Scientific Committee on Consumer Safety

SCCS

OPINION on

Titanium dioxide (TiO₂)

used in cosmetic products

The SCCS adopted this document
By written procedure on 7 August 2020
ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to the finalisation of this Opinion.

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https://ec.europa.eu/transparency/regexpert/index.cfm
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 (TiO₂) 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 TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ in a typical hair styling aerosol spray product is safe up to a maximum concentration of 1.64 % for general consumers, and 1.0 % 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 products based on only one type of TiO₂ 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 TiO₂ 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 TiO₂ 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.


Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Titanium dioxide (TiO₂), preliminary version of 7 August 2020, SCCS/1617/20
About the Scientific Committees

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

These committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Both are made up of independent experts.

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

SCCS

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

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ISSN ISBN

Doi ND

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm
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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

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 Triethoxycaprylsilane 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 nano form of TiO₂. More specifically, this dossier is confined to the uses of TiO₂ (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 TiO₂ 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\textsubscript{2} materials are described, two pigmentary TiO\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2} as such.

In developing this Opinion, the SCCS considered the safe use of TiO\textsubscript{2} in cosmetics on the basis of safety assessment of TiO\textsubscript{2} via inhalation route, despite the recent CLP CMR2 classification for inhalation exposure. In this context, this Opinion is focused on the safety assessment of the pigmentary TiO\textsubscript{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\textsubscript{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\textsubscript{2} as such. Consequently, the Opinion has only discussed in any detail the information relating to pigmentary TiO\textsubscript{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

<table>
<thead>
<tr>
<th>CAS number</th>
<th>EC number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium dioxide</td>
<td>13463-67-7</td>
</tr>
<tr>
<td>Anatase</td>
<td>1317-70-0</td>
</tr>
<tr>
<td>Rutile</td>
<td>1317-80-2</td>
</tr>
</tbody>
</table>
3.1.1.5 Structural formula

Figure 1: Structural formula of TiO$_2$ and its crystal form

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$_2$)

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 2 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$_2$O$_3$, 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 TiO₂ to improve the formulation in hydrophilic and hydrophobic solvents.

- **Group 1b**: uncoated TiO₂ 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 TiO₂ materials**

This group, comprising nanoforms of TiO₂, 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 TiO₂ and other metal oxide layers.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>TiO₂ content</th>
<th>Coating</th>
<th>Crystal phase control agents</th>
<th>Other ingredient layers physically fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (Pigmentary TiO₂ - coated)</td>
<td>&gt; 95%</td>
<td>Hydrophilic coating Hydrophobic coating</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1b (Pigmentary TiO₂ - uncoated)</td>
<td>&gt; 99%</td>
<td>-</td>
<td>Alumina, sodium or potassium, and phosphate</td>
<td>-</td>
</tr>
<tr>
<td>3 (Pearlescent pigments)</td>
<td>1 – 75%</td>
<td>-</td>
<td>Mica, Silica, Alumina, Fluorphlogopite, Potassium, Aluminum Silicate, Calcium Aluminum Borosilicate, Calcium Sodium Borosilicate, Synthetic Fluorophlogopite</td>
<td>Fe₂O₃, Fe₃O₄, Cr₂O₃, SiO₂, Al₂O₃, Carmine, Ferric Ferrocyanide, BaSO₄, SnO₂</td>
</tr>
</tbody>
</table>

* No information is provided on the materials in group-2 (nano TiO₂), as these are considered as not relevant for this submission by the Applicant.

**SCCS comment**

The SCCS is of the opinion that only pigmentary TiO₂ (group 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 TiO₂. 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 TiO₂ as such.

Furthermore, contrary to the Applicant’s suggestion, the SCCS has regarded it relevant to consider group-2 (comprising nano TiO₂ materials) for this evaluation, because pigmentary TiO₂ 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.

### 3.1.5 Impurities / accompanying contaminants

| No information provided |

### 3.1.6 Solubility

| Insoluble in water and organic solvents³ |

### 3.1.7 Partition coefficient (Log Pow)

| Not relevant |

### 3.1.8 Additional physical and chemical specifications

<table>
<thead>
<tr>
<th>Colour Index</th>
<th>77891; Pigment white</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>1855 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>2900 °C</td>
</tr>
<tr>
<td>Chrystal forms</td>
<td>Anatase; Rutile</td>
</tr>
<tr>
<td>Density</td>
<td>3.9-4.1 g/m³ (R4-R6)</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>2.55 – 2.75 (R4-R6)(see details below)</td>
</tr>
<tr>
<td>pH</td>
<td>Not found</td>
</tr>
<tr>
<td>pKa</td>
<td>Not applicable for uncoated TiO₂</td>
</tr>
<tr>
<td>UV-VIS absorption spectrum</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

Detailed information on different TiO₂ materials (R4-R9) dossier is given below:

---

Opinion on Titanium dioxide (TiO$_2$)

<table>
<thead>
<tr>
<th>Sample Parameters</th>
<th>R1 TiO$_2$ (Rutile)</th>
<th>R2 TiO$_2$ (Rutile)</th>
<th>R4 201902981611 (Anatase)</th>
<th>R6 201602981613 (Rutile)</th>
<th>R7 Lot 0143 (Rutile)</th>
<th>R9 Lot 1024 (Rutile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter</td>
<td>1.0µm</td>
<td>6.0µm</td>
<td>6.0µm</td>
<td>1.5µm</td>
<td>1.5µm</td>
<td>6.0µm</td>
</tr>
<tr>
<td>Minimum diameter</td>
<td>0.03µm</td>
<td>0.03µm</td>
<td>0.03µm</td>
<td>0.03µm</td>
<td>0.03µm</td>
<td>0.03µm</td>
</tr>
<tr>
<td>Particle density</td>
<td>4.1g/cm$^3$</td>
<td>4.1g/cm$^3$</td>
<td>3.9g/cm$^3$</td>
<td>4.1g/cm$^3$</td>
<td>4.1g/cm$^3$</td>
<td>4.1g/cm$^3$</td>
</tr>
<tr>
<td>Refractive Index</td>
<td>2.75</td>
<td>2.75</td>
<td>2.55</td>
<td>2.75</td>
<td>2.75</td>
<td>2.75</td>
</tr>
<tr>
<td>Particle absorption</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-Sphericity factor</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Calibration Standard Parameters

<table>
<thead>
<tr>
<th>Fluid Parameters (Gradient)</th>
<th>Fluid Density</th>
<th>Fluid refractive index</th>
<th>Fluid Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.064 g/ml</td>
<td>1.357</td>
<td>1.325</td>
</tr>
<tr>
<td></td>
<td>1.064 g/ml</td>
<td>1.357</td>
<td>1.325</td>
</tr>
<tr>
<td></td>
<td>1.064 g/ml</td>
<td>1.357</td>
<td>1.325</td>
</tr>
<tr>
<td></td>
<td>1.064 g/ml</td>
<td>1.357</td>
<td>1.325</td>
</tr>
</tbody>
</table>

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.
Opinion on Titanium dioxide (TiO₂)

Intertek, 2019
TDMA, 2019

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

Group 1: Pigmentary TiO₂ (Uncoated and Coated)

Pigmentary TiO₂ (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, 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).

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Crystal Phase TiO₂</th>
<th>TiO₂ content in reference material (RM)</th>
<th>Description of Coating</th>
<th>Median minimal external dimension by number (µm)</th>
<th>Geometric Standard Deviation (exp((ln(x50)-ln(x10))/1,282))</th>
<th>Number-based fraction of particle size &lt;0.1µm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R4</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Hydrophilic Surface</td>
<td>0.145</td>
<td>1.30</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R6</td>
<td>Rutile</td>
<td>&gt;97%</td>
<td>Hydrophilic Coating</td>
<td>0.168</td>
<td>1.32</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>R7</td>
<td>Rutile</td>
<td>&gt;97%</td>
<td>Hydrophilic Coating</td>
<td>0.183</td>
<td>1.87</td>
<td>17.0</td>
</tr>
<tr>
<td></td>
<td>R9</td>
<td>Rutile</td>
<td>&gt;96%</td>
<td>Hydrophilic Coating</td>
<td>0.228</td>
<td>2.14</td>
<td>15.1</td>
</tr>
<tr>
<td>1b</td>
<td>A*</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.140</td>
<td>1.30</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>B*</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.101</td>
<td>1.35</td>
<td>49.6</td>
</tr>
<tr>
<td></td>
<td>C*</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.110</td>
<td>1.29</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td>D*</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.173</td>
<td>1.40</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>E*</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.101</td>
<td>1.32</td>
<td>47.0</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Rutile</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.151</td>
<td>ND</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* data from the TDMA E171 dossier submitted to EFSA (2018)(TDMA, 2019)

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 TiO₂ 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):

<table>
<thead>
<tr>
<th>TDMA 2019, (page 9)</th>
<th>Current SCCS opinion, Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median minimal external dimension by number (µm)</td>
<td>Number-based fraction of particle size &lt;0.1µm (%)</td>
</tr>
<tr>
<td>A</td>
<td>138 nm</td>
</tr>
<tr>
<td>B</td>
<td>105 nm</td>
</tr>
<tr>
<td>C</td>
<td>113 nm</td>
</tr>
<tr>
<td>D</td>
<td>166 nm</td>
</tr>
<tr>
<td>E</td>
<td>104 nm</td>
</tr>
</tbody>
</table>

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 TiO₂ 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 TiO₂-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.

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 TiO₂ 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 TiO₂ 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, 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 TiO₂ group 1a

Figure 4: SEM image and particle size distribution of sample D TiO₂ group 1b

Additional measurements using the Differential Centrifugal sedimentation (DC) method was 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

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Crystal Phase TiO₂</th>
<th>TiO₂ content in referenc e material</th>
<th>Description of coating</th>
<th>CPS DC Median x 50 volume (µm)</th>
<th>Geometric Standard Deviation (GSD) exp((ln(x50)- ln(x10))/1,282)</th>
<th>Fraction of particles &lt; 0.1 um mass/ volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R4</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Hydrophilic Surface Treating</td>
<td>0.370</td>
<td>1.24</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>R6</td>
<td>Rutile</td>
<td>&gt;97%</td>
<td>Hydrophilic Coating</td>
<td>0.287</td>
<td>1.17</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>R7</td>
<td>Rutile</td>
<td>&gt;80%</td>
<td>Hydrophilic Coating</td>
<td>0.361</td>
<td>1.18</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>R9</td>
<td>Rutile</td>
<td>&gt;80%</td>
<td>Hydrophilic Coating</td>
<td>0.600</td>
<td>1.19</td>
<td>0</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.280</td>
<td>1.51</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.267</td>
<td>1.49</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.269</td>
<td>1.43</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.373</td>
<td>1.42</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>Anatase</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td>0.306</td>
<td>1.62</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Rutile</td>
<td>&gt;99%</td>
<td>Uncoated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since the CMR2 classification concerns TiO₂ 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 TiO₂ 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 TiO₂ 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 <10 µm MMAD of pigmentary TiO₂

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total Dustiness [%]</th>
<th>Fraction in airborne particles&lt; 10 µm [%]</th>
<th>Fraction in total mass&lt; 10 µm [%]</th>
<th>TiO₂ dust with MMAD&lt;10 µm generated by EN17199 small rotating drum [%]</th>
<th>Respirable dustiness calculated by the SCCS (according to Evans et al, 2013) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E171-E and representative for R4</td>
<td>47.5</td>
<td>1.8</td>
<td>0.9</td>
<td>-</td>
<td>15.8</td>
</tr>
<tr>
<td>G3-1 Representative for sample F</td>
<td>22.4</td>
<td>1.6</td>
<td>0.3</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>G4-19 Representative for R6</td>
<td>9.6</td>
<td>16.1</td>
<td>1.5</td>
<td>-</td>
<td>3.2</td>
</tr>
<tr>
<td>G9-5 Representative for R7 and R9</td>
<td>47.9</td>
<td>1.7</td>
<td>0.8</td>
<td>-</td>
<td>15.9</td>
</tr>
</tbody>
</table>

SCCS comments

The Applicant stated that E171-E is a representative of R4 material in the abovementioned dust measurements. Although this is inconsistent, because R4 is a surface-treated TiO₂ 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 TiO₂ 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 stable⁴

#### SCCS overall comments on physicochemical characterisation

The Applicant has described physicochemical characterisation of different TiO₂ materials. A distinction is made between surface-treated or coated TiO₂ materials (group 1a) and uncoated TiO₂ materials (group 1b). Table 1 mentions the pigmentary TiO₂ 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: because 'TiO₂' is coated with metal oxides like SiO₂, Al₂O₃, ZrO₂ or CeO₂, amongst other to improve dispersibility and processability in formulations. Hydrophilic and hydrophobic organic compounds (e.g. dimethicone or caprylylsilanes) are added to TiO₂ 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 TiO₂ 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, the SCCS has regarded ‘R4’ as the only relevant TiO₂ 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 TiO₂ 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 TiO₂ (>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 Entry for TiO₂ in GESTIS-databases of hazardous substances; provided by IFA, http://gestis.itrust.de/nxt/gateway.dii/gestis_en/000000.xml?f=templates&fn=default.htm&vid=gestis eng:sdmbeng
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 a very different arrangement of the particles at low magnification 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.


**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$_2$ (group 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

3.2.1 Dermal / percutaneous absorption

3.2.2 Other studies on toxicokinetics

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 (Stelling et al., 2014). Within mathematical exposure models, default assumptions (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**

<table>
<thead>
<tr>
<th>Number of participating cosmetic product manufacturers</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of TiO$_2$-containing products reported</td>
<td>807*</td>
</tr>
<tr>
<td>Number of products associated to potential non-intended inhalation exposure</td>
<td>171</td>
</tr>
</tbody>
</table>

*only products that can lead to inhalation exposure

*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.

*Additional data provided by the Applicant upon SCCS request:

Out of the formulations reported in the TiO$_2$ use survey, the experts analyzed all cosmetic product dosage forms reported and hand-picked those that could lead to 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:
Opinion on Titanium dioxide (TiO$_2$)

- 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:
   - presence of TiO$_2$
   - physical form of the product (e.g. liquid, paste, powder, ...)
   - product dosage form (spray, powders and applicators used)
   - 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.

The following products were selected for field exposure studies.

Ref 2.
Table 6: List of products selected for TiO\textsubscript{2} lung exposure associated with consumer use

<table>
<thead>
<tr>
<th>Product category</th>
<th>Dosage form</th>
<th>Product</th>
<th>TiO\textsubscript{2} content in the formulation (%)</th>
<th>Particle droplet fraction &lt;10 μm (%)</th>
<th>RM code for TiO\textsubscript{2} material used in product</th>
<th>TiO\textsubscript{2}-based raw material</th>
<th>Raw material Median Particle Size Volume based (μm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling</td>
<td>Aerosol spray</td>
<td>F8</td>
<td>1.0</td>
<td>15.94</td>
<td>R4</td>
<td>Pigmentary coated</td>
<td>0.145</td>
</tr>
<tr>
<td>Make-up Powder for Face</td>
<td>Loose powder</td>
<td>FZ</td>
<td>20</td>
<td>45</td>
<td>R4</td>
<td>Pigmentary coated</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Note: Table 6 shows TiO\textsubscript{2} concentrations from airborne particles in the respirable and thoracic size fractions from direct exposure measurement of each product type. Despite high TiO\textsubscript{2} percent used in some other cosmetic products (e.g. sun products and self-tanning with 0.09-20.50 % of TiO\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2} concentrations in the different subcategories were provided 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 (DLS for sprays and 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 TiO₂ as explained by the Applicant (i.e. pigmentary TiO₂ 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 products, 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 products) 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, 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 10 m³ 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; 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 TiO₂ 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 TiO₂ by chemical analysis. TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ 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 TiO₂ concentrations per application in the respirable and thoracic fractions as determined experimentally using realistic simulations of product application (mean from 5 applications).

<table>
<thead>
<tr>
<th></th>
<th>TiO₂ concentration in the formulation (%)</th>
<th>Amount of product per application (g)</th>
<th>TiO₂ concentration (µg/m³) per application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respirable fraction ¹</td>
</tr>
<tr>
<td>Hair Styling Aerosol Spray</td>
<td>1.0</td>
<td>7.43</td>
<td>266.7</td>
</tr>
<tr>
<td>Product F8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose Powder for Face Make-</td>
<td>20</td>
<td>0.088</td>
<td>7.38</td>
</tr>
<tr>
<td>up Product FZ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ i.e. contained in product droplets of < 5 µm

² i.e. contained in product droplets of < 10 µm

³ values below LOQ

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 TiO₂/filter or < 1.23 µg TiO₂/m³), whereas for the powders this additional analysis was not required and the LOQ was reported as 667 ng TiO₂/filter or < 2.5 µg TiO₂/m³ 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 TiO₂ per filter (corresponds to: respirable < 2.5 µg TiO₂/m³; thoracic < 4.4 µg TiO₂/m³). For the respirable size fractions, the TiO₂ 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 TiO₂/filter) corresponding to < 1.23 µg TiO₂/m³.
Powder extract:

All filter samples were analysed as a 1:4 dilution 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.

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:

$$\text{TiO}_2 \text{ lung exposure dose (μg/application)} = \frac{\text{TiO}_2 \text{ concentration (μg/m}^3\text{)}}{1000} \times \text{human breathing rate (13 L/minute)} \times \text{residence time in the room (20 minutes)}$$

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.

<table>
<thead>
<tr>
<th></th>
<th>TiO$_2$ conc in the formulation (%)</th>
<th>TiO$_2$ conc Respirable fraction (μg/m$^3$)</th>
<th>TiO$_2$ inhaled dose Respirable fraction (μg/application)</th>
<th>TiO$_2$ conc Thoracic fraction (μg/m$^3$)</th>
<th>TiO$_2$ inhaled dose Thoracic fraction (μg/application)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>1.0</td>
<td>266.7</td>
<td>69.3</td>
<td>480.4</td>
<td>125</td>
</tr>
<tr>
<td>Loose Powder for Face Make-up</td>
<td>20</td>
<td>7.38</td>
<td>1.92</td>
<td>39.80</td>
<td>10.35</td>
</tr>
</tbody>
</table>
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 9: TiO$_2$ lung exposure dose (inhaled dose) thoracic fraction per day

<table>
<thead>
<tr>
<th>Product</th>
<th>TiO$_2$ in the formulation (%)</th>
<th>TiO$_2$ concentration Thoracic fraction ($\mu$g/m$^3$)</th>
<th>TiO$_2$ inhaled dose Thoracic fraction ($\mu$g/application)</th>
<th>Product frequency of use/day</th>
<th>TiO$_2$ inhaled dose Thoracic fraction ($\mu$g/day)</th>
<th>TiO$_2$ pulmonary deposited dose ($\mu$g/application)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>1.0</td>
<td>480.4</td>
<td>125</td>
<td>1</td>
<td>125</td>
<td>21.25</td>
</tr>
<tr>
<td>Loose Powder for Face Make-up Product FZ</td>
<td>20</td>
<td>39.80</td>
<td>10.35</td>
<td>1</td>
<td>10.35</td>
<td>1.76</td>
</tr>
</tbody>
</table>

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.
Furthermore, the P95 for product frequency mentioned in Ficheux et al. (2015) is 2 (instead of 1). For real worst-case conditions, these values should therefore be doubled.

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 TiO₂ pulmonary deposited dose has been added to Table 9 (right column), where values are quoted from Appendix 7 of the dossier.

**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 TiO₂ 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 TiO₂ raw material provided by EM measurement and the corresponding mass/volume determined by CPS DC methods (see Table 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 TiO₂ 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**

<table>
<thead>
<tr>
<th></th>
<th>TiO₂ inhaled dose Thoracic fraction² (µg/day)</th>
<th>(a) TiO₂ nano particle inhaled (lung dose) in number¹ (Number Particles/day)</th>
<th>(b) TiO₂ nano particle inhaled (lung dose) in mass/volume² (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>125</td>
<td>1.37E+03</td>
<td>1.25E+00</td>
</tr>
<tr>
<td>Loose Powder for Face Make-up Product FZ</td>
<td>10.35</td>
<td>1.13E+02</td>
<td>1.04E-01</td>
</tr>
</tbody>
</table>

¹. Exposure to nano content of TiO₂ in number feret.min from R4 in products with the highest measured TiO₂ exposure

Number of nano particles in TiO₂ inhaled (lung exposure) dose thoracic fraction =


Number nano,TiO₂-thoracic = mTiO₂-thoracic/m particle. * f nano

With

Mass of TiO₂ constituent Particle = Volume of constituent Particle * Density of constituent particle

= (4/3*Π *(d/2)³ * rho)
where \( \rho \) is skeletal density of TiO\( _2 \) = 4 \( \mu \)g/\( \mu \)m\(^3\) 

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 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.**

<table>
<thead>
<tr>
<th>SEM Median x50 feret.min number (µm)</th>
<th>Fraction &lt; 0.1µm mass/volume (%)</th>
<th>Fraction &lt; 0.1µm particle number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.100 (i)</td>
<td>2.0 (ii)</td>
<td>50.0 (iii)</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th></th>
<th>TiO( _2 ) inhaled (lung exposure) dose thoracic fraction (µg/day)</th>
<th>(a) TiO( _2 ) nano particle inhaled (lung dose) in number feret.min(^1) (Number Particles/day)</th>
<th>(b) TiO( _2 ) nano particle inhaled (lung dose) in mass/volume (µg/day)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>125</td>
<td>9.79E+03</td>
<td>2.50</td>
</tr>
<tr>
<td>Loose Powder for Face Make-up Product FZ</td>
<td>10.35</td>
<td>2.47E+03</td>
<td>0.21</td>
</tr>
<tr>
<td>Combined exposure</td>
<td><strong>135</strong></td>
<td><strong>1.23E+04</strong></td>
<td><strong>2.7</strong></td>
</tr>
</tbody>
</table>

\(^1\) Calculation nano content of TiO\( _2 \) in number feret.min using worst case sample E

\(^2\)

With
Mass of TiO\(_2\) constituent Particle = Volume of constituent Particle * Density of constituent particle

\[
\mu g/\mu m^3 = \frac{(4/3) \pi \times (d/2)^3 \times \rho}{\text{where } \rho \text{ is skeletal density of TiO}_2 = 4}
\]

2. Calculation nano content of TiO\(_2\) in mass/volume using worst case sample F

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 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 an exposure calculation 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.

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 ConsExpWeb (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 approximately 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). TiO₂ 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 TiO₂ is estimated at $6.3 \times 10^{-5}$ mg/kg bw (60 kg bw) = **3.78 µg/d**

### ConsExpo Web - Assessment settings

| Frequency: | 438 per year |
| Exposure model: | Exposure to spray – Spraying |
| Spray duration: | 0.24 minute |
| Exposure duration: | 20 minute |
| Weight fraction substance: | 1% (TiO₂ content in F8 product) |
| Room volume: | 60 m³ |
| 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/cm³ |
| Inhalation cut off diameter: | 10 µm |
| Aerosol diameter distribution: | LogNormal |
| Median diameter: | 46.5 µm |
| Arithmic diameter 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 $\times 10^{-2}$ mg/m³

- 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 $\times 10^{-2}$ mg/m³

- Mean concentration on day of exposure (average air concentration over the day (accounts for the number of events on one day))
  - 2.0 $\times 10^{-4}$ mg/m³

- Year average concentration (mean daily air concentration averaged over a year)
  - 2.0 $\times 10^{-4}$ mg/m³

- External event dose (the amount that can potentially be absorbed per kg body weight during one event)
  - 5.2 $\times 10^{-5}$ 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 $\times 10^{-5}$ mg/kg bw (61 kg bw)

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 parameter included in the ConsExpo model in consistence with workplace regulatory provisions requiring hair salons ventilation (25 m³/h/person in France, 100 m³/h in Germany). In addition, the room size used for the study was 10 m³ whereas hair salon volume is much higher since it is reasonable to consider a salon surface of approx. 25 m² and volume of 60 m³. Nevertheless, according to the Applicant, the lung exposure estimates obtained from both approaches remain low compared to the derived TiO₂ safe reference
dose of 24000 µg/day (developed below) and support that the professional lung exposure to TiO₂ 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 has been made by the Applicant that the frequency of application of TiO₂-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 conservative assumption that all the hairsprays contain TiO₂, which is conservative since not all the hairsprays available on the market contain TiO₂.

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 be 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 m³) 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 m³/h/person as a minimal requirement. This could translate to a conservative lower bound on ventilation of 50 m³/h. With a room volume of 60 m³, 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 m³ room with 0.8 per hour ventilation) and a frequency of 2190 per year representing approximately 10 applications per working day, the estimated lung exposure to TiO₂ is \(3.7 \times 10^{-4}\) mg/kg bw (60 kg bw) = 22.08 µg/d. This is higher than the value proposed by the Applicant. The SCCS has further concerns regarding the derived human reference value (see below), and therefore the exposure value for hairdressers is considered to be much lower than the proposed safe level.

Table 13: **ConsExpo Web - Assessment settings used by the SCCS**
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body weight 60 kg</td>
</tr>
<tr>
<td>2</td>
<td>Scenario WORKER SCCS</td>
</tr>
<tr>
<td>3</td>
<td>Frequency 2.19E+03 per year</td>
</tr>
<tr>
<td>4</td>
<td>Description</td>
</tr>
<tr>
<td>5</td>
<td>Inhalation</td>
</tr>
<tr>
<td>6</td>
<td>Exposure model Exposure to spray - Spraying</td>
</tr>
<tr>
<td>7</td>
<td>Spray duration 0.24 minute</td>
</tr>
<tr>
<td>8</td>
<td>Exposure duration 20 minute</td>
</tr>
<tr>
<td>9</td>
<td>Product in pure form No</td>
</tr>
<tr>
<td>10</td>
<td>Molecular weight matrix</td>
</tr>
<tr>
<td>11</td>
<td>The product is used in dilution No</td>
</tr>
<tr>
<td>12</td>
<td>Weight fraction substance 1 %</td>
</tr>
<tr>
<td>13</td>
<td>Room volume 60 m³</td>
</tr>
<tr>
<td>14</td>
<td>Room height 2.5 m</td>
</tr>
<tr>
<td>15</td>
<td>Ventilation rate 0.8 per hour</td>
</tr>
<tr>
<td>16</td>
<td>Inhalation rate 13 l/min</td>
</tr>
<tr>
<td>17</td>
<td>Spraying towards person No</td>
</tr>
<tr>
<td>18</td>
<td>Mass generation rate 0.4 g/s</td>
</tr>
<tr>
<td>19</td>
<td>Airborne fraction 0.2</td>
</tr>
<tr>
<td>20</td>
<td>Density non volatile 1.5 g/cm³</td>
</tr>
<tr>
<td>21</td>
<td>Inhalation cut off diameter 10 µm</td>
</tr>
<tr>
<td>22</td>
<td>Aerosol diameter distribution LogNormal</td>
</tr>
<tr>
<td>23</td>
<td>Median diameter 46.5 µm</td>
</tr>
<tr>
<td>24</td>
<td>Arithmetic coefficient of variation 2.1</td>
</tr>
<tr>
<td>25</td>
<td>Maximum diameter 50 µm</td>
</tr>
<tr>
<td>26</td>
<td>Include oral non-respirable material exposure No</td>
</tr>
<tr>
<td>27</td>
<td>Absorption model n.a.</td>
</tr>
<tr>
<td>28</td>
<td>Dermal</td>
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<tr>
<td>29</td>
<td>Exposure model n.a.</td>
</tr>
<tr>
<td>30</td>
<td>Absorption model n.a.</td>
</tr>
<tr>
<td>31</td>
<td>Oral</td>
</tr>
<tr>
<td>32</td>
<td>Exposure model n.a.</td>
</tr>
<tr>
<td>33</td>
<td>Absorption model n.a.</td>
</tr>
<tr>
<td>34</td>
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</tr>
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</table>

**Results for scenario WORKER SCCS SCENRAIO**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>35</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Inhalation</td>
</tr>
<tr>
<td>37</td>
<td>Mean event concentration 0.0144 mg/m³</td>
</tr>
<tr>
<td>38</td>
<td>Peak concentration (TWA 15 min) 0.0159 mg/m³</td>
</tr>
<tr>
<td>39</td>
<td><strong>Mean concentration on day of exposure</strong> 0.0012 mg/m³</td>
</tr>
<tr>
<td>40</td>
<td>Year average concentration 0.0012 mg/m³</td>
</tr>
<tr>
<td>41</td>
<td>External event dose 6.13E-05 mg/kg bw</td>
</tr>
<tr>
<td>42</td>
<td><strong>External dose on day of exposure</strong> 0.000368 mg/kg bw</td>
</tr>
<tr>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>
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 (\textit{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 \textit{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 \textit{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\textsubscript{2} materials used in cosmetic products do not pose a genotoxic risk.

SCCS comments on genotoxicity

The SCCS considered in a previous Opinion on TiO\textsubscript{2} (SCCS/1583/17) that, where internal exposure of the lungs is possible, there is a possibility that nano-TiO\textsubscript{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\textsubscript{2} at the EU level, that the main mechanism to explain the effects induced by TiO\textsubscript{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\textsubscript{2} particles. However, a direct interaction with DNA could not be excluded, since TiO\textsubscript{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\textsubscript{2} genotoxicity data has been given. It concluded that 'orally ingested TiO\textsubscript{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\textsubscript{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.

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\textsubscript{2} may exert genotoxic effects where internal exposure of the lungs is possible. The genotoxic effects of TiO\textsubscript{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\textsubscript{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\textsubscript{2}, but a nanomaterial designated as “P25” (not commercially used for any applications).
In the 2-year chronic inhalation study by Lee at 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/m$^3$ 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/m$^3$ in this study. However, exposure concentrations above 50 mg/m$^3$ 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/m$^3$ 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/m$^3$, 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/m$^3$ 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, β-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/m$^3$ 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.
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 TiO₂. [...] 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 TiO₂ 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 TiO₂ 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 therefore 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 TiO₂ in sprayables (SCCS/1583/17):

'Various scientific and regulatory bodies have considered TiO₂ as a possible carcinogen to humans when inhaled. Recently, TiO₂ has been classified as Carc. Cat 1B-H350i considering that a causal relationship had been established between TiO₂ 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 TiO₂.

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 TiO₂. It is considered that this mode of action is principally due to the biopersistence and poor solubility of the TiO₂ particles. However, a genotoxic effect by direct interaction with DNA cannot be excluded since TiO₂ was found in the cell nucleus in various in vitro and in vivo studies’.

<table>
<thead>
<tr>
<th>3.4.8 Photo-induced toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.8.1 Phototoxicity / photo-irritation and photosensitisation</td>
</tr>
<tr>
<td>/</td>
</tr>
<tr>
<td>3.4.8.2 Photomutagenicity / photoclastogenicity</td>
</tr>
<tr>
<td>/</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3.4.9 Human data</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
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</tbody>
</table>
3.4.10 Derivation of a safe Human Reference Value

According to the Applicant, the mechanism of tumour formation in laboratory rats exposed to TiO₂ 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 defense 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 TiO₂-specific chemically-induced effect.

Inhalation exposure to pigmentary TiO₂ 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 TiO₂ 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 TiO₂ inhalation exposure, specifically in TiO₂ 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 TiO₂ 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 TiO₂ comparable to TiO₂ 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/m³ as the Point of Departure (POD) for human safety assessment of inhalation exposure to TiO₂.

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/m³ 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 in Muhle et al. (1991) 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)

<table>
<thead>
<tr>
<th>MPPD Parameter</th>
<th>Rat</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Vol (mL)</td>
<td>2.1</td>
<td>860</td>
</tr>
<tr>
<td>Breaths/ min</td>
<td>102</td>
<td>16</td>
</tr>
<tr>
<td>VE (mL/min)</td>
<td>214.2</td>
<td>13760</td>
</tr>
<tr>
<td>Fractional deposition (PU)</td>
<td>0.0424</td>
<td>0.1287</td>
</tr>
<tr>
<td>Alveolar surface area (m$^2$)</td>
<td>0.4</td>
<td>102</td>
</tr>
<tr>
<td>DAF</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>24-hour Adjusted HEC (mg/m$^3$.day )</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

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

The Applicant chose the Muhle et al. (1991) 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/m³ (instead of 1.25 mg/m³, 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/cm³), 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 Human is 860 ml, according the default parameter of MPPD it should be 625 ml;
- the breath rate in Human is 16, the value of this parameter should be 12 (default parameter);
- The reference of the alveolar surface (in m²) in rat and human is missing. Literature indicates other values for alveolar surface, however, the values chosen by the Applicant are in the same range of the published values.

According to the Applicant, the theoretical deposition to the lung HEC is 24000 µg/day (1.2 mg/m³ x 20 m³/day), where 20 m³ 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.

The SCCS considers the deposition in 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/m³) x 20 m³/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>
<thead>
<tr>
<th>MPPD Parameter</th>
<th>Calculations by the Applicant</th>
<th>Calculations by the SCCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tidal Vol (mL)</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Breaths/min</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>VE (mL/min)</td>
<td>214.2</td>
<td>214.2</td>
</tr>
<tr>
<td>Fractional deposition (PU)</td>
<td>0.0424</td>
<td>0.0449</td>
</tr>
</tbody>
</table>

Table 15: Comparison of calculations of HEC and estimated deposition values calculated by the Applicant and the SCCS using different key studies
Opinion on Titanium dioxide (\(\text{TiO}_2\))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Human</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar surface area (m(^2))</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Tidal Vol (mL)</td>
<td>860</td>
<td>860</td>
</tr>
<tr>
<td>Breaths/min</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>VE (mL/min)</td>
<td>13760</td>
<td>13760</td>
</tr>
<tr>
<td>Fractional deposition (PU)</td>
<td>0.1287</td>
<td>0.1534</td>
</tr>
<tr>
<td>Alveolar surface area (m(^2))</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>DAF</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>24-hour Adjusted HEC (mg/m(^3).day)</td>
<td>1.2</td>
<td>1.03</td>
</tr>
<tr>
<td>Estimated deposition value (µg/day)</td>
<td>24000</td>
<td>3173 (in the pulmonary region)</td>
</tr>
<tr>
<td>Steady state Adjusted HEC (mg/m(^3).day)</td>
<td>Not calculated</td>
<td>0.15</td>
</tr>
<tr>
<td>Estimated deposition value (µg/day) at steady state</td>
<td>Not calculated</td>
<td>456</td>
</tr>
</tbody>
</table>

1Yeh-Schum symmetric per Kuempel et al. (2015) and Thompson et al. (2016)
2Values in red are divergent (between SCCS calculations and Applicant's calculations)
3This HEC at steady state takes account the elimination constant in rat and human, expressed in days:
   Elimination constant = \(-\ln(0.5)/\text{elimination half-time (MAK 2012, ANSES 2019)}\)
   In rat, the Elimination constant = \(-\ln(0.5)/60 = 0.0116/\text{day.}\)
   In human, Elimination constant= \(-\ln(0.5)/400 = 0.00173/\text{day.}\)
4A 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) study has been used (instead of 5 mg/m\(^3\) from Mühle 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).
5For the calculations based on Bermudez et al. (2004) study, the SCCS has used the default parameter for the tidal volume in humans (625 ml) and the breath rate in humans (12) leading to a ventilation rate of 7500 (ml/min). For the alveolar surface, the SCCS used 57.22 m\(^2\) for Human, and 0.297 m\(^2\) for rat.
6Furthermore, 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.
7The Deposition value at non steady state was calculated as: deposition rate in human x NOAEC = 802 µg/day (1.608 mg/d x 0.5).

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

<table>
<thead>
<tr>
<th>MPPD Parameter</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAEC =0.5</td>
<td></td>
</tr>
</tbody>
</table>
Opinion on Titanium dioxide (TiO₂)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Vol (mL)</td>
<td>2.1</td>
</tr>
<tr>
<td>Breaths/min</td>
<td>102</td>
</tr>
<tr>
<td>VE (mL/min)</td>
<td>214.2</td>
</tr>
<tr>
<td>Fractional deposition (PU)</td>
<td>0.056</td>
</tr>
<tr>
<td>Alveolar surface area (m²)</td>
<td>0.297</td>
</tr>
<tr>
<td>Clearance</td>
<td>Not used</td>
</tr>
<tr>
<td>deposition rate ¹</td>
<td>0.00308448</td>
</tr>
</tbody>
</table>

**Human**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Vol (mL)</td>
<td>625</td>
</tr>
<tr>
<td>Breaths/min</td>
<td>12</td>
</tr>
<tr>
<td>VE (mL/min)</td>
<td>7500</td>
</tr>
<tr>
<td>Fractional deposition (PU)</td>
<td>0.1485</td>
</tr>
<tr>
<td>Alveolar surface area (m²)</td>
<td>57</td>
</tr>
<tr>
<td>Clearance Human</td>
<td>Not used</td>
</tr>
<tr>
<td>deposition rate ²</td>
<td>1.6038</td>
</tr>
<tr>
<td>DAF</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**24-hour Adjusted HEC (mg/m³.day)**

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.185</td>
</tr>
</tbody>
</table>

¹ Deposition rate rat = 0.056 x (2.1/1000000) x 102 x 60 x 6 x 5/7 = 0.003084 m³/day
² Tidal volume of the rat
³ Respiratory rate of the rat
⁴ Exposure time of the study, expressed in days
⁵ Deposition rate human = 0.1485 x (625/1000000) x 12 x 60 x 24 = 1.6038 m³/day
⁶ Tidal volume of human
⁷ Respiratory rate of human
⁸ Exposure time, expressed in days

Using the NOAEC and the parameters from this study, the SCCS has calculated the following:

- 24 hour adjusted HEC = 0.185 mg/m³/day
- Deposition value (fractional deposition) then becomes 802 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/m³ 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 TiO₂ derived by different institutions

<table>
<thead>
<tr>
<th>Institution (year)</th>
<th>Main TiO₂ material</th>
<th>Reference value</th>
<th>Critical endpoint</th>
<th>Time adjustment and dose metrics</th>
<th>Uncertainty factors</th>
<th>POD</th>
<th>Key study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANSES (2020)</td>
<td>P25 (nano)</td>
<td>Workers: Lung</td>
<td>Temporal and allometric</td>
<td>225 UF inter</td>
<td>NOAEC = 0.5</td>
<td>Bermudez et al., 2004</td>
<td></td>
</tr>
</tbody>
</table>
**Opinion on Titanium dioxide (TiO₂)**

<table>
<thead>
<tr>
<th>NIOSH (2011)*</th>
<th>Various (fine and ultrafine)</th>
<th>0.80 µg/m³ General population: 0.12 µg/m³</th>
<th>Inflammation adjustment MPPD model</th>
<th>species = 2.5 UF intra species = 10 UF study duration= 3 UF Database = 3</th>
<th>mg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIOSH (2011)</strong></td>
<td>Various (fine and ultrafine)</td>
<td>For FP: 0.04 mg/m³</td>
<td>Lung Inflammation 10 hr/day during a 40-hour work week, 45 years. Internal lung doses</td>
<td>For FP: 0.9 mg/m³ For UFP: 0.11 mg/m³ 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)</td>
<td>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)</td>
</tr>
<tr>
<td>NIOSH (2011)*</td>
<td>Various (fine and ultrafine)</td>
<td>2.4 mg/m³ for fine TiO₂ 0.3 mg/m³ for ultrafine (including engineered nanoscale) TiO₂</td>
<td>Lung cancer 10 hr/day during a 40-hour work week, 45 years. Internal lung doses</td>
<td>Working Life Time cancer risk approach 1 excess case per 1,000 workers Equal sensitivity of lungs tissues between rats and humans assumed</td>
<td>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)</td>
</tr>
<tr>
<td>MAK</td>
<td>Various</td>
<td>0.3 mg/m³ × material density</td>
<td>Lung Inflammation</td>
<td>Different Approaches considered Reference value derived according to the general threshold value for biopersistent granular dusts, not valid for ultrafine particles</td>
<td>MAK, 2012</td>
</tr>
</tbody>
</table>

---

1. 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 exposure.

risk of lung tumors due to exposure to TiO2. 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 TiO2. (...) 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 TiO2 on lung tumors rather than pulmonary inflammation. However, NIOSH notes that extremely
low-level exposures to TiO2—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
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 TiO2 considers the most sensitive adverse effects in rats
associated with chronic inhalation exposure to TiO2. From the evidence presented, the
pivotal study corroborates a NOAEC of 5 mg/m³ 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 TiO2 (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 available 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 TiO2. The SCCS considered it
relevant for the assessment of pigmentary TiO2 materials because the latter contain a
significant fraction of nano-scale particles that 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 TiO2-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 by inhalation, 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 to 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).


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\textsubscript{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\textsubscript{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\textsubscript{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.

**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\textsubscript{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\textsubscript{2} exposure) and the calculated MOS (167 for aggregated deterministic exposure), the consumer inhalation exposure to TiO\textsubscript{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.

![Table 17: Applicant’s calculation of Margin of Safety (Note: only those products are shown here that use R4 pigmentary TiO\textsubscript{2} and are therefore relevant for the SCCS assessment)](image-url)
Opinion on Titanium dioxide ($\text{TiO}_2$)

<table>
<thead>
<tr>
<th>Product</th>
<th>TiO$_2$ concentration in the formulation (%)</th>
<th>TiO$_2$ Human deposition in pulmonar y region (µg/day)</th>
<th>Measured TiO$_2$ concentration Thoracic fraction (µg/m$^3$)</th>
<th>TiO$_2$ inhaled (lung exposure) dose thoracic fraction (µg/day)</th>
<th>TiO$_2$ pulmonary deposited dose (µg/day)</th>
<th>Margin of Safety$	extsuperscript{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>1</td>
<td>802</td>
<td>480.4</td>
<td>125</td>
<td>19.6</td>
<td>41</td>
</tr>
<tr>
<td>Loose Powder for Face Make-up Product FZ</td>
<td>20</td>
<td></td>
<td>39.8</td>
<td>10.35</td>
<td>1.60</td>
<td>501</td>
</tr>
<tr>
<td>Combined exposure of the above 2</td>
<td></td>
<td></td>
<td>135</td>
<td>21.2</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

$\textsuperscript{1}$ Data from section 2. 20 min average air concentration

$\textsuperscript{2}$ TiO$_2$ inhaled dose (µg/day) = Measured TiO$_2$ concentration Thoracic fraction (µg/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).

$\textsuperscript{3}$ 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 comments

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, using 0.5 mg/m$^3$ as the NOAEC.

The Human deposition value was calculated according 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 rate in human x NOAEC = 802 µg/day (1.608 mg/dx 0.5)

This corresponds to the breathing rate of a person for 24-hour continuous exposure i.e. 7 days per week, and 60 kg of average consumer body weight.

Table 18: The SCCS calculation of the Margin of Safety with HEC at non-steady state
1 this fraction of inhaled material deposited in the pulmonary region has been calculated by the applicant (see Appendix 7 of the dossier). The average deposition fraction is 17%.

\[
\text{TiO}_2 \text{ pulmonary deposited dose (µg/day)} = \frac{\text{Measured TiO}_2 \text{ concentration Thoracic fraction (µg/m}^3\text{) /1000 (conversion m}^3\text{ to L) x human breathing rate (12 L/minutes) x residence time in the room (20 minutes) x frequency of use per day (according to the product uses) x 0.17.}}
\]

Margin of Safety = \(\frac{\text{Safe Human deposition in pulmonary region(µg/day)} \text{ / TiO}_2 \text{ pulmonary deposited dose, where HEC is 802 µg/day.}}\)

**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 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**        |                 |
| 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\(^1\) | 0.00308448 |
| **Human**      |                 |
| Tidal Vol (mL) | 625             |
| Breaths/min    | 12              |
| VE (mL/min)    | 7500            |
| Fractional deposition (PU) | 0.1485 |
| Alveolar surface area (m2) | 57 |
| Clearance Human | Not used |
| deposition rate\(^2\) | 0.5346 |
| **DAF**        | 1.11            |
| **8-hour Adjusted HEC (mg/m3.day)** | 0.554 |

\(^1\) Deposition rate (rat) = 0.056 \times (2.1/1000000) \times 102 \times 60 \times 6 \times 5/7

\(^2\) Deposition rate (human) = 0.1485 \times (625/1000000) \times 12 \times 60 \times 8

For the safety assessment for hairdressers, the SCCS has used the deposition value values in the Table 20.
The Deposition value was calculated as follow: Deposition rate human x NOAEC = 267.3 µg/day (0.5346 mg/d x 0.5), (representing the amount that can reach the alveoli).

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

<table>
<thead>
<tr>
<th>TiO₂ conc. in the formulation (%)</th>
<th>Human equivalent pulmonary exposure dose (µg/day)</th>
<th>estimated TiO₂ lung exposure (µg/days) Estimated by consexpo (see chapter 3.3)</th>
<th>TiO₂ pulmonary deposited dose (µg/day)¹</th>
<th>Margin of Safety²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>1.0</td>
<td>267.3</td>
<td>22.08</td>
<td>3.75</td>
</tr>
</tbody>
</table>

¹ calculated with Consexpo with an average deposition fraction of 17%.
² Margin of Safety = safe Human equivalent pulmonary exposure dose / TiO₂ pulmonary deposited dose, where HEC is 267.3 µg/day.

A further consideration in the SCCS opinion is that hairdressers are also consumers and therefore the exposure expected for a general consumer should also be added in the MOS calculation (Table 20b):

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

<table>
<thead>
<tr>
<th>TiO₂ conc. in the formulation (%)</th>
<th>Human equivalent pulmonary exposure dose (µg/day)</th>
<th>estimated TiO₂ lung exposure (µg/days) Estimated by consexpo (see chapter 3.3)</th>
<th>TiO₂ pulmonary deposited dose (µg/day)¹</th>
<th>Margin of Safety²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Styling Aerosol Spray Product F8</td>
<td>1.0</td>
<td>267.3</td>
<td>147.08 (125 from consumer exposure + 22.08 from occupational exposure)</td>
<td>25</td>
</tr>
</tbody>
</table>

¹ occupational and consumer exposure with an average deposition fraction of 17%.
² Margin of Safety = safe Human equivalent pulmonary exposure dose / TiO₂ pulmonary deposited dose, where HEC is 267.3 µg/day.

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 products based on only one type of TiO₂ material (pigmentary, anatase, surface-treated). 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 hairdresser.

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$_2$. In 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 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

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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 any 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**

Recurrent 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 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, using 0.5 mg/m\(^3\) as the NOAEC.

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 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 opinion, an 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 1.64 % for the general consumer, and 1.0 % 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 products 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.
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 (TiO2) 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 TiO2 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 TiO2 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 TiO2 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 TiO2 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 TiO2 in a typical hair styling aerosol spray product is safe up to a maximum concentration of 1.64 % for general consumers, and 1.0 % 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 products based on only one type of TiO2 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 TiO2 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 TiO2 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

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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