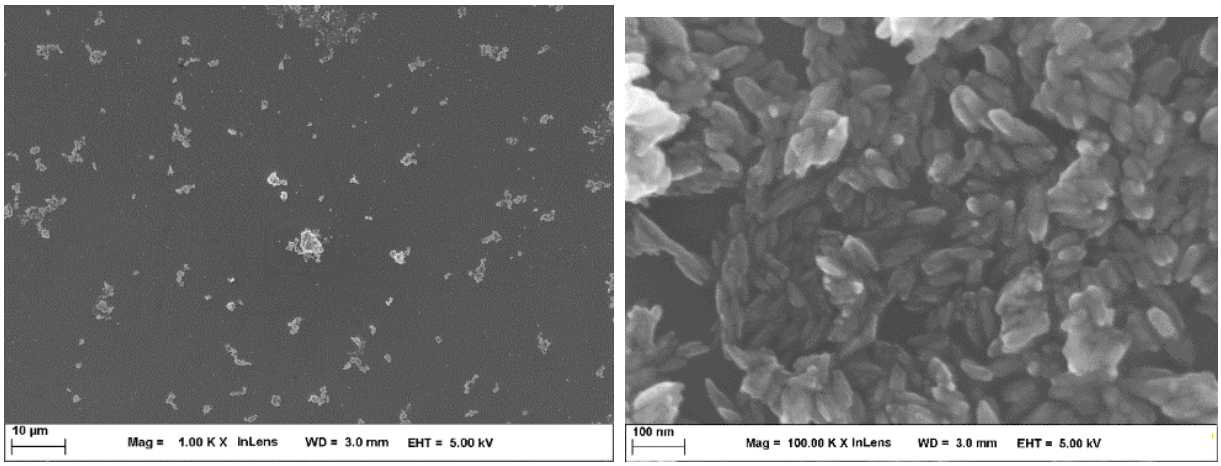


Figure 2: Electron microscopy of Eclipse 70

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.3 Molecular weight

Provided by the Applicant:

Core material: Titanium dioxide – 79.9 g/mol
Coating materials: Aluminium hydroxide –78.004 g/mol
Sodium myristoyl sarcosinate – 321.4 g/mol
Dimethicone – 236.53 g/mol

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.4 Purity, composition and substance codes

Provided by the Applicant:

The composition / purity of Eclipse 70 is reported in **Table 1**.

Table 1. Typical composition of Eclipse 70

Components	% w/w	CAS No.	EINECS No.
Ultrafine titanium dioxide	**70**	-	-
Titanium dioxide	(80-90)	13463-67-7	236-675-5
Aluminium hydroxide	(10-20)	21645-51-2	244-492-7
Sodium myristoyl sarcosinate	**14**	30364-51-3	250-151-3
Dimethicone	**10**	63148-62-9	Not regulated
Aluminium hydroxide	**6**	21645-51-2	244-492-7

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment

The SCCS has noted that the nanomaterial under current evaluation is composed of core TiO_2 nanoparticles that constitute 70% w/w of the material, which is surface coated sequentially with aluminium hydroxide (up to 6% w/w), sodium myristoyl sarcosinate (up to 14% w/w), and dimethicone (up to 10% w/w). This means that, in the final form, Eclipse 70 nanoparticles are composed of up to 30% w/w of the coating materials.

3.1.5 Impurities / accompanying contaminants

Provided by the Applicant:

The technical data sheet of Eclipse 70 reports that the material does not contain heavy metals (e.g., Hg, Cd, Pb, As, or Sb) beyond generally accepted limits.
The sample has been mineralised in a solution containing 4.5 mL HNO_3, 1.5 mL HCl and 1 mL HF. During 2 hours at 100°C. It is noticed that the full mineralization has not been achieved. Typical impurities of Eclipse 70, measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES), are shown in **Table 2.**

Table 2. Typical impurities of Eclipse 70

Element	Technique	Results (%)
Ag	ICP-AES	< 0.00025
Al	**ICP-AES**	**3.82**
As	ICP-AES	< 0.0025
B	ICP-AES	< 0.0010
Ba	ICP-AES	< 0.00025
Be	ICP-AES	< 0.0025
Bi	ICP-AES	< 0.00025
Ca	ICP-AES	0.0047
Cd	ICP-AES	< 0.00025
Co	ICP-AES	0.072
Cr	ICP-AES	< 0.0013
Cu	ICP-AES	< 0.025
Fe	ICP-AES	0.0042
K	ICP-AES	0.0016
Li	ICP-AES	< 0.00025
Mg	ICP-AES	0.00073
Mn	ICP-AES	< 0.00025
Mo	ICP-AES	< 0.00025

Na	ICP-AES	0.027
Ni	ICP-AES	< 0.00025
P	ICP-AES	0.0089
Pb	ICP-AES	< 0.0025
S	ICP-AES	0.098
Sb	ICP-AES	0.012
Se	ICP-AES	< 0.0025
Si	ICP-AES	0.038
Sn	ICP-AES	< 0.050
Sr	ICP-AES	< 0.00025
Ti	**ICP-AES**	**37.4**
Tl	ICP-AES	0.017
V	ICP-AES	0.0017
Zn	ICP-AES	< 0.050

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

3.1.6 Solubility

Provided by the Applicant:

Titanium dioxide is insoluble in water and organic solvents. It also has a very low dissociation constant in water and aqueous systems, and thus can be considered insoluble, also under physiological conditions (SCCS, 2014).

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.7 Partition coefficient (Log P_{ow})

Provided by the Applicant:

Not applicable for uncoated titanium dioxide.

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment
Whilst the SCCS agrees that measurement of octanol/water partition coefficient is not applicable to uncoated titanium dioxide particles, Eclipse 70 has a surface coating composed of inorganic/organic substances (resulting in a hydrophobic surface), which may affect partitioning between hydrophilic/lipophilic phases. The OECD TG 126 may be followed in this regard to provide hydrophobicity index of Eclipse 70.

3.1.8 Additional physical and chemical specifications

Provided by the Applicant:

Crystallinity: Rutile titanium dioxide
Mean aspect ratio: 2.81
Surface specific area: 15.14 m^2/g
Density: 2.2045 ± 0.0009 g/cm^3 (measurement by Helium pycnometry)
VSSA(*): 33.38 cm^2/cm^3

Zeta potential: 6.109 mV
UV-Vis spectroscopy: Two absorption peaks are observable.
One peak at 210 nm (Absorption = 0.7691), one peak at 357 nm (Absorption = 0.6355).

(*): Volume Specific Surface Area

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment

The SCCS has noted that the Specific Surface Area of the materials tested for skin penetration (789455-Miyoshi_Eclipse-Microscopy_Final_26Apr23.pdf, page 29/37) is 5.8 times higher than the one reported above (87.6 m^2/g versus 15.14 m^2/g). The Applicant needs to confirm which value is correct, or whether they reflect variation between the two different batches of the material.

3.1.9 Particle size

Provided by the Applicant:

Particle/aggregate size distribution analysis of Eclipse 70 was first performed using laser diffraction (LD) which produces distributions weighted according to the intensity of light scattered by each size of particle/aggregate. The D10 range is reported as 1.42-1.45 µm, while the D90 is reported as 5.02- 5.73 µm. This represents a mean size ranging between 3.14 to 3.47 µm. Details are provided in the following Figures.

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

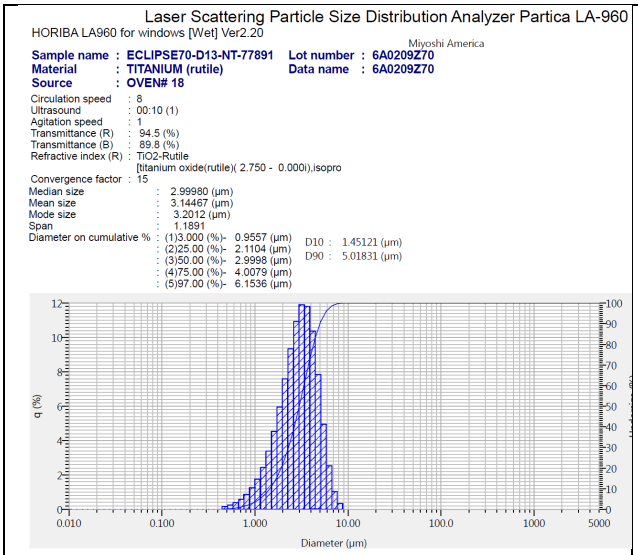


Figure 3a: Laser scattering particle size distribution *(From Ref.: Annex 1_Laser scattering particle size distribution-PSD-6A0209Z70.pdf)*

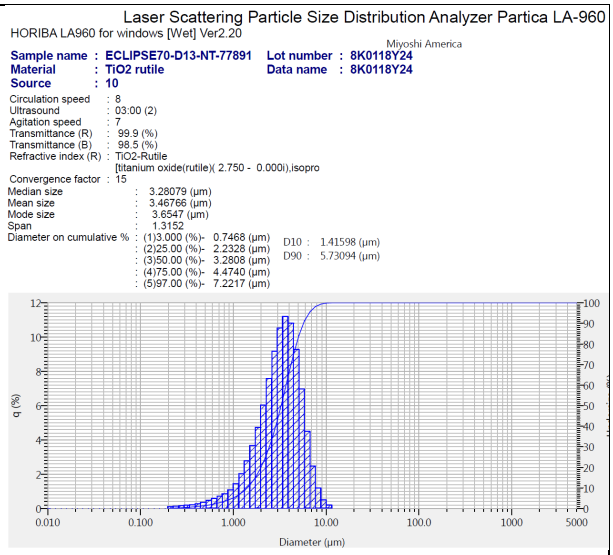


Figure 3b: Laser scattering particle size distribution *(From Ref.: Annex 1_Laser scattering particle size distribution-PSD-8K0118Y24.pdf)*

Table 3: Laser scattering size distribution (number based): D10, D50, D90 and Dmean for two batches *(data extracted by the SCCS from Annex 1_Laser scattering particle size distribution-PSD-6A0209Z70.pdf and Annex 1_Laser scattering particle size distribution-PSD-8K0118Y24.pdf)*

Materials ECLIPSE70-D13-NT-77891	**D10** (µm)	**D50** (µm)	**D90** (µm)	**Dmean** (µm)
Lot 6A0209Z70	1.45121	2.99980	5.01831	3.14467
Lot 8K0118Y24	1.41598	3.28079	1.41598	3.46766

SCCS comment

The SCCS considers that the use of methods based on laser diffraction is only appropriate for larger sized agglomerates/aggregate, and not for particle size measurement of constituent particles in the nano scale.

3.1.10 Microscopy

3.1.10.1 Morphological observation of particles by SEM

From Applicants:

SEM observations reveal the presence of particles with a needle – like morphology. Some of these particles appear to have nanometric dimensions (< 100 nm).

