Safety and efficacy of a feed additive consisting of titanium dioxide for all animal species (Titanium Dioxide Manufacturers Association)

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Abstract
Following a request from the European Commission, the EFSA was asked to deliver a scientific opinion on the safety and efficacy of titanium dioxide (TiO₂) for all animal species. TiO₂ is applied to be used as a sensory additive (functional group: colourants; i) substances that add or restore colour in feedingstuffs). The specification for TiO₂ used as feed additive meets the specifications of TiO₂ used as food additive. The EFSA Panel on Food Additive and Flavourings (FAF) concluded that TiO₂ (E171) can no longer be considered as safe when used as a food additive. The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) endorses this conclusion and considers that it also applies to TiO₂ as a feed additive for all animal species. TiO₂ is absorbed to a low extent; however, particles of TiO₂ can accumulate in the body due to their long half-life. The genotoxicity of TiO₂ particles cannot be ruled out raising potential concerns on the safety of the additive for the target species (especially for long-living animals and reproductive animals), consumers and user. Considering this fact and the absence of specific data related to its use as a feed additive, the Panel cannot conclude on the safety of TiO₂ for the target species, consumers and environment. In the absence of studies with the additive under assessment, the Panel cannot conclude on the assessment of the effects of the additive on eyes and skin. TiO₂ is potentially carcinogenic to workers if inhaled. The concern for genotoxicity of TiO₂ particles cannot be ruled out, this should be considered as an additional potential concern to users handling the additive. TiO₂ is efficacious in colouring the food for cats and dogs at a minimum content of 1%.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003\(^1\) establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7. In particular, Article 10(2) of that Regulation also specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, at the latest one year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC\(^2\) for additives with a limited authorisation period, and within a maximum of seven years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC\(^3\).

The European Commission received a request from the company Kronos International, Inc.\(^4\) for the re-evaluation of the additive consisting of titanium dioxide, when used as a feed additive for all animal species (category: 2. sensory additive; functional group: (a) colourants/substances that add or restore colour in feedingstuff).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1)\(^5\) (authorisation of a feed additive or new use of a feed additive) and Article 10(2) (re-evaluation of an authorised feed additive). The particulars and documents in support of the application were considered valid by EFSA as of 13 April 2011.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of titanium dioxide, when used under the proposed conditions of use (see Section 3.1.4).

1.2. Additional information

Titanium dioxide is included in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. It is authorised for its use in cats and dogs as colourant additive (colouring agents authorised for colouring foodstuffs by Community rules in application of Article 9t (b) of Council Directive 70/524/EEC).\(^6\) The additive is also authorised for all species or categories of animals with the exception of cats and dogs for animal feedingstuffs only in products processed from: (i) waste products of foodstuffs, (ii) other base substances, with the exception of cereals and manioc flour, denatured by means of these agents or coloured during technical preparation to ensure the necessary identification during manufacture. No maximum levels of titanium dioxide in feeds are established in the EU.

The use of titanium dioxide as feed additive has never been assessed in the EU. The applicant asks for the re-evaluation of the use of the additive for all species or categories of animals.

It is noted that that titanium dioxide occurs in three different crystallised forms, anatase, rutile and brookite. The present application concerns only the anatase and rutile forms of titanium dioxide.

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\(^1\) Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

\(^2\) Directive 70/524/EEC of 23 November 1970 concerning additives in feeding-stuffs. OJ L 270, 14.12.1970, p. 1.

\(^3\) Council Directive 82/471/EEC of 30 June 1982 concerning certain products used in animal nutrition. OJ L 213, 21.7.1982, p. 8.

\(^4\) Kronos International, Inc. Peschstraße 5, 51373, Leverkusen, Germany. During the assessment, the Company has been changed to Titanium Dioxide Manufacturers Association (TDMA), a sector group of Cefic, Rue Beillard 40, b. 15, 1040 Brussels, Belgium.

\(^5\) Originally the European Commission forwarded the application as a new use of the additive in feed for all animal species except cats and dogs. During the assessment, the applicant clarified that they wanted to keep the provisions of the current authorisation: Titanium dioxide is authorised for its use in cats and dogs as colourant additive (colouring agents authorised for colouring foodstuffs by Community rules). The additive is also authorised for all species or categories of animals with the exception of cats and dogs for animal feedingstuffs only in products processed from: i) waste products of foodstuffs, ii) other base substances, with the exception of cereals and manioc flour, denatured by means of these agents or coloured during technical preparation to ensure the necessary identification during manufacture.

\(^6\) List of the authorised additives in feedingstuffs (1) published in application of Article 9t (b) of Council Directive 70/524/EEC concerning additives in feedingstuffs. OJ C 50, 25.2.2004, p. 1.
Titanium dioxide (TiO₂, E 171) is authorised as a food additive in the EU according to Annex II of Regulation (EC) No 1333/2008 and specifications have been defined in Commission Regulation (EU) No 231/2012.

Titanium dioxide (TiO₂) (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 colourant 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. TiO₂ is also used as a filler in cosmetic products (not subject to specific regulatory restrictions).

In addition, TiO₂ is widely used as an excipient in medicinal products, mainly as a colour/opacifier in oral and cutaneous dosage forms. TiO₂ for use in medicinal products needs to meet the requirements defined in the European Pharmacopoeia. Colouring matter should comply with the requirements of European Union Directive 2001/83/EC. Current EU legislation laying down specific purity criteria concerning colours for use in foodstuffs (Commission Regulation (EU) No 231/2012) also applies to medicinal products (as detailed in Directive 2009/35/EC).

Several assessment bodies evaluated the safety of TiO₂. The text below provides an overview of the previous assessments considering separately the evaluations for orally administered TiO₂ and TiO₂ applied via dermal and inhalation route.

**Orally administered TiO₂**

TiO₂ was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1969 (JECFA, 1970) and by the Scientific Committee on Food (SCF) in 1975 and 1977 (European Commission, 1975, 1977). The British Industrial Biological Research Association (BIBRA) issued a toxicity profile on TiO₂ in 1990 (BIBRA, 1990). TiO₂ was reviewed by TemaNord in 2002 (TemaNord, 2002) and assessed by EFSA in 2004 (EFSA, 2005).

In 1969, JECFA did not establish a limit on the intake of TiO₂ (anatase and rutile forms were not distinguished), considering that the available information indicated ‘that it is free from toxic effects on account of its insolubility and inertness’. An acceptable daily intake (ADI) ‘not limited except for good manufacturing practice’ was allocated (JECFA, 1970).

In 1975, the SCF did not establish an ADI for TiO₂ because they ‘felt able to accept the use of this colouring matter for the surface and mass colouring of sugar confectionary only, without the need for further investigations’. In a later SCF evaluation (1977), it was indicated that new information on other potential uses and specifications had been presented to the Committee, and subsequently, they included TiO₂ in the category ‘colours for which an ADI was not established but which could be used in food’.

In 2002, TemaNord reviewed TiO₂ and concluded that ‘the available data do not currently meet requirements. However, the inertness of the substance and the lack of absorption and tissue storage does not warrant further testing or a re-evaluation of the safety in use of this compound’ (TemaNord, 2002).

In 2004, the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food (AFC Panel) evaluated the safety of using platelet forms of rutile TiO₂ as an alternative to the permitted anatase form. The AFC Panel concluded that the bioavailability of these forms was essentially the same, that the toxicological database would, therefore, be applicable to either form and that the platelet forms of rutile TiO₂ could be used to replace anatase TiO₂ in any of its current applications (EFSA, 2005).

In 2010, the International Agency for Research on Cancer (IARC) re-evaluated TiO₂ and revised the classification as ‘possibly carcinogenic to humans (Group 2B)’ based on an excess incidence of lung tumours in inhalation studies. It was stated that ‘No increases were observed among mice and hamsters exposed intratracheally. Other studies that used different routes of administration did not observe excesses in tumour incidence’ (IARC, 2010).

In 2011, the EFSA FEEDAP Panel started the re-evaluation of TiO₂ as feed additive for all animal species. At that time, the re-evaluation of the safety of the TiO₂ titanium dioxide (E 171), performed...
under the frame of Regulation (EC) No 257/2010, was not started yet. A number of coordination activities were put in place within EFSA in order to coordinate the assessment of TiO₂ as feed and food additives.

In 2015, the Organisation for Economic Co-operation and Development (OECD) published different Series on the Safety of Manufactured Nanomaterials among which there is a dossier on TiO₂ manufactured nanomaterials. Detailed information on results and tests performed can be found in the technical dossiers of the particular TiO₂ nanomaterials (OECD, 2015).

In a Scientific Report by the Food Standard Agency of New Zealand (FSANZ) published in 2016 (FSANZ, 2016) on ‘The potential health risks associated with nanotechnologies in existing food additives’, it is reported that all forms of TiO₂ (nano- and microsized) in the diet are poorly absorbed from the gastrointestinal tract. Overall, this review concluded that there is limited information available to support a contemporary risk assessment of nano-TiO₂ in food. There are no epidemiology studies available regarding possible associations with adverse health outcomes. However, the long history of use has not given rise to reports of adverse effects.

In 2016, the EFSA Panel on Food Additives and Nutrient sources added to Food (ANS Panel) completed the re-evaluation of the safety of the food additive TiO₂ performed under the frame of Regulation (EC) No 257/2010 (EFSA ANS Panel, 2016). In that opinion, the ANS Panel had concluded that the food additive did not raise concerns with respect to genotoxicity and carcinogenicity, but was unable to establish a health-based guidance value (HBGV) because of certain deficiencies identified in the available toxicological data set, in particular with respect to the investigation of potential reproductive toxicity. Another important source of uncertainty identified during the re-evaluation concerned the characterisation of the material used as the food additive. On the basis of the information available at that time, the EFSA ANS Panel considered that ‘E 171 mainly consisted of microsized TiO₂ particles, with a nano-sized (< 100 nm) fraction less than 3.2% by mass’ (EFSA ANS Panel, 2016). Uncertainties around the identity and characterisation of E 171 were however highlighted, noting that no limits for the particle size of E 171 were set in the EU specifications. After the publication of the ANS Panel opinion, the re-evaluation of TiO₂ as feed additive was put on hold with the request of an extended one-generation reproductive toxicity (EOGRTS) study.

The European Commission followed up on the recommendations issued by the EFSA ANS Panel and, in January 2017, published a call for data addressed to interested business operators (IBOs) and requesting their commitment to provide the data requested to reduce the uncertainties underpinning the conclusions of the ANS Panel opinion. These included data on the characterisation of the material and the performance of a new extended one-generation reproductive toxicity study (EOGRTS) in rodents, to be conducted in accordance with the latest OECD Guidance applicable and with test material representative of the food additive on the EU market.

In January 2017, the publication of a study by Bettini et al. (2017) raised some concerns on the potential promoting effect on the development of colon cancer. The authors found an increase in the number and size of Aberrant Crypt Foci (ACF), putative preneoplastic lesions in the colon of rats treated with dimethylhydrazine to initiate colon carcinogenesis and given food-grade TiO₂ particles (10 mg/kg body weight (bw) per day) via drinking water for 100 days. This observation led to an opinion of the French Agency for Food, Environmental and Occupational Health & safety (ANSES) in April 2017 on the dietary exposure to nanoparticles of TiO₂ (ANSES, 2017). In that opinion, the ANSES concluded that the data available did not put the 2016 EFSA assessment in question.

A subsequent scientific opinion was issued by the ANS Panel in June 2018 to address a request from the European Commission for the evaluation of four publications – among them, Bettini et al. (2017) previously considered by ANSES – raising concerns on the safety of the food additive. Having reviewed these publications, the ANS Panel maintained the conclusions reached in 2016, but recommended the inclusion of biomarkers for putative pre-cancerous lesions in the colon to be included in the ongoing EOGRTS as additional parameters to be investigated (EFSA ANS Panel, 2018).

In July 2018, the EFSA Scientific Committee published a Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health (EFSA Scientific Committee, 2018) updating the 2011 Guidance Document on

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10 Commission regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19.

11 The genotoxicity studies retrieved from the literature search (Technical dossier/Supplementary information February 2102) were considered in the assessment of the ANS Panel in 2016 (EFSA ANS Panel, 2016).
nanomaterials (EFSA Scientific Committee, 2011) and clarifying that conventional materials containing a fraction of nanoparticles require specific risk assessment considerations, which were detailed in the document.

While the follow-up activities for the generation of new data were ongoing, in April 2019, the French Government decided to take risk management action introducing a ban on foods containing the additive E 171. The French decree, that entered into force on 1 January 2020, was based by the application of the precautionary principle to the latest advice issued by ANSES (ANSES, 2019). The ban on foods containing the food additive E 171 in France has been reconfirmed for the current year, pending the finalisation of the assessment by EFSA. In 2019, EFSA published a statement on the review of the risks related to the exposure to E 171 performed by ANSES (EFSA, 2019).

As a follow-up to the re-evaluation of E 171 completed by the ANS Panel in 2016, in 2018 the European Commission requested EFSA to assess a proposal for an amendment of the EU specifications for the food additive (E 171) based on the data on particle size and particle size distribution that had been provided by the IBOs in response to the first part of the European Commission call for data. The related scientific opinion was published by the EFSA FAF Panel (EFSA FAF Panel on Food Additive and Flavourings) in 2019 (EFSA FAF Panel, 2019). The FAF Panel recommended to include into the EU specifications for titanium dioxide (E 171) the parameter of median minimum external dimension by particle number > 100 nm (measured by electron microscopy), which is equivalent to less than 50% of constituent particles by number with a minimum external dimension < 100 nm. Furthermore, the FAF Panel also concluded that the toxicological database should be revisited in line with the data requirements specified in the 2018 EFSA ‘Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain’ (EFSA Scientific Committee, 2018). Due to the presence of a fraction of nanoparticles in E 171, the food additive falls under the scope of the EFSA guidance on nanotechnology in its present version. Since its 2018 revision, this document covers not only engineered nanomaterials but also those materials containing a fraction of particles that is less than 50% in the number–size distribution, with one or more external dimensions in the size range 1–100 nm.

Based on the recommendations from the 2019 scientific opinion of the FAF Panel, the European Commission made a proposal for amending the definition and specifications of E 171, introducing limits with respect to the particle size and particle size distribution in the food additive in Regulation (EU) No 231/2012. In October 2020, the European Parliament called on the Commission to withdraw its draft regulation, to apply the precautionary principle and to remove TiO2 (E 171) from the list of food additives authorised by the Union.4

In 2019, the Office for Risk Assessment and Research of the Nederlandse Voedsel- en Warenautoriteit (NVWA) delivered an opinion on possible health effects of the food additive TiO2 (NVWA, 2019). The opinion concluded that studies conducted since 2016 in mice and rats provide an indication of tumour promotion by E 171 in the intestinal tract, but should be considered ‘exploratory’ since they were not conducted in accordance with OECD guidelines. With regard to the EOGRT study (on-going at the time), the opinion concluded that an examination of immunotoxicological effects is important given recent studies, in addition to potential reprotoxicological effects. The opinion also concluded that an examination for potential promotion of colon cancer by E 171 should be examined, but considered it doubtful whether the performance of an EOGRT or chronic exposure test would be a suitable test system. In addition to this, further research in humans was considered required to establish any relevance of experimental findings to man.

In 2020, the European Commission requested EFSA to reassess the safety of the food additive TiO2 (E 171) taking into account all new relevant data available to EFSA since the completion of its re-evaluation of TiO2 (E 171) as a food additive in 2016. The FAF Panel finished its assessment in 2021 (EFSA FAF Panel, 2021) and concluded that, on the basis of all currently available evidence along with all the uncertainties, in particular the fact that genotoxicity concern could not be ruled out, E171 can no longer be considered as safe when used as a food additive. The Panel also concluded that the conclusions apply to E171 as described in Commission Regulation (EU) No 231/2012 as well as to E171 specified by the EFSA FAF Panel (EFSA FAF Panel, 2019).

**TiO2 applied via dermal and inhalation route**

In 2000, the Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) evaluated TiO2 as a cosmetic product. The SCCNFP concluded that TiO2 is photocatalytic in UV light, but that it did not give rise to concern for human use (SCCNFP, 2000).
The Scientific Committee on Consumer Safety (SCCS) issued an Opinion on TiO₂ (nanoform) in 2013 (SCCS, 2013a,b), and a commentary on this opinion was released in 2015 (SCCS and Chaudhry, 2015). The aim of these reports was to provide an answer to the question of the European Commission on whether the use of TiO₂ in its nanoform as a UV filter in cosmetic products (e.g. sunscreens), at a concentration up to maximum 25.0%, was safe for the consumers. In that opinion, SCCS concluded that the use of TiO₂ (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 TiO₂ nanoparticles (such as powders or sprayable products) cannot be considered safe. Furthermore, SCCS issued an additional opinion in 2018 on TiO₂ (nano form) as UV filter in sprays (SCCS, 2018); it concluded that ‘the information provided is insufficient to allow assessment of the safety of the use of nano-TiO₂ in spray applications that could lead to exposure of the consumer’s lungs’. Finally, SCCS provided an opinion on TiO₂ (nano form) coated with Cetyl Phosphate, Manganese Dioxide or Triethoxycaprylylsilane as UV filter in dermally applied cosmetics (SCCS, 2017). 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 Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) concluded in its scientific opinion of 14 September 2017 that titanium dioxide met the criteria in Regulation (EC) No 1272/2008\textsuperscript{12} for classification as a carcinogen in category 2 by inhalation (ECHA, RAC, 2017). The adopted harmonised classification and labelling was later included in an amendment of Regulation (EC) No 1272/2008 as indicated in Commission Delegated Regulation (EU) 2020/217\textsuperscript{13}. The new entry in Annex VI to Regulation (EC) No 1272/2008 applies to titanium dioxide in powder form containing 1% or more of particles with aerodynamic diameter ≤ 10 μm.

In 2020, the SCCS published an opinion on TiO₂ used in cosmetic products that lead to exposure by inhalation (SCCS, 2020). The aim of the report was to provide an answer to the question of the European Commission on whether, in light of the data provided and of the possible classification as Carcinogen Cat. 2 (inhalation) in Annex VI to Regulation (EC) no. 1272/2008 (see below), TiO₂ is considered safe when used as a UV filter (entry 27 Annex VI) in cosmetic products up to a maximum concentration of 25%, as a colourant (entry 143 Annex IV) and as an ingredient in all other cosmetic products. The SCCS concluded that the use of pigmentary 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. In this report, SCCS 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. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier\textsuperscript{14} in support of the authorisation request for the use of titanium dioxide as a feed additive.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports and experts’ knowledge, to deliver the present output.

\textsuperscript{12} Regulation (EC) No 1272/2008 of the European parliament and of the council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1.

\textsuperscript{13} Commission delegated regulation (EU) 2020/217 of 4 October 2019 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures and correcting that Regulation. OJ L 44, 18.2.2020, p. 1.

\textsuperscript{14} FEED dossier reference: FAD-2010-0297.
EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of the active substance in animal feed. The Executive Summary of the EURL report can be found in Annex A.15

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance is in line with the principles laid down in Regulation (EC) No 429/200816 and the relevant guidance documents: guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012c), Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d), Guidance on the assessment of additives intended to be used in pets and other non food-producing animals (EFSA FEEDAP Panel, 2011b), Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health (EFSA Scientific Committee, 2018).

3. Assessment

Titanium dioxide (in both anatase and rutile structure) is applied to be used as a sensory additive (functional group: colourants; (i) substances that add or restore colour in feedingstuffs) for direct use in feed for cats and dogs; for all other animal species, it is intended to be used in feedingstuffs only in products processed from: (i) waste products of foodstuffs or (ii) other base substances, with the exception of cereals and manioc flour, denaturated by means of these agents or coloured during technical preparation to ensure the necessary identification during manufacture, in line with the current authorisation.6

3.1. Characterisation of the additive

Titanium dioxide (TiO₂), Chemical Abstracts Service (CAS) Registry number 13463-67-7, European Inventory of Existing Commercial Chemical Substances (EINECS) number 236-675-5 and Colour Index (C.I.) number 77,891, is an inorganic substance with the molecular formula TiO₂ and a molecular weight of 79.88 g/mol. The active substance is identical to the additive.

TiO₂ occurs in three different crystallised forms, rutile (tetragonal, CAS Registry number 1317-80-2), anatase (tetragonal, CAS Registry number 1317-70-0) and brookite (orthorhombic, CAS Registry number 12188-41-9). Rutile and anatase are the most common forms crystallised in a tetragonal system differing mainly in the angle of the crystal pyramid. The present application concerns only the anatase and rutile forms of TiO₂.

The applicant stated that the specification for TiO₂ used as feed additive complies with the monograph of the European Pharmacopoeia (monograph 01/2008:0150) and it meets the specifications of Directive 95/45/EC17 for TiO₂ used as food additive (currently replaced by Commission Regulation (EU) No 231/2012: content not less than 99% on an alumina and silica-free basis, loss on drying < 0.5%, loss on ignition < 1.0%, aluminium oxide and/or silicon dioxide: < 2.0%).

Analytical data to confirm the compliance with the specifications were provided for five batches of each form of the additive, and comply with the thresholds set by Commission Regulation (EU) No 231/2012.

The same batches were analysed for impurities. The analytical values for Al₂O₃ comply with the thresholds set by Commission Regulation (EU) No 231/2012 and European Pharmacopoeia.

15 The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2010-0297.pdf
16 Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of the applications and the assessment of the applications and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.
17 Commission directive 95/45/EC of 26 July 1995 laying down specific purity criteria concerning colours for use in foodstuffs. 1995L0045 — EN — 25.08.1999 — 001.001 — 1.
18 Commission regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1.
The manufacturer provided specifications.

The content of polychlorinated dibenzo-p-dioxin and dibenzofuran (PCDD/F) and dioxin-like polychlorinated biphenyls (DL-PCBs), measured in three batches each. Non-dioxin-like PCBs were not measured. The levels of the impurities were considered of no concern.

3.1.1. Physical properties of the additive, including particle size and particle size distribution

The additive is a white powder insoluble in water. The melting point is > 1,800°C (rutile and anatase), the density of the rutile form is 4,200 kg/m³ and the one of anatase is 3,900 kg/m³. The apparent density of both forms is 600 kg/m³.

The dusting potential of the anatase form was determined in one batch using a modified Stauber-Heubach method being 150 g/kg.22 No data on the dusting potential of the rutile product was provided.

The information on particle size distribution of TiO₂ included in the current dossier22 was also evaluated in the assessment of the ANS Panel (EFSA ANS Panel, 2016).23 The average particle size of 11 commercial samples of TiO₂ (E 171) was measured in dispersions, using different methods of dispersion (ultra Turrax, ultrasonic probe, high-shear/high-speed mixer) and different measurement methods (laser diffraction, spinning disc centrifuge, transmission electron microscopy (TEM)). The results showed an average particle size of 169–680 nm; the smaller particle sizes were reported from application of the TEM measurement technique. The weight percentage of particles with a size < 100 nm ranged between 0.0% and 3.2%. Other limited information from anatase and rutile (E 171) samples was also submitted.

The above analytical data were evaluated together with data on particle size characteristics of TiO₂ used as a food/feed additive provided by other interested parties24 and additional information available from public literature in the ANS Panel opinion (EFSA ANS Panel, 2016).

Overall, the analytical data, provided by interested parties on the particle size distribution of food-grade TiO₂ confirmed the small percentage in the nanoscale (< 100 nm), but that actual values depended on the method used. From this information, a percentage value of 3.2% of nanoparticles by mass was considered by the Panel to be reasonable to address in a conservative way a preliminary content estimate in the food additive TiO₂ (E 171).25 At the time of that assessment, it was also noted that according to the data provided by industries and from the literature, TiO₂ (E 171) as a food additive would not be considered as a nanomaterial according to the EU Recommendation on the definition of a nanomaterial.25 However, it was recommended that the EU specifications for TiO₂ (E 171) should include a characterisation of particle size distribution using appropriate statistical descriptors (e.g. range, median, quartiles) as well as the percentage (in number and by mass) of particles in the nanoscale (with at least one dimension < 100 nm) present in TiO₂.

22 Supplementary information/February 2012/Annex 1.
23 E-mail message sent on 19 June 2013.
24 The interested parties who submitted data for the assessment of TiO₂ as food additive gave the permission to use the data submitted to EFSA for the assessment of TiO₂ as feed additive (ICAM letter dated 15 September 2015, TDMA letter dated 18 September 2015, Colorcon letter dated 14 September 2015).
25 In Commission Recommendation of 18 October 2011 on the definition of nanomaterial, 2011/696/EU nanomaterials are defined as follows: ‘Nanomaterial’ means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm.
(E 171) used as a food additive. The measuring methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2011).’

The FEEDAP Panel noted that, as a follow-up to the re-evaluation of E 171 completed by the ANS Panel in 2016, in 2018, the European Commission requested EFSA to assess a proposal for an amendment of the EU specifications for the food additive (E 171) based on the data on particle size and particle size distribution that had been provided by the interested food business operators in response to the first part of the European Commission call for data. The related scientific opinion was adopted by the FAF Panel in June 2019 (EFSA FAF Panel, 2019). In that opinion, the FAF Panel recommended that the EU specifications for E 171 include the parameter of median minimum external dimension by particle number should be higher than 100 nm, measured by electron microscopy, which is equivalent to less than 50% of constituent particles by number with a minimum external dimension below 100 nm (EFSA FAF Panel, 2019).

The FEEDAP Panel considers that the assessments above apply to TiO2 when used as feed additive.

3.1.2. Manufacturing process

3.1.3. Stability and homogeneity

Stability studies are not required for metal oxides. No data on the capacity of homogeneous distribution of the additive in complete feed were submitted.

3.1.4. Conditions of use

TiO2 is intended to be used as a colourant in feedingstuffs for all animal species without a maximum use level or age restriction. For animal species and categories other than dogs and cats, the applicant proposed the restriction to (i) waste products of foodstuffs and (ii) other base substances, with the exception of cereals and manioc flour, denaturated by means of these agents or coloured during technical preparation to ensure the necessary identification during manufacture.

The applicant reported that, with particular reference to the pet food market, typical application rates are in the range 0.2–1%, the maximum level used being 3%.26

3.2. Safety

In support of the safety of the additive, the applicant submitted in the dossier the evaluations performed by JECFA in 1969 (JECFA, 1970), by the Scientific Committee on Food (SCF) in 1975 and 1977 (European Commission, 1975, 1977), by EFSA in 2004 (EFSA, 2005), by the United States Environmental Protection Agency (EPA) in 2005, by the SCCNFP (2000) and by IARC in 2010.

In addition, the European Chemicals Bureau (2000)27 IUCLID4 data set was submitted, together with a full paper on the mortality among workers employed in the titanium dioxide production industry in Europe (Boffetta et al., 2004).

Moreover, the applicant submitted: (i) a literature search on genotoxicity,28 (ii) papers on the use of titanium dioxide as a digestibility marker to support the safety of titanium dioxide in ruminant and non-ruminant animals29 and (iii) a new EOGRT study carried out according to OECD test guidelines (TG) 433 and a 14 days palatability study in rats.30

The FEEDAP Panel noted that, since the time of the submission of the data in the dossier, more recent evaluations on the safety of titanium dioxide were published (EFSA ANS Panel, 2016, 2018;

26 Supplementary information/April 2012/Annex 14.
27 Technical dossier/Section III/Annex III.6.
28 Technical dossier/Supplementary information February 2012. The genotoxicity studies retrieved from the literature search were considered in the assessment of the ANS Panel in 2016 (EFSA ANS Panel, 2016).
29 Technical dossier/Supplementary information February 2012/Annex 2.
30 Technical dossier/Supplementary information April 2021.
EFSA, 2019; EFSA FAF Panel, 2019, 2021; ECHA, RAC, 2017) which have to be taken into consideration for the present assessment.

### 3.2.1. Safety of titanium dioxide

In 2020, the European Commission requested EFSA to reassess the safety of the food additive TiO₂, taking into account all new relevant data available to EFSA since the completion of its re-evaluation of titanium dioxide (E 171) as a food additive in 2016. These include the data generated by a consortium of IBOs in response to the call for data from the European Commission as follow-up of the re-evaluation of E 171 (an EOGRT study carried out according to OECD test guidelines (TG) 433 submitted also for the assessment of the safety of TiO₂ as feed additive) and new data retrieved from the published literature and considered to be in line with the data requirements specified in the 2018 EFSA ‘Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain’ (EFSA Scientific Committee, 2018).

Studies performed with (i) the food additive titanium dioxide (E 171), (ii) titanium dioxide – other than E 171 – containing a fraction of particles < 100 nm or (iii) nano titanium dioxide (TiO₂ NPs) have been evaluated in the FAF opinion for the assessment of E 171 (EFSA FAF Panel, 2021).

The FAF Panel noted that, ‘In mice, E 171 has a low oral systemic availability, probably not greater than 0.5%. In studies in rats with TiO₂ NPs, the oral systemic availability was also low (most probably < 1%) but higher than that of E171 and TiO₂ NPs were detected in blood and tissues. For absorbed TiO₂ particles, half-lives of 200-450 days were estimated by the Panel.’

Based on the data available, the FAF Panel concluded as follows:

Concerning the content of nanoparticles in E 171 the Panel considered that:

- according to the Regulation EU (No) 231/2012 there is currently no limitation for the content of nanoparticles in E 171.
- according to data received from interested business operators, less than 50% of constituent particles in E 171 have a minimum external dimension below 100 nm by number (EFSA FAF Panel, 2019).
- the percentage by number of constituent particles below 30 nm was in the order of 1 percent or less in samples of pristine E 171 or in E 171 extracted from foods analysed after dispersion.
- TiO₂ particles in pristine E 171 likely form large agglomerates. When dispersion procedures are applied, these agglomerates may deagglomerate, resulting in increased numbers of ‘free’ nanoparticles. The extent of agglomeration and number of ‘free’ nanoparticles present may be further affected by the conditions in food and the gastrointestinal tract environment.

Accordingly, the Panel concluded that studies with TiO₂ nanoparticles were relevant in the current risk assessment of E 171. However, studies performed with TiO₂ NPs that predominantly consisted of particles smaller than 30 nm were considered to be of limited relevance.

Concerning absorption and toxicity of TiO₂ particles that are present in E171, the Panel concluded that:

- the absorption of TiO₂ particles is low; however, they can accumulate in the body due to their long half-life;
- studies on general and organ toxicity, including the newly performed EOGRT study with E171, did not indicate adverse effects of E 171 up to a dose of 1,000 mg/kg bw per day. Also, no effects were seen in studies retrieved from the literature with TiO₂ NP > 30 nm up to the highest dose tested of 100 mg/kg bw per day;
- no effects on reproductive and developