Scientific Committee on Consumer Safety

SCCS

OPINION on

Titanium dioxide (TiO_2) used in cosmetic products that lead to exposure by inhalation

The SCCS adopted this document
by written procedure on 6 October 2020

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All Declarations of Working Group members are available on the following webpage: https://ec.europa.eu/transparency/regexpert/index.cfm

This Opinion has been subject to a commenting period of the minimum four weeks after its initial publication due to legislative constraints (from 10 August until 07 September 2020). Comments received during this time period were considered by the SCCS. The final version has been amended, in particular in the following sections: SCCS comment in physicochemical section, Tables 9b, 13b, 15a, 18a, 18b, 20b and 20c in exposure assessment section, toxicokinetic section, SCCS comment in genotoxicity section, SCCS comment in margin of safety section.

1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided and of the possible classification as Carcinogen Cat. 2 (inhalation) in Annex VI to Regulation (EC) n.1272/2008, does the SCCS consider Titanium dioxide safe when used as a UV-filter (entry 27 Annex VI) in cosmetic products up to a maximum concentration of 25 %, as a colorant (entry 143 Annex IV) and as an ingredient in all other cosmetic products?

On the basis of safety assessment, the SCCS is of the opinion that the use of pigmentary titanium dioxide (TiO_2) up to a maximum concentration of 25% in a typical hair styling aerosol spray product is not safe for either general consumers or hairdressers.

The safety assessment has shown that the use of pigmentary TiO_2 in loose powder up to a maximum concentration of 25% in a typical face make-up application is safe for the general consumer.

It needs to be noted that these conclusions are based on safety assessment of TiO_2 in the context of possible classification as category-2 carcinogen (via inhalation). This means that the conclusions drawn in this Opinion are applicable to the use of pigmentary TiO_2 in a cosmetic product that may give rise to consumer exposure by the inhalation route (i.e. aerosol, spray and powder form products). As such, the Opinion is not applicable to any pearlescent pigment because of the composite nature of such materials, of which TiO_2 is only a minor constituent.

2. Alternatively, if up to 25% use is not considered safe, what is according to the SCCS, the maximum concentration considered safe for use of Titanium dioxide as an ingredient in cosmetic products?

In the SCCS's opinion, the use of pigmentary TiO_2 in a typical hair styling aerosol spray product is safe up to a maximum concentration of 1.4 % for general consumers, and 1.1 % for hairdressers.

3. Does the SCCS have any further scientific concerns with regard to the use of Titanium dioxide in cosmetic products?

It needs to be emphasised that the SCCS conclusions have been drawn from a *very selected group of cosmetic product*s based on *only one type of TiO_2 material* (pigmentary, anatase, surface-treated). In the absence of more information, it may not be clear whether these conclusions would be applicable to the use of pigmentary TiO_2 materials in other similar types of cosmetic applications that may be on the market. In this regard, the SCCS is of the opinion that other applications of pigmentary TiO_2 materials can also be considered safe if the MoS calculation is performed as detailed in the current Opinion, *and* if the resultant MoS for the combined use of different products is above 25 for general consumers and for hairdressers.

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

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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 authorised both as a colorant under entry 143 of Annex IV and as a UV-filter under entries 27 and 27a (nano form) of Annex VI to Regulation (EC) No 1223/2009. TiO_2 is also used as a filler in cosmetic products (not subject to specific regulatory restrictions). In 2000, SCCNFP concluded that the toxicological profile of TiO_2 (Opinion SCCNFP/0005/98): 'does not give rise to concern in human use since the substance is not absorbed through the skin'.

In July 2013, the SCCS delivered a new Opinion on TiO_2 (nano) (SCCS/1516/1311). In that Opinion, the SCCS concluded that the use of TiO_2 (nano) as UV-filter in sunscreens and at a concentration up to 25% can be considered not to pose any risk of adverse effects in humans. The SCCS also considered that applications that might lead to inhalation exposure to TiO_2 nanoparticles (such as powders or sprayable products) cannot be considered safe.

In 2014, the SCCS provided clarification of the meaning of the term 'sprayable application/products' (Opinion SCCS/1539/14). Furthermore, SCCS issued an additional Opinion in 2018 (SCCS/1583/17) on TiO_2 (nano form) as UV-Filter in sprays; it concluded that 'the information provided is insufficient to allow assessment of the safety of the use of nano-TiO_2 in spray applications that could lead to exposure of the consumer's lungs'.

Finally, SCCS provided an Opinion on TiO_2 (nano form) coated with Cetyl Phosphate, Manganese Dioxide or Triethoxycaprylylsilane as UV-filter in dermally-applied cosmetics (SCCS/1580/16). The Opinion confirmed previous assessment: safe use in cosmetics for products intended for application on skin. However, this Opinion does not apply to applications that might lead to exposure of the consumer's lungs by inhalation.

The European Risk Assessment Committee (RAC) of ECHA issued in September 2017 an Opinion recommending a Carcinogen Category 2 classification (i.e. as a suspected human carcinogen) of TiO_2 (CAS 13463-67-7) by inhalation route only.

Following this RAC recommendation, the European Commission on 4 October 2019 adopted[1] for TiO_2 a classification as a 'Carcinogen Category 2 (inhalation)' for the purposes of adaptation to technical and scientific progress of the Regulation (EC) No 1272/2008 (CLP Regulation Annex VI entry); this classification applies to TiO_2 'in powder form containing 1% or more of particles with an aerodynamic diameter of ≤ 10 μm'.

In addition, the following note applies to the classification of mixtures containing TiO_2: 'The classification as a carcinogen by inhalation applies only to mixtures placed on the market in powder form containing 1% or more of titanium dioxide which is in the form of or incorporated in particles with an aerodynamic diameter of ≤ 10 μm'.

In January 2020, industry submitted a dossier to support the safety of TiO_2 according to Article 15(1) Regulation (EC) n.1223/2009. Since the nano form of TiO_2 is already restricted under entry 27a of Annex VI to Regulation 1223/2009 (i.e. not to be used in applications that may lead to exposure of the end-user's lungs by inhalation), this dossier covers only the non

[1] COMMISSION DELEGATED REGULATION (EU) 2020/217 of 4 October 2019 https://eur-lex.europa.eu/eli/reg_del/2020/217/oj

nano form of TiO_2. More specifically, this dossier is confined to the uses of TiO_2 (non nano) in cosmetic products that may give rise to consumer exposure by the inhalation route (i.e. aerosol, spray and powder form products).

The Commission requests the SCCS to carry out a safety assessment on TiO_2 in view of the information provided, for the purpose of the adoption of the necessary measures in accordance with Article 15(1) Regulation (EC) n.1223/2009.

Terms of reference

1. In light of the data provided and of the possible classification as Carcinogen Cat. 2 (inhalation) in Annex VI to Regulation (EC) n.1272/2008, does the SCCS consider Titanium dioxide safe when used as a UV-filter (entry 27 Annex VI) in cosmetic products up to a maximum concentration of 25 %, as a colorant (entry 143 Annex IV) and as an ingredient in all other cosmetic products?

2. Alternatively, if up to 25% use is not considered safe, what is according to the SCCS, the maximum concentration considered safe for use of Titanium dioxide as an ingredient in cosmetic products?

3. Does the SCCS have any further scientific concerns with regard to the use of Titanium dioxide in cosmetic products?

3. OPINION

Preamble

The Applicant provided a dossier in which three groups of TiO_2 materials are described, two pigmentary TiO_2 (either coated or uncoated), and one pearlescent pigment. The latter group relates to a composite mixture comprising different materials (e.g. mica, silica, etc), to which TiO_2 has only been applied as a coating layer. According to the Applicant, this group has been included in the dossier to give a full picture of the compositional variety of non-nano TiO_2 raw materials used in cosmetic products. The dossier, therefore, contained information that is beyond the scope inferred from the formal application of the CLP CMR2 classification, which refers to TiO_2 as such.

In developing this Opinion, the SCCS considered the safe use of TiO_2 in cosmetics on the basis of safety assessment of TiO_2 via inhalation route, because of the recent CLP CMR2 classification for inhalation exposure. In this context, this Opinion is focused on the safety assessment of the pigmentary TiO_2 materials that were presented in the dossier for use in the two product categories evaluated. The Opinion has not evaluated the pearlescent pigments included in the dossier because they are composed of different materials and contain TiO_2 only as a minor constituent. In the SCCS's view, the physicochemical and toxicological properties of such materials are likely to be driven by the mixture composition, not TiO_2 as such. Consequently, the Opinion has only discussed in any detail the information relating to pigmentary TiO_2 materials, and has excluded the pearlescent pigments specified in the dossier from the current evaluation.

During the evaluation, the SCCS sought clarification and more information on certain aspects from the Applicant. In response, the Applicant provided a document with additional information and clarifications. These have been marked as 'additional information provided by the Applicant upon SCCS request' throughout the Opinion.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Titanium Dioxide

3.1.1.2 Chemical names

Titanium dioxide, Titanium (IV) oxide

3.1.1.3 Trade names and abbreviations

S75

3.1.1.4 CAS / EC number

	CAS number	EC number
Titanium dioxide	13463-67-7	236-675-5
Anatase	1317-70-0	215-280-1
Rutile	1317-80-2	215-282-2

3.1.1.5 Structural formula

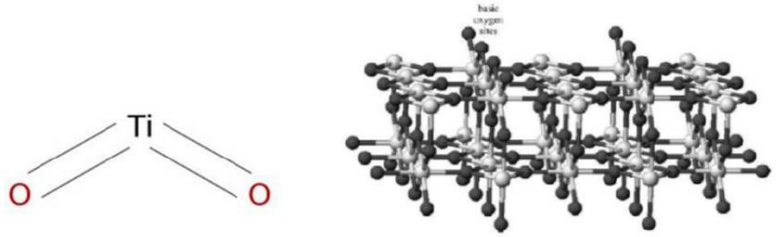

Figure 1: Structural formula of TiO_2 and its crystal form (noted by the SCCS as rutile)

Ref. 1

SCCS comment

TiO_2 can exist in three crystalline forms (brookite, anatase and rutile). The image depicted in Figure 1 is the rutile phase (according to Ganyecz et, 2019), whereas the most relevant material assessed in this Opinion is anatase.

Ref: Ganyecz *et al*., 2019

3.1.1.6 Empirical formula

TiO_2

3.1.2 Physical form

Solid white powder

3.1.3 Molecular weight

79.866 g/mol

3.1.4 Purity, composition and substance codes

Purity[2] of TiO_2 is > 99% (pigmentary TiO_2)

[2] CPR, Annex IV, TiO_2 must comply with the "purity criteria as set out in Commission Directive 95/ 45/EC (E 171)", which was replaced by Commission Regulation (EU) No 231/2012 of 9 March 2012 [4] laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council; FDA USP monograph

General description of composition provided by the Applicant (Ref 1)

For the purpose of this submission, a general description of TiO_2-based raw materials is presented below. TiO_2-based raw materials used in cosmetics can be divided into 3 different groups:

Group 1: Pigmentary TiO_2 (uncoated and coated)

Pigmentary TiO_2 is mostly used for its opacifying properties by light scattering. The preferred particle size of pigmentary TiO_2 for providing white opacity to any application is determined by physical properties. A particle scatters electromagnetic radiation with a wavelength that is twice the particle diameter. Hence green light with a wavelength of 550 nm is scattered most strongly by particles of 275 nm diameter. Therefore, pigmentary TiO_2 is manufactured intentionally with average particle sizes > 100 nm to provide opacity and needed colour effects. This pigmentary TiO_2 group is further divided in two subgroups:

- *Group 1a*: TiO_2 is coated with metal oxides like SiO_2, Al_2O_3, ZrO_2 or CeO_2, amongst others to improve dispersibility and processability in formulations. Hydrophilic and hydrophobic organic compounds (e.g. dimethicone or caprylylsilanes) are added to TiO_2 to improve the formulation in hydrophilic and hydrophobic solvents.

- *Group 1b*: uncoated TiO_2 has no surface treatments or coatings and is of high purity although it may contain small quantities (< 0.5%) of primary particle growth and crystal phase control agents (alumina, sodium or potassium, and phosphate) that are added prior to the calcination process. It is also being used and regulated as food additive (E171).

Group 2: Nano TiO_2 materials

This group, comprising nanoforms of TiO_2, is considered by the Applicant as not relevant for this submission.

Group 3: pearlescent pigments

The pearlescent pigments are composed of various substrates that are coated with TiO_2 and other metal oxide layers.

Table 1 below gives a typical composition of the materials included in the current dossier.

Table 1: Typical composition of TiO_2-based raw materials i.e. pigmentary TiO_2 (group 1a, coated and 1b uncoated) covered in the Applicant's dossier.

Group	**TiO_2 content**	**Coating**	**Crystal phase control agents**	**Other ingredient layers physically fixed**
1a (Pigmentary TiO_2 - coated)	> 95%	Hydrophilic coating Hydrophobic coating	-	-
1b (Pigmentary	> 99%	-	Alumina, sodium or potassium, and phosphate	-

TiO_2 - uncoated)				
3 (Pearlescent pigments)	1 – 75%	-	Mica, Silica, Alumina, Fluorphlogopite, Potassium, Aluminum Silicate, Calcium Aluminum Borosilicate, Calcium Sodium Borosilicate, Synthetic Fluorophlogopite	Fe_2O_3, Fe_3O_4, Cr_2O_3, SiO_2, Al_2O_3, Carmine, Ferric Ferrocyanide, $BaSO_4$, SnO_2

Note: No information is provided in this Table on the materials in group 2 (nano TiO_2), as these are considered as not relevant for this submission by the Applicant.

Ref. 1

SCCS comment

The SCCS is of the opinion that only pigmentary TiO_2 (groups 1a and 1b) can be considered for safety assessment in the context of CLP CMR2 classification, because they are mainly composed of titanium dioxide. The Opinion will not consider the materials in group-3 (pearlescent pigments) as they are composites of different materials that contain TiO_2. In the SCCS's view, the physicochemical and toxicological properties of such materials are likely to be driven by the mixture composition and not by TiO_2 as such.

Furthermore, contrary to the Applicant's suggestion, the SCCS has regarded it relevant to consider group 2 (comprising nano TiO_2 materials) for this evaluation, because pigmentary TiO_2 materials also contain a significant fraction of nano-scale particles. In the SCCS's view, safety assessment of such a fraction is crucially important for the estimation of inhalation exposure of the alveolar region of the lungs.

No experimental data have been provided on the analysis of the purity of the TiO_2 material. These data should be provided.

3.1.5 Impurities / accompanying contaminants

No information provided

3.1.6 Solubility

Insoluble in water and organic solvents[3]

3.1.7 Partition coefficient (Log Pow)

Not relevant

[3] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance

3.1.8 Additional physical and chemical specifications

Colour Index	77891; Pigment white
Melting point	1855 ºC
Boiling point	2900 ºC
Chrystal forms	Anatase; Rutile
Density	3.9- 4.1 g/m^3 (R4-R6)
Refractive Index	2.55 – 2.75 (R4-R6)(see details below)
pH	Not found
pKa	Not applicable for uncoated TiO_2
UV-VIS absorption spectrum	Not provided

Detailed information on different TiO_2 materials (R4-R9) dossier is given below:

Sample Parameters	R1 TiO2 Powder (Rutile)	R2 TiO2 Powder (Rutile)	R4 201902981611 (Anatase)	R6 201602981613 (Rutile)	R7 Lot 0143 (Rutile)	R9 Lot 1024 (Rutile)
Maximum diameter	1.0µm	6.0µm	6.0µm	1.5µm	1.5µm	6.0µm
Minimum diameter	0.03µm	0.03µm	0.03µm	0.03µm	0.03µm	0.03µm
Particle density	4.1g/cm^3	4.1g/cm^3	3.9g/cm^3	4.1g/cm^3	4.1g/cm^3	4.1g/cm^3
Refractive index	2.75	2.75	2.55	2.75	2.75	2.75
Particle absorption	0.2	0.2	0.2	0.2	0.2	0.2
Non-Sphericity factor	1.3	1.3	1.3	1.3	1.3	1.3
Calibration Standard Parameters						
Peak diameter	0.483µm	0.483µm	0.483µm	0.483µm	0.483µm	0.483µm
Half height peak width	0.3µm	0.3µm	0.3µm	0.3µm	0.3µm	0.3µm
Particle density	1.385g/ml	1.385g/ml	1.385g/ml	1.385g/ml	1.385g/ml	1.385g/ml
Fluid Parameters (Gradient)						
Fluid Density	1.064 g/ml	1.064 g/ml	1.064 g/ml	1.064 g/ml	1.064 g/ml	1.064 g/ml
Fluid refractive index	1.357	1.357	1.357	1.357	1.357	1.357
Fluid Viscosity	1.3cps	1.3cps	1.3cps	1.3cps	1.3cps	1.3cps

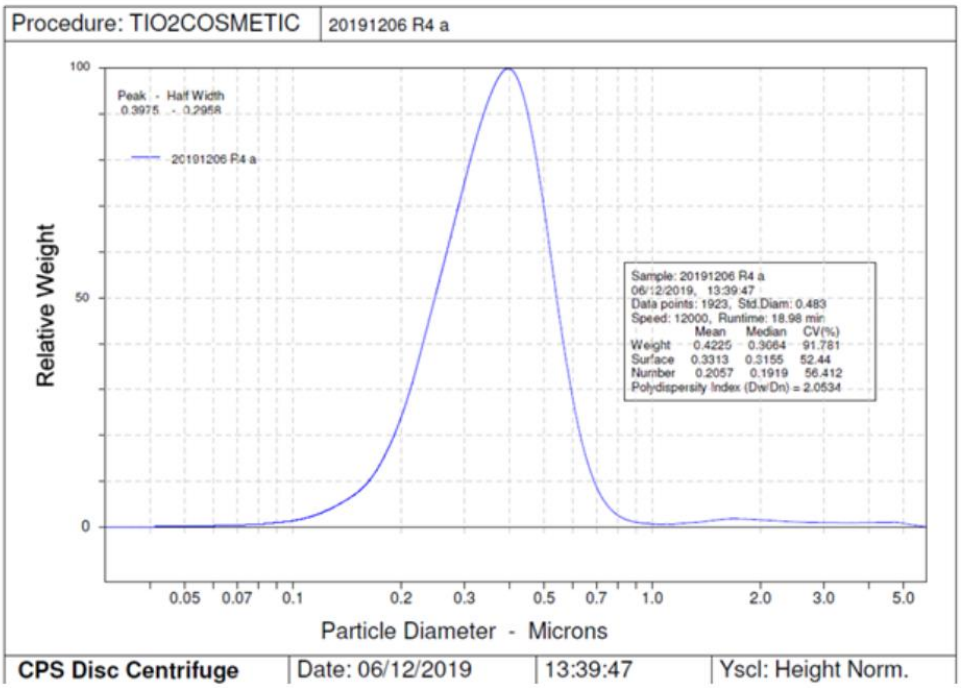

Figure 2: Detailed information on CPS disc centrifuge analysis of R4 material

Ref: Armstrong, 2019

SCCS comment

Information on additional physical and chemical specifications was only given for the coated pigmentary forms of TiO_2 (R4-R9). No information was provided for the uncoated forms, and this should be provided.

3.1.9 Particle shape, particle size and distribution

The basic physicochemical information regarding particle size of TiO_2 raw materials provided by the Applicant is given below. For this, the Applicant analysed several batches of TiO_2 materials belonging to group 1 (pigmentary TiO_2) which, in their opinion, are representative of the materials used in cosmetics.

Ref. 1
Intertek, 2019
TDMA, 2019

General description provided by the Applicant of the particle shape, size and distribution

Group 1: Pigmentary TiO_2 (Uncoated and Coated)
Pigmentary TiO_2 (group 1a and b) is a solid, white, odourless powder. Particles are usually of nearly spherical shape (Figure 3 and Figure 4) with aspect ratios between 1.1 to 1.6 (EFSA Food Ingredients and Packaging (FAF) panel, 2019).
The number based median of particle size range in feret.min number of group 1 materials has a range between 0.1 micron up to several microns based on the Scanning Electron Microscopy (SEM) method (number-based particle size).

Table 2: Crystal phase, purity, median particle size, Geometric Standard Deviation (GSD) and fraction particle size < 0.1 µm (Q0<0.1µm) (SEM method).

Group	ID	Crystal Phase TiO_2	TiO_2 content in reference material (RM)	Description of Coating	Median minimal external dimension by number (µm)	Geometric Standard Deviation (exp((ln(x50)-ln(x10))/1,282)	Number-based fraction of particle size <0.1µm (%)
1a	R4	Anatase	>99%	Hydrophilic Surface Treating	0.145	1.30	7.3
	R6	Rutile	>97%	Hydrophilic Coating	0.168	1.32	3.8
	R7	Rutile	>97%	Hydrophilic Coating	0.183	1.87	17.0
	R9	Rutile	>96%	Hydrophilic Coating	0.228	2.14	15.1
1b	A*	Anatase	>99%	Uncoated	0.140	1.30	18.0
	B*	Anatase	>99%	Uncoated	0.101	1.35	49.6
	C*	Anatase	>99%	Uncoated	0.110	1.29	37.0

	D *	Anatase	>99%	Uncoated	0.173	1.40	10.0
	E*	Anatase	>99%	Uncoated	0.101	1.32	47.0
	F	Rutile	>99%	Uncoated	0.151	ND	5.6

* data from the TDMA E171 dossier submitted to EFSA Nutrient sources added to Food (ANS) Panel (2018)(Titanium Dioxide Manufacturers Association (TDMA), 2019)

Ref. 1

SCCS comments

For further clarity, the SCCS has amended the description in the heading of column 6 to '*Median minimal external dimension by number*'. In addition, following Applicant's clarification, 'PSD' has been replaced with 'Geometric Standard Deviation' and 'Q0' is replaced with '*Number based fraction of particle size*' <0.1 µm.

The SCCS has also checked the information provided in the dossier on uncoated TiO_2 particles (A, B, C, D, and E), and found it to be similar to that provided in the TDMA dossier (2019) (see the Table below):

	TDMA 2019 (page 9)		**Current SCCS opinion, Table 2**	
	Median minimal external dimension by number (µm)	Number-based fraction of particle size <0.1µm (%)	Median minimal external dimension by number (µm)	Number-based fraction of particle size <0.1µm (%)
A	138 nm	18.4 %	140 nm	18 %
B	105 nm	45.6 %	101 nm	49.6 %
C	113 nm	36.2 %	110 nm	37.0 %
D	166 nm	11.4 %	173 nm	10.0 %
E	104 nm	45.0 %	101 nm	47.0 %

Furthermore, the SCCS requested information in regard to some of the materials in Table 2 of the dossier because the median particle sizes were reported as 101 nm, which is very close to the threshold for considering them nanomaterials. Also, the smallest median size of TiO_2 particles in the selected products was 145 nm and it was not clear how this could be related to the Applicant's statement that the test products were chosen based on 'Lowest particle size of the TiO_2-based raw material in the formulations'.

According to the information provided by the Applicant, particle sizes of the samples R4, R6, R7 and R9 by SEM were determined by an independent testing and certification company, and the particle sizes of samples A-F by three E171 manufacturers in Europe for an EFSA report on the safety of E171 in food. This led to the results being very different and not comparable because the difference between group 1a and group 1b materials came from analysis by different laboratories.

Ref. 2

The SCCS considers this statement as the Applicant's own opinion, which is not supported by scientific argumentation.

Another request was raised by the SCCS for clarification on whether the raw materials used in the representative products were (partly) in nanoform. From the results of the product selection discussed further below, it seemed that the only relevant raw material for this evaluation is R4, which has a particle number based fraction of 7.3% in the size range <0.1 µm (see Table 2 of this Opinion).

The SCCS also asked for the data provided by the companies from the product survey as these data were not provided.

According to the Applicant, the nano content of TiO_2 can be calculated from the formulation and SEM data from the raw material. For a material to be defined as non-nano, amongst other criteria that need to be met, the number of particles in the range of 1-100 nm (i.e. the nano tail) must be less than 50% according to the guideline issued by the SCCS in 2019 regarding safety assessment of nanomaterials in cosmetics (SCCS/1611/2019). According to the Applicant, the TiO_2 raw materials defended in this dossier all have a nano tail smaller than 50%, and thus by definition are not nanomaterials.

Ref. 2

The SCCS noted that the Applicant had referred to the Commission Recommendation for Definition of a Nanomaterial (2011/696/EU). However, this has not yet been applied to the definition of nanomaterial under Cosmetic Regulation (EC) No 1223/2009. Therefore, the existing definition given in the EU Cosmetic Regulation provides the legal definition of nanomaterial in relation to cosmetic ingredients, i.e. 'An insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm'. In any case, the materials listed in the dossier contain significant fractions of the particles that are in the nanoscale.

From the Applicant's dossier:

Particles are usually of nearly spherical shape with aspect ratios between 1.1 to 1.6 (EFSA, FAF panel, 2019). Examples of SEM images and particle size distribution curves for group 1a and 1b are presented in Figure 3 and Figure 4 respectively.

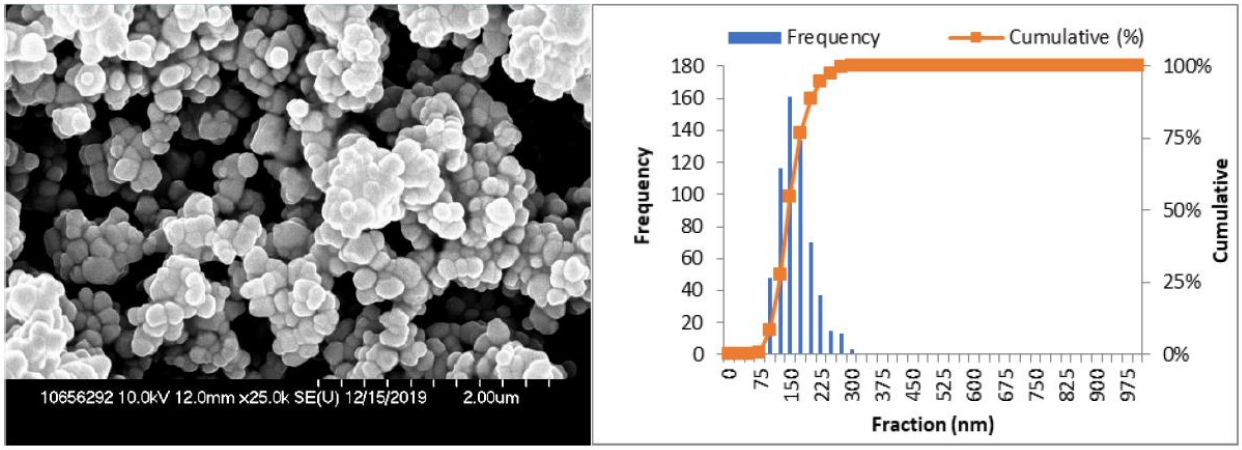

Figure 3: SEM image and particle size distribution R4 TiO_2 group 1a

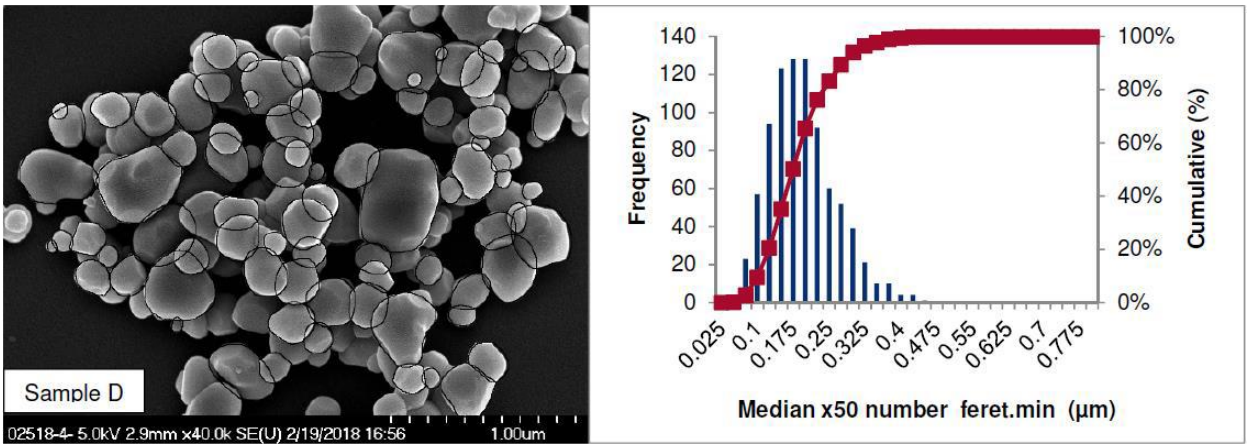

Figure 4: SEM image and particle size distribution of sample D TiO_2 group 1b

Additional measurements using the Differential Centrifugal sedimentation (DC) method were conducted to provide volume-based particle size results that can be used to assess the agglomeration / aggregation state of the materials, and to convert doses based on number into mass / volume, the latter being more adequate for risk assessment (SCCS/1611/19). These results are described in Table 3 below.

Table 3: Crystal phase, purity, coating description, particle size, Geometric Standard Deviation (GSD) and fraction particle < 0.1 µm (Q3<0.1µm) using CPS DC method

Group	**ID**	**Crystal Phase TiO_2**	**TiO_2 content in reference material**	**Description of coating**	**CPS DC Median x 50 volume (µm)**	**Geometric Standard Deviation (GSD) exp((ln(x50)-ln(x10))/1,282)**	**Fraction of particles < 0.1 µm mass/ volume (%)**
1a	R4	Anatase	>99%	Hydrophilic Surface Treating	0.370	1.24	1
	R6	Rutile	>97%	Hydrophilic Coating	0.287	1.17	2.5
	R7	Rutile	>80%	Hydrophilic Coating	0.361	1.18	0.05
	R9	Rutile	>80%	Hydrophilic Coating	0.600	1.19	0
1b	A	Anatase	>99%	Uncoated	0.280	1.51	0.99
	B	Anatase	>99%	Uncoated	0.267	1.49	1.26
	C	Anatase	>99%	Uncoated	0.269	1.43	1.02
	D	Anatase	>99%	Uncoated	0.373	1.42	0.22
	E	Anatase	>99%	Uncoated	0.306	1.62	1.52
	F	Rutile	>99%	Uncoated			

Ref. 1

Since the CMR2 classification concerns TiO_2 materials in powder form containing 1% or more of particles with an aerodynamic diameter of ≤10 µm, the SCCS requested additional information on the fraction of pigmentary TiO_2 materials <10 µm. These were not given in Tables 2 and 3.

Additional data provided by the Applicant upon SCCS request
The exposure to the cosmetic consumer is via the finished cosmetic formulation, in particular the droplet or powder size of the formulation is relevant to the safety assessment of the final cosmetic formulation. The aim of the dossier is to demonstrate that TiO_2 does not present a safety concern with respect to the CMR classification, when used in applications that may result in inhalation exposure.

Therefore, in accordance with test method DIN EN 481, dust fractions defined as the inhalable, thoracic and respirable fractions were measured for

- sample E
- products similar to sample F (uncoated rutile pigment),
- R4 (surface treated anatase pigment, similar to sample E),
- R6 (alumina and silica coated rutile pigment),
- R7 (alumina and zirconia coated rutile pigment) and
- R9 (alumina and zirconia coated rutile pigment with coarser particle size):

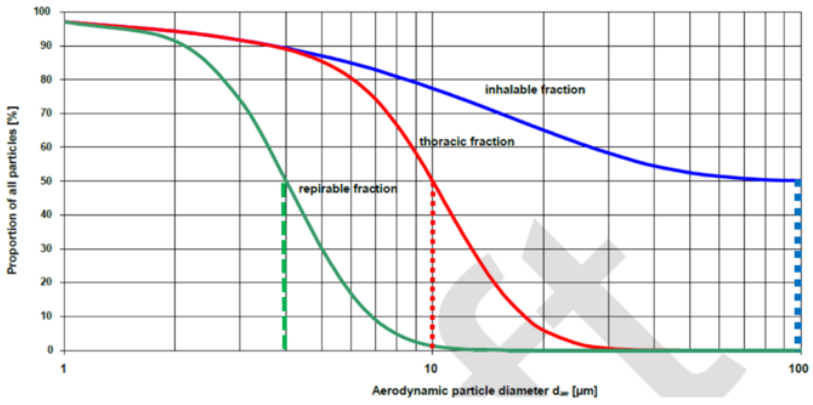

Figure 5: Separation curves for inhalable, thoracic and respirable fractions in accordance with DIN EN 481

The modified Heubach procedure was applied according to DIN 55992-1:2006 ("Determination of a parameter for the dust formation of pigments and extenders – Part 1: Rotation method").

The Table below shows the total dustiness in column 2 as the percentage of dust created in the rotary drum that passed through a filter membrane of 100 µm pore size. The particle size fraction <10 µm medium aerodynamic diameter (MAD) was calculated based on the dust fractions (column 3) and based on the full sample (column 4).

Table 4: Examples for fraction <10µm MMAD of pigmentary TiO_2

Sample	**Total Dustiness [%]**	**Fraction in airborne particles< 10 µm [%]**	**Fraction in total mass< 10 µm [%]**	**TiO_2 dust with MMAD<10 µm generated by EN17199 small**	***Respirable dustiness calculated by the SCCS (according to Evans et al, 2013)***

				rotating drum [%]	***[%]***
E171-E and representative for R4	47.5	1.8	0.9	-	*15.8*
G3-1 Representative for sample F	22.4	1.6	0.3	-	*7.5*
G4-19 Representative for R6	9.6	16.1	1.5	-	*3.2*
G9-5 Representative for R7 and R9	47.9	1.7	0.8	-	*15.9*

Note: MMAD = Mass median aerodynamic diameter

Ref 2.

SCCS comments

The Applicant stated that E171-E is a representative of R4 material in the above-mentioned dust measurements. Although this is inconsistent, because R4 is a surface-treated TiO_2 material and sample E an uncoated material, the SCCS has acknowledged that surface treatment may not be relevant for dust measurements.

Table 4 describes the fraction of the particles with the aerodynamic diameter of <10 µm to be around 1% for all the pigmentary TiO_2 materials analysed, including material 'E' that has been considered by the Applicant as representative of R4 (not R4 itself). The SCCS does not agree with the estimated values because a study of several powders by Evans et al. (2013) has reported that respirable dustiness is generally around one third of the total dustiness of a fine/nanoscale material. Therefore, the SCCS is of the view that the respirable dustiness of 'E' could be as high as around 16% - i.e. 1/3 of the total dustiness (see column 6 added by the SCCS to Table 4).

3.1.10 Homogeneity and Stability

Chemically inert; Light resistant; Thermally stable[4]

SCCS overall comments on physicochemical characterisation

The Applicant has described physicochemical characterisation of different TiO_2 materials. A distinction is made between surface-treated or coated TiO_2 materials (group 1a) and uncoated TiO_2 materials (group 1b). Table 1 mentions the pigmentary TiO_2 materials belonging to group 1-a that includes R4, R6, R7 and R9, where R4 is mentioned as a hydrophilic surface-treated material, and R6, R7, R9 as having either hydrophilic or hydrophobic surface treatment/coating. These coatings have been described as follows: 'TiO_2 is coated with metal oxides like SiO_2, Al_2O_3, ZrO_2 or CeO_2, amongst other to improve dispersibility and processability in formulations. Hydrophilic and hydrophobic organic compounds (e.g. dimethicone or caprylylsilanes) are added to TiO_2 to improve the formulation in hydrophilic and hydrophobic solvents'.

Further analysis of the materials mentioned in group 1b (A-E) is provided in the TDMA report that had been used for EFSA re-evaluation of E171. According to the Applicant's description of dust fractions (Table 4), E171-E (uncoated) is described as a representative of R4. This is questionable because R4 is described as a surface-treated/ coated TiO_2 material, whereas E171-E is uncoated. For this reason, the SCCS has accepted R4 as a representative material of group 1a, but not of group 1b. Furthermore, out of all the materials included in the dossier,

[4] Entry for TiO_2 in GESTIS-databases of hazardous substances; provided by IFA
http://gestis.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates&fn=default.htm&vid=gestiseng:sdbeng

the SCCS has regarded 'R4' as the only relevant TiO_2 material for the current evaluation because it is the only material that is used in the cosmetic applications evaluated in this Opinion (see below).

The Applicant has also applied data read-across from other published studies to the material 'R4'. For this purpose, R4 has been regarded by the Applicant as comparable to another TiO_2 material 'BayerTitan-T' that had been used in a study by Muhle et al. (1991). The SCCS has however noted certain discrepancies in this regard:

1. R4 is comprised of anatase phase of TiO_2 (>99% pure) with a hydrophilic surface treatment, whereas BayerTitan-T is rutile phase, for which no further specifications were provided by the Applicant.
2. A study by Miles *et al.* (2008) characterised particle size distribution of Bayertitan-T that had been used in other studies as a diluent for the preparation of positive control material to investigate pulmonary effects of quartz via intratracheal instillation in rats. The SEM characterisation of Bayertitan-T by Miles *et al.* (2008) showed the median diameter to be 0.5 µm and a mass mean geometric diameter (MMGD) of 0.81 µm. In comparison, the median diameter for R4 has been reported by the Applicant as 0.370 µm and MMGD (reported as GSD) as 1.24 µm (see Table-3).
3. For Bayertitan-T, Muhle *et al.* (1991) noted the MMAD (mass median aerodynamic diameter) to be about 1.1 µm with a respirable fraction of 78% without describing the measurement technique used. The range of particle size distribution was not given and no indication was provided on the aggregation/ agglomeration state of the material.
4. Intertek (2019) reported individual particle size of R4 as determined by SEM with a minimum measured particle diameter of sub-100 nm. The median Feret.min for R4 was found to be 145 nm (144.95). Also, two SEM images were provided for R4 that showed the structure of the TiO_2 sample at different magnifications. The left image in Figure 6 below shows at low magnification a very different arrangement of the particles to that observed in the first two samples. Rather than aggregating/ agglomerating into clusters, the material seemed to have formed a more even layer across the SEM stub. The right image shows larger constituent particles than the previous two samples, although the level of clumping is similar to that shown for the first sample.

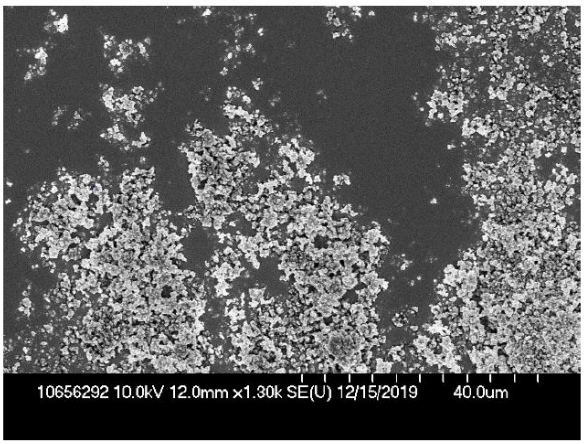

Image: 1346086-10656292-2005_050
Micron bar: 10 x 4.0 µm = 40.0 µm

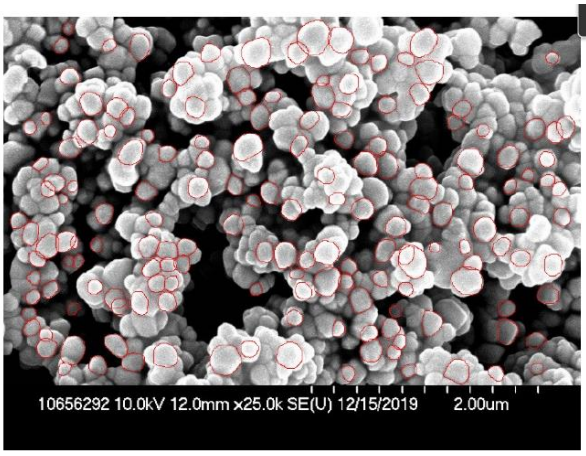

Image: 1346086-10656292-2005_046-M
Micron bar: 10 x 0.2 µm = 2.00 µm

Figure 6: 10656292 : R4

5. Armstrong (2019) reported CPS Disc Centrifuge measurements, coupled with light absorption measurement for R4. The maximum diameter is reported as 6 µm, and the minimum diameter 0.03 µm (30 nm). The median size (expressed in weight) is reported to range from 0.3336 to 0.3763 µm (3 runs), with the mean size (expressed in weight) range from 0.4225 to 0.4530 µm (3 runs).

In this regard, a review by Wang and Fan (2014) concluded that detailed characterisation of TiO_2 nanoparticles is essential in terms of size, crystal phase, dispersion and agglomeration status, surface coating, and chemical composition to understand the production of reactive oxygen species in studies on pulmonary inflammation. In view of this, and due to the above noted discrepancies in material characteristics, the SCCS concluded that R4 and Bayertitan-T are not comparable materials because of the differences in crystalline phase, particle sizes, and agglomeration/ aggregation states.

As mentioned before, the SCCS has regarded that only pigmentary TiO_2 (groups 1a and 1b) can be considered for safety assessment in this Opinion in the context of CLP CMR2 classification, because they are mainly composed of titanium dioxide. The Opinion has not considered the materials in group-3 (pearlescent pigment) because they are composed of various materials and contain TiO_2 only as a minor part, and because the physicochemical and toxicological properties of such a material are likely to be driven by the mixture composition and not by TiO_2 as such.

The SCCS has also regarded group-2 materials (comprising nanoform of TiO_2) relevant for this evaluation because the pigmentary TiO_2 materials contain a significant fraction of particles in the nano-scale. In the SCCS view, safety assessment of such a fraction is crucially important for the estimation of inhalation exposure of alveolar region of the lungs.

3.2 TOXICOKINETICS

No data provided by the Applicant.

Information from open literature (from SCCS/1583/17):
Depending on size, inhaled nano-TiO_2 is distributed to the nasopharyngeal, tracheobronchial and alveolar regions of the respiratory tract. In part, deposited material is eliminated via mucociliar clearance. Particles having reached the alveolar region are taken up by macrophages and are then eliminated from the body by alveolar clearance. High concentrations have been reported to impair alveolar clearance and to concomitantly increase lung retention half-lives. Compared to microsized TiO_2, nano-TiO2 was also observed to a greater extent in lung-associated lymph nodes indicating epithelial translocation into the interstitium. There are further reports on the detection of nano-TiO_2 in the cytoplasm of pneumocytes I cells, in the capillary endothelium, the connective tissue or as free particles in the alveolar space (e.g. Ferin *et al.*, 1992; Bermudez *et al.*, 2004; Eydner *et al.*, 2012). Rapid translocation of a small amount (about 2%) of the lung-deposited material accompanied by subsequent accumulation was reported for a variety of secondary target organs (liver > kidney > blood > spleen > heart > brain) after endotracheal intubation. However, amounts were low compared to those retained in the lung until the end of the observation period. The sum of amounts found in the above-mentioned tissues was lower than that reported for the remainder of the body (Kreyling et al., 2010). Studies by Wang *et al.* (2008a, 2008b) on murine brain reported that intra-nasally instilled TiO_2 NPs (80 nm rutile, 155 nm anatase; 500 µg/ml; 2, 10, 20, and 30 days) can be taken up by sensory nerves and translocate to the brain.

SCCS comments
The information on kinetics and deposition of inhaled TiO_2 in the lungs and other organs is insufficient and therefore a more extensive evaluation of kinetics/deposition of the particles is needed.

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

TiO_2 is a white, insoluble, inert substance with a high refractive index that, according to the Applicant, makes it ideally suited for providing benefits including opacity to many applications in cosmetics. It is generally used as a colourant in cosmetic products. It is also mentioned that, for decades, TiO_2 has been used mainly in make-up, sun care products, hair products, skin care and oral-care. In its non-pigment form, TiO_2 also absorbs and scatters both UVA and UVB rays making it a key ingredient for UV-protection.

Ref. 1

3.3.2 Evaluation of consumer exposure from TiO_2-containing cosmetic products

According to the Applicant, for consumers exposed to cosmetic products containing TiO_2, there are typically no safety concerns by the inhalation route since cosmetic products are primarily intended to be applied on the skin and are not likely to be deliberately inhaled. However, depending on the product type and consumer use scenario there is the potential for non-intended exposure by inhalation. Therefore, although dermal contact is the dominant exposure route, cosmetic pressurized aerosols, pump sprays and loose powders have to be evaluated regarding non-intended inhalation exposure.

Inhalation exposure assessment is usually conducted in a tiered approach starting with *in silico* exposure (mathematical models) as an initial estimate, which may be followed up in a second step by measurement during simulated use of the product as the most realistic approach (Steiling *et al.*, 2014). Within mathematical exposure models, default assumptions (e.g. for room size, exposure duration, human breathing rate, etc.) are used as input (e.g. for room size, exposure duration, human breathing rate, etc.) are used as input parameters to the model. However, these models are generally rather conservative and may overestimate lung exposure, as compared to real life conditions. Furthermore, adequate input parameters may not be available for some product types adding further uncertainty to the produced exposure estimates. For the purpose of the present submission, the inhalation exposure assessment for cosmetic pressurized aerosols, pump sprays and cosmetic powders is based on real measured exposure with representative formulations of each product category/type.

Ref. 1

3.3.2.1 Selection of TiO_2 containing cosmetic products for field exposure studies

According to the Applicant, a European use survey was carried out at the level of the cosmetic industry to allow identification of the worst case finished product in terms of potential for TiO_2 inhalation exposure. In addition, a survey has been carried out among the suppliers of TiO_2 raw materials. The companies were instructed to report:

- The product category/types and dosage forms containing TiO_2, and that can lead to inhalation exposure
- The different types of TiO_2 in each formulation and respective concentrations
- Total TiO_2 concentration in each formulation
- The proportion (%) of particles < 10 µm in powder products
- The proportion (%) of sprayed droplets < 10 µm for sprays
- The particle size of TiO_2 raw materials used in each formulation

Table 5: Results of the European survey conducted by the Applicant for identification of representative products

Number of participating cosmetic product manufacturers	11
Total number of TiO_2-containing products reported	807*
Number of products associated to potential non-intended inhalation exposure	171

*only products that can lead to inhalation exposure

Ref 1.

Additional data provided by the Applicant upon SCCS request:

Upon request of the SCCS, the Applicant provided additional data on the surveys. According to the information, the representativeness of the cosmetic manufacturers responding to the survey via market share was 67% in select sub-categories of the overall Beauty and Personal care industry (Eastern and Western Europe – Euromonitor data for 2019 market – Accessed June 2020).

In addition to that, the Mintel Global New Products Database has been used to further verify that the 6 product types on which the developed risk assessment later in the Opinion is based covers the entirety of the cosmetic products on the market that could lead to exposure to TiO_2 by inhalation.

The searches performed in this commercial database (accessed June 2020) for cosmetic products containing TiO_2 and that could lead to exposure by inhalation did, according to the Applicant, not result in identification of cosmetic products – in dosage form and/or exposure scenario – not covered by the product categories and product types reported in the industry survey carried out by Cosmetic Europe in 2018.

According to the Applicant, this further validates the representativeness of the Cosmetics Europe cosmetic product survey and supports the relevance of the "worst case scenario" identified accordingly.

Ref 2.

Additional data provided by the Applicant upon SCCS request:

Out of the formulations reported in the TiO_2 use survey, the experts analysed all cosmetic product dosage forms reported and hand-picked those that could lead to a significant inhalation exposure. Further refining was performed considering products presented in aerosol spray, loose powder, pressed powder and pump spray. The range of concentration of TiO_2 within these products varied from 0.01% to 58 % and covered both UV filter use and colorant use.

Specific TiO_2 concentrations in relevant product categories are:

- Perfume category: 0.03-0.06 %
- Hair Styling and Hair colour: 0.01-3.83 % (maximum concentration was found in a rinse off and loose powder)
- Products with antiperspirant activity: 0.01-0.20%
- Make up: 0.37-58.00% (the highest is a compact powder eye shadow)
- Sun products and self-tanning: 0.09 – 20.50 % (The highest concentration is a pressed powder)

The Applicant further stated that, to ensure the dossier covers all the cosmetic products in the scope of the CMR ban, the studies to measure TiO_2 exposure and presented risk assessment were conducted on worst-case cosmetic products in terms of potential for TiO_2 inhalation exposure as identified from the cosmetic product survey. The identification of representative and worst-case cosmetic products selected for the exposure studies and subsequent risk assessment was completed according to the below process steps. For practical and confidentiality reasons, some were carried out by respondent companies (steps 1-2) and some others by the consortium (steps 3-4):

1. Identification by cosmetic companies within their product portfolio, of products containing TiO_2 and likely to cause exposure by inhalation according to the following criteria:
    i. presence of TiO_2
    ii. physical form of the product (e.g. liquid, paste, powder, …)
    iii. product dosage form (spray, powders and applicators used)
    iv. exposure scenario (*i.e.* mode, frequency and duration of product application)

2. Respondent companies reported to the consortium "worst case products" (for potential to produce inhalation exposure) for each product dosage form (spray, powder) in each product category based on the following criteria:
    - products with the highest TiO_2 concentrations
    - sprays with the largest fraction of droplets < 10 µm according to available in-house data (droplet size distribution measurement using laser diffraction technique or extrapolation of the measurement results from close-related products)
    - powders with the largest fraction of particles < 10 µm (particle size distribution measurement using laser diffraction technique or extrapolation of the measurement results from close-related products)
    - particle size of TiO_2 raw materials in the formulation

3. All the "worst-case products" provided by each respondent company were pooled together by product category. Identification of the final worst-case products in each category was carried out by the applicant based on the following criteria:
        - Highest TiO_2 concentration
        - Product dosage form (spray or powder)
        - Largest fraction of particles/droplets < 10 µm
        - Particle size of TiO_2-based raw materials in the reported formulation

4. Final refinement was carried out by comparing the exposure scenarios across the different product categories. The products in the categories with the highest potential for inhalation exposure were selected for exposure testing.

Ref 2.

The following products were selected for field exposure studies.

Table 6: List of products selected for TiO_2 lung exposure associated with consumer use

Product category	**Dosage form**	**Product**	**TiO_2 content in the formulation (%)**	**Particle droplet fraction <10 µm (%)**	**Raw Material (RM) code for TiO_2 material used in product**	**TiO_2-based raw material**	**Raw material Median Particle Size Volume based (µm)***
Hair Styling	Aerosol spray	F8	1.0	15.94	R4	Pigmentary coated	0.145
Make-up Powder for Face	Loose powder	FZ	20	45	R4	Pigmentary coated	0.145

Ref 1.

Note: Table 6 shows TiO_2 concentrations from airborne particles in the respirable and thoracic size fractions from direct exposure measurement of each the product type. Despite high TiO_2 percent used in some other cosmetic products (e.g. sun products and self-tanning with 0.09-20.50 % of $Ti0_2$ in the formulation), these products were not considered by the SCCS for the estimation of consumer exposure and in the MOS calculation because they have no significant influence on the inhalation exposure to TiO_2 compared to hair spray or Make-up Powder for Face. Therefore, only two product types considered by the SCCS for this opinion (hair spray and make-up powder for face) that give rise to the highest exposure by inhalation are represented in this Table.

SCCS comments

With respect to the two different surveys that have been reported by the Applicant, the results are given in terms of absolute number of cosmetic product manufacturers who responded to the study, but the *response rate to the survey* has not been given (not even after a request by the SCCS for additional information).

Other results in Table 5 are the total number of TiO_2 containing cosmetic products reported, and the number of products associated with the potential for non-intended inhalation exposure. For safety assessment in the context of this Opinion, it is crucial for the SCCS to know the *market coverage of the products*, as well as the *market share of TiO_2 types* covered by the current dossier. Although the market share has been reported as 67% in select sub-categories of the overall Beauty and Personal care industry, this information is insufficient because no details are given on the subcategories for which the 67% value holds true. The SCCS has therefore deduced from the given information that the overall representativeness for the Beauty and Personal care industry is lower than 67%.

Also, the ranges of TiO_2 concentrations in the different subcategories were provided by the Applicant in response to the SCCS request for additional information. However, it is not clear for every product category how these concentrations map up to the selection of the worst case products listed in Table 6.

Another crucial aspect missing in the worst-case considerations/ criteria is the type of nozzles and dispensers used in the spray can (aerosol spray). These two parameters are essentially required for the SCCS to evaluate potential exposure of the consumer.

The protocols used for the measurement of particle droplet fractions have not been specified. According to the Applicant, these methods (Dynamic light scattering (DLS) for sprays and Selective laser sintering (SLS) for powder) have been used by the industry for many years, and the data were already available from the cosmetic companies. Since no data from the survey are reported by the Applicant, the relevance of the choice of representative material cannot be evaluated by the SCCS. In addition to the data on spray distribution, data on the raw material are also necessary to enable ascertaining the representativeness and the choice of a worst case. Furthermore, the different types/ categories of TiO_2 as explained by the

Applicant (i.e. pigmentary TiO_2 either coated or uncoated, and pearlescent pigments) are too broad, and give no additional information on characterisation of the raw materials for use in safety assessment of the specific products.

Only data on raw material R4 are given in any detail. This material has been considered by the SCCS for the current evaluation because exclusion of the products containing pearlescent pigments left only two product types – both containing R4 dispersion (Table 6).

3.3.2.2 Evaluation of consumer lung exposure using field exposure studies

3.3.2.2.1 Experimental measurement of lung exposure

According to the Applicant, realistic simulations of lung exposure using a mannequin were performed at the Fraunhofer Institute according to the relevant intended use of the selected finished product~~s~~, i.e. Hair Styling Aerosol Spray (F8).

Because the adherence of the cosmetic powders to the skin during the intended application is a key factor determining the inhalation exposure, simulations of lung exposure for selected Loose Powders for face make-up (FZ product~~s~~) were conducted using human volunteers. A total of five individual applications (n = 5) were carried out for each tested product. Each application procedure (exposure scenario) was designed to simulate normal use conditions according to the relevant published data on product use (Loretz *et al.*, 2006; Steiling *et al.*, 2012; 2014; 2018; SCCS 2018). In the absence of published data on the application amount of a product (e.g. perfume), data were extrapolated from a category of products with comparable exposure scenario (deodorants). A room volume of $10m^3$ was used as the exposure chamber, which represents a size of a standard bathroom assumed for safety assessment (RIVM, 2014; Rothe *et al.*, 2011). To cover worst-case surrounding conditions in which a consumer may use the products, there was no ventilation and no exchange of room air during exposure measurements.

For characterization of the inhalation exposure potential, spray and dust clouds are characterized according to the health-relevant particle size fractions defined for airborne suspended particulate matter in the international standards CEN 481 (CEN, 1993; American Conference of Governmental Industrial Hygienists (ACGIH), 1997). These are the respirable, the thoracic and the inhalable fraction of airborne aerosols, i.e. aerosols not deposited on any surface and that remain airborne. The inhalable fraction is defined as all particles that can enter the respiratory tract during normal breathing. The thoracic particles pass through the head airways and reach the trachea and bronchi. The respirable particles reach the peripheral airways, i.e. the bronchioli and the alveolar lung region. The respirable concentration represents approximately the concentration in the size range smaller than 5 µm. The extrathoracic fraction of inhaled particles represents those particles that fail to penetrate beyond the larynx, i.e. the inhalable minus the thoracic fraction. The thoracic fraction represents the range of particles smaller than 10 µm. The aerosol size fraction smaller than 10 µm i.e. that passes through the upper respiratory tract and reaches the thorax, was of particular interest for the measurement of TiO_2 concentration following simulated exposure conditions.

For a direct exposure measurement, airborne particles of the respirable and thoracic size fraction generated during the simulations were collected in the breathing zone or simulated breathing zone of the mannequin using the RESPICON® personal aerosol monitor (Helmut Hund GmbH, Wetzlar, Germany) according to CEN 481 and ACGIH standard. A RESPICON® is a combination of a two-stage virtual impactor (for aerodynamic size classification), three sampling filter cassettes (contain filter plates) for measurement of the average mass concentration in the three size fractions (respirable, thoracic and inhalable) by chemical analysis of the collected material, and three light scattering photometers for on-line concentration monitoring (constant angle light scattering sensor) (Koch et al., 1999). The

breathing zone was sampled for 20 minutes (time of the application itself plus the worst-case post-application residence time).

After the exposure periods, the aerosols collected on the internal filters of the RESPICON® were analysed for TiO_2 by chemical analysis. TiO_2 was quantified by bulk chemical elemental analysis of titanium by using the ICP-MS (Inductively Coupled Plasma - Mass Spectrometry) technique. Based on the amount of TiO_2 on the relevant filters, the average value for the time-average concentration for the five applications is determined for the respirable and the thoracic size regime. The limit of quantification (LOQ) of the TiO_2 determination on the filters was 600 ng (for a 1:4 dilution of the sample extracts). Half of this LOQ for the filters corresponds to an LOQ of the methodology for the inhaled dose in the thoracic size range of about 400 ng per application and for the respirable range of about 200 ng.

Table 7 provides results of TiO_2 concentrations from airborne particles in the respirable and thoracic size fractions from direct exposure measurement of each tested product. The amount of product per application is also reported and shows that each exposure scenario was designed in respect of the normal use conditions of the product category.

Ref. 1

Table 7: Amount of product used and TiO_2 concentrations per application in the respirable and thoracic fractions as determined experimentally using realistic simulations of product application (mean from 5 applications).

	TiO_2 concentration in the formulation (%)	Amount of product per application (g)	**TiO_2 concentration ($\mu g/m^3$) per application**	
			Respirable fraction [1]	**Thoracic fraction** [2]
Hair Styling Aerosol Spray Product F8	1.0	7.43	**266.7**	**480.4**
Loose Powder for Face Make-up Product FZ	20	0.088	**7.38**	**39.80**

[1] i.e. contained in product droplets of < 5 µm
[2] i.e. contained in product droplets of < 10 µm

Additional information regarding the LOQ being higher for the powder than for the sprays was provided by the Applicant upon SCCS request. According to this information, there is a difference in the LOQs as there was some additional semi-quantitative analysis conducted for the sprays resulting in the reporting of the LOQ for the respirable fraction as ½ LOQ (i.e. 333 ng TiO_2/filter or < 1.23 µg TiO_2/m^3), whereas for the powders this additional analysis was not required and the LOQ was reported as 667 ng TiO_2/filter or < 2.5 µg TiO_2/m^3 for the respirable fraction.

For further detail:

> Sprays extract:
>
> *All filter samples were analysed as a 1:4 dilutions and in technical duplicates after acidic digest. The analytical LOQ was set as 5 ng Ti/mL which equals 667 ng TiO_2 per filter (corresponds to: respirable < 2.5 µg TiO_2/m^3; thoracic < 4.4 µg TiO_2/m^3). For the respirable size fractions, the TiO_2 concentrations were below the LOQ. Based on the semi-quantitative analysis results (values below 2.5 ng/mL) data for the respirable fraction were reported as ½ LOQ (333 ng TiO_2/filter) corresponding to < 1.23 µg TiO_2/m^3.*

Powder extract:

All filter samples were analysed as a 1:4 dilutions and in technical duplicates after acidic digest. The analytical LOQ was set as 5 ng Ti/mL which equals 667 ng TiO_2 per filter (corresponds to: respirable < 2.5 µg TiO_2/m^3; thoracic < 4.4 µg TiO_2/m^3). For respirable size fraction, the TiO_2 concentrations were below the LOQ.

Product usage per application was based on a range (73 to 175 mg) taken from two publications (Steiling *et al*, 2018 and Ficheux *et al*, 2016, bottom and top of range, respectively). The final amount of product used per application (and reported) is based on human volunteers using the product in a simulated use scenario. Consequently, there will be some differences in the usage due to the variation in the volunteer using the product. However, while 88 mg is lower than the P95 of Ficheux *et al*, 2016 (which is also the upper end of the range quoted above), it is nevertheless within the range established at the commencement of the studies and also above the P50 of Ficheux *et al*, 2016. Therefore, the value of 88 mg does not seem unreasonable.

Ref. 2

SCCS comment
According to the explanation provided by the Applicant, the use amount reflects the normal use and not the worst case.

3.3.2.2.2 Conversion into TiO_2 lung exposure doses (i.e. inhaled doses)

To convert TiO_2 concentrations obtained from experimental measures into inhaled or lung exposure doses, human physiological parameters such as breathing rate must be considered. For human adults (60 kg), the respiratory minute volume during light physical work is generally assumed to be approximately 13 L/minute (Finley et al., 1994; Salem and Katz, 2006).

The lung exposure doses per application of each product are calculated with the following formula and are reported in Table 8:

TiO_2 lung exposure dose (µg/application) = TiO_2 concentration (µg/m^3)/1000 (conversion m^3 to L) x human breathing rate (13 L/minute) x residence time in the room (20 minutes)

Table 8: TiO_2 lung exposure dose (inhaled dose) per application converted from TiO_2 concentrations in the respirable and thoracic fractions determined experimentally using realistic simulations of product application.

	TiO_2 conc in the formulation (%)	TiO_2 conc Respirable fraction (µg/m^3)	**TiO_2 inhaled dose Respirable fraction (µg/application)**	TiO_2 conc Thoracic fraction (µg/m^3)	**TiO_2 inhaled dose Thoracic fraction (µg/application)**
Hair Styling Aerosol Spray Product F8	1.0	266.7	**69.3**	480.4	**125**

Loose Powder for Face Make-up Product FZ	20	7.38	**1.92**	39.80	**10.35**

The experimental TiO_2 lung exposure measurements (field exposure studies) simulated a single application of the selected product. For the lung exposure dose per day calculation, the frequency of use per day of each product category was taken from SCCS Notes of Guidance (2018) or from relevant literature when there is no guidance, i.e. for Perfumes and Loose powder face make-up products (Steiling et al., 2012; 2018).

Table 9a: TiO_2 lung exposure dose (inhaled dose) thoracic fraction per day

	TiO_2 conc. in the formulation (%)	TiO_2 concentration Thoracic fraction ($\mu g/m^3$)	TiO_2 inhaled dose Thoracic fraction (µg/ application)	Product frequency of use/day	TiO_2 inhaled dose Thoracic fraction (µg/day)	TiO_2 pulmonary deposited dose (µg/ application)
Hair Styling Aerosol Spray Product F8	1.0	480.4	125	1	125	21.25
Loose Powder for Face Make-up Product FZ	20	39.80	10.35	1	10.35	1.76

Lung exposure to TiO_2 particles contained in spray products is evidently dependent on the TiO_2 concentration, the size of the product droplets delivered upon the spray use and the application procedure. The potential for inhalation exposure to TiO_2 in cosmetic powders appeared to be significantly influenced by the composition of the formulations and specifically by the content in binders. Loose powders are therefore regarded as worst case scenario and cover the potential exposure to TiO_2 due to pressed powder use.

The TiO_2 lung exposure doses (thoracic fraction per day) obtained for each of the products tested in the field exposure studies were used for the risk assessment of consumer exposures to TiO_2 resulting from the use of cosmetic products, which makes it more conservative than selecting the more relevant respirable fraction. This lung exposure dose, derived from thoracic fraction, did not include clearance that further increased the theoretical inhalation exposure.

Ref.1

SCCS comment

The SCCS is of the opinion that the product frequency used by the Applicant in Table 9 is not a reflection of worst-case conditions. The SCCS notes of Guidance (SCCS/1602/18) describe a default value of product frequency for hair styling products of 1.14/ day. For loose powder make-up foundation there is no explicit default value in the SCCS Notes of Guidance, but for other make-up products, such as eye shadow, the NoG describes a default value of 2/ day. Based on the findings that make-up products are usually applied together (Garcia-Hidalgo et al., 2017), these values can therefore be extrapolated to make-up powder. The value of 2 is

further confirmed by Ficheux *et al.* (2015) who report a P95 of 2/day for the frequency of use of loose powder make-up. Therefore, the SCCS will be using the frequency values of 1.14/day for hair styling products and 2/day for loose powder products for the calculation of exposure.

Furthermore, the SCCS considers that the deposition in the pulmonary region is the relevant dose metric, not the inhalable fraction or the thoracic fraction (see further reasoning in the following sections). Therefore, another column with TiO_2 pulmonary deposited dose has been added to Table 9 (right column), where values are quoted from Appendix 7 of the dossier.

The SCCS has recalculated the pulmonary-deposited dose according the product frequency and a human breathing rate of 12 L/min (instead of 13 L/min). Results are presented in Table 9b.

Table 9b: TiO_2 lung exposure dose (inhaled dose) thoracic fraction calculated by the SCCS

	TiO_2 conc. in the formulation (%)	TiO_2 concentration Thoracic fraction ($\mu g/m^3$)	Product frequency of use/day	TiO_2 pulmonary deposited dose (µg/ days)
Hair Styling Aerosol Spray Product F8	1.0	480.4	1.14	22.34
Loose Powder for Face Make-up Product FZ	20	39.80	2	3.2

The average deposition fraction is 17%.

TiO_2 pulmonary deposited dose (µg/day) = Measured TiO_2 concentration Thoracic fraction ($\mu g/m^3$) /1000 (conversion m^3 to L) x human breathing rate (12 L/min) x residence time in the room (20 min) x frequency of use per day (according to the product uses) x 0.17.

Additional information provided by the Applicant upon SCCS request

The SCCS had sought an estimate of the exposure based on particle numbers, and the corresponding risk assessment for all of the products, because two of the products had shown median particle sizes near the threshold for nanomaterials, and the weight-based assessment by Respicons had shown that there was a potential for exposure.

In response, the Applicant stated that the nano content in terms of number of particles and the corresponding mass/volume in the TiO_2 exposure doses measured for each of the studied cosmetic products in the exposure studies can be estimated from the nano particle count in number of the TiO_2 raw material provided by EM measurement and the corresponding mass/volume determined by CPS DC methods (see Tables 2 and 3 of the current Opinion).

In Table 10 below, the exposure estimates in terms of particle number (column a) and mass/volume (column b) are calculated for marketed hairsprays (F8) and loose powders (FZ), which yielded the two highest measured TiO_2 exposure values.

According to the Applicant, the nano content is technically unavoidable. Therefore, it should be considered as an unavoidable trace impurity.

Ref. 1

Table 10: Exposure estimates calculated for Hairsprays and loose powder

	TiO_2 inhaled dose Thoracic fraction[2] (µg/day)	**(a) TiO_2 nano particle inhaled (lung dose) in number[1] (Number Particles/day)**	**(b) TiO_2 nano particle inhaled (lung dose) in mass/volume[2] (µg/day)**
Hair Styling Aerosol Spray Product F8	125	1.37E+03	1.25E+00
Loose Powder for Face Make-up Product FZ	10.35	1.13E+02	1.04E-01

[1.] *Exposure to nano content of TiO_2 in number feret.min from R4 in products with the highest measured TiO_2 exposure*

Number of nano particles in TiO_2 inhaled (lung exposure) dose thoracic fraction =
Mass TiO_2 in TiO_2 inhaled (lung exposure) dose thoracic fraction / (Mass of TiO_2 constituent particle) * Nano Fraction in R4 raw material.

$$Number_{nano\text{-}TiO2\text{-}thoracic} = mTiO_{2\text{-}thoracic}/m_{particle.} * f_{nano}$$

With
Mass of TiO_2 constituent Particle = Volume of constituent Particle * Density of constituent particle

$$= (4/3*\Pi *(d/2)^3 x \text{ rho})$$

where rho is skeletal density of TiO_2 = 4 µg/µm^3

[2.] *Exposure to nano content of TiO_2 in mass/volume from R4 in products with the highest measured TiO_2 exposure*

Mass/volume of nano particles in TiO_2 inhaled (lung exposure) dose thoracic fraction =
Mass TiO_2 in TiO_2 inhaled (lung exposure) dose thoracic fraction * Nano Fraction in R4 raw material

According to the Applicant, the exposure values calculated accordingly for the nano content of R4 raw material when contained in the tested products are far below the nano content of the safe reference value calculated based on Bayertitan-T parameters.

In a worst case approach, in the Table 12? below, virtual worst case exposure estimates for the nano content in particle number (column a) and mass/volume (column b) for all tested cosmetic products from measured TiO_2 lung exposures is given. As a conservative approach, the worst-case parameters for particle size and nano content are in the table below.

Table 11: Simulated analytical parameters of TiO_2 raw material used to determine the worst-case exposure estimates to the nano content.

SEM Median x50 feret.min number (µm)	**Fraction < 0.1µm mass/volume (%)**	**Fraction < 0.1µm particle number (%)**
0.100 (i)	2.0 (ii)	50.0 (iii)

i. Smallest particle size of pigmentary TiO_2
ii. 2% nano content which corresponds to an applied dispersion energy which would be much above the one that could be expected in living biological systems
iii. Nano content of a TiO_2 pigment with diameter 0,100 µm number feret.min

Table 12: Exposure estimate from virtual worst-case exposure scenario

	TiO_2 inhaled (lung exposure) dose thoracic fraction (µg/day)	**(a) TiO_2 nano particle inhaled (lung dose) in number feret.min[1] (Number Particles/day)**	**(b) TiO_2 nano particle inhaled (lung dose) in mass/volume (µg/day)[2]**
Hair Styling Aerosol Spray Product F8	125	9.79E+03	2.50
Loose Powder for Face Make-up Product FZ	10.35	2.47E+03	0.21
Combined exposure	**135**	**1.23+04**	**2.7**

1. *Calculation nano content of TiO_2 in number feret.min using worst-case sample E*

Number of nano particles in TiO_2 inhaled (lung exposure) dose thoracic fraction = Mass TiO_2 in TiO_2 inhaled (lung exposure) dose thoracic fraction / (Mass of TiO_2 constituent particle) * Nano Fraction in raw material

With
Mass of TiO_2 constituent Particle = Volume of constituent Particle * Density of constituent particle

= $(4/3*\Pi *(d/2)^3 x$ rho) where rho is skeletal density of TiO_2 = 4 µg/µm^3

2. *Calculation nano content of TiO_2 in mass/volume using worst-case sample E*

Mass/volume of nano particles in TiO_2 inhaled (lung exposure) dose thoracic fraction = Mass TiO_2 in TiO_2 inhaled (lung exposure) dose thoracic fraction * Nano Fraction in raw material

Ref. 2

SCCS overall comments on exposure assessment

The SCCS is of the view that the exposure assessment should have taken into account the small respirable particles, especially those in the nanoscale, in the assessment of inhalation exposure as they are most likely to reach and deposit in the alveolar region of the lung of the exposed consumer.

As a result, the exposure calculation by the Applicant based on only the estimated particle number is not valid. This should have been measured and not estimated through approximation/calculation.

In addition, the basis for exposure calculation by the Applicant is not given, and there is a lack of clarity on the actual raw materials used. The Applicant has provided statements to say that representative materials were chosen for exposure estimation without any data on particle size ranges, crystal phases, etc.

Additional information provided by the Applicant upon SCCS request on hairdressers' exposure

The Applicant provided an evaluation of professional exposure by inhalation from Titanium Dioxide (non-nano form) containing aerosol hair spray product.

Ref. 3

According to the Applicant, the approaches detailed below were used. The lung exposure estimates were based on the aerosol hair spray product F8 with the highest TiO_2 content (1%) identified from the use survey performed by the cosmetic companies. The lung exposure estimates obtained were low compared to the derived TiO_2 safe reference dose of 24000 µg/day (developed in the submission as described below in the Opinion). According to the Applicant, the professional exposure to TiO_2 resulting from the use of the hairspray product remains on the safe side.

Approach 1: Use of the exposure measurements from the field inhalation exposure study

Realistic simulations of consumer exposure using F8 product were conducted to simulate lung exposure (data detailed in the exposure section above). The number of applications per day of hair styling product category by a hairdresser is estimated to be 9 (Lafon *et al.*, 2014). The Applicant assumed that 1/3 of applied styling products represent hair sprays since not all the styling products applied by the hairdresser are hairsprays.

Based on the above, the hairdresser lung exposure is estimated as follows:

- TiO_2 concentration (thoracic fraction) from F8 exposure: 480.4 µg/m^3 per application
- Resulting inhaled dose: 125 µg per application
- Number of applications per day of hair sprays by hairdresser: 3
- Estimated lung exposure to TiO_2: 375 µg/d (125 µg/d x 3)

Approach 2: Use of the mathematical model ConsExpo Web (www.consexpoweb.nl)

Default and input parameters as well as detailed results are presented below. For the hairdresser use exposure estimation, the input parameter for the condition "Spraying towards person" is "No". The default frequency of 438 per year represents approximatively 2 applications per day considering a hairdresser works 47 weeks per year (52 minus 5 weeks of vacation) and 5 days/week (438 divided by 235). TiO_2 concentration in F8 product is 1% and product particles droplet size below 10 µm as airborne fraction is 16% (20% was used as input parameter).

The lung exposure to TiO_2 is estimated at 6.3×10^{-5} mg/kg bw (60 kg bw) = **3.78 µg/d**

Table 13a: ConsExpo Web - Assessment settings used by the Applicant

Frequency:	438 per year
Exposure model:	Exposure to spray – Spraying
Spray duration:	0.24 minute
Exposure duration:	20 minute
Weight fraction substance:	1% (TiO_2 content in F8 product)
Room volume:	60 m^3
Room height:	2.5 m
Ventilation rate:	2 per hour
Inhalation rate:	13 L /min
Spraying towards person:	No (=> professional use)
Mass generation rate:	0.4 g/s
Airborne fraction:	0.2 (F8 product is 0.16)
Density nonvolatile:	1.5 g/cm^3
Inhalation cut off diameter:	10 µm
Aerosol diameter distribution: -	LogNormal
Median diameter: -	46.5 µm
Arithmic coefficient of variation: -	2.1
Maximum diameter:	50 µm
Mean event concentration (average air concentration on exposure event. Note: depends strongly on chosen exposure duration)	1.2×10^{-2} mg/m^3
Peak concentration (TWA 15 min) (peak concentration (TWA 15 min) is the 15-minute time weighted average of the air concentration. In case the exposure duration is less than 15 minutes, the mean event air concentration is given instead.)	1.4×10^{-2} mg/m^3
Mean concentration on day of exposure (average air concentration over the day (accounts for the number of events on one day))	2.0×10^{-4} mg/m^3
Year average concentration (mean daily air concentration averaged over a year)	2.0×10^{-4} mg/m^3
External event dose (the amount that can potentially be absorbed per kg body weight during one event)	5.2×10^{-5} mg/kg bw
External dose on day of exposure (the amount that can potentially be absorbed per kg body weight during one day)	6.3×10^{-5} mg/kg bw (61 kg bw)

Note: TWA = time weighted average

According to the Applicant, the estimated lung exposure derived from the mathematical model ConsExpo is far lower than the one obtained from the simulated use of hairspray by the consumer suggesting that the latter is very conservative. Indeed, during the performed consumer use simulations there was no ventilation in the room whereas ventilation is an input parameters included in the ConsExpo model in consistence with workplace regulatory provisions requiring hair salons ventilation (25 m^3/h/person in France, 100 m^3/h in Germany). In addition, the room size used for the study was 10 m^3 whereas hair salon volume is much higher since it is reasonable to consider a salon surface of approx. 25 m^2 and volume of 60 m^3. Nevertheless, according to the Applicant, the lung exposure estimates obtained from both approaches remain low compared to the derived TiO_2 safe reference dose of 24000 µg/day (developed below) and support that the professional lung exposure to TiO_2 resulting from the use of the hair spray product remains on the safe side.

Ref. 3

SCCS comments on the hairdressers' exposure

In the exposure calculations for hairdressers, the assumption was made by the Applicant that the frequency of application of TiO_2-containing hairspray by the hairdressers is only 2-3 times per day. The SCCS is of the opinion that this is not realistic and is too low. The worst-case assumption should be that a hairdresser has one preferred hairspray that he/she uses most of the time, and that the application number could be the total number of treatments during a day (9 according to Lafon *et al.,* 2014). To clarify this assumption, the SCCS requested more information about what this assumption had been based on.

According to the Applicant, the 9 products cited in the provided reference cover all the hair styling product types i.e. hairsprays, waxes, gels, creams, etc, that a hairdresser may apply to clients on a working day basis. The estimation was made that among all hair styling product categories, 1/3 were hairsprays. Then, the resulting hairdresser exposure scenario was based on the assumption that all the hairsprays contain TiO_2, which is conservative since not all the hairsprays available on the market contain TiO_2.

The SCCS does not regard this reasoning as convincing and, as already explained, considers that a realistic assumption for the number of applications by a hairdresser should be 9-10 per day.

Also, although the ConsExpo model can be used for the calculation of professional exposure, the defaults for this model have been developed for consumer use. Therefore, any extrapolation of a consumer scenario to an occupational exposure setting should have been done with other due considerations. For example, the ConsExpo spray model assumes instantaneous mixing of the released material into the air of the room, and that the exposure during spraying is for a very short duration. In the short time span of a few minutes, the instant mixing assumption does not hold very well. Aerosol concentrations in the vicinity of the hairdresser will be significantly higher than in more remote parts of the room. It would arguably make more sense to use the 'near-field' model option of use 'on person'. Even though the spray is not formally used on the hairdresser, this option would more plausibly simulate the near-field nature of the exposure. Alternatively, a limited room size (of say 10 m^3) could be assumed to account for the fact that the spray will only partly disperse in the room in the short time considered.

Furthermore, when using the larger room volume that is more representative of the occupational circumstances, the corresponding ventilation should be used in the simulation. The assessment mentioned a requirement of 25 m^3/h/person as a minimal requirement. This could translate to a conservative lower bound on ventilation of 50 m^3/h. With a room volume of 60 m^3, this would correspond to a ventilation fold of 0.8 per hour, rather than the 2 per hour assumed in the assessment.

With these adjustments (i.e. use 'on person' spraying in a 60 m^3 room with 0.8 per hour ventilation and a frequency of 10 applications per working day, the mean concentration on day of exposure is 2 µg /m^3.
The estimated TiO_2 pulmonary deposited dose (µg/days) is equal to 1.96 µg/ days.
The following equation was used:
TiO_2 pulmonary deposited dose (µg/days) =*mean concentration on the day of exposure x breathing rate x 8 hours of exposure x 0.17 (average deposition fraction)*

Table 13b: ConsExpo Web - Assessment settings used by the SCCS

Substance
Name TiO_2
Body weight 60 kg
Scenario TiO_2 SCCS SEPT
Frequency 10 / per day
Description

Inhalation			
Exposure model	Exposure to spray - Spraying		
Spray duration	0.24	minute	
Exposure duration	20	minute	
Product in pure form	No		
Molecular weight matrix			
The product is used in dilution	No		
Weight fraction substance	1	%	
Room volume	60	m^3	
Room height	2.5	m	
Ventilation rate	0.8	per hour	
Inhalation rate	12 L /min		
Spraying towards person	No		
Mass generation rate	0.4	g/s	
Airborne fraction	0.2		
Density non volatile	1.5	g/cm^3	
Inhalation cut off diameter	10	µm	
Aerosol diameter distribution	LogNormal		
Median diameter	46.5	µm	
Arithmetic coefficient of variation	2.1		
Maximum diameter	50	µm	
Include oral non-respirable material exposure	No		
Absorption model	n.a.		
Dermal			
Exposure model	n.a.		
Absorption model	n.a.		
Oral			
Exposure model	n.a.		
Absorption model	n.a.		
Results for scenario TiO_2 SCCS SEPT			
Inhalation			
Mean event concentration	0.0144	mg/m^3	
Peak concentration (TWA 15 min)	0.0159	mg/m^3	
Mean concentration on day of exposure	0.002	mg/m^3	
Year average concentration	0.002	mg/m^3	
External event dose	5.75E-05	mg/kg bw	
External dose on day of exposure	0.000575	mg/kg bw	

3.4 TOXICOLOGICAL EVALUATION

According to the Applicant:

- Over the past 20 years, the SCCS and its predecessors issued several opinions on different TiO_2 materials (SCCNFP, 2000; SCCS, 2014) following dermal and oral exposure routes, overall confirming the safe use of this ingredient in cosmetic products, sometimes with restrictions on specific cosmetic product types and/or specifications. In fact, TiO_2 is of low acute toxicity by the oral and dermal routes, and exposure results in slight or no irritation to skin and mucous membranes. The lack of TiO_2 skin sensitization potential is reported by numerous studies which are all negative (REACH dossier https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15560).
- Available safety data show the absence of systemic effects including lack of reproductive and developmental toxicity or carcinogenic effects following exposures by the oral or dermal routes. The favourable safety profile of TiO_2 is substantiated by the evaluations carried out by other authoritative and scientific bodies (EFSA, 2016; 2018 & 2019; ANSES, 2017 and US FDA, 2019).
- The European Risk Assessment Committee (RAC) of ECHA issued in September 2017 an opinion suggesting a CMR2 classification (i.e. as a suspected human carcinogen) of TiO_2 by the inhalation route (ECHA, 2017). The hazard classification was based on the occurrence of lung tumours in rats, due to "lung overload" after lifetime inhalation exposure to high dose levels of TiO_2. Inflammation and lung overload are also observed from subchronic inhalation toxicity studies. There is, however, strong evidence that the carcinogenic effects in rats are not due to a direct genotoxic mechanism as detailed below. Therefore, a threshold for tumour occurrence in rats can be assumed and used for the safety assessment of inhalation exposure to TiO_2 in humans.

Ref. 1

3.4.1. Irritation and corrosivity

3.4.1.1 Skin irritation

/

3.4.1.2 Mucous membrane irritation / eye irritation

/

3.4.2 Skin sensitisation

/

3.4.3 Acute toxicity

3.4.3.1 Acute oral toxicity

/

3.4.3.2 Acute dermal toxicity

/

3.4.3.3 Acute inhalation toxicity

/

3.4.4 Repeated dose toxicity

3.4.4.1 Sub-chronic (90 days) inhalation toxicity

According to the Applicant, several sub-chronic (90 days) TiO_2 inhalation exposure studies performed in rats, mice and hamsters have been reported (Ferin et al., 1992; Everitt et al., 2000; Bermudez et al., 2002; 2004). No other findings than substantial responses of inflammation and overload associated with diminishing particle clearance in a dose dependent manner, and histologically clear indications of epithelial hypertrophy and hyperplasia were observed. Only the very high doses led to the above persistent adverse effects in the rat which appeared to be oversensitive to high lung burden of insoluble dusts such as TiO_2 in comparison to the mouse or hamster.

Ref. 1

3.4.4.3 Chronic (> 12 months) toxicity

/

3.4.5 Reproductive toxicity

/

3.4.5.1 Fertility and reproduction toxicity

/

3.4.5.2 Developmental Toxicity

/

3.4.6 Mutagenicity / genotoxicity

According to the Applicant, TiO_2 has been extensively studied according to internationally recognized testing guidelines for studies evaluating gene mutations (in bacteria or mammalian cells) and chromosomal damage (*in vitro and in vivo*) as well as in numerous non-standard models. There is a large body of evidence in literature showing that TiO_2 materials, irrespective of their coating status, crystalline phase and particle size are devoid of any genotoxic potential. This large panel of studies was reviewed by several scientific authoritative bodies (IARC,2010; SCCNFP, 2000; SCCS, 2014; EFSA, 2016, ECHA, 2017), who did not raise concerns with respect to a genotoxicity potential of TiO_2.

In its review of available genotoxicity data on TiO_2, the IARC (2010) concluded that most of the *in vitro* genotoxicity studies with TiO_2 exposure were negative despite the high rate of

false positive results. Further, an EFSA panel (2016) noted that positive genotoxicity results may have been due to experimental conditions associated with the induction of oxidative stress. The studies showing a positive association between the so-called group of Poorly Soluble Low Toxicity (PSLT) particles exposures and genotoxicity are generally consistent with the mechanism that sub-toxic concentrations of PSLT particles can cause inflammation and oxidative stress, which may lead to mutations. Oxidative stress is considered the underlying mechanism of the proliferation and genotoxic responses to PSLT particles including TiO_2 (Donaldson *et al.*, 1996; Shi *et al.,* 1998; Vallyathan *et al.*, 1998; Knaapen *et al.*, 2002; Donaldson and Stone, 2003). Overall negative results were obtained in *in vivo* genotoxicity studies with micro sized TiO_2 (IARC, 2010). Thus, there is a large body of evidence that TiO_2 has no direct genotoxic potential.

Taking into account the entire set of available literature data, previous submissions to the SCCS and its predecessors and reviews performed by scientific authoritative bodies, it can be concluded that TiO_2 materials used in cosmetic products do not pose a genotoxic risk.

Ref. 1

SCCS comments on genotoxicity

The SCCS considered in a previous Opinion on TiO_2 (SCCS/1583/17) that, where internal exposure of the lungs is possible, there is a possibility that nano-TiO_2 may exert genotoxic effects, most probably through indirect (e.g. oxidative stress) or secondary mechanisms (as a result of inflammation caused by immune cells), although direct interaction with the genetic material cannot be excluded.

ECHA (2017) concluded in its Opinion proposing harmonised classification and labelling of TiO_2 at the EU level, that the main mechanism to explain the effects induced by TiO_2, in common with effects seen with other substances, was inflammation and an indirect genotoxic effect through production of reactive oxygen species (ROS) arising from the biopersistence and insolubility of all forms of TiO_2 particles. However, a direct interaction with DNA could not be excluded, since TiO_2 was found in the cell nucleus in various *in vitro* and *in vivo* studies.

In 2016, EFSA published their 'Re-evaluation of titanium dioxide (E 171) as a food additive', in which a thorough and detailed summary and discussion of TiO_2 genotoxicity data has been given. It concluded that 'orally ingested TiO_2 particles (micro- and nanosized) are unlikely to represent a genotoxic hazard *in vivo*.' A review of data from the available open literature performed by the EFSA panel indicated that microsized TiO_2, with a defined size >100 nm or designed as 'fine rutile or anatase' produces mixed results (both negative and positive) in genotoxicity tests *in vitro.* Based on this, new studies with regard to genotoxicity were requested (EFSA 2018, EFSA 2019).

In concordance with the conclusion of EFSA (2016) and ECHA (2017), as well as in consideration of a review of other published studies, the SCCS is of the opinion that TiO_2 may exert genotoxic effects where internal exposure of the lungs is possible. The genotoxic effects of TiO_2 most probably manifest through an indirect mechanism (oxidative stress), or secondary mechanisms (e.g. oxidative stress and inflammation caused by immune cells). The SCCS therefore considers it plausible that there is a practical threshold for this mode of action and therefore a risk assessment could be carried out for its use in cosmetic products.

3.4.6.1 Mutagenicity / genotoxicity *in vitro*

/

3.4.6.2 Mutagenicity / genotoxicity *in vivo*

/

3.4.7 Carcinogenicity

According to the Applicant, three carcinogenicity inhalation studies in rats with TiO_2 were identified after an extensive literature review (Lee *et al.*, 1985; Muhle *et al.,* 1991; Heinrich *et al.*, 1995).

The study performed by Heinrich *et al.* (1995) was excluded from the current submission because the test material was not pigmentary TiO_2, but a nanomaterial designated as "P25" (not commercially used for any applications).

In the 2-year chronic inhalation study by Lee *et al.* (1985), male and female CD rats were exposed to pigmentary TiO_2 (uncoated rutile, purity 99%) at concentrations of 10, 50, or 250 mg/m³ for six hours a day, five days a week. The majority of the TiO_2 particles was of respirable size. Lung tumours occurred at 250 mg/m³ in this study. However, exposure concentrations above 50 mg/m³ clearly exceeded the maximum tolerated dose and were accompanied by a considerable cessation of alveolar clearance. An increased incidence of inflammatory reactions in the lungs and trachea was observed in the exposed groups as well as rhinitis and metaplasia of the respiratory epithelium. Inflammatory reactions and squamous metaplasia in the anterior nasal cavity were also found in the animals exposed to the lowest concentration. In addition, no analysis of bronchoalveolar lavage fluid (most sensitive end point) was carried out, therefore a No Observed Adverse Effect Concentration (NOAEC) cannot be derived on the basis of this study. ECHA (2017) also discounted this study because of the above limitations, assuming an exceedance of 60% volumetric alveolar macrophage loading thereby associated with complete cessation of alveolar clearance. Likewise, the National Institute for Occupational Safety and Health (NIOSH, 2011) designated the top exposure concentration of 250 mg/m³ as an excessive dose not relevant for human risk assessment. The authors of the study themselves noted that, due to excessive loading in the lungs of rats exposed chronically at 250 mg/m³, the lung tumours were different from common human lung cancers in terms of tumour type, anatomic location, tumourigenesis and lack of tumour metastasis. Overall, the biological relevance of these lung tumours for humans was deemed questionable.

In the study reported by Muhle *et al.* (1991), TiO_2 was used as a negative control dust in a two-year inhalation study with toner particles. Male and female Fischer 344 rats were exposed for 6 hours per day, 5 days per week to 5 mg/m³ pigmentary TiO_2 (rutile purity 99.5%, MMAD about 1.1 µm) with a particle size respirable fraction of 78%. A separate group of animals was used to monitor particle retention, alveolar clearance, bronchoalveolar lavage and other parameters. The animals were kept without further exposure for an additional 1.5 month observation period. The average amount of TiO_2 retained in the rat lung after 24 months was 3.2 mg for males and 2.24 mg for females. Inhalation of TiO_2 showed no signs of overt toxicity and other parameters such as body weight, food consumption, organ weights and chemistry data did not differ from untreated controls. A slight and non-significant increase in fibrosis and a significant increase in percent polymorphonuclear leucocytes was observed at 15 months, both effects were not significantly increased following 24 months of exposure, indicating that the exposure was not sufficient to cause a sustained pulmonary inflammation or fibrosis. No significant increase in lung tumours was observed. Lung clearance half-life (by 85Sr-labelled PS particles) was reduced by 20% after 9 and 21 months. In bronchoalveolar lavage analysis, a reduction of macrophages after 15 and 24 months was measured and polymorphonuclear leukocytes were increased only after 15 months. The number of leukocytes did not statistically differ from untreated controls. Furthermore, there were no effects on lactate dehydrogenase activity, ß-glucuronidase activity or protein levels as measured by bronchoalveolar lavage analysis. No significant fibrosis was detected in the terminal histopathological investigation.

In conclusion, the test concentration of 5 mg/m³ can be regarded as a true NOAEC based on the lack of relevant signs of inflammation.

Similarly, to the inhalation toxicity in general, the rat is a particularly sensitive model to lung tumours caused by Poorly Soluble Low Toxicity (PSLT) particles. This is further supported by the absence of such carcinogenic effect in other non-rodent species following inhalation exposure. Because of physiological species differences, even under theoretical conditions of very high inhalation exposures to TiO_2 powders over very long periods, it is highly unlikely that humans would be prone to TiO_2-induced lung tumours. Human epidemiology studies in TiO_2 workers have consistently shown absence of elevated of any cancer risk.

Ref. 1

SCCS comments

The SCCS is of the Opinion that Applicant's statement on the carcinogenicity studies does not reflect correctly the following two conclusions of the ECHA report:

1. *'ECHA (2017) also discounted this study because of the above limitations, assuming an exceedance of 60% volumetric alveolar macrophage loading thereby associated with complete cessation of alveolar clearance'.*

Whereas the ECHA Opinion states that *'Because of the complete cessation of alveolar clearance, RAC takes the view that the results of the Lee et al. (1985) rat study should not have a determining influence on classification of TiO_2. […] RAC takes the view that these exposure conditions represent excessive exposure which invalidates the results of the Lee et al. (1985) study on their own for classification purposes.'*

2. *'Human epidemiology studies in TiO_2 workers have consistently shown absence of any elevated cancer risk'.*

Whereas according to the ECHA Opinion, '….*RAC concluded that the epidemiological data was not sufficient to conclude on a carcinogenicity classification as the exposure data was inconclusive and that the epidemiological data could not overrule the outcome of the animal studies.'*

The SCCS is of the opinion that the CMR2 classification of TiO_2 cannot be disputed because of an official body's conclusion on its classification and subsequent inclusion in the CLP regulation by the Commission. In the absence of a conclusive evidence to suggest otherwise, the position remains that the carcinogenic effects observed in animals are also possible in humans. In this regard, the following text is repeated as a summary of the available carcinogenicity studies from a previous opinion on TiO_2 in sprayables (SCCS/1583/17):

'Various scientific and regulatory bodies have considered TiO_2 as a possible carcinogen to humans when inhaled. Recently, TiO_2 has been classified as Carc. Cat 1B-H350i considering that a causal relationship had been established between TiO_2 and an increase of both malignant and benign lung tumours in one species (rat), reported in two studies by inhalation and two studies by instillation. Since data provided cannot distinguish if a specific characteristic is linked to such effect, this classification is proposed to be applied to all existing possible crystalline forms, morphologies and surface chemistries in all possible combinations of TiO_2.

Although the detailed mode of action is still unclear, an inflammatory process and indirect genotoxic effect by ROS production seems to be the major mechanism to explain the effects induced by TiO_2. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO_2 particles. However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO_2 was found in the cell nucleus in various *in vitro* and *in vivo* studies'.

3.4.8 Photo-induced toxicity

3.4.8.1 Phototoxicity / photo-irritation and photosensitisation

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3.4.8.2 Photomutagenicity / photoclastogenicity

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3.4.9 Human data

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3.4.10 Derivation of a safe Human Reference Value

According to the Applicant, the mechanism of tumour formation in laboratory rats exposed to TiO_2 and other so-called "poorly soluble particles of low toxicity" (PSLT) particles is a well-understood mechanism. The latter involves a cascade of events, triggered by "lung overload" from PSLT particles, including sustained inflammation, production of reactive oxygen species, depletion of antioxidants, cell proliferation and eventually gene mutations. Reactive oxygen species within cells may damage DNA and potentially induce mutations. The existence of a non-linear, dose-related effect with a threshold that triggers inflammation and overwhelms the body's antioxidant and DNA repair mechanisms is well described (Greim and Ziegler-Skylakakis, 2007). Under conditions of particle exposure that do not overwhelm host defence mechanisms (e.g., anti-oxidants, DNA repair) and hence do not elicit inflammatory or proliferative responses, no genotoxic effects are observed. The RAC also clearly designated the rat lung tumours as being elicited merely by a "physical, particle effect" and not a TiO_2-specific chemically-induced effect.

Inhalation exposure to pigmentary TiO_2 under conditions of excessive pulmonary overload associated with complete cessation of lung clearance is known to produce primarily benign lung tumours in rats only, but no tumours in other experimental rodent species (Hext et al. 2005). The rat is considered uniquely sensitive to the formation of lung tumours when exposed under conditions of particle overload to TiO_2 and other PSLT (Levy, 1994; Hext *et al.* 2005). Although particle overload is observed in other experimental species such as mice, a sequence of events that leads to fibroproliferative disease, septal fibrosis, hyperplasia and eventually lung tumours is only initiated in rats. Similar pathological changes are not observed in other experimental rodent species, nor in non-human primates or in humans. In addition, detailed epidemiological investigations have shown no causal relationship between TiO_2 inhalation exposure, specifically in TiO_2 workers, and cancer risk in humans.

According to the Adverse Outcome Pathway (AOP) in Rats (as summarized in the ECETOC Technical Report 122, 2013), the onset of chronic inflammation is required prior to the occurrence of proliferative changes. Thus, any chosen NOAEC should be based on the absence of inflammatory changes inducing increased inflammatory cells, inflammation-specific cytokines, enzymes specific to cytotoxicity or hyperplasia of the pulmonary epithelium. As a consequence, the lack of significant signs of inflammation, is set as relevant parameter for the NOAEC identification.

As TiO_2 is recognized not to be a direct genotoxic and in light of the above mechanism of tumour formation in rats, a threshold below which no relevant adverse effects occur can be identified. The existence of a non-linear dose-related effect with a threshold that triggers inflammation is indeed well described (ToxStrategies 2020).

On the basis of the following evidences:

- The test material in the Muhle *et al.* (1991) study is a pigmentary TiO_2 comparable to TiO_2 raw materials used in cosmetics
- Absence of sustained inflammation in rats and no observed lung tumours,

The Applicant identified Muhle *et al.* (1991) rat inhalation study as the pivotal and considered the NOAEC of 5 mg/m^3 as the Point of Departure (POD) for human safety assessment of inhalation exposure to TiO_2.

Ref. 1

Calculation of human equivalent concentration (HEC) by the Applicant

For deriving the human equivalent concentration (HEC) or human equivalent lung exposure dose (ToxStrategies, 2020), the concentration value of NOAEC 5 mg/m^3 obtained was first adjusted for exposure of 6 hours per day, 5 days per week to a chronic exposure of 24 h per day, 7 days per week to yield the concentration value of 0.89 mg/m^3/day (=5 mg/m^3 x 6/24 x 5/7).

A dosimetric adjustment factor (DAF) was then used to convert 0.89 mg/m^3/day to a continuous-exposure HEC based on species-specific information on deposition, pulmonary surface area, and breathing volume. Deposition per pulmonary surface area is the key dose metric for inflammatory effects. This DAF is also known as the regional deposited dose ratio (RDDR) (US EPA, 1994). The DAF was calculated using Applied Research Associates' Windows-based Multi Pathway Particle Deposition (MPPD) v3.04 to estimate the pulmonary deposition fraction to the human and rat lungs. The human model used was Yeh Schum symmetrical (minute volume, breathing frequency, and pulmonary surface area are shown in Table 4). The deposition fraction to the rat lung was based on the rat Sprague-Dawley symmetrical model, using the time-weighted average bodyweight for male rats and whole body exposure as per experimental conditions in Muhle *et al.* (1991).

This depositional fraction was combined with standard rat breathing rates and pulmonary surface area measurements for computing the DAF. The calculated DAF was 1.3. Therefore, the 24-hour time-weighted equivalent rodent exposure of 0.89 mg/m^3-day was multiplied by 1.3, resulting in an adjusted HEC of 1.2 mg/m^3/day (Table 13). Since all of this TiO_2 is inhalable, the theoretical deposition to the lung HEC is 24000 µg/day (1.2 mg/m^3 x 20 m^3/day) where 20 m^3 corresponds to the breathing rate of a person for 24-hour continuous exposure i.e. 7 days per week, and 60 kg of the average consumer body weight.

Table 14: Summary of the parameters for MPPD model used to derive HEC (by the Applicant)

	MPPD Parameter
Rat	
Tidal Vol (mL)	2.1
Breaths/min	102
VE (mL/min)	214.2
Fractional deposition (PU)	0.0424
Alveolar surface area (m^2)	0.4
Human	
Tidal Vol (mL)	860
Breaths/min	16
VE (mL/min)	13760
Fractional deposition (PU)	0.1287 [1]

Alveolar surface area (m^2)	102
DAF	**1.3**
24-hour Adjusted HEC (mg/m^3.day)	**1.2**

[1]Yeh-Schum symmetric per Kuempel et al. (2015) and Thompson et al. (2016)

According to the Applicant, the estimated deposition value of 24000 µg/day (HEC or human equivalent lung exposure dose) is thus the reference value for consumer exposure to non-nano TiO_2 taken forward for the risk assessment. This human lung exposure dose covers all the TiO_2 materials used in cosmetics (i.e. group 1 and group 3) as the rat lung tumours are elicited merely by a "physical, particle effect" and not a TiO_2-specific chemically-induced effect (ECHA, 2017) and because, as demonstrated by Warheit and Brown (2019) surface modifications and particle size alone of TiO_2 materials have little or no impact on the lung toxicity of TiO_2 particles following pulmonary exposures.

Ref. 1

SCCS comments on the derivation of HEC and the estimated deposition values

The Applicant chose the Muhle *et al.* (1991) work as the key study for the calculations of HEC.

As first step, the SCCS recalculated the HEC based on the parameters provided, which resulted in a slightly different HEC of 1.03 mg/m^3 (instead of 1.25 mg/m^3, see column 3 of Table 14). Furthermore, the SCCS examined the calculations done by the Applicant with the MPPD software and found that information and references for some of the parameters used were missing:

- particle properties: density (4.3g/cm^3), MMAD (1.1µm), GSD (1.6)(now added to the Table);
- the breath rate (value of 102) in rat seems to correspond to nose only exposure, the value of this parameter should be 115 (whole body exposure);
- the tidal volume in humans is 860 ml, according the default parameter of MPPD2 it should be 625 ml;
- the breath rate in humans is 16/min, the value of this parameter should be 12/min (default parameter);
- The reference for the alveolar surface (in m^2) in rats and humans is missing. Literature indicates other values for alveolar surface, however, the values chosen by the Applicant are in the same range as the published values.

According to the Applicant, the theoretical deposition to the lung HEC is 24000 µg/day (1.2 mg/m^3 x 20 m^3/day), where 20 m^3 corresponds to the breathing rate of a person for 24-hour continuous exposure i.e. 7 days per week; and 60 kg is used as average consumer body weight.

The SCCS considers the deposition in the pulmonary region as the most relevant dose metric for the current assessment, and not the inhalable fraction. Based on the same equation used by the applicant, the SCCS has derived the corresponding deposition value as being equal to the fractional deposition x HEC (mg/m^3) x 20 m^3/day, which results in a value of 3173 µg/ day (i.e. the amount that reaches the alveoli). However, the SCCS has considered it more appropriate to use the same approach for calculation of the particle deposition in the pulmonary region as used by MAK (2012) and ANSES (2017) (see Table 15b).

Table 15a: Comparison of calculations of HEC and estimated deposition values calculated by the Applicant and the SCCS using Muhle et al, 1991

	Calculations by the Applicant	**Calculations by the SCCS**
	Muhle *et al.*, 1991	
NOAEC (mg/m^3)	5	
Time adjustment	(6h/24hr)x(5 days/7 days)	
Density	4.3	
MMAD (um)	1.1	
GSD	1.6	
MPPD Parameter		
Rat		
Tidal Vol (mL)	2.1	2.1
Breaths/min	102	102
VE (mL/min)	214.2	214.2
Fractional deposition (PU)	0.0424	0.0449
Alveolar surface area (m^2)	0.4	0.4
Human		
Tidal Vol (mL)	860	860
Breaths/min	16	16
VE (mL/min)	13760	13760
Fractional deposition (PU)	0.1287 [1]	0.1534
Alveolar surface area (m^2)	102	102
DAF	**1.3**	**1.2**
24-hour Adjusted HEC (mg/m^3.day)	**1.2**	**1.03**
HEC (ug/day)	**24000**	**21153**
Estimated deposition value (µg/day)	**3120[2]**	**3173 (in the pulmonary region)**
Steady state Adjusted HEC (mg/m^3.day)[2]	**Not calculated**	**0.15**
Estimated deposition value (µg/day) at steady state	**Not calculated**	**456**

[1] Yeh-Schum symmetric per Kuempel *et al.* (2015) and Thompson et al. (2016)
Values in red are divergent (between SCCS calculations and Applicant's calculations)
[2] Estimated deposition value (µg/day) = HEC x Fractional deposition (PU)
This HEC at steady state takes account the elimination constant in rat and human, expressed in days:
Elimination constant = −ln(0.5)/elimination half-time (MAK 2012, ANSES 2019)
In rat, the Elimination constant = -(ln0.5)/60 = 0.0116/day.
In human, Elimination constant= -(ln0.5)/400 = 0.00173/day.

A different study (Bermudez *et al.*, 2004) has been used as the key study in an ANSES report to derive a toxicity reference value TRV (see below). In this study, the pulmonary responses of rats after sub-chronic inhalation of ultrafine TiO_2 (P25) particles have been described. For the reasons mentioned below, the SCCS has also decided to use the Bermudez et al. (2004) study as the key study to derive the point of departure for the safety assessment of the TiO_2 materials in the current Opinion. Therefore, a NOAEC of 0.5 mg/m^3 from Bermudez *et al.* (2004) has been used (instead of 5 mg/m^3 from Muhle *et al.*, 1991) as the point of departure, which is based on inflammation evidenced in the BALF and pulmonary lesions at 2 mg/m^3 (minimal hypertrophy and hyperplasia of type II alveolar epithelial cells).

For the calculations based on Bermudez *et al.* (2004), the SCCS has used the default parameter for the tidal volume in humans (625 ml) and the breath rate in humans (12/min) leading to a ventilation rate of 7500 (ml/min). For the alveolar surface, the SCCS used 57.22 m^2 for humans, and 0.297 m^2 for rats.

Furthermore, the parameters for tidal volume as well as for number of breaths have been changed into 625 and 12 respectively, which results in the ventilation rate (VE) of 7500. These parameters were changed according to the numbers in the MPPD as default parameter.

The Deposition value at non steady state was calculated as: Fractional deposition in human x 24-h HEC (Human Equivalent Concentration)x 20 m^3/day), where 20 m^3 corresponds to the breathing rate of a person for 24-hour continuous exposure = **766 µg/day.** In Table 15b the SCCS has not adjusted NOAEC (5 days /week) and has based the calculation on a 6 hours exposure of rats.

Table 15 b: calculations of HEC and estimated deposition values calculated by the SCCS using Bermudez et al. 2004

	MPPD Parameter
Rat	NOAEC =0.5
Tidal Vol (mL)	2.1
Breaths/min	102
VE (mL/min)	214.2
Fractional deposition (PU)	0.056
Alveolar surface area (m2)	0.297
Clearance	Not used
deposition rate[1]	0.00431827
Human	
Tidal Vol (mL)	625
Breaths/min	12
VE (mL/min)	7500
Fractional deposition (PU)	0.1485
Alveolar surface area (m^2)	57
Clearance Human	Not used
deposition rate [2]	1.6038
DAF	**0.52**
24-hour Adjusted HEC (mg/m^3/day)	**0.258**

[1] Deposition rate rat = 0.056 x (2.1/1000000) x 102 x 60 x 6 = 0.003084 m^3/day
2.1 ml = tidal volume of the rat
102/min = respiratory rate of the rat
60 min x 6h x 5/7j = exposure time of the study, expressed in days

[2]Deposition rate human = 0.1485 x (625/1000000) x 12 x 60 x 24 = 1.6038 m^3/day
625 ml = tidal volume of human
12/min = respiratory rate of human
60 min x 24h = exposure time, expressed in days

Using the NOAEC and the parameters from this study, the SCCS has calculated the following 24 hour adjusted HEC and the estimated deposition value based on Bermudez *et al.* (2004) (see Table 15b):

- 24 hour adjusted HEC = 0.258 mg/m^3/day
- Deposition value (fractional deposition) then becomes 766 µg/day in the pulmonary region.

This indicates that the Human Equivalent Concentration (HEC) or lung exposure dose of 24000 µg/day derived by the Applicant from Muhle *et al.* (1991) study using a NOAEC of 5 mg/m^3 is far too high when compared with the reference values derived by the SCCS (Table 15b) and by other institutions (Table 16).

Table 16: Reference values for TiO_2 derived by different institutions

Institution (year)	**Main TiO_2 material**	**Reference value**	**Critical endpoint**	**Time adjustment and dose metrics**	**Uncertainty factors**	**POD**	**Key study**
ANSES (2020)	P25 (nano)	Workers: 0.80 µg/m^3 General population: 0.12 µg/m^3	Lung Inflammation	Temporal and allometric adjustment MPPD model	225 UF inter species = 2.5 UF intra species = 10 UF study duration= 3 UF Database = 3	NOAEC = 0.5 mg/m^3	Bermudez *et al.*, 2004
NIOSH (2011)*	Various (fine and ultrafine)	For fine particles (FP): 0.04 mg/m^3 For ultrafine particles (UFP): 0.004 mg/m^3 for ultrafine (including engineered nanoscale) TiO_2	Lung Inflammation	10 hr/day during a 40-hour work week, 45 years. Internal lung doses MPPD model	25 UF inter species = 2.5 UF intra species = 10	For FP: 0.9 mg/m^3 For UFP: 0.11 mg/m^3	For FP and UFP : Rat studies: Tran *et al.* (1999), Cullen *et al.* (2002), and the combined data from Bermudez *et al.* (2002) and Bermudez *et al.* (2004)

NIOSH (2011)*	Various (fine and ultrafine)	2.4 mg/m^3 for fine TiO_2 0.3 mg/m^3 for ultrafine (including engineered nanoscale) TiO_2	Lung cancer	10 hr/day during a 40-hour work week, 45 years. Internal lung doses MPPD model	Working Life Time cancer risk approach 1 excess case per 1,000 workers Equal sensitivity of lungs tissues between rats and humans assumed	For Fine Particles : Rat studies: Lee *et al.* (1985, 1986), Muhle *et al.* (1989,1991, 1994) and Bellmann *et al.* (1991) For Ultrafine Particles: Heinrich *et al.* (1995); Rat studies : Muhle*et al.* (1994)
MAK	Various	0.3 mg/m^3 × material density	Lung Inflammation	Different Approaches considered	Reference value derived according to according to the general threshold value for biopersistent granular dusts, not valid for ultrafine particles	MAK, 2012

* NIOSH (2011): The pulmonary inflammation-based exposure concentrations are expected to entirely prevent the development of toxicity secondary to pulmonary inflammation, resulting in zero excess risk of lung tumors due to exposure to TiO_2. In contrast, the lung tumor-based exposure concentrations are designed to allow a small, but nonzero, excess risk of lung tumors due to occupational exposure to TiO_2. (…) It is possible that the 4% PMN response used in this analysis as the benchmark response level for pulmonary inflammation is overly protective and that a somewhat greater inflammatory response is required for tumor initiation. It is also possible that the 25-fold uncertainty factor applied to the critical dose estimate for pulmonary inflammation may be overly conservative, since pulmonary inflammation is an early event in the sequence of events leading to lung tumors. However, NIOSH has not previously used early events or secondary toxicity as a rationale for applying smaller than normal uncertainty factors. Given that in this case the primary objective of preventing pulmonary inflammation is to prevent the development of lung tumors, and given that lung tumors can be adequately controlled by exposures many-fold higher than the inflammation-based exposure concentrations, NIOSH has concluded that it is appropriate to base RELs for TiO_2 on lung tumors rather than pulmonary inflammation. However, NIOSH notes that extremely low-level exposures to TiO_2—i.e., at concentrations less than the pulmonary inflammation-based RELs—may pose no excess risk of lung tumors.

Refs: https://www.anses.fr/en/content/titanium-dioxide-nanoparticle-form-anses-defines-toxicity-reference-value-trv-chronic
https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf
Hartwig A., MAC commission (2019)

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MoS)

3.5.1 Toxicological Point of Departure

According to the Applicant, the point of departure that shall be used in the risk assessment of consumer inhalation exposure to TiO_2 considers the most sensitive adverse effects in rats associated with chronic inhalation exposure to TiO_2. From the evidence presented, the pivotal study corroborates a NOAEC of 5 mg/m^3 on the basis of the absence of inflammatory response in the rat lung (Muhle et al., 1991). On the basis of the above, the Applicant has considered the use of this NOAEC value to be protective of any adverse effects possibly associated with inhalation exposures to TiO_2 (as indicated above). This NOAEC was converted by the Applicant into a human equivalent lung exposure dose of 24000 µg/day by taking into account the adaptation of the rat study exposure schedule (from 6h/day, 5 days/week to 24 h/day, 7 days/week), and interspecies differences in pulmonary deposition and breathing volumes between rats and humans.

Ref.1

SCCS comments

Selection of the key study for derivation of toxicological point of departure

As discussed above, having considered the various relevant studies, the SCCS has regarded Bermudez *et al.* (2004) as the key study for deriving the toxicological point of departure for safety assessment. This is because the SCCS has noted a number of shortcomings in regard to the study by Muhle *et al.* (1991).

The Bermudez *et al.* (2004) study used P25, which is comprised of uncoated nanoparticles (NPs) of a mixture of 80% rutile and 20% anatase forms of TiO_2. The SCCS considered it relevant for the assessment of pigmentary TiO_2 materials because the latter contain a significant fraction of nano-scale particles that in the SCCS opinion are most important to consider in the estimation of inhalation exposure of the alveolar region of the lungs. In this regard, the SCCS agrees with the following reasons given in the ANSES report for regarding Bermudez *et al.* (2004) as the pivotal study:

1. All of the available human studies on TiO_2-NP are considered inadequate and they do not allow the establishment of a TRV;
2. In animals, only few studies with repeated exposure are available for the inhalation route. Repeated-dose toxicity studies conducted by instillation are also found in the literature. As stated in the OECD (2018), those studies cannot be used for risk assessment, mainly because such an exposure bypasses the upper respiratory tract and therefore cannot be used as a representative of inhalation exposure;
3. Bermudez *et al.* (2004) is the most robust study available for the inhalation route, with the longest duration of exposure (13 weeks). The TiO_2-NP used (P25; 80% anatase/20% rutile; about 21 nm) is one of the OECD reference materials and is fully characterised (OECD 2015);
4. Moreover, compared to most other studies available, the concentrations used (0.5, 2 and 10 mg/m^3) in the Bermudez *et al.* (2004) study are adequate to observe a dose-response relationship and to identify a no-observed effect concentration. The study was carried out in three rodent species (mice, rats and hamsters), which also allows a comparative assessment of the sensitivity of different species to TiO_2-NP under the same protocol;
5. The findings reported in rats with the TiO_2-NP (P25) are considered relevant for humans, because of:
    a. the lack of specific mechanistic data to adequately compare humans and rats and their sensitivity to TiO_2-NP exposure;

b. a slower lung clearance of particles in humans compared to rats;
c. and similar qualitative lung response to dust between humans and rats

Considering all these elements, the study of Bermudez *et al.* (2004) remains the most reliable study for the selection of a point of departure for risk assessment. It has to be noted that all other repeated-dose toxicity studies performed with several concentrations by inhalation, even if performed on other forms of TiO_2-NP, support the qualitative and quantitative results obtained by Bermudez *et al.* (2004).

Ref: https://www.anses.fr/en/content/titanium-dioxide-nanoparticle-form-anses-defines-toxicity-reference-value-trv-chronic

Read-across of toxicological data from other TiO_2 materials

Despite the apparent discrepancies in the material characteristics (R4 being anatase and surface-treated, and Bayertitan-T and P25 being rutile and uncoated), the SCCS has accepted the Applicant's data read-across from toxicological studies on other materials for the current safety evaluation of R4. This is because of the indications from published studies that the pulmonary effects caused by these types of TiO_2 materials are likely to be comparable (or comparatively lower for anatase and thus the use of rutile in these studies could represent a worst-case):

1. Ferin and Oberdörster (1985) exposed rats to an aerosol of either anatase or rutile and determined the TiO_2 retention in the lung for up to 132 days post exposure. Particle clearance from the lung, calculated from the retention data, was similar in both the anatase and the rutile groups with $T_{1/2}$ of 51 or 53 days, respectively. The study also carried out a pulmonary cell response test on other rats. Lung lavage was performed and the harvested cells counted after intratracheal instillation of anatase and rutile (0.5 or 5.0 mg/rat). This also yielded similar results for both types of TiO_2 in terms of cell counts, alveolar macrophages (AM), peroxidase positive AM, and polymorphonuclear leukocytes. The authors concluded that there was no difference between toxicological effects of rutile and anatase, and no indication that the crystal lattices of TiO_2 altered the biological effects of TiO_2 particles (via inhalation).
2. A study by Warheit and Brown (2019) indicated that pulmonary exposure to surface modifications and particle size alone of TiO_2 materials have little or no impact on the lung toxicity of TiO_2 particles.
3. Danielsen *et al.* (2020) studied the pulmonary toxicity of four anatase nanomaterials with varying sizes and shapes and found that all of them induced pulmonary inflammation and pulmonary acute phase response, but no genotoxicity in mice after intratracheal exposure. They also compared their results with the data from previous studies on rutile TiO_2 nanomaterials to conclude that, in general, anatase nanomaterials induce less inflammation than rutile nanomaterials when normalised to surface area, and the inflammatory and acute phase response was greatest and more persistent for the TiO_2 tubes.

3.5.2 Exposure data

According to the Applicant, the inhalation exposure assessment has been performed according to the SCCS Notes of Guidance 10th revision (SCCS/1602/18). The products tested in field exposure studies were chosen on the basis of criteria allowing identification of worst case exposure to TiO_2 resulting from the use of cosmetic products. In addition, a deterministic and overly conservative aggregate exposure assessment - assuming that all the evaluated products are used by an individual each day - was performed.

Ref.1

SCCS comments

Detailed SCCS comments on the exposure data are given under section 3.3.

3.5.3 Margin of Safety calculation

According to the Applicant, in the case of TiO_2 risk assessment, there is clear evidence that there is no need to account for all the usual uncertainty factors because:

- The dose metric used for the risk assessment is the target organ exposure dose (lung dose), applying interspecies toxicokinetic uncertainty factors is therefore not necessary
- The observed effects are rat specific, applying interspecies toxicodynamic uncertainty factors is therefore not necessary

Thus, according to the Applicant, a Margin of safety value of **10** would be sufficiently protective to consumers' health. Considering the built-in conservatism of the point of departure (POD) derivation, the conservatism of the exposure data used (product types with the highest potential for TiO_2 exposure) and the calculated MoS (**167** for aggregated deterministic exposure), the consumer inhalation exposure to TiO_2 resulting from the use of cosmetic products is unlikely to pose a consumer health risk.

As shown in the Table below, the derived margin of safety value is above 10 for each individual product (MoS values ranging from about 200 to > 100000) as well as for the deterministic aggregate exposure.

Ref.1

Table 17: Applicant's calculation of Margin of Safety (Note: only those products are shown here that use R4 pigmentary TiO_2 and are therefore relevant for the SCCS assessment)

	Human equivalent lung exposure dose (µg/day)	Measured TiO_2 concentration Thoracic fraction ($\mu g/m^3$)[1]	TiO_2 inhaled (lung exposure) dose thoracic fraction[2] (µg/day)	Margin of Safety[3]
Hair Styling Aerosol Spray Product F8	24000	480.4	125	192
Loose Powder for Face Make-up Product FZ		39.8	10.35	2319

[1] Data from section 2. 20 min average air concentration
[2] TiO_2 inhaled dose (µg/day) = Measured TiO_2 concentration Thoracic fraction ($\mu g/m^3$) /1000 (conversion m^3 to L) x human breathing rate (13 L/minutes) x residence time in the room (20 minutes) x frequency of use per day (according to the product uses).
[3] Margin of Safety = Safe human equivalent lung exposure dose / TiO_2 inhaled (lung dose) dose thoracic, where HEC is 24 000 µg/day (see Section IV(c)).

SCCS comment

For general consumers

As explained above, in the SCCS Opinion, the Margin of Safety (MoS) should be calculated based on the toxicological point of departure derived from Bermudez *et al.* (2004) study, which is an NOAEC of 0.5 mg/m^3.

The Human deposition value was calculated according to the MPPD software (v3.4), see chapter 3.4.10. The SCCS considers it important to take the fractional deposition into account because of the concerns for the nano-scale fraction reaching the alveoli. Furthermore, in the SCCS Opinion, the relevant dose metric should be the deposition of particles in the pulmonary region (pulmonary deposited dose) and not the inhalable fraction. The TiO_2 pulmonary deposited dose is calculated as follows:

Deposition fraction in human x HEC x 20 m^3 = 766 µg/day

This corresponds to the breathing rate of a person for 24-hour continuous exposure.

The SCCS recalculated the pulmonary-deposited dose according to the product use frequency given in chapter 3.3.2.2. The SCCS calculation of the Margin of Safety (MoS) with HEC at non-steady state is presented in Table 18a.

Table 18a: The SCCS calculation of the Margin of Safety with HEC at non-steady state

	TiO_2 concentration in the formulation (%)	Safe Human deposition in pulmonary region (µg/day)	Measured TiO_2 concentration Thoracic fraction (µg/m^3)	TiO_2 pulmonary deposited dose (µg/day)[1]	Margin of Safety[2]
Hair Styling Aerosol Spray Product F8	1	766	480.4	22.34	34
Loose Powder for Face Make-up Product FZ	20		39.8	3.24	236
Combined exposure of the above 2 product types				25.6	30

The average deposition fraction is 17%.
TiO_2 pulmonary deposited dose (µg/day) = Measured TiO_2 concentration Thoracic fraction (µg/m^3) /1000 (conversion m^3 to L) x human breathing rate (12 L/min) x residence time in the room (20 min) x frequency of use per day (according to the product uses) x 0.17.
[2]Margin of Safety = Safe Human deposition in pulmonary region (µg/day)/ TiO_2 pulmonary deposited dose, where Safe Human deposition is 766 µg/day.

Recalculation by the SCCS of the levels that can be considered safe indicated that **the use of pigmentary TiO_2 in a typical hair styling aerosol spray product would be safe up to a maximum concentration of 1.4 % for the general consumer**.

The MoS associated with a TiO_2 concentration in the formulation of 25% as proposed in the mandate is 1.36 for Hair Styling Aerosol Spray Product F8, and 189 for Loose Powder for Face Make-up Product FZ (Table 18b)**.**

Table 18b: The SCCS calculation of the Margin of Safety for the general consumer at a product concentration of 25%

	TiO_2 concentration in the formulation (%)	MoS
Hair Styling Aerosol Spray Product F8	**25**	**1.36**
Loose Powder for Face Make-up Product FZ	**25**	**189**

For hairdressers:

For estimating hairdressers' exposure, the SCCS also considers the deposition in the pulmonary region at non steady state as the relevant dose metric and not the inhalable fraction, but the pulmonary deposited dose (µg/day) with the time adjustment for 8 hours of exposure (See Table 19).

Table 19: Calculation of HEC and estimated deposition values at non steady state for hairdresser by the SCCS

	MPPD Parameter
Rat	0.5
Tidal Vol (mL)	2.1
Breaths/min	102
VE (mL/min)	214.2
Fractional deposition (PU)	0.056
Alveolar surface area (m^2)	0.297
Clearance	Not used
deposition rate[1]	0.00431827
Human	
Tidal Vol (mL)	625
Breaths/min	12
VE (mL/min)	7500
Fractional deposition (PU)	0.1485
Alveolar surface area (m^2)	57
Clearance Human	Not used
deposition rate[1]	0.5346
DAF	**1.55**
8-hour Adjusted HEC (mg/m^3.day)	**0.775**

[1]Deposition rate (rat) = 0.056 x (2.1/1000000) x 102 x 60 x 6 x 5/7
[2]Deposition rate (human) = 0.1485 x (625/1000000) x 12 x 60 x 8

For the safety assessment for hairdressers, the SCCS has used the deposition value mentioned in Table 19.

The Deposition value at non steady state was calculated as: deposition rate in human x 24-h HEC (Human Equivalent Concentration)x 10 m^3/day), where 10 m^3 corresponds to the breathing rate of a person for 8-hour continuous exposure
= **1151** µg/day

Table 20a: The SCCS calculation of the Margin of Safety with HEC at non steady state for hairdressers with ConsExpo exposure estimation

	TiO_2 conc. in the formulation (%)	Human equivalent pulmonary exposure dose (µg/day)	Estimated TiO_2 lung exposure (µg/days) Estimated by ConsExpo (see chapter 3.3)	**TiO_2 pulmonary deposited dose (µg/day)[1]**	Margin of Safety[2]
Hair Styling Aerosol Spray Product F8	1.0	**1151**	11.47	1.95	587

[1] calculated with ConsExpo with an average deposition fraction of 17%.
TiO_2 pulmonary deposited dose (µg/day) = estimated TiO_2 lung exposure x0.17.
[2] Margin of Safety = safe Human equivalent pulmonary exposure dose / TiO_2 pulmonary deposited dose, where HEC is 1151 µg/day.

Important Note: A further consideration in the SCCS opinion is that hairdressers are also consumers and therefore the exposure expected for a general consumer also needs to be added to the exposure accrued in the workplace for the MoS calculation (Table 20b). In addition, the human equivalent pulmonary exposure dose for the hairdressers should be the same as for general consumer, e.g. 766 µg/day.

Table 20b: The SCCS calculation of the Margin of Safety with HEC at non steady state for hairdressers with ConsExpo exposure estimation (with adapted HEC for general consumer)

	TiO_2 conc. in the formulation (%)	Human equivalent pulmonary exposure dose (µg/day)	estimated TiO_2 lung exposure (µg/days) estimated by consexpo (see chapter 3.3)	**TiO_2 pulmonary deposited dose (µg/day)[1]**	Margin of Safety[2]
Hair Styling Aerosol Spray Product F8	1.0	**766**	162 (150.5 from consumer exposure +11.5 from occupational exposure)	27.6	28

[1] occupational and consumer exposure with an average deposition fraction of 17%.
TiO_2 pulmonary deposited dose (µg/day) = estimated TiO_2 lung exposure x0.17.
[2] Margin of Safety = safe Human equivalent pulmonary exposure dose / TiO_2 pulmonary deposited dose, where HEC is 766 µg/day.

Recalculation by the SCCS of the levels that can be considered safe indicated that **the use of pigmentary TiO_2 in a typical hair styling aerosol spray product would be safe up to a maximum concentration of 1.11 % for the hairdresser**.

The SCCS calculated the MoS associated with a TiO_2 concentration in the formulation of 25%. This resulted in a MOS of 1.12 for Hair Styling Aerosol Spray Product F8.

Table 20c: The SCCS calculation of the Margin of Safety for the hairdresser at a product concentration of 25%

	TiO_2 concentration in the formulation (%)	MoS
Hair Styling Aerosol Spray Product F8	**25**	**1.12**

The SCCS is of the opinion that these product levels should not be compared to a MoS of 10 but to a MoS of 25, as in the opinion of the SCCS an additional factor of 2.5 (toxicodynamic difference between rats and humans) and a factor of 10 for interindividual variability among workers should be applied in the safety calculation.

It needs to be emphasised that the SCCS conclusions have been drawn from a *very selected group of cosmetic product*s based on *only one type of TiO_2 material* (pigmentary, anatase, surface-treated). The SCCS is of the opinion that more data would be needed for a comprehensive estimation of the combined TiO_2 exposure via inhalation from all product categories that could lead to inhalation exposure.
In the absence of more information, it may not be clear whether these conclusions would be applicable to similar cosmetic applications containing other types of pigmentary TiO_2 materials that may be on the market. In this regard, the SCCS is of the opinion that other similar applications of pigmentary TiO_2 materials can also be considered safe if the MoS calculation is performed in the way as detailed in the current Opinion, and if the resultant MoS is above 25 for the general consumer and for the hair dresser.

3.6 DISCUSSION

The focus of the current opinion is on the question whether TiO_2 materials can be considered safe for use in cosmetic products despite the recent CLP CMR2 classification for inhalation exposure.

The safety of the materials has been evaluated on the basis of the data relating to potential exposure of the consumer via the inhalation route.

Physicochemical properties

The Applicant described physicochemical characterisation of different TiO_2 materials that include pigmentary TiO_2 (group-1) and pearlescent pigments (group-3). Nanoforms of TiO_2 (group-2) were not described because the Applicant considered these being not relevant for the submission. The Applicant made a further distinction between pigmentary TiO_2 materials in terms of coated or surface-treated (group 1a) and uncoated (group 1b) materials and provided description of different physicochemical characteristics of the materials.

Having considered the information, the SCCS has regarded that only pigmentary TiO_2 can be considered for safety assessment in this Opinion, because they are mainly composed of TiO_2. The Opinion has not considered the pearlescent pigments because they are composed of various materials and contain TiO_2 only as minor constituent. In SCCS's view, the physicochemical and toxicological properties of such materials are likely to be driven by the

mixture composition and not TiO_2 as such. Consequently, the Opinion has only included and discussed the information relating to pigmentary TiO_2 materials, and excluded the pearlescent pigments specified in the dossier from the current evaluation.

The SCCS has also regarded group-2 (comprising of nano TiO_2 materials) as relevant for this evaluation because the pigmentary TiO_2 materials also contain a significant fraction of the particles in the nano-scale. In the SCCS's view, safety assessment of such a fraction is crucially important in the estimation of inhalation exposure of alveolar region of the lungs.

Within the pigmentary TiO_2 materials in group 1a, R4 has been regarded as the most relevant for current evaluation because of its use in different relevant products. Other materials (A-E) in group 1b have been analysed in the TDMA report that was used for the EFSA re-evaluation of E171. In the Applicant's description of dust fractions of the various materials (Table 4), E171-E (uncoated) has been described as a representative of R4. However, R4 has been described in the dossier as a surface-treated/coated TiO_2 material and therefore the claim that it is representative of both the 1a and 1b groups of pigmentary TiO_2 materials is not justified.

Toxicokinetics

No data provided by the Applicant.

The information on kinetics and deposition of inhaled TiO_2 in the lungs and other organs is insufficient and therefore a more extensive evaluation of kinetics/deposition of the particles is needed.

Exposure Assessment

The SCCS has evaluated the information provided on the two different surveys reported by the Applicant for the identification and selection of representative and worst-case products on the market and found it to be insufficient. Vital information (response rate to the survey, market coverage and market share of products) was not provided, even after it was requested by the SCCS. The data on the ranges of TiO_2 concentrations in different product subcategories were not sufficient to allow identification of the worst-case products. Another crucial aspect missing in the worst-case considerations/ criteria is the information on the type of nozzle and dispenser used in spray cans (aerosol spray). Furthermore, the protocols for the measurement of particle droplet fractions were not specified, except mentioning that DLS for sprays and SLS for powders were the methods used by industry for many years, and that the data were already available from cosmetic companies. Although different types/categories of the materials were explained by the Applicant (i.e. coated or uncoated pigmentary TiO_2, and pearlescent pigments), the descriptions were too broad for use in a safety assessment of the specific products without having more detailed information on the characterisation of the raw materials. In this regard, the applicant only provided statements to say that representative materials were chosen without any data on particle size ranges, crystal phases etc.

Because of such shortcomings, the relevance of the choice of representative materials used in cosmetic products for the materials presented in the dossier could not be evaluated by the SCCS for safety assessment.

Only data on the pigmentary TiO_2 material R4 were given in detail. The exclusion of the products containing pearlescent pigments resulted in only two product types remaining that contain R4 dispersion for evaluation in the current Opinion.

For the reasons discussed under section 3.3, the SCCS regards the exposure calculations based on particle number as inappropriate as these should have been measured and not estimated through approximation/calculation. The SCCS is of the view that the exposure assessment should have taken into account the fraction of respirable particles in the nanoscale in the assessment of inhalation exposure. The SCCS considers it important to take the fractional deposition into account because of the concerns for the nano-scale particles as they

are most likely to reach and deposit in the alveolar region of the lung of the exposed consumer. Therefore, in the SCCS Opinion, the relevant dose metric is the deposition in pulmonary region (pulmonary deposited dose) and not the inhalable fraction. In view of this, the SCCS has recalculated the potential exposure in terms of the fractional deposition of relevant fractions of TiO_2 particle in the alveolar region of the lung. These values were calculated both for the general consumer and the hairdresser (assuming a non-steady state scenario).

Toxicological Evaluation

Repeated dose toxicity

According to the Applicant, several sub-chronic (90 days) TiO_2 inhalation exposure studies performed in rats, mice and hamsters have been reported (Ferin *et al.*, 1992; Everitt *et al.*, 2000; Bermudez *et al.,* 2002; 2004). No other findings were observed apart from substantial responses of inflammation and overload associated with diminishing particle clearance in a dose dependent manner, and histologically clear indications of epithelial hypertrophy and hyperplasia. Only the very high doses led to the above persistent adverse effects in the rat, which appeared to be oversensitive to high lung burden of insoluble dusts such as TiO_2 in comparison to the mouse or hamster.

Mutagenicity / genotoxicity

The SCCS considered in a previous Opinion on TiO_2 (SCCS/1583/17) that, where internal exposure of the lungs is possible, there is a possibility that nano-TiO_2 may exert genotoxic effects, most probably through indirect (e.g. oxidative stress) or secondary mechanisms (as a result of inflammation caused by immune cells), although direct interaction with the genetic material cannot be excluded.

In concordance with the conclusion of the recent evaluations by EFSA (2016) and ECHA (2017), as well as in consideration of a review of the published data, the SCCS is of the opinion that TiO_2 may exert genotoxic effects where internal exposure of the lungs is possible. The genotoxic effects most probably manifest through indirect mechanism (oxidative stress) or secondary mechanisms (e.g. oxidative stress and inflammation caused by immune cells). The SCCS therefore considers it plausible that there is a practical threshold for this mode of action.

Carcinogenicity

For the reasons discussed under section 3.4.7, the SCCS is of the opinion that the CMR2 classification of TiO_2 cannot be disputed after an official body's conclusion on its classification and subsequent inclusion in the CLP regulation by the Commission. In the absence of any conclusive evidence to suggest otherwise, the position therefore remains that the carcinogenic effects observed in animals are also possible in humans. Since data provided cannot distinguish if a specific characteristic is linked to such an effect, this classification is proposed to be applied to all existing possible crystalline forms, morphologies and surface chemistries in all possible combinations of TiO_2.

Although the detailed mode of action is still unclear, an inflammatory process and indirect genotoxic effect by ROS production seems to be the major mechanism to explain the effects induced by TiO_2. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO_2 particles. However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO_2 was found in the cell nucleus in various *in vitro* and *in vivo* studies.

Derivation of a safe Human Reference Value

The Applicant chose Muhle *et al.* (1991) as the key study for the calculations of HEC. However, the SCCS noted a number of shortcomings in the Muhle *et al.* (1991) study (see section 3.4.10), and deemed another study by Bermudez *et al.* (2004) as the key study for deriving the toxicological point of departure for safety assessment of the TiO_2 materials in the current Opinion. The Bermudez *et al.* (2004) study used P25, which is comprised of uncoated nanoparticles of a mixture of 80% rutile and 20% anatase forms of titanium dioxide. The SCCS considered it relevant for the assessment of pigmentary TiO_2 materials because the latter also contain a sizeable fraction of nano-scale particles that are very important to consider in the estimation of exposure of the alveolar region of the lungs.

The SCCS regards the deposition of particles in the pulmonary region as the relevant dose metric instead of the inhalable fraction. Estimation of human reference value on these basis resulted in a much lower value than that derived by the Applicant (section 3.3.2.2.1).

Safety Evaluation (including calculation of the MoS)

Based on the NOAEC from the Bermudez *et al,* (2004) study (0.5 mg/m^3) and the deposition in the pulmonary region, the SCCS calculated a MoS for the two products relevant for this Opinion.

As explained in section 3.5.1, despite the apparent discrepancies in the material characteristics (R4 being anatase and surface-treated, and Bayertitan-T and P25 being rutile and uncoated), the SCCS has accepted the data read-across from the toxicological studies for the current safety evaluation of R4. This is because of the indications from published studies that the pulmonary effects caused by these types of TiO_2 materials are likely to be comparable (or comparatively lower for anatase and thus the use of rutile in these studies may represent a worst-case).

Margin of Safety calculation

According to the SCCS, the margin of safety (MoS) should be calculated based on the toxicological point of departure derived from the Bermudez *et al.* (2004) study, which is an NOAEC of 0.5 mg/m^3.

For exposure estimation, the SCCS calculated the human deposition value using the MPPD software (v3.4) (section 3.4.10). For this, the SCCS considers it important to take the fractional deposition into account because of the concerns for the nano-scale fraction reaching the alveoli. In the SCCS Opinion, the relevant dose metric is the deposition in the pulmonary region (pulmonary deposited dose) and not the inhalable fraction.

In addition, the use levels of TiO_2 in the products under current assessment should not be compared to a MoS of 10 for the general consumer as it only takes into account interindividual human variability. In the SCCS view a factor of 2.5 needs to be added to reflect toxicodynamic differences between rats and humans. Thus, a MoS of 25 should be used in the safety assessment for the general consumer and for hairdressers.

The calculation of the MoS by the SCCS showed that the use of pigmentary titanium dioxide (TiO_2) up to a maximum concentration of 25% in a typical hair styling aerosol spray product is not safe for both general consumers and for hairdressers (considering MoS of 25).

Recalculation by the SCCS of the levels that can be considered safe indicated that the use of pigmentary TiO_2 in a typical hair styling aerosol spray product would be safe up to a maximum concentration of 1.4 % for the general consumer, and 1.11 % for the hairdresser.

The MoS indicated that the use of pigmentary TiO_2 in loose powder up to a maximum concentration of 25% in a typical face make-up application would be safe for the general consumer.

It needs to be emphasised that the SCCS conclusions have been drawn from a *very selected group of cosmetic product*s based on *only one type of TiO_2 material* (pigmentary, anatase, surface-treated). The SCCS is of the opinion that more data would be needed for a comprehensive estimation of the combined TiO2 exposure via inhalation from all product categories that could lead to inhalation exposure.

In the absence of more information, it may not be clear whether these conclusions would be applicable to the use of pigmentary TiO_2 materials in other similar types of cosmetic applications that may be on the market. In this regard, the SCCS is of the opinion that other applications of pigmentary TiO_2 materials can also be considered safe if the MoS calculation is performed as detailed in the current Opinion, *and* if the resultant MoS for the combined use of different products is above 25 for general consumers and for hairdressers.

4. CONCLUSION

1. In light of the data provided and of the possible classification as Carcinogen Cat. 2 (inhalation) in Annex VI to Regulation (EC) n.1272/2008, does the SCCS consider Titanium dioxide safe when used as a UV-filter (entry 27 Annex VI) in cosmetic products up to a maximum concentration of 25 %, as a colorant (entry 143 Annex IV) and as an ingredient in all other cosmetic products?

On the basis of safety assessment, the SCCS is of the opinion that the use of pigmentary titanium dioxide (TiO_2) up to a maximum concentration of 25% in a typical hair styling aerosol spray product is not safe for either general consumers or hairdressers.

The safety assessment has shown that the use of pigmentary TiO_2 in loose powder up to a maximum concentration of 25% in a typical face make-up application is safe for the general consumer.

It needs to be noted that these conclusions are based on safety assessment of TiO_2 in the context of possible classification as category-2 carcinogen (via inhalation). This means that the conclusions drawn in this Opinion are applicable to the use of pigmentary TiO_2 in a cosmetic product that may give rise to consumer exposure by the inhalation route (i.e. aerosol, spray and powder form products). As such, the Opinion is not applicable to any pearlescent pigment because of the composite nature of such materials, of which TiO_2 is only a minor constituent.

2. Alternatively, if up to 25% use is not considered safe, what is according to the SCCS, the maximum concentration considered safe for use of Titanium dioxide as an ingredient in cosmetic products?

In the SCCS's opinion, the use of pigmentary TiO_2 in a typical hair styling aerosol spray product is safe up to a maximum concentration of 1.4 % for general consumers, and 1.1 % for hairdressers.

3. Does the SCCS have any further scientific concerns with regard to the use of Titanium dioxide in cosmetic products?

It needs to be emphasised that the SCCS conclusions have been drawn from a *very selected group of cosmetic product*s based on *only one type of TiO_2 material* (pigmentary, anatase, surface-treated). In the absence of more information, it may not be clear whether these conclusions would be applicable to the use of pigmentary TiO_2 materials in other similar types of cosmetic applications that may be on the market. In this regard, the SCCS is of the opinion that other applications of pigmentary TiO_2 materials can also be considered safe if the MoS calculation is performed as detailed in the current Opinion, *and* if the resultant MoS for the combined use of different products is above 25 for general consumers and for hairdressers.

5. MINORITY OPINION

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6. REFERENCES

1. Cosmetics Europe (2020). Dossier on the Human Safety Evaluation of Titanium Dioxide (non-nano form) in Cosmetics. (Submission I with focus on inhalation exposure). Cosmetics Europe Nº S75
2. Cosmetics Europe (2020). Additional data to Dossier on the Human Safety Evaluation of TITANIUM DIOXIDE (NON-NANO FORM) in Cosmetics (Submission I with focus on inhalation exposure)-response to SCCS questions
3. Cosmetic Europe (2020). Evaluation of professional exposure by inhalation from Titanium Dioxide (non-nano form) containing aerosol hair spray product

Other references

American Conference of Governmental Industrial Hygienists (ACGIH) (1997). Threshold Limit Values and Biological Exposure Indices. Available at https://www.nsc.org/Portals/0/Documents/facultyportal/Documents/fih-6e-appendix-b.pdf

Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) (2017). AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à une demande d'avis relatif à l'exposition alimentaire aux nanoparticules de dioxyde de titane.

Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) (2019). Toxicological Reference Value (TRV) Establishment of Chronic Reference Value by inhalation for Titanium Dioxide under nanoform. https://www.anses.fr/en/content/titanium-dioxide-nanoparticle-form-anses-defines-toxicity-reference-value-trv-chronic

Armstrong L. (2019). Intertek test report Particle size analysis of TiO_2 samples by Differential Centrifugal Sedimentation. REPORT NO. IWTN/W000011089RL001

Bermudez E, Mangum JB, Asgharian B, Wong BA, Reverdy EE, Janszen DB, Hext PM, Warheit DB, Everitt D. (2002). Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles (publication), Toxicol. Sci. 70, 86-97

Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, Everitt JI (2004) Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles (publication), Toxicol. Sci. 77: 347 – 357

Boffetta P, Soutar A, Cherry JW, Granath F, Andersen A, Anttila A, Blettner M, Gaborieau V, Klug SJ, Langard S, Luce D, Merletti F, Miller B, Mirabelli D, Pukkala E, Adami HO, Weiderpass E (2004). Mortality among workers employed in the titanium dioxide production industry in Europe, Cancer Causes Control. 15, 697-706

CEN 481, 1993. Workplace Atmospheres - Size Fraction Definitions for Measurement of Airborne Particles, European Standard EN 481: 1993E, CEN European Committee for Standardization

Commission Recommendation on the definition of nanomaterial (2011/696/EU): https://ec.europa.eu/research/industrial_technologies/pdf/policy/commission-recommendation-on-the-definition-of-nanomater-18102011_en.pdf

Donaldson K, Beswick PH, Gilmour PS (1996). Free radical activity associated with the surface of particles: a unifying factor in determining biological activity. Toxicol Letters. 88:293–298.

Donaldson K, Stone V. (2003). Current hypotheses on the mechanisms of toxicity of ultrafine particles. Ann Ist Super Sanita. 2003;39(3):405-10.

ECETOC (2013). Poorly Soluble Particles/Lung Overload, European Centre for Ecotoxicology and Toxicology of Chemicals, Technical Report No. 122

ECHA, REACH registration dossier https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15560)(last visited July 2020).

ECHA (2017). Committee for Risk Assessment RAC, Opinion proposing harmonised classification and labelling at EU level of Titanium dioxide, Document: CLH-O-0000001412-86-163/F.
https://echa.europa.eu/documents/10162/682fac9f-5b01-86d3-2f70-3d40277a53c2

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food),(2016). Scientific Opinion on the re-evaluation of titanium dioxide (E 171) as a food additive. EFSA Journal 2016; 14(9): 4545, 83 pp. doi.org/10.2903/j.efsa.2016.4545 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4545

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food),(2018). Scientific Opinion on the evaluation of four new studies on the potential toxicity of titanium dioxide used as a food additive (E 171). EFSA Journal 2018; 16(7): 5366, 27 pp. doi.org/10.2903/j.efsa.2018. 5366
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5366

EFSA (2019). EFSA statement on the review of the risks related to the exposure to the food additive titanium dioxide (E 171) performed by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). EFSA Journal 2019;17(6): 5714, 11 pp

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings)(2019). Scientific opinion on the proposed amendment of the EU specifications for titanium dioxide (E 171) with respect to the inclusion of additional parameters related to its particle size distribution. EFSA Journal 2019;17(7):5760, 23 pp. https://doi.org/10.2903/j.efsa.2019.5760

Evans, D. E., Turkevich, L. A., Roettgers, C. T., Deye, G. J., & Baron, P. A. (2013). Dustiness of fine and nanoscale powders. The Annals of occupational hygiene, 57(2), 261–277. https://doi.org/10.1093/annhyg/mes060

Everitt JI, Mangum JB, Bermudez E, Wong BA, Asgharian B, Reverdy EE, Hext PM, Warheit DB (2000) Comparison of selected pulmonary responses of rats, mice, and Syrian hamsters to inhaled pigmentary titanium dioxide. Inhalat Toxicol 12, Suppl 3: 275-282

Eydner M, Schaudien D, Creutzenberg O, Ernst H, Hansen T, Baumgärtner W, Rittinghausen, S.; 2012. Impacts after inhalation of nano- and fine-sized titanium dioxide particles: morphological changes, translocation within the rat lung, and evaluation of particle deposition using the relative deposition index. Inhalation Toxicology (9):557-69.

Ferin J. and Oberdörster G. (1985) Biological effects and toxicity assessment of titanium dioxides: anatase and rutile, American Industrial Hygiene Association Journal, 46:2, 69-72, DOI: 10.1080/15298668591394419).

Ferin J, Oberdörster G, Penney DP (1992) Pulmonary retention of ultrafine and fine particles in rats. Am J Respir Cell Mol Biol 6: 535-542

Ficheux AS, Chevillotte G, Wesolek N, Morisset T, Dornic N, Bernard A, Bertho A, Romanet A, Leroy L, Mercat AC, Creusot T, Simon E, Roudot AC (2016). Consumption of cosmetic

products by the French population. Second part: Amount Data. Food and Chemical Toxicology 90, 130-41

Finley B, Proctor D, Scott P, Harrington N, Paustenbach D, Price P (1994). Recommended Distributions for Exposure Factors Frequently Used in Health Risk Assessment. Risk analysis 14(4)

Ganyecz A, Mezei P, Kállay M (2019). Oxygen reduction reaction on TiO_2 rutile (1 1 0) surface in the presence of bridging hydroxyl groups. Comp and Theor. Chemistry, 1168, 112607

Garcia-Hidalgo E, von Goetz N, Siegrist M, Hungerbühler K. (2017). Use-patterns of personal care and household cleaning products in Switzerland. Food and Chemical Toxicology 99, pp 24-39. doi: 10.1016/j.fct.2016.10.030.

Greim H and Ziegler-Skylakakis K (2007). Risk assessment for biopersistent granular particles. Inhalation Toxicolology. 19(Suppl 1): 199–204

Hartwig, A. MAK Commission (2019). Titianium dioxide. Respirable fraction. DOI: 10.1002/3527600418.mb1346367d0067

Hashem MM, Abo-El-Sooud K, Abd-Elhakim YM, Badr YA, El-Metwally AE, Bahy-El-Dien A. The long-term oral exposure to titanium dioxide impaired immune functions and triggered cytotoxic and genotoxic impacts in rats. J Trace ElemMed Biol. 2020 Jul;60:126473. doi: 10.1016/j.jtemb.2020.126473. Epub 2020 Feb 21. PMID: 32142956.

Heinrich U, Fuhst R, Rittinghausen S, Creutzenberg O, Bellmann B, Koch W, Levsen K (1995). Chronic inhalation exposure of Wistar rats and two different strains of mice to Diesel engine exhaust, Carbon Black and Titanium Dioxide Inhalation Toxicology, 7, 533-556

Hext PM, Tomenson JA, Thompson P (2005). Titanium Dioxide: Inhalation Toxicology and Epidemiology. Ann. occup. Hyg., Vol. 49, No. 6, pp. 461–472

IARC (2010) Titanium dioxide, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 93, 193-214
https://publications.iarc.fr/Book-And-Report-Series/IarcMonographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Carbon-BlackTitanium-Dioxide-And-Talc-2010

Intertek technical report (2019). Particle Size Distribution Analysis by SEM. REPORT REFERENCE: 1346086_SEM.

Knaapen AM, Albrecht C, Becker A, Höhr D, Winzer A, Haenen GR, Borm PJA, Shins RPF (2002). DNA damage in lung epithelial cells isolated from rats exposed to quartz: role of surface reactivity and neutrophilic inflammation. Carcinogenesis 23(7): 1111–1120

Koch W, Dunkhorst W, Lödding H (1999). Design and performance of a new personal aerosol monitor. Aerosol Science Technol 31: 231-246

Kreyling W, Wenk A, Semmler-Behnke W, 2010. Quantitative biokinetic analysis of radioactively labelled, inhaled Titanium dioxide Nanoparticles in a rat model. UBA-FB Nr: 001357 4. Umweltbundesamt.

Kuempel ED, Sweeney LM, Morris JB, Jarabek AM (2015). Advances in Inhalation Dosimetry Models and Methods for Occupational Risk Assessment and Exposure Limit Derivation, J. Occupat. Environmental Health, 12, S18-S40

Lafon D, Anoma G, Bouslama M, Collot Fertey D, Fontaine B, Garnier R, Gautier MA, Guilleux A, Ould Elhkim M, Labro MT, Picot C, Radauceanu A, Roudot AC, Sater N et al. (2014).

Exposition aux produits cosmétiques et risque pour la grossesse chez les professionnels de la coiffure. INRS TC 147

Lee KP, Trochimowicz HJ, Reinhardt CF (1985). Pulmonary Responses of Rats Exposed to Titanium Dioxide (TiO_2) by Inhalation for Two Years. Toxicol. Appl. Pharmacol., 79,179192.

Levy LS, (1994). Squamous Lung Lesions Associated with Chronic Exposure by Inhalation of Rats to p-Aramid Fibrils (Fine Fiber Dust) and to Titanium Dioxide: Findings of a Pathology Workshop, Mohr, U. (Ed.): Toxic and carcinogenic effects of solid particles in the respiratory tract, ILSI Press, 473-478

Loretz L, Api MA, Barraj L, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YAL, Re T, Renskers K, Scrafford C, Vater S (2006). Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food and Chemical Toxicology 44 (2006) 2008–2018

MAK 2012. "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)[MAK Value Documentation, 2012] " In The MAK Collection for Occupational Health and Safety (eds)

MAK (2012) Allgemeiner Staubgrenzwert (A-Fraktion) (Granuläre biobeständige Stäube (GBS)) [MAK Value Documentation in German language, 2012]. published: 08 May 2014 https://doi.org/10.1002/3527600418.mb0230stwd0053

Miles W,, Moll W.F., Hamilton R.D. & Brown R.K. (2008) Physicochemical and Mineralogical Characterization of test materials used in 28-day and 90-day intratracheal instillation toxicology studies in rats, Inhalation Toxicology, 20:11, 981-993, DOI: 10.1080/08958370802077943.

Muhle H, Bellmann B, Creutzenberg O, Dasenbrock C, Ernst H, Kilpper R, MacKenzie J.C, Morrow P, Mohr U, Takenaka S, Mermelstein R (19919. Pulmonary response to toner upon chronic inhalation exposure in rats, Fundamental and applied toxicology, 17(2), 280-299

National Institute for Occupational Safety and Health (NIOSH, 2011). Current Intelligence Bulletin 63, Occupational Exposureto Titanium Dioxide, DEPARTMENT OF HEALTH AND HUMAN SERVICES, Centers for Disease Control and Prevention, DHHS (NIOSH) Publication No. 2011–160, April 2011. https://www.cdc.gov/niosh/docs/2011160/pdfs/2011-160.pdf

Proquin H, Rodríguez-Ibarra C, Moonen CG, Urrutia Ortega IM, Briedé JJ, deKok TM, van Loveren H, Chirino YI. Titanium dioxide food additive (E171) induces ROS formation and genotoxicity: contribution of micro and nano-sized fractions. Mutagenesis. 2017 Jan;32(1):139-149. doi: 10.1093/mutage/gew051. Epub 2016 Oct 27. Erratum in: Mutagenesis. 2018 Sep 17;33(3):267-268. PMID: 27789654.

RIVM (2014). RIVM report 090013003/2014. General Fact Sheet. General default parameters for estimating consumer exposure – Updated version 2014. J.D. te Biesebeek, M.M. Nijkamp, B.G.H. Bokkers, S.W.P. Wijnhoven.

Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C (2011). Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. Toxicol Lett. 8-28, 205(2):97-104

Salem H and Katz SA (eds, 2006). Inhalation toxicology , 2nd edition,, CRC Press, Taylor & Francis Group, Boca Raton, FL, USA

Scientific Committee on Consumer Safety (SCCS, 2014) Scientific Committee on Consumer Safety Opinion on Titanium Dioxide (nano form) (SCCS/1516/13). 22 July 2013. https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_136.pdf

Scientific Committee on Consumer Safety (SCCS, 2015). Opinion for clarification of the meaning of the term "sprayable applications/products" for the nano forms of Carbon Black CI 77266, Titanium Oxide and Zinc Oxide. (SCCS/1539/14) https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_163.pdf

Scientific Committee on Consumer Safety (SCCS, 2017). Opinion on Titanium Dioxide (nano form) as UV-Filter in sprays, 19 January 2018, SCCS 1583/17. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_206.pdf

Scientific Committee on Consumer Safety (SCCS, 2018). The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 10th revision (SCCS/1602/18) https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf

Scientific Committee on Consumer Safety (SCCS, 2019). Guidance on the Safety Assessment of Nanomaterials in Cosmetics, 30-31 October 2019, SCCS/1611/19. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_233.pdf

Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP, 2000). Opinion of the Scientific Committee on Cosmetic Products and Non-food Products intended for consumers concerning Titanium Dioxide. 24 October 2000, SCCNFP/0005/98, https://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out135_en.pdf

Shi X, Castranova V, Halliwell B, Vallyathan V (1998). Reactive oxygen species and silica induced carcinogenesis. J Toxicol Environ Health, Part B, 1: 181–197

Steiling W, Almeida JF, Vandecasteele HA, Gilpin S, Kawamoto T, O'Keeffe L, Pappa G, Rettinger K, Rothe H, Bowden AM (2018). Principles for the safety evaluation of cosmetic powders. Toxicology Letters 297 (2018) 8–18

Steiling W, Bascompta M, Carthewc P, Catalano G, Corea N, D'Haese A, Jackson P, Kromidas L, Meurice P, Rothe H, Singah M (2014). Principle considerations for the risk assessment of sprayed consumer products. Toxicology Letters 227 (2014) 41–49

Steiling W, Buttgereit P, Hall B, O'Keeffe L, Safford B, Tozer S, Coroama M (2012). Skin exposure to deodorants/antiperspirants in aerosol form. Food and Chemical Toxicology 50 (2012) 2206–2215

Titanium Dioxide Manufacturers Association (TDMA) (2019). Data on Particle Size and Particle Size Distribution for Titanium Dioxide (E171).

Thompson CM, Suh M, Mittal L, Wikoff DS, Welsh B, Protor DM (2016). Development of linear and threshold no significant risk levels for inhalation exposure to titanium dioxide using systematic review and mode of action considerations, Regulatory Toxicol. Pharmacol., 80, 60-70

ToxStrategies report (2020). Mode-of-Action Review and Determination of a Human Equivalent Concentration for Use in Risk Assessment of Fine Pigment-Grade Titanium Dioxide in Personal Care and Cosmetic, confidential business information, unpublished, 15 January 2020

US EPA (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry EPA/600/8-90/066F. Washington (DC), United States Environmental Protection Agency.
https://19january2017snapshot.epa.gov/risk/methods-derivationinhalation-reference-concentrations-and-application-inhalation-dosimetry_.html

US FDA (2019). Department of Health and Human Services, Food and Drug Administration, 21 CFR Parts 201, 310, 347 and 352, RIN 0910–AF43, Sunscreen Drug Products for Overthe-Counter Human Use, Federal Register, Vol. 84, No. 38, 26 February 2019, Proposed Rules

Vallyathan V, Shi X, Castranova V (1998). Reactive oxygen species: their relation to pneumoconiosis and carcinogenesis. Environmental Health Perspectives. 106(Suppl 5): 1151–1155

Wang J, Chen C, Liu Y, Jiao F, Li W, Lao F, Li Y, Li B, Ge C, Zhou G, Gao Y, Zhao Y and Chai Z, 2008a. Potential neurological lesion after nasal instillation of TiO2 nanoparticles in the anatase and rutile crystal phases. Toxicol Lett 183(1-3), 72-80.

Wang J, Liu Y, Jiao F, Lao F, Li W, Gu Y, Li Y, Ge C, Zhou G, Li B, Zhao Y, Chai Z and Chen C, 2008b. Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO2 nanoparticles. Toxicology 254(1-2), 82-90.

Wang J. and Fan Y. (2014) Lung Injury Induced by TiO_2 Nanoparticles Depends on Their Structural Features: Size, Shape, Crystal Phases, and Surface Coating, Int. J. Mol. Sci. 15: 22258-22278, doi:10.3390/ijms151222258.

Warheit DB and Brown SC (2019). What is the impact of surface modifications and particle size on commercial titanium dioxide particle samples? – A review of *in vivo* pulmonary and oral toxicity studies – Revised 11-6-2018, Toxicol. Letters, 302, 42-59

7. GLOSSARY OF TERMS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

8. LIST OF ABBREVIATIONS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

Additional abbreviations and glossary of terms, specific for this Opinion:
ACGIH: American Conference of Governmental Industrial Hygienists
ANS: Nutrient Sources added to Food
AM: alveolar macrophage
DAF: dosimetric adjustment factor
DC: differential centrifugal sedimentation
DLS: dynamic light scattering
FAF: food ingredients and packaging
FP: fine powder
GSD: geometrical standard deviation
HEC: human equivalent concentration
HRV: human reference value
ICP-MS: inductively coupled plasma - mass spectrometry

LOQ: limit of quantification
MAD: medium aerodynamic diameter
MMAD: mass median aerodynamic diameter
MPPD: multi pathway particle deposition
NIOSH: national institute for occupational safety and health
PSLT: poorly soluble particles of low toxicity
Pulmonary deposited dose: deposition of particles in the pulmonary region
PSLT: poorly soluble low toxicity
RDDR: regional deposited dose region
RM: raw material
RAC: risk assessment committee
RDDR: regional deposited dose ratio
SEM: scanning electron microscopy
SLS: Selective laser sintering
TDMA: Titanium Dioxide Manufacturers Association
TRV: toxicity reference value
UF: uncertainty factor
UFP: ultra-fine particle
VE: ventilation rate
TWA: time weighted average