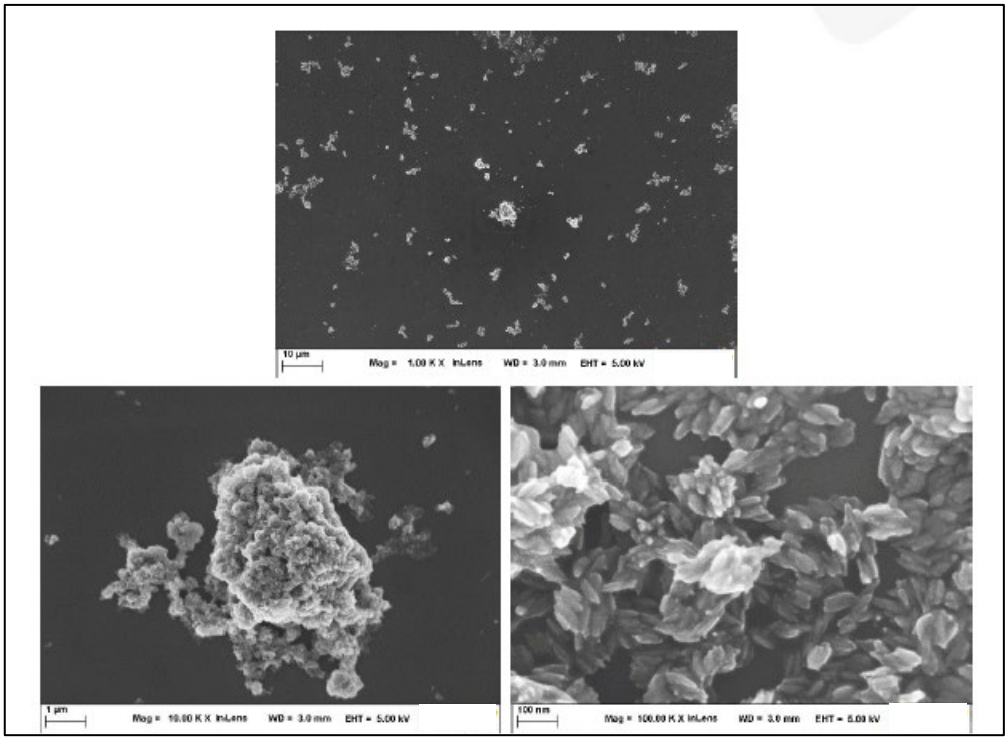


Figure 4: SEM observations (secondary electron mode) of sample 2303-E01 32 782 (from Annex 1_Material characterisation report_PC_RAPPORT #A2302555 - MIYOSHI EUROPE en-US.pdf and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf)

The elemental analysis by EDX carried out on the sample reveals that these particles are mainly composed of Carbon (C), Oxygen (O) and Titanium (Ti), a minority of Aluminium (Al), as well as traces of Sulfur (S).
It should be noted that the Silicon (Si) detected in EDC probably comes from the Silicon Wafer used as a support for analysis.

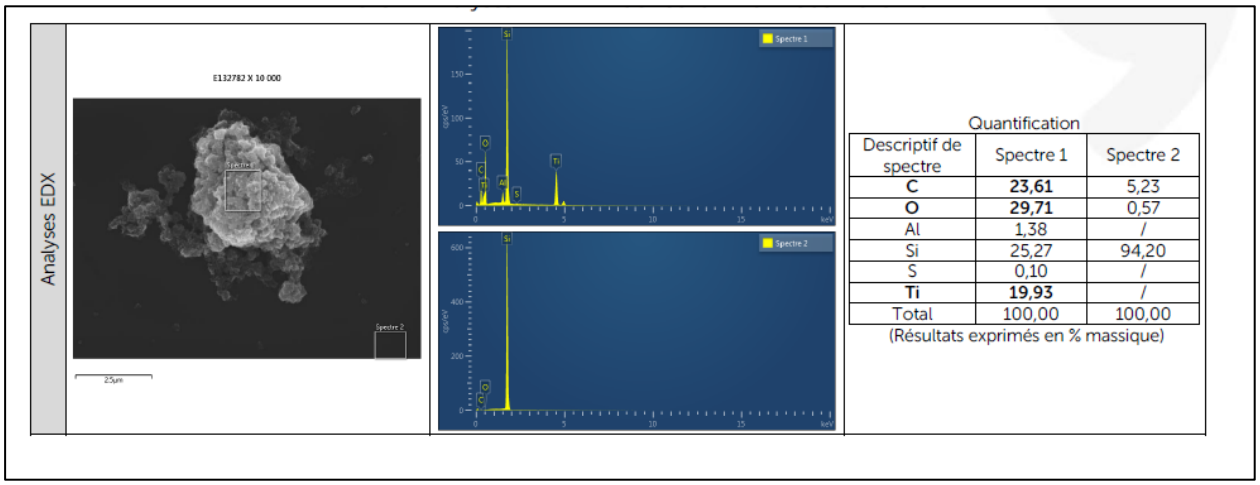


Figure 5: SEM – EDX analysis of Sample 2303-E01 32 782 (from Appendix - RAPPORT #A2302555 - MIYOSHI EUROPE.pdf)

SCCS comment

Only a single sentence is provided in the submission to describe how samples were prepared prior to measurement of particle size distribution: "A dispersion of the sample is made in a 10 mL volume of Isopropanol. 2.5 µL of this solution is then deposited in a Silicon Wafer using a Spin Coating technique".

Despite the SCCS request for further information, no more details were provided by the Applicant on the sample preparation method used. The SCCS considers the provided information as inadequate because appropriate sample preparation to achieve adequate dispersion of nanoparticles is crucial for physicochemical characterisation and toxicological testing of nanomaterials (SCCS Guidance on Nanomaterials: SCCS/1655/23).

3.1.10.2 Primary particle size distribution

Provided by the Applicant:

The primary particle size distribution of Eclipse 70 (raw powder) was analysed by scanning electron microscopy (SEM), showing a monomodal distribution with a peak centred at about 20 nm (**Figure 7**).

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

A count of 305 particles was performed using an image analyzer. The minimum Feret diameter was chosen as the dimensional parameter. This dimension was preferred because in the definition, the term "one or more dimensions" is mentioned. The counted particles were chosen randomly on the Wafer. Only particles with a discriminable physical countour were counted. The size of the primary particles has priority over the agglomerates or aggregates, since the latter will be considered as nanomaterials if the particles that compose them are nanometric.

A selection of SEM images, with and without the counting performed, is presented in the following Figures.

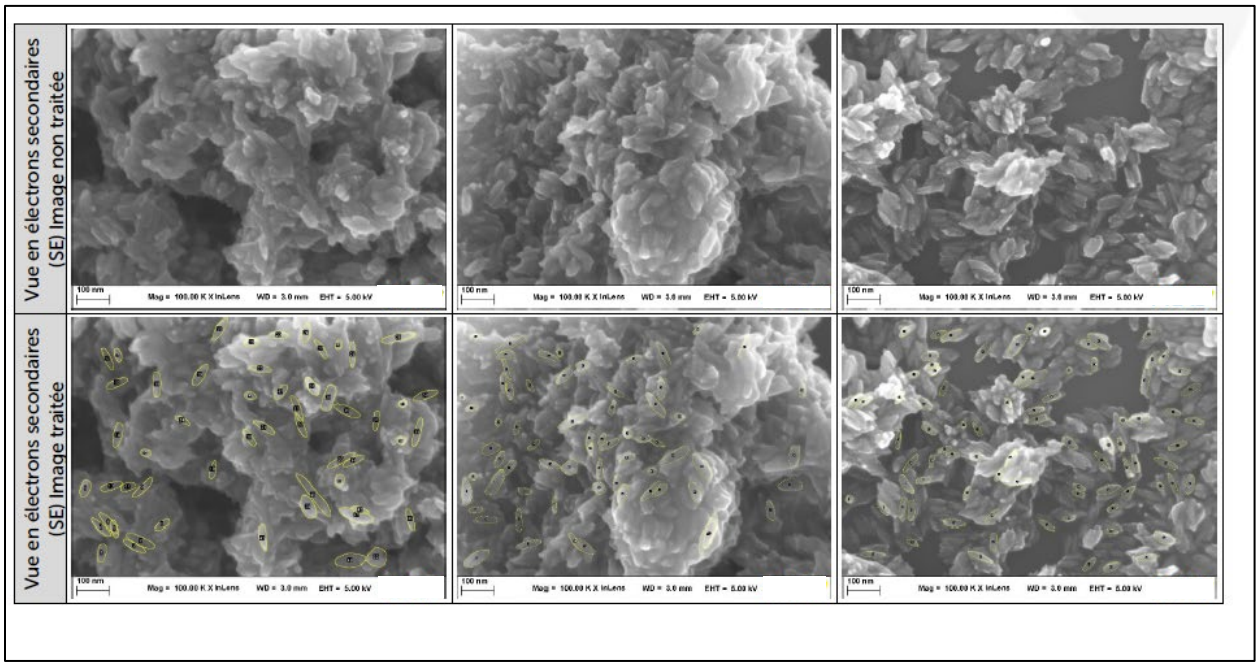


Figure 6: SEM micrographs of Sample 2303-E01 32 782 (from Appendix - RAPPORT #A2302555 - MIYOSHI EUROPE)

Ref.: RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

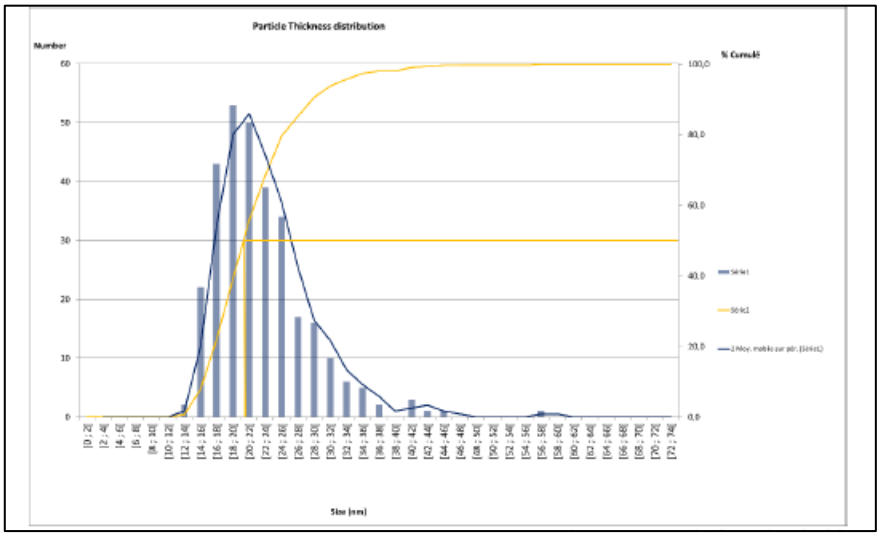


Figure 7: Particle size distribution of Eclipse 70 measured by SEM (sample 2303-E0132782)

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf
and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

The particle size distribution of the sample is monomodal with a peak centered at about 20 nm. The particle size ranges from 12 to 56 nm.

The results of the particle size distribution (% cumulative) show that more than 50% of the particles in the numerical size distribution have a size less than 100 nm. Overall, average particle size was reported as 22.4 nm, d10 as 16.3 nm and d90 as 30.0 nm.

The results are listed in the Table below.

Table 4: Size distribution determined by SEM (average value, D10%, D50%, % nanoparticles, aspect ratio)

Sample Reference	Average Value (nm)	Value at 10% cumulative (nm)	Median Value* (nm) (50% cumulative, according to 2022/C 229/01)	% of nanoparticles in the sample of particles analyzed*	Aspect Ratio
2303-E0132782 *ECLIPSE70-D13-NT-77891*	22.4	16.3	**20.9**	**100**	**2.81**

Ref.: Annex 1_Material characterisation report_PC_RAPPORT #A2302555 - MIYOSHI EUROPE en-US.pdf and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

SCCS comment

Figure 7 shows particle size distribution of Eclipse 70 measured by SEM (sample 2303-E0132782). However, it is not clear how the line was drawn and whether it is based on a mathematical model. It is notable from the Figure that the particle size distribution is not completely monomodal.

Also, aspect ratio of the nanoparticles is given but no explanation is provided on how the aspect ratio was determined. In the absence of information on full aspect ratio distribution based on individual particle size measurements, it is not clear if the given aspect ratio is a median/mean value.

Provided by the Applicant:

Summary of the Particle size of Eclipse 70 based on Laser scattering and SEM analyses:

Table 5. Particle size of Eclipse 70

Material Code	Particle size distribution					
	Laser scattering analyser (um)			Number weighted median based on SEM (nm)		
	D10	D90	Mean size	D10	D90	Mean size
Eclipse 70	1.42 – 1.45	5.02 – 5.73	3.14 – 3.47	16.3	30.0	22.4

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment

Despite the uncertainty due to the lack of details on particle dispersion, the information provided on particle size distribution measured by electron microscopy shows that median particle size of Eclipse 70 is around 21 nm. Since up to 30% (w/w) of the material is comprised of coating substances, the actual median size of core TiO_2 nanoparticle is most likely below 21 nm. This renders Eclipse 70 outside the particle size range covered in the SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014):

"….have a median particle size based on number size distribution of 30 to 100 nm (measured by different methods) as submitted in the dossier, or larger. Thus, whilst primary particle size may be smaller (around 10 nm), the median particle size of TiO_2 nanomaterials in a cosmetic formulation must not be smaller than 30 nm in terms of number-based size distribution".

In response to the SCCS request for further information, the Applicant provided the following explanation:

"While the coating represents a significant proportion by weight, the overall thickness of the coating layer is only a few nanometers. We have analysed the particle size of both untreated and treated particles (using the same method, SEM by number, and the same lot) and have found a very comparable D50 (median particle size). The difference in particle size between the untreated and treated particles is
not significant, indicating that the coating does not significantly affect the overall PSD."

In the absence of any supporting data, the SCCS regards the Applicant's narrative statement as unsatisfactory, and maintains the view that the median particle size range of Eclipse 70 is most likely outside that covered in the previous SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014).

3.1.11 Crystal structure

Provided by the Applicant:

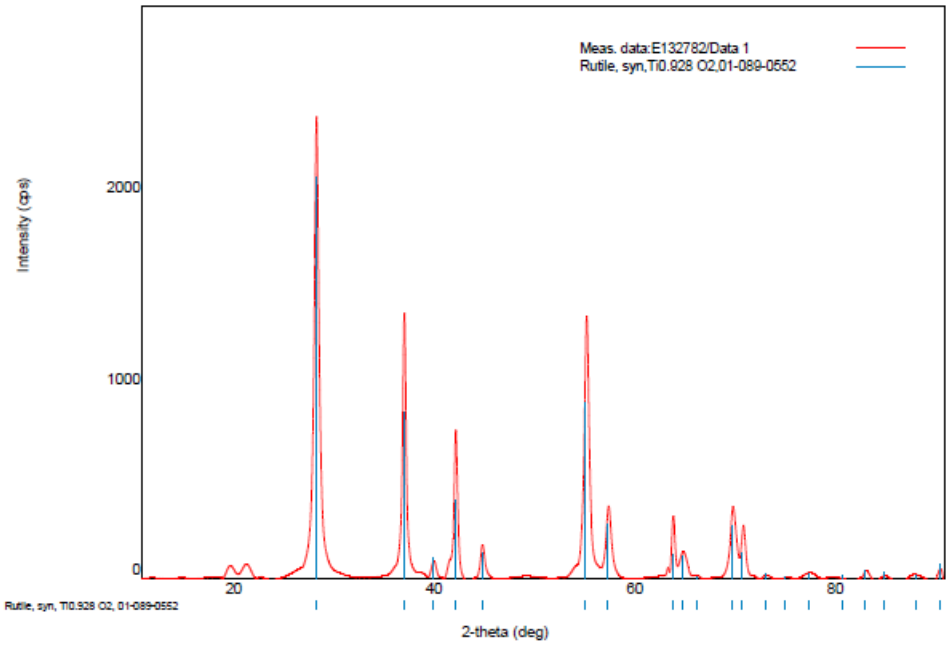


Figure 8: X – ray diffraction pattern provided by Applicant (from Ref. RAPPORT #A2302555 - MIYOSHI EUROPE.pdf)

The crystal phases identified for this sample are as follows:

Table 6

Reference Sample / Référence Echantillon	Identified crystal phases / Phases cristallines identifiées	ICDD sheet / Fiche ICDD
2303-E0132782 *ECLIPSE70-D13-NT-77891*	**Rutile TiO_2 / TiO_2 rutile**	**01-089-0552**

Ref.: Annex 1_Material characterisation report_PC_RAPPORT #A2302555 - MIYOSHI EUROPE en-US.pdf and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

SCCS comment

The SCCS has noted that some minor XRD peaks have not been identified in the data provided in the submission.

3.1.12 UV absorption

Provided by the Applicant:

Two absorption peaks are observable. One at 210 nm (Abs.) 0.7691) and one at 357 nm (Abs. = 0.6355).

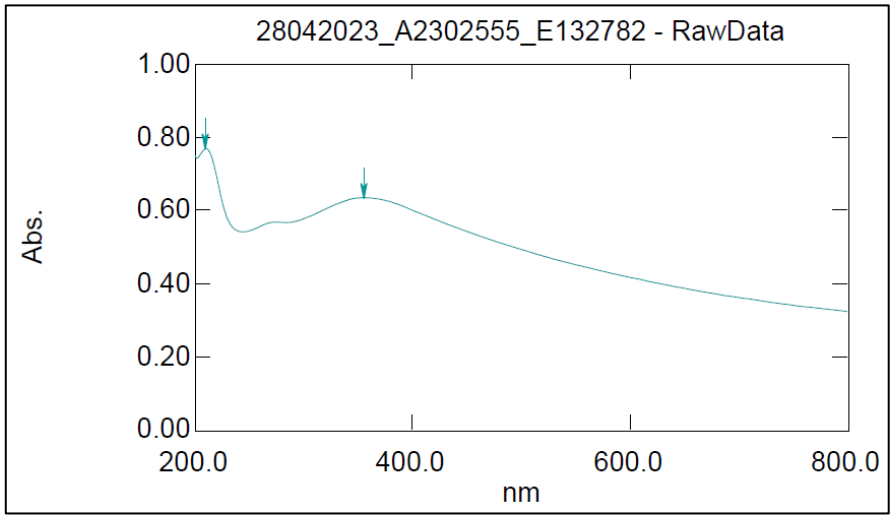


Figure 9: UV – visible spectrometry spectrum

Table 7: Absorption UV – visible peaks

Absorption peak (nm)	Absorption
210	**0.7691**
357	**0.6355**

From Ref.: Annex 1_Material characterisation report_PC_RAPPORT #A2302555 - MIYOSHI EUROPE en-US.pdf and RAPPORT #A2302555 - MIYOSHI EUROPE.pdf

3.1.13 Surface characteristics

SCCS comment
No specific information is provided about the surface characteristics of Eclipse 70. However, from the information provided on coating materials, it can be anticipated that the surface characteristics of fully coated Eclipse 70 would be determined by the outermost layer of dimethicone (i.e. the coated nanoparticles will be hydrophobic).

3.1.14 Droplet size in formulations

/

3.1.15 Homogeneity and stability

Provided by the Applicant:

Based on stability information reported in the confidential **Annex I**, it is concluded that an optimum manufacturing process is needed to develop strong hydrophobic surfaces, and stable surface treatment.

The manufacturing process described above (see 'Physical form' paragraph) respects Good Manufacturing Practices and is strictly controlled for any deviation. Should any modification occur, its potential consequences are investigated, reported, and resolved. The end-product must respect the same Quality Control parameters to be released (hydrophobicity and proportion of treatment).

Stability testing is performed under strictly defined conditions, allowing the shelf life to be set at 3 years.

Different samples are taken during the manufacturing process to ensure the homogeneity of treatment within the batch.

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment
The Applicant provided data from a test to indicate stability of the coating. The purpose of the test was described as to confirm ECLIPSE 70 surface treatment stability with comparing incorrect surface treatment process sample. The reported method involved, dispersing, filtering, making a 'press-cake' and dropping 1-2 water droplet on press-cake, and monitoring contact angle at 0 sec, 20 sec, 60 sec, 15 min, 30 min and 45 min.

In response to the SCCS request for further information, the Applicant provided the following explanation:

"The water droplet contact angle test is used to confirm the stability of the surface treatment, even after applying an isopropanol (IPA) washing process, which is rougher than normal condition of use. This test indicates that our product, with our specific process, maintains a high contact angle, which signifies that the pigment retains its water resistance effect even after the IPA washing process. To further prove the stability of the coating over time, we have conducted hydrophobicity tests over a longer period, specifically up to 48 months (see results in annex II of this document). These results demonstrate that the coated TiO_2 remains stable and retains its water resistance properties even after an extended period, providing additional evidence of the coating's stability during the shelf-life of the product."

The Applicant also provided a Table (Table 8) to indicate stability of the coating in terms of maintenance of hydrophobicity over 48 months (Float test, and Stir test).

Table 8

Test	Method	Specification	0 Month (2-15-2018)	2 Month (4-15-2018)	3 Month (5-15-2018)	6 Month (8-15-2018)	12 Months (2-15-2019)	24 Months (2-15-2020)	36 Months (2-15-2021)	48 Months (2-15-2022)
Appearance, Color, Odor and Feel	Q-C001	Matches Std	Matches Std	Matches Std	Matches Std	Matches Std	Matches Std	Matches Std	Matches Std	Matches std.
Loss on Drying	Q-C015	Less than 2.0%	0.60%	1.0%	1.2%	1.2%	1.7%	1.88%	1.59%	1.19%
Float Test (Hydrophobicity)	Q-C014	Floats on still water for more than 1 hour	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Stir Test (Hydrophobicity)	Q-C028	≥5.0/≥5.0/≥5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0	5.0/5.0/5.0
TiO2 Content	Q-E018	55.0 – 65.0 %	58.7%	61.17%	60.70%	61.34%	60.53%	60.78%	61.16%	60.57%
Microbial Content	Q-D002	Less than 100 cfu/gm, No gram negative	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

The SCCS regards the provided information unsatisfactory because validity and relevance of the used method have not been established in terms of how the measurement of a change in the water contact angle (over short intervals, and an overall short period of time) could be considered to depict long term stability of the coating on the nanomaterial. Similarly, details have not been provided on the 'Float' and 'Stir' methods to enable assessment of their validity and relevance to demonstrate stability of the coating.

3.1.16 Other parameters of characterisation

Provided by the Applicant:

Melting point: Not provided
Boiling point: Not applicable
Flash point: Not applicable
Vapour pressure: Not applicable
Density: Not provided
Viscosity: Not provided
pKa: Not provided
Refractive index: Not provided

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.1.17 Summary on supplementary physicochemical characterisation

Provided by the Applicant:

Table 9. Additional parameters for the identification and characterisation of Eclipse 70

Material code	Crystal size (nm) (XRD)	Aspect ratio (L/W)	UV absorption (extinction coefficient)	Zeta potential (mV)	Photo-catalytic activity (%)	Photo-stability	Coating stability
Eclipse 70	N/A	2.81	210 nm and 357 nm	6.109	0.74	N/A	Stable

Ref.: Table 2, 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment
The SCCS is of the view that where evidence is provided to show that photocatalytic activity remained quenched over a long period of time, it could be considered an indirect way of ascertaining stability of a coating on a photoreactive/photocatalytic nanomaterial. In this regard, the Applicant provided data on photocatalytic activity (Table-9) to indicate that it is below the acceptable level of 10%, compared to the same material without surface coating. However, the provided evidence only comprised of plate images without any detail on how photocatalytic activity was measured, calculated, or what it was compared with to conclude that it was within the acceptable limit.

In response to the SCCS request for further information, the Applicant provided the following explanation: "The method outlined in SCCS/1516/13 was followed for testing. The photocatalytic activity was measured on the coated test sample and the non-coated control. The activity of the test sample was compared with that of the control. The measured activity values for the test and control samples were 39.49 and 0.29, respectively. The final calculated activity was 0.74% (0.29/39.49=0.74%). As per the SCCS NoG (2023), the activity of the coated material should not be more than 10% compared to the non-coated control to be considered acceptable. In our case, the calculated activity of 0.74% falls well below this limit, indicating that the photocatalytic activity of the coated material remains quenched."

In the absence of detailed information, the SCCS regards the Applicant's narrative statement as unsatisfactory and reiterate that full experimental details of the test should be provided to enable evaluation of the validity of the results.

3.2 TOXICOKINETICS

Provided by the Applicant:

Eclipse 70 is reported to have a stable coating during long-term storage, hence no release of individual coating materials is expected under the proposed use conditions. From the toxicological evaluation point of view, the core and coating materials were considered as one entity.

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

SCCS comment
The SCCS regards the Applicant's narrative statement as unsatisfactory and considers that stability of the composite coating has not been demonstrated either directly (see 3.1.15) or indirectly (see 3.1.17).

3.2.1 Dermal / percutaneous absorption

An OECD Test Guideline 428 compliant in vitro percutaneous absorption study has been provided in the submission. The study was conducted with a representative cosmetic formulation containing 10% w/w of Eclipse70.

In vitro percutaneous absorption (human skin)

Guideline:	OECD TG 428
Test system:	Human skin (Split-thickness)
Test substance:	10% (w/w) amino acid treated nano-titanium dioxide with dimethicone (ECLIPSE70-D13-NT-77891, abbreviated Eclipse 70) in a representative sunscreen formulation (A69-14-36A-MOD)

Formulation batch:	92-114
TiO_2 content in the formulation:	6.07% (w/w)
Conversion factor:	2.76 (to convert from titanium to Eclipse 70)
Route:	Topical application
Application technique:	Static diffusion
Thickness of skin:	350-400 µm
Duration:	24 hours
Washing of test formulation:	Yes
Dose of test formulation:	5 mg/cm^2
Applied mass:	529 µg/cm^2
Surface area of exposed skin:	0.64 cm^2
Number of samples:	12
No of donors:	4
No of cells per donor:	3
Membrane integrity:	Yes
Receptor fluid:	Physiological saline
Sampling:	0.5, 1, 2, 4, 8 and 24 hours
Analytical method:	Inductively coupled plasma mass spectrometry (ICP-MS)
Exposure time:	24 hours
GLP:	Yes
Study period:	2022-23

Method:

The *in vitro* absorption of Eclipse 70 in a representative sunscreen formulation at 10% was investigated in a GLP-compliant study conducted according to OECD Test Guideline 428. Healthy split-thickness human skin membranes (350-400 µm) with an exposure area of 0.64 cm2 were mounted into static diffusion cells with receptor fluid present in the receptor chamber. A skin surface temperature of 32 ± 1 C was maintained throughout the experiment. An initial electrical resistance barrier integrity assessment was performed for all skin samples, and skin samples exhibiting a resistance greater than 7.7 kΩ were accepted in the study. The test formulation was applied at a dose of 5 mg/cm2 to twelve skin membranes from four different donors. The cells were open to the atmosphere. An analytical method capable of detecting the presence of elemental titanium by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) was developed for all relevant samples (i.e., mock doses, receptor fluid, skin wash, tissue swabs, tape strips, donor wash, receptor wash, epidermis, and dermis). The skin membranes were dosed with test formulation, a non-dosed control group served to determine the background levels of titanium in the test system. The percutaneous absorption was assessed by collecting receptor fluid samples at 0.5, 1-, 2-, 4-, and 8-hours post-dosing. At 24 hours post-dosing, the exposure was terminated by washing the skin surface with a commercial hand wash soap concentrate, followed by rinsing with a dilute soap solution (2%, v/v) and drying of the surface with tissue swabs. The 24-hour receptor fluid was collected from the receptor chamber and retained for analysis. The skin was removed from the static cells, the *stratum corneum* tape-stripped, and the skin was divided into exposed and unexposed skin sections. The exposed skin was separated by scraping the epidermis from the dermis using a scalpel. The receptor chambers were rinsed with 2% nitric acid, which was retained for subsequent analysis.

All samples taken were analysed for titanium by inductively coupled plasma mass spectrometry (ICP-MS) using a method validated by the contract laboratory. The titanium levels in the tissue samples and the tape strips were provided as elemental titanium per sample. The titanium content in the receptor fluid, donor and receptor chamber wash was provided as concentration (ng Ti/mL). To convert the levels of elemental titanium to that of Eclipse 70, a conversion factor of 2.75 was applied.

Results:
The ICP-MS analysis revealed that most of the epidermis, dermis, receptor fluid and receptor wash values were below the method's limit of quantification (LOQ), similar to what was observed in the blank control group. The initial development and validation of the method was complex due to titanium being a challenging and ubiquitous analyte, which is present in nature in higher amounts than most trace elements. Only in single test samples (e.g., cell 7 at the 0.5-hour measurement), the measured value slightly exceeded the LOQ of 10 ng/mL. Overall, the absorption profiles looked similar for all test samples with absorption of Eclipse 70 being below the LOQ throughout the experimental period. The same was observed in the blank control group. Hence, it should be noted that the actual concentration of titanium values provided below in Tables 7 and 8 [of the submission], will be between zero (best case, lower bound) and the LOQ value (worst case, upper bound). Although the pre-dose values showed titanium contents greater than the LOQ, the pre-dose values were set at 0.00 ng/mL as the formulation had not been introduced at that time point. Where the measured values were below the LOQ, the LOQ value was applied as worst case to all calculations. The mass balance for all individual samples was within 100 ± 15% except for six cells (i.e., cells 2, 3, 4, 5, 7, 9 which revealed a mass balance >115%). The mean mass balance was 113.33% of the applied dose at 24 hours post-dose. The high mass balance was a result of almost all samples being below the LOQ. None of the cells were rejected, and the results were provided as mean values (n = 12).

Table 10 presents the mean absorption results and distribution at 24 hours post dose obtained for the Eclipse test sunscreen formulation. Most of the applied dose was washed off at 24 hours post application (i.e., 7.42 and 98.89% recovered in the skin wash and tissue swabs, respectively). At 24 hours post dosing, a further 0.08% was recovered in the donor chamber wash. The material recovered in the donor wash was almost certainly the material that was dislodged from the skin during the washing procedure. Therefore, the total dislodgeable dose was 106.40% of the applied dose. The mean total unabsorbed dose was 110.74% of the applied dose. This consisted of the dislodgeable dose, unexposed skin (0.82%) and the Eclipse 70 associated with the *stratum corneum* (3.53%).

The amounts retained in the *stratum corneum* at 24 hours were not considered dermally absorbed. With the worst-case assumption of absorption at the LOQ, the totally absorbed dose, the sum of the receptor fluid (0.25%) and receptor chamber wash (0.08%), was calculated to be 0.33%. With the same worst-case assumption, the epidermis and dermis contained 1.44% and 0.82% of the applied dose, respectively. Due to epidermal removal during the tape stripping, the values from the *stratum corneum* for cells 5, 8, 10 and 11 (*stratum corneum* (SC) 11-15 and SC 16-20 values for cell 5, SC 6-10 and SC 11-15 values for cell 11, SC 6-10 value for cell 10 and SC 16-20 value for cell 8) were added to the epidermis, resulting in the values for epidermis above the LOQ of 0.82%. Considering the upper bound levels (measurements below the LOQ was considered as equal to the LOQ), the dermal delivery, the sum of absorbed dose and exposed skin (epidermis and dermis), was calculated to be 2.58%. Since most receptor fluid values were below the LOQ, it was not possible to determine the extent of absorption. To present the most conservative risk assessment value, the potentially absorbable dose value has been calculated and reported in the study report. However, it should be pointed out that this value is "worst-case".

Table 10. *In vitro* percutaneous absorption of Eclipse 70 through human skin in terms of % applied dose and amount per skin unit area (upper bound levels)

	ECLIPSE 70			
Test Formulation	Eclipse Test Sunscreen			
Concentration of Test Item (w/w)	10%			
Applied Mass (µg/cm²)	529			
Number of Samples	12			
Distribution	% Applied dose		µg/cm²	
	Mean	**SD**	**Mean**	**SD**
Donor chamber wash	0.08	0.02	0.433	0.129
Dislodgeable Dose	106.40	7.76	562	41.0
Stratum corneum	3.53	1.01	18.7	5.35
Unexposed Skin	0.82	0.00	4.31	0.00
Total unabsorbed dose	110.74	8.05	585	42.6
Epidermis	1.44@	0.83	7.62@	4.41
Dermis	0.82$	0.00	4.31$	0.00
Receptor Fluid (RF)	0.25$	0.00	1.30$	0.00622
Receptor Wash (RW)	0.08$	0.00	0.431$	0.00
Total Absorbed Dose (RF+RW)	0.33	0.00	1.73	0.00622
Dermal Delivery	**2.58**	**0.83**	**13.7**	**4.41**
Potentially absorbable dose	5.25	0.80	27.7	4.24
Mass balance	113.33	8.09	599	42.7

$ Below limit of quantification.
@ Above the limit of quantification (LOQ) for 4 cells out of 12. The values for the 8 cells were below LOQ of 0.82%
Dislodgeable dose = skin wash 24 hours + tissue swab 24 hours + donor chamber wash.
Stratum corneum = tape strips 1 to 20.
Total unabsorbed dose = dislodgeable dose + *stratum corneum* + unexposed skin.
Total absorbed dose = cumulative receptor fluid + receptor chamber wash.
Dermal delivery = absorbed dose + epidermis + dermis.
Potentially absorbable dose = dermal delivery + *stratum corneum* 3-20.
Mass balance = unabsorbed dose + dermal delivery.

The distribution of Eclipse 70, by mass, at 24 hours post dose as shown in **Table 10** reflects the upper bound levels while measurements below the LOQ were considered as equal to the LOQ. The mass balance, total dislodgeable dose, unabsorbed dose, absorbed dose and dermal delivery were 599, 562, 585, 1.73 and 13.7 µg/cm2, respectively.

Of the 12 cells dosed with Eclipse test sunscreen, 4 cells (i.e., cells 5/8/10/11) had the epidermis removed during the tape stripping procedures. Although representative *stratum corneum* values have been added to the epidermis values for these cells as a "worst-case" scenario, there is a possibility that these *stratum corneum* values did not contain any levels of active ingredient even with epidermis removed. In addition to the skin samples dosed with the test sunscreen, a blank control group was tested. This group was included to ascertain the intrinsic levels of background titanium associated with the test system and to enable the correction of the Eclipse test sunscreen data to account for this, if appropriate. Although the donor wash and tissue swabs displayed slightly increased titanium content, the amount was deemed small enough to be negligible. Therefore, data adjustment was not considered to be required.

Conclusion

In the dermal absorption study conducted by Kravcenko (2023a), no absorption of Eclipse 70 above the limit of quantification was observed. Hence, the actual concentration would be between zero (best case; lower bound) and the LOQ value (worst case; upper bound). The absorption profiles looked similar for tested samples including the blank controls. Most of the applied dose (106.4%) was removed at 24 hours post dosing by washing the skin samples,

indicating that the applied Eclipse 70 was present in the dislodgeable dose. The mean total recovery of 113.3% was within the SCCS acceptance criteria of 85-115%.

(Kravcenko, 2023a)

B. Identification of Eclipse 70 in human skin following *in vitro* percutaneous absorption by Transmission Electron Microscopy (TEM)

In addition to afore mentioned study, a separate study investigating the presence of Eclipse 70 (titanium) in human skin by electron microscopy following topical application of Eclipse 70 present at 10% (in a representative sunscreen formulation (A69-14-36A-MOD)) to human skin membranes was conducted. For this purpose, the Eclipse 70 containing sunscreen formulation was applied to the mounted human split-thickness skin membranes at a rate of 5 mg/cm2 (3.2 mg). The skin membranes were mounted in static diffusion cells. The cells were positioned in a manifold heated to maintain a skin surface temperature of 32°C ± 1°C and the receptor fluid volume made up to the pre-calibrated line. The receptor fluid was mixed using a magnetic stirrer flea which was placed in the receptor chamber. An electrical resistance barrier integrity assessment was performed and any skin sample exhibiting resistance lower than 7.7 kΩ was excluded from subsequent absorption measurements.

A positive displacement pipette was used to apply the formulation evenly over the surface of the skin membranes. Two control samples of human skin membranes were treated in the same manner but left un-dosed. The cells were dismantled, and the skin under the cell flange (unexposed skin site) was cut off from the exposed skin site. Only the exposed skin was retained for analysis. The 24-hour post-dose exposed skin samples were cut in half. Each skin piece was individually fixed using Modified Karnovsky's Fixative. The samples were sent in cold packs for further processing and sectioning before TEM analysis. Samples were processed for TEM through 0.1M phosphate buffer rinses, post-fixed in 1% osmium tetroxide in 0.1M phosphate buffer, rinsed in distilled water, dehydrated through a graded ethanol series (50, 70, 95, and 100% ethanol), transitioned through propylene oxide, infiltrated with Epon-Araldite resin (1:1 resin-propylene oxide, 3:1 resin propylene oxide, pure resin), and embedded in pure Epon-Araldite resin. The blocks were thick sectioned at approximately 0.5 microns, with sections mounted on glass slides and stained with 1% Toluidine blue. Selected blocks were trimmed to allow thin sectioning at approximately 70-90 nm, with the sections mounted on copper grids. The grids were examined on a JEOL JEM-1400+ transmission electron microscope (TEM) without post-staining to avoid obscuring the heavy metal test substance. The examination included reviewing the full length of the epidermis and adjacent dermis visible on each grid, with special attention to any electron-dense features in size range of approximately 10-200 nm.

Results

All examined skin samples revealed recognisable features of *stratum corneum*, epidermal-dermal border and upper dermal tissue. Examination of control samples included representative images of any electrondense features, which primarily consisted of cytoplasmic bodies, which could be consistent with melanosomes, especially near the epidermal-dermal border. Some of these bodies were also present in the cytoplasm of the outer corneocytes. Small amounts of amorphous material, possibly degraded desmosomes or lipids could also be seen between and along the outermost corneocytes and was of similar electron density to the melanosome-like bodies.

Examination of most of the dosed samples (cell 2, 5 and 6) revealed very strongly electron-dense material but only along the outer *stratum corneum*. The material was darker than the melanosome-like bodies and degraded desmosomes. At higher magnifications the material was seen to be made up of particles of regular size and shape, consistent with images of the test item. Cell 4 had very little of the electron-dense material present, with just a few particles evident along outer corneocytes.

Conclusion

The electron microscopy images obtained in this study demonstrated that the titanium dioxide present in the Eclipse sunscreen formulation remained on the surface of the skin along the outer *stratum corneum* (SC). No titanium could be visualised in the inner layer of the SC or in the epidermis or dermis.

(Kravcenko, 2023b)

Overall conclusions of the Applicant on dermal absorption of Eclipse 70

In line with previously conducted dermal absorption studies with coated and uncoated titanium dioxide (nano form), the study conducted with a representative sunscreen formulation containing 10% Eclipse 70 did not provide any evidence for dermal absorption. For almost all samples, the titanium levels measured by ICP MS in epidermis, dermis, receptor fluid and receptor wash were below the methods limit of quantification (LOQ) and not different to the blank controls.

This finding was confirmed by an additional study conducted by the applicant, who investigated in a similar test set-up and dermal absorption experiment the presence of Eclipse 70 applied topically to skin a sunscreen formation in the skin by TEM. This study demonstrated that all titanium dioxide (Eclipse 70) applied to the skin membranes remained on the surface of the skin along the outer *stratum corneum*. As it was not possible to accurately quantify the concentrations and knowing that the actual concentrations of titanium in the different skin samples are between zero (best case, lower bound) and the LOQ (worst case, upper bound), the study report presents the study results by considering lower bound (zero) and upper bound (LOQ) levels (see **Table 11**).

Table 11: Absorption values obtained through human split-thickness skin, considering lower bound (zero) and upper bound (LOQ) levels.

Test substance	Amino acid treated nano-titanium dioxide with dimethicone (Eclipse 70) (lower bound - LOQ values reported as zero / best-case scenario)	Amino acid treated nano-titanium dioxide with dimethicone (eclipse 70) (upper bound - LOQ values / worst-case scenario)
Test Formulation	Eclipse Test Sunscreen	
Concentration of Test Item (w/w)	10% (corresponding to 6.05% titanium dioxide (w/w))	
Applied Mass (µg/cm²)	529	
Number of Samples	12	
Distribution	% Applied Dose)	
Donor Chamber Wash	0.06 %	0.08 %
Dislodgeable Dose	106.38 %	106.40 %
Stratum corneum	0.27 %	3.53 %
Unexposed Skin	0.00 %	0.82 %
Total Unabsorbed Dose	106.64 %	110.74 %
Epidermis	0.35 %	1.44 %
Dermis	0.00 %	0.82 %
Total Absorbed Dose	0.00 %	0.33 %
Dermal Delivery	0.36 %	2.58 %
Potentially Absorbable Dose	0.44 %	5.25 %
Mass Balance	107.00 %	113.33 %

Dislodgeable dose = skin wash 24 h + tissue swab 24 h + donor chamber wash.
Stratum corneum = tape strips 1 to 20.
Total unabsorbed dose = dislodgeable dose + *stratum corneum* + unexposed skin.
Total absorbed dose = cumulative receptor fluid + receptor chamber wash.
Dermal delivery = absorbed dose + epidermis + dermis.
Potentially absorbable dose = dermal delivery + *stratum corneum* 3-20.
Mass balance = unabsorbed dose + dermal delivery.

The results indicate that most of the applied dose (106.4%) was removed at 24 hours post dose by washing the skin samples, suggesting that the applied Eclipse 70 (TiO_2) was entirely present in the dislodgeable dose. Since most of the percent absorption values were below the LOQ, it was not possible to accurately determine the extent of absorption. Hence, considering lower (LOQ values reported as zero) and upper bound (LOQ values) absorption levels through skin, the theoretical worst case dermal delivery was 0.36 and 2.58%, respectively. The dermal delivery reflects the sum of the epidermis, dermis and receptor fluid and wash. The mass balance was 107.00 and 113.33%, respectively.

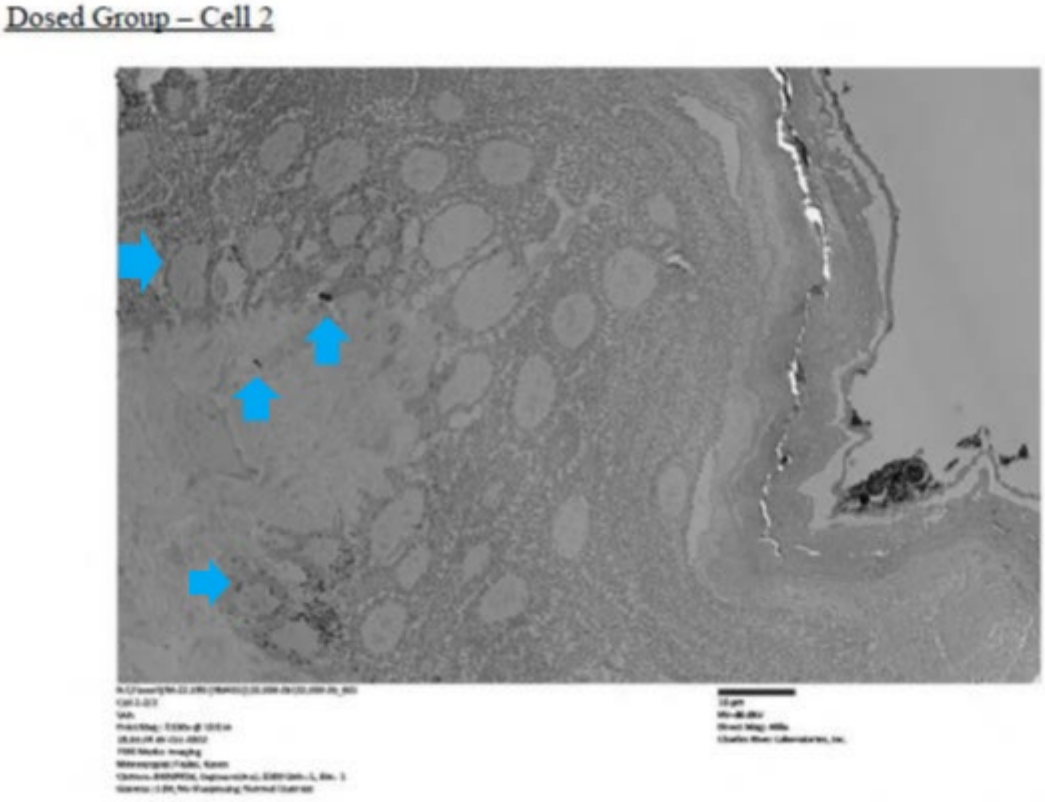
In summary, following the topical application of a sunscreen formulation containing 10% Eclipse 70, no absorption through the human skin of the test substance was observed beyond the most upper layers of the *stratum corneum*. The absorption measured throughout the experiment was below the LOQ for all layers. The mean total recovery (i.e., 107-113% considering the lower or upper bound) was within the SCCS acceptance criteria of 85-115%.

SCCS comment

Despite the mentioned limitations regarding the sensitivity of the analytical method in terms of LOQ, the estimated lower and upper bound values indicate that there was a certain level of Ti present in the epidermis and dermis layers of the skin (Table 11), indicating potential absorption of the nanoparticles through the skin.

Furthermore, the provided TEM images of skin sections show dark spots in several places below stratum corneum (see a typical example in Figure 10 below). No information is provided on the chemical identity of these spots. This information is needed (e.g. via SEM or TEM coupled with EDX) to exclude the possibility that these are TiO_2 nanoparticles to support the lack of dermal absorption of Eclipse 70 nanoparticles.

Figure 10: TEM Image of skin section



3.2.2 Other studies on toxicokinetics

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3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

Provided by the Applicant:

In the EU, titanium dioxide (nano form) is approved for use as an UV-filter in a concentration up to 25% in cosmetic products. The substance is regulated in Annex VI, entry 27a of the Cosmetics Regulation. The maximum use concentrations of Eclipse 70 in cosmetic sun protection factor (SPF) products are presented in **Table 12**.

Table 12: Maximum concentrations of Eclipse 70 in cosmetic products

Product category	Product types	Maximum use (% w/w) in finished products
Sun protection factor (SPF) products (ingredient used as UV-filter)		
Sun care cosmetics	Face sun protection - lotion/cream (includes all face creams with SPF)	10
	Body sun protection - lotion/cream	10
	Make-up: Liquid foundation with SPF	10

Ref.: 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

3.4 TOXICOLOGICAL EVALUATION

The toxicological studies provided in the submission relate to oral absorption, acute toxicity, skin/eye irritation, skin sensitisation, repeated dose toxicity, mutagenicity/genotoxicity, and photo-induced toxicity of titanium dioxide. Also, the lack of studies on reproductive and developmental toxicity and carcinogenicity was indicated, with inconclusive reports on dermal carcinogenicity. It was also mentioned that inhalation is not a relevant route of exposure for Eclipse 70. The submission also contained hazard profiles of the three individual coating materials to regard that they do not affect the particle properties or raise additional safety concerns.

SCCS comment

The SCCS has noted that, with the exception of a dermal absorption study, the provided toxicological data mainly relate to uncoated nanoparticles of titanium dioxide, and not to Eclipse 70 as a whole entity (i.e. inclusive of the composite coating). The provided toxicological studies are therefore not discussed in detail in this Opinion because it is not possible to relate the information to Eclipse 70.

In the absence of specific toxicological data on Eclipse 70, the SCCS considers that it is not possible to derive a meaningful conclusion on the (lack of) toxicological hazard of Eclipse 70 without a clear evidence to demonstrate that: 1) Eclipse 70 nanoparticles have a similar physicochemical profile to other TiO_2 nanomaterials already assessed by the SCCS; 2) the composite coating is stable for the duration of the product shelf life; and 3) that there is no dermal absorption of Eclipse 70 nanoparticles.

Information provided by the Applicant on individual components of the coating

Aluminium hydroxide

Aluminium hydroxide is included in the EU 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 (EC

CosIng, 2023). The material has not been evaluated by the SCCS as a coating material on any nanomaterial. As per the Cosmetic Ingredient Review (CIR)'s Expert Panel report, an orally administered aluminium in aluminium hydroxide has low bioavailability (<0.01%) and is excreted primarily in the faeces. The systemically absorbed aluminium in aluminium hydroxide is excreted primarily in the urine (CIR, 2016). Dermal absorption was calculated from an exposure study with female volunteers after application of antiperspirant per axilla. The antiperspirant contained aluminium chlorhydrate which had been doped with radioactive 26Al and the volunteers were biomonitored for 26Al in 24 hour-urine. The study result yielded an overall percentage of bioavailable Al of 0.00192% (SCCS, 2023). Aluminium hydroxide can be considered to be of low acute oral toxicity, based on an oral LD50 value of >2000 mg/kg bw in rats study. In rabbits' skin and eye irritation studies, undiluted aluminium hydroxide was determined to be non-irritating to skin but slightly irritating to eyes. In a guinea pig maximization test (GPMT), there was no skin sensitization reactions reported for aluminium hydroxide (ECHA, 2023c) There were no effects on immunological parameters in humans when orally administered with aluminium hydroxide (equal to 59 mg Al) 3 times daily for 6 weeks (CIR, 2016). Considering the available genotoxicity data, the SCCS was of the opinion that under the scenarios of dermal exposure in cosmetics, aluminium is not likely to pose a risk of genotoxic effects (SCCS, 2023). There was no indication of carcinogenicity at dietary doses up to 850 mg Al/kg bw/day in animal studies, and the SCCS considered that carcinogenicity is not expected at Al exposure levels that are achieved via cosmetic use (SCCS, 2023). In an oral reproductive toxicity study conducted with aluminium salts in mice, rabbits and dogs, testicular toxicity, decreased sperm quality, decrease of testicular weigh, degeneration of germinal epithelium and reduced fertility were observed. No effects on male fertility were observed in one rat study where aluminium nitrate was administered by gavage, however, histopathology examination data of testes was not provided for this study. No effects on female fertility were seen in rats after exposure for two weeks before mating and during gestation to aluminium nitrate by gavage or dissolved in drinking water (EFSA, 2008). In developmental toxicity studies in mice and rats, there were no significant maternal or developmental toxicity effects reported in animals orally administered up to 300 mg/kg bw/day aluminium hydroxide (103.8 mg Al/kg bw/day) and 768 mg/kg bw/day aluminium hydroxide (266 mg Al/kg bw/day), respectively (ECHA, 2023c). Effects of oral aluminium exposure (as lactate or chloride) on brain development have been studied in mice. LOAELs for impaired performance of reflexes and simple behaviours in the offspring ranged from maternal doses of 50 to 500 mg Al/kg bw/day. In one study, NOAELs of 10 mg Al/kg bw/day in the mother during pregnancy and 42 mg/ kg bw/day during lactation could also be identified. However, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice. The European Food Safety Authority (EFSA) expert panel concluded that a value of 1 mg Al/kg bw/week, representing a rounded value between the Tolerable Weekly Intakes (TWIs) provided by using the LOAEL 50 mg Al/kg bw/day and NOAEL 10 mg Al/kg bw/day approaches, should be established as the TWI (EFSA, 2008). In a recent drinking water developmental and chronic neurotoxicity study, the rats were exposed to aluminium citrate (30, 100 and 300 mg Al/kg bw/day), one of the more soluble aluminium compounds. Aluminium citrate was generally well tolerated in the dams at all doses, except the high dose (300 mg Al/kg bw/day) where diarrhoea occurred in 8 of the treated dams. The developmental toxicity NOAEL 30 mg AI/kg bw/day was reported, based on reported treatment related renal damage and reduced grip strength in the pups (Poirier et al., 2011, SCCS, 2022). The maternal toxicity NOAEL can be considered as 300 mg Al/kg bw/day. The SCCS in its recent opinion on the safety of aluminium in cosmetic products, derived the systemic NOAEL (NOAELsys) as 180 µg Al/kg bw/day from Poirier et al. study NOAEL, after adjustment for the rat oral bioavailability (0.6%) of aluminium citrate (SCCS, 2023). Aluminium hydroxide was reported to be used in leave-on products up to 10.1% (in eye products) and in rinse-off products up to 8.8% (in oral hygiene products). The CIR Expert Panel concluded that aluminium hydroxide is safe in the present practices of use and concentration described in its 2016 safety assessment (CIR, 2016).

Sodium myristoyl sarcosinate (SMS)

Sodium myristoyl sarcosinate (SMS) is included in the EU CosIng database as a cosmetic ingredient. 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 (EC, 2023). The material has so far not been evaluated by the SCCS as a coating on any nanomaterial. The following provides a short summary of the toxicokinetic and toxicological information available for SMS. Most of the information has been generated for the close structural analogue sodium lauroyl sarcosinate (SLS) The acute oral LD50 values for sodium lauroyl sarcosinate (SLS) ranged from 2000 to >5000 mg/kg bw in rodents. The acute dermal LD50 value for SMS was >2000 mg/kg bw in rats. The acute inhalation LC50 value for SLS 50 to 500 mg/m3 in rats (CIR, 2001, 2021). This information suggests SMS to be of low acute oral and dermal toxicity. A formulation containing 30% SMS was not irritating to rabbit skin (CIR, 2021). In a Bovine Corneal Opacity and Permeability (BCOP) test, a 20% SMS solution in physiological saline was considered severely irritating to corrosive. A mixture of 30% SMS and sodium myristate was severely irritating to rabbit eyes and considered a primary eye irritant (CIR, 2021). SMS did not exhibit peptide reactive properties in the Direct Peptide Reactivity Assay (DPRA) according to the OECD Test Guideline 442C. SMS induced luciferase activity in LuSens cells in the LuSens assay according to the OECD Test Guideline 442D. SMS did not induce dendritic cell activation in the Human Cell Line Activation Test (h-CLAT) according to the OECD Test Guideline 442E (ECHA, 2023c). In a GPMT, there was no skin sensitization response following exposure to 5% SLS, a structural analogue of SMS (ECHA, 2023d). In a human repeat-insult patch test (HRIPT), 5% SLS, a structural analogue of SMS was not assessed to be a skin sensitiser (CIR, 2001). Considering the overall weight of evidence, SMS is not considered to be a skin sensitiser.

In a subchronic oral toxicity study conducted in rats, the animals were orally administered the structural analogue SLS at dose levels of 0, 30, 100 or 250 mg/kg bw/day for 90 days. The NOAEL and LOAEL were established at 100 and 250 mg/kg bw/day, respectively (CIR, 2021). In a 2-year chronic dietary toxicity study conducted in rats, the animals were fed SLS at the dose levels of 0, 0.05, 0.2 and 1% (equivalent to 0, 39.4, 157.8 and 789 mg/kg bw/day for 2 years (CIR, 2001, US EPA, 1988). The low dose group was fed 0.05% SLS in the daily diet for the first 6 months of the study and 2% SLS in the diet (equivalent to 1578 mg/kg bw/day) for the remaining 18 months. At 1, 3 and 6 months, no significant differences were observed in lesions, fertility, mortality, haematology, or body weight gain between rats of the control and treated groups. At 24 months, the only consistent difference that could be attributed to the test substance was minor hyperplasia of the stratified squamous epithelium with excess keratin formation of the cardiac mucosa of the stomach in rats receiving the highest exposure to the test substance, 0.05% dose group (2% in the diet after 6 months) and 1% dose group (CIR, 2001). Based on the study results, the NOAEL was established at ≥2% (equivalent to 1578 mg/kg bw/day) (ECHA, 2023b).

SMS was tested negative in an in vitro genotoxicity battery of tests, i.e., bacterial reverse mutation assay (Ames test), chromosome aberration study in using human lymphocytes and mouse lymphoma assay (ECHA, 2023c). Based on the study results, SMS is not expected to be genotoxic. As per the CIR's Expert Panel report, fatty acyl sarcosines and their salts are not considered likely carcinogens as they and their metabolites "do not belong to any class of compounds that contains a significant number of mutagens or oncogens" (CIR, 2021). Considering the weight of evidence, SMS is not expected to have a carcinogenic potential. In a 2-year chronic dietary toxicity study conducted in rats, the feeding of up to 2% SLS did not adversely affect fertility of rats (CIR, 2021). In two oral pre-natal developmental toxicity studies conducted in rats and rabbits for SLS, there were no developmental or teratogenic effects were reported up to highest tested dose levels of 250 and 500 mg/kg bw/day, respectively. The maternal toxicity NOAELs were established at 30 and >500 mg/kg bw/day and the developmental toxicity NOAELs were established at >250 and >500 mg/kg bw/day, respectively (CIR, 2021, ECHA, 2023d). SMS was reported to be used in leave-on products up to 5% (in eye products) and in rinse-off products up to 6%. The CIR Expert Panel concluded that SMS is safe as used in cosmetics when formulated to be nonirritating.

The CIR Expert Panel also cautioned that Sarcosinate salts should not be used in cosmetic products in which N-nitroso compounds can be formed (CIR, 2021).

Dimethicone

Dimethicone is included in the EU 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 (EC, 2023). Dimethicone has been evaluated by the SCCS as a coating on nano-forms of titanium oxide (SCCS, 2014). Several acute toxicokinetic studies in dogs, rats, and a monkey reported minimal gastrointestinal absorption of dimethicone and up to 99.99% recovery of the administered dose via excretion. In a repeated dose study, beagle dogs were fed 91% dimethicone at a dose of 300 mg/kg bw/day for 120 days in the diet. Although one female showed atrophy of the spleen, and another female had slightly reddened rugae near the stomach and mucus in the intestine, dimethicone was not detected in any organs or considered absorbed (CIR, 2022).

In a dermal absorption study conducted in male rats, an occlusive patch containing [14C] dimethicone was applied to male CD rats for 24 h. radioactivity tracing demonstrated that 70% of the administered dimethicone dose was found on the patch materials, 11.4% was present at the site of application, and none was found in the blood. Minimal amounts were found in the faeces (0.01%) and carbon dioxide traps (0.001%) (CIR, 2022). Considering an oral LD50 values of >10000 mg/kg bw in rats, dermal LD50 values of >2000 mg/kg bw in rats and rabbits, and inhalation LC50 values of >695 to >11500 mg/m3 in rats, dimethicone is considered to be of low acute oral and dermal toxicity and moderate inhalation toxicity (CIR, 2003, ECETOC, 2003). Most dermal irritation studies using rabbits identified dimethicone as a minimal irritant (CIR, 2003). Most of the eye irritation studies conducted with varying viscosities dimethicone following the Draize protocol revealed transient mild to minimal irritation with transient conjunctival reaction as the most frequently observed adverse effect (CIR, 2003). Conjunctival redness is assumed to be due to the physical effect of the silicone causing disruption of the tear film and hence producing eye dryness (ECETOC, 2003).

Dimethicone (undiluted and 79%) was not a sensitizer in 4 assays using mice and guinea pigs (CIR, 2003). A 5% dimethicone was not assessed to be a skin irritant or sensitiser in a HRIPT study (CIR, 2003). Oral administration of dimethicone fluids of various viscosities in the diet in 28-day and 90-day studies did not result in any systemic toxicologically relevant effects up to highest tested dose, 100000 ppm in diet (equivalent to 18000 mg/kg bw/day for 28 day rat study, 4600 to 5300 mg/kg bw/day for 90 day rat studies and 18,800 mg/kg bw/day for 90 day mice study) (ECETOC, 2003, US EPA, 1988). Dimethicone was tested negative in an in vitro (Ames test, BALB/C-3T3 mouse cell transformation assay, CHO/HGPRT forward mutation assay and Chinese hamster ovary (CHO) chromosome aberration assay) and in vivo (mice micronucleus assay) genotoxicity tests (CIR, 2003).

In a 2-year combined chronic toxicity/carcinogenicity study, rats were dosed with 10 cSt dimethicone for 103 weeks. There were no treatment-related macroscopic or microscopic (neoplastic or non-neoplastic) findings at any dose level and a freestanding NOEL in rats was determined to be at the highest tested dose of 1000 mg/kg bw/day (ECETOC, 2003, JECFA, 2011).

In a 26-month dietary carcinogenicity study performed in rats, no toxicologically relevant treatment-related effects or increased incidences of any non-neoplastic or neoplastic lesions were reported in females/male animals up to highest tested dimethicone dose of 1742/2055 mg/kg bw/day. The EFSA panel considered 1742/2055 mg/kg bw/day as the study NOAEL (EFSA, 2020).

In a 76-week carcinogenicity dietary study, mice were orally fed with 91% dimethicone at 0.25% and 2.5% (equivalent to 520 and 5200 mg/kg bw/day) in diet. Another group received a single 0.2 mL subcutaneous injection of dimethicone (201 mg) into the left flank. The study author concluded that there was no treatment-related increase in the incidence of malignant or benign tumours in the mice groups receiving dimethicone by either oral diet or subcutaneous injection. Also, no treatment-related toxic effects were observed (CIR, 2003).

In a dermal lifetime carcinogenicity study, mice were treated topically with motor oil with an

unknown amount of dimethicone. No application site dermal neoplasms were microscopically confirmed in treated or control mice. Ulceration at the application site was observed in 8% of treated mice compared to 2.6% of control mice. One treated mouse had a palpable skin mass at the application site during week 65, which reverted by week 67. Epidermal hyperplasia at the application site was more evident in treated mice (17/50) than in control mice (1/115), suggesting to the study author slight dermal irritation (CIR, 2003). Overall, the CIR expert panel and EFSA panel concluded that dimethicone is negative in both oral and dermal carcinogenicity studies (CIR, 2003, EFSA, 2020).

In a three-generation reproductive toxicity study performed in rats, the animals were fed 0, 0.01 or 0.1% dimethicone in the diet (equivalent to 0, 4.5 or 45 mg/kg bw/day). The survival rate of the parent generation offspring was slightly higher in the high dose group as compared to controls, but lower in the generation F1 offspring. However, the study report authors considered these findings to be of questionable significance in the absence of other signs of toxicity. No other significant differences were reported. The EFSA panel noted that the study details provided was limited and the highest dose only 45 mg/kg bw/day (EFSA, 2020). In two male rats, reproductive toxicity studies, no treatment-related changes in any of the investigated reproductive parameters were reported in either animals orally dosed with 1000 mg/kg bw/day or dermally applied with 3000 mg/kg bw/day 350 cSt dimethicone for 4 weeks (ECETOC, 2003).

In three prenatal developmental toxicity studies, administration of dimethicone up to 3800 mg/kg bw/day by gavage in rats and dietary dimethicone up to 756 mg/kg bw/day in rabbits did not induce significant treatment-related adverse effects in the incidence of external, visceral, or skeletal abnormalities (CIR, 2003, EFSA, 2020). In similar dermal prenatal developmental toxicity studies in rabbits, no treatment related adverse effects were observed in the only tested dose, 200 mg/kg bw/day (CIR, 2003). In another developmental toxicity study, cross-linked silicone gel was implanted into rats and rabbits at doses of 3, 10 and 30 mL/kg bw equivalent to 2.8, 9.5 and 28.5 g/kg bw/day. Based on the absence of treatment related toxicity, parental as well as developmental NOEL was 28.5 g/kg bw (ECETOC, 2003).

In a prenatal oral gavage developmental toxicity study, rabbits were dosed orally with 10 or 350 cSt dimethicone at doses of 0, 33, 300 and 1000 mg/kg bw/day and the NOAEL for developmental toxicity was considered to be 1000 mg/kg bw/day (ECETOC, 2003). Based on the results of the above studies it can be concluded that the potential of dimethicone to be a reproductive or developmental toxicant is low.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) level for dimethicone of 0 to 1.5 mg/kg bw/day (only to compounds with a relative molecular mass in the range of 200–300) (CIR, 2003, JECFA, 2011). The EFSA panel established an ADI of 17 mg/kg bw/day for dimethyl polysiloxane (E 900) using the NOAEL 1742 mg/kg bw/day from 26-month dietary carcinogenicity study (EFSA, 2020).

Dimethicone was reported to be used in leave-on products up to 85% and in rinse-off products up to 23.4%. The CIR Expert Panel concluded that dimethicone is safe in cosmetics in the present practices of use and reported concentration ranges when formulated to be non-irritating, with the exception that the available data are insufficient to make a determination of safety for use in products that may be incidentally inhaled when applied using airbrush devices (CIR, 2022).

SCCS comment

The SCCS has noted the provided information relating to toxicological hazard of the three individual components of the coating. It is worth highlighting that although each of the substances has been noted in CosIng database for use in cosmetic products, none has yet been assessed for safety as a colorant, preservative, or UV-filter, or included in any of the Annexes of the Cosmetic Products Regulation (EC) No 1223/2009.

The SCCS has also noted that the information relating to sodium myristoyl sarcosinate is mainly derived from studies on a structural analogue – sodium lauroyl sarcosinate. Citing ECHA (2023), it is mentioned that sodium myristoyl sarcosinate was tested negative in an *in vitro* genotoxicity battery of tests, i.e., bacterial reverse mutation assay (Ames test), mouse

lymphoma assay, and chromosomal aberration study using human lymphocytes. The SCCS requires original study reports in this regard to be able to assess the validity and relevance of the tests to the current evaluation.

Overall, the SCCS considers that the information on toxicological hazard of the individual coating constituents will be useful when uncertainties and data gaps relating to the potential modulation of the properties and toxicokinetic behaviour of TiO_2 nanoparticles have been clarified.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

According to the Applicant:
Eclipse 70 consists of a core titanium dioxide particle (nano form; up to 70% w/w) and three coating materials, namely, sodium myristoyl sarcosinate (SMS; up to 14% w/w), dimethicone (up to 10% w/w), and aluminium hydroxide (up to 6% w/w).

As presented in **Section 3.1** [of the Applicant's submission], Eclipse 70 is a stable coated titanium dioxide particle (nano form), meaning that the core particle and the coating materials can be considered one entity from a toxicological point of view.

As discussed in **Section 3.3.1** [of the Applicant's submission], the results from a recent OECD Test Guideline 428 compliant dermal absorption study with Eclipse 70 suggests no significant absorption through human skin.

The absorption measured throughout the experiment was below the LOQ for all skin layers. The mean total recovery (i.e., 107-113% considering the lower or upper bound) was within the SCCS acceptance criteria of 85-115%. Further, the imaging of the skin sections using TEM analysis did not show any nanoparticles of titanium dioxide beyond the uppermost layers of the *stratum corneum*. Titanium dioxide (nano form) has an overall low toxicity profile and the data available on the three coatings indicates that they do not affect the particle properties or raise additional safety concerns. Given the low skin penetration potential of Eclipse 70 and the overall low toxicity profile of its individual constituents, the calculation of margins of safety (MoS) to evaluate its safety when used as a UV-filter at concentrations of up to 10% w/w in dermally applied cosmetic products is not considered necessary. Exposure by the oral and inhalation routes is assumed to be an unlikely under normal and reasonably foreseeable conditions of use.

SCCS comments
The focus of the current submission was to demonstrate that the TiO_2 nanomaterial with the new composite coating could be considered safe on the basis of similarity in terms of physicochemical and toxicokinetic aspects to other TiO_2 nanomaterials that have already been assessed by the SCCS (SCCS/1516/13 - Revision of 22 April 2014).

As discussed in previous sections, the available information indicates Eclipse 70 to be most likely outside the physicochemical and toxicokinetic properties of the TiO_2 nanomaterials covered in the SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014). The SCCS therefore considers that, in the absence of specific toxicological data on Eclipse 70, safety evaluation of Eclipse 70 is not possible - either on the basis of a similarity to the previously assessed TiO_2 nanomaterials, or on the basis of the additional information provided in the current submission.

3.6 DISCUSSION

Chemical and physical specifications

Chemical composition: The nanomaterial under current evaluation is composed of core TiO_2 nanoparticles that constitute 70% w/w of the material, which is surface coated sequentially with aluminium hydroxide (up to 6% w/w), sodium myristoyl sarcosinate (up to 14% w/w), and dimethicone (up to 10% w/w). This means that, in the final form, Eclipse 70 nanoparticles are composed of up to 30% w/w of the coating materials. The information provided on chemical formula, structure and molecular weight for dimethicone (CAS number 63148-62-9) needs to be corrected as it relates to another discrete compound 'dimeticone' (octamethyltrisiloxane; CAS Number: 28349-86-2).

No specific information is provided about the surface characteristics of Eclipse 70. However, from the information provided on coating materials, it can be anticipated that the surface characteristics of fully coated Eclipse 70 would be determined by the outermost layer of dimethicone (i.e. the coated nanoparticles will be hydrophobic). Whilst the SCCS agrees that measurement of octanol/water partition coefficient is not applicable to uncoated titanium dioxide particles, Eclipse 70 has a surface coating composed of inorganic/organic substances (resulting in a hydrophobic surface), which may affect partitioning between hydrophilic/lipophilic phases. The OECD TG 126 may be followed in this regard to provide hydrophobicity index of Eclipse 70.

Particle size distribution: The provided information on sample preparation prior to measurement of particle size distribution is limited to a single sentence: "A dispersion of the sample is made in a 10 mL volume of Isopropanol. 2.5 µL of this solution is then deposited in a Silicon Wafer using a Spin Coating technique". Despite the SCCS request for further information, no more details were provided. The SCCS considers the information as inadequate because appropriate sample preparation to achieve adequate dispersion of nanoparticles is crucial for physicochemical characterisation and toxicological testing of nanomaterials (SCCS Guidance on Nanomaterials: SCCS/1655/23).

The SCCS considers that the use of methods based on laser diffraction is only appropriate for larger sized agglomerates/aggregate, and not for particle size measurement of constituent particles in the nano scale.

Particle size distribution of Eclipse 70, measured by SEM (sample 2303-E0132782), is also provided but it is not clear how the line is drawn and whether it is based on a mathematical model. It is notable from Figure 7 that the particle size distribution is not completely monomodal. Also some minor XRD peaks have not been identified in the data provided in the submission.

Despite the uncertainty due to the lack of details on particle dispersion, the information provided on particle size distribution measured by electron microscopy shows that median particle size of Eclipse 70 is around 21 nm. Since up to 30% (w/w) of the material is comprised of coating substances, the actual median size of core TiO_2 nanoparticle is most likely below 21 nm. This renders Eclipse 70 outside the particle size range covered in the SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014):

"….have a median particle size based on number size distribution of 30 to 100 nm (measured by different methods) as submitted in the dossier, or larger. Thus, whilst primary particle size may be smaller (around 10 nm), the median particle size of TiO_2 nanomaterials in a cosmetic formulation must not be smaller than 30 nm in terms of number-based size distribution".

In response to the SCCS request for further information, the Applicant provided explanation that while the coating represents a significant proportion by weight, the overall thickness of the coating layer is only a few nanometers. It was claimed that analysis of the particle size of

both untreated and treated particles (using the same method, SEM by number, and the same lot) showed a very comparable D50 (median particle size). In the absence of any supporting data, the SCCS regards the Applicant's narrative statement as unsatisfactory, and maintains the view that the median particle size range of Eclipse 70 is most likely outside that covered in the previous SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014).

Aspect ratio: The aspect ratio of the nanoparticles is given but no explanation is provided on how it was determined. In the absence of information on full aspect ratio distribution based on individual particle size measurements, it is not clear if the given aspect ratio is a median/mean value. The SCCS has also noted that the specific surface area of the materials tested for skin penetration is 5.8 times higher than the one reported above (87.6 m^2/g versus 15.14 m^2/g). The Applicant needs to confirm which value is correct, or whether they reflect a variation between the two different batches of the material.

Stability of the coating: The Applicant provided data from a test to indicate stability of the coating. The reported method involved, dispersing, filtering, making a 'press-cake' and dropping 1-2 water droplet on press-cake, and monitoring contact angle at 0 sec, 20 sec, 60 sec, 15 min, 30 min and 45 min. In response to the SCCS request for further information, the Applicant explained that the water droplet contact angle test was used to confirm the stability of the surface treatment, even after applying an isopropanol (IPA) washing process. Other hydrophobicity tests were also conducted over a longer period (up to 48 months), which demonstrated that the coated TiO_2 remains stable and retains its water resistance properties. The SCCS regards the provided information unsatisfactory because validity and relevance of the used method have not been established in terms of how the measurement of a change in the water contact angle (over short intervals, and an overall short period of time) could be considered to depict long term stability of the coating on the nanomaterial. Similarly, details have not been provided on the 'Float' and 'Stir' methods used in the long term tests to enable assessment of their validity and relevance to demonstrate stability of the coating.

Photocatalytic activity: The SCCS is of the view that where evidence is provided to show that photocatalytic activity remained quenched over a long period of time, it could be considered an indirect way of ascertaining stability of a coating on a photoreactive/photocatalytic nanomaterial. In this regard, the Applicant provided data on photocatalytic activity (Table-9) to indicate that it is below the acceptable level of 10%, compared to the same material without surface coating. However, the provided evidence only comprised of plate images without any detail on how photocatalytic activity was measured, calculated, or what it was compared with to conclude that it was within the acceptable limit.

In response to the SCCS request for further information, the Applicant explained that the method outlined in SCCS/1516/13 was followed for testing. The photocatalytic activity was measured on the coated test sample and the non-coated control. Since the activity of the coated test sample was below 10% compared to the non-coated control, the Applicant concluded that the photocatalytic activity of the coated material remained quenched. In the absence of detailed information, the SCCS regards the Applicant's narrative statement as unsatisfactory and reiterates that full experimental details of the test should be provided to enable evaluation of the validity of the results.

Toxicokinetics: Only limited information is provided on toxicokinetics of Eclipse 70. The SCCS regards the Applicant's narrative statement on the stability of the composite coating as unsatisfactory and considers that stability of the composite coating has not been demonstrated either directly (see 3.1.15) or indirectly (see 3.1.17).

Dermal/percutaneous absorption: Despite the mentioned limitations regarding the sensitivity of the analytical method in terms of LOQ, the estimated lower and upper bound values provided in the submission indicate that there was a certain level of Ti present in the epidermis and dermis layers of the skin, indicating potential absorption of the nanoparticles through the skin.

Furthermore, the provided TEM images of skin sections show dark spots in several places below stratum corneum (see a typical example in the Figure below). No information is provided on the chemical identity of these spots. This information is needed (e.g. via SEM or TEM coupled with EDX) to exclude the possibility that these are TiO_2 nanoparticles to support the lack of dermal absorption of Eclipse 70 nanoparticles.

Exposure assessment

The information provided by the Applicant on exposure assessment is limited to describing the use levels in different cosmetic products

Toxicological evaluation

Titanium dioxide: The SCCS has noted that, with the exception of a dermal absorption study, the provided toxicological data mainly relate to uncoated nanoparticles of titanium dioxide, and not to Eclipse 70 as a whole entity (i.e. inclusive of the composite coating). The provided toxicological studies are therefore not discussed in detail in this Opinion because it is not possible to relate the information to Eclipse 70.

In the absence of specific toxicological data on Eclipse 70, the SCCS considers that it is not possible to derive a meaningful conclusion on the (lack of) toxicological hazard of Eclipse 70 without a clear evidence to demonstrate that: 1) Eclipse 70 nanoparticles have a similar physicochemical profile to other TiO_2 nanomaterials already assessed by the SCCS; 2) the composite coating is stable for the duration of the product shelf life; and 3) that there is no dermal absorption of Eclipse 70 nanoparticles.

Individual components of the coating: The SCCS has noted the provided information relating to toxicological hazard of the three individual components of the coating. It is worth highlighting that although each of the substances has been noted in CosIng database for use in cosmetic products, none has yet been assessed for safety as a colorant, preservative, or UV-filter, or included in any of the Annexes of the Cosmetic Products Regulation (EC) No 1223/2009.

The SCCS has also noted that the information relating to sodium myristoyl sarcosinate is mainly derived from studies on a structural analogue – sodium lauroyl sarcosinate. Citing ECHA (2023), it is mentioned that sodium myristoyl sarcosinate was tested negative in an *in vitro* genotoxicity battery of tests, i.e., bacterial reverse mutation assay (Ames test), mouse lymphoma assay, and chromosomal aberration study using human lymphocytes. The SCCS requires original study reports in this regard to be able to assess the validity and relevance of the tests to the current evaluation.

Overall, the SCCS considers that the information on toxicological hazard of the individual coating constituents will be useful when uncertainties and data gaps relating to the potential modulation of the properties and toxicokinetic behaviour of TiO_2 nanoparticles have been clarified.

Safety evaluation

The focus of the current submission was to demonstrate that the TiO_2 nanomaterial with the new composite coating could be considered safe on the basis of similarity in terms of physicochemical and toxicokinetic aspects to other TiO_2 nanomaterials that have already been assessed by the SCCS (SCCS/1516/13 - Revision of 22 April 2014).

As discussed in previous sections, the available information indicates Eclipse 70 to be most likely outside the physicochemical and toxicokinetic properties of the TiO_2 nanomaterials

covered in the SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014). The SCCS therefore considers that, in the absence of specific toxicological data on Eclipse 70, safety evaluation of Eclipse 70 is not possible - either on the basis of a similarity to the previously assessed TiO_2 nanomaterials, or on the basis of the additional information provided in the current submission.

4. CONCLUSION

1. In light of the data provided, does the SCCS consider safe the use of Titanium Dioxide (nano) coated with a combination of w/w 6% Aluminium Hydroxide, 14% Sodium Myristoyl Sarcosinate and 10% Dimethicone, for use as UV filter in dermally applied cosmetic products?

   Considering all the provided information, the SCCS is of the view that there are a number of uncertainties and data gaps that do not allow a conclusion on the safety of titanium dioxide (nano) coated with a combination of w/w 6% aluminium hydroxide, 14% sodium myristoyl sarcosinate and 10% dimethicone (Eclipse 70) - either on the basis of a similarity to the TiO_2 nanomaterials previously assessed by the SCCS, or on the basis of the additional information provided in the current submission.

2. Does the SCCS have any further scientific concerns regarding the use of Titanium Dioxide (nano) coated with the above-mentioned materials when used as UV-filter in dermally applied cosmetic products?

   The provided information has not demonstrated a similarity of the titanium dioxide with the above-mentioned composite coating (Eclipse 70) to other TiO_2 nanomaterials assessed in the previous SCCS Opinion (SCCS/1516/13 - Revision of 22 April 2014) in terms of physicochemical characteristics, stability of the coating, and the lack of dermal absorption of the nanoparticles. If these aspects cannot be addressed, additional data on physicochemical, toxicological and exposure aspects specifically relating to the nanomaterial under evaluation (Eclipse 70) will be needed to conclude on the safety of its use in cosmetic products.

5. MINORITY OPINION

None.

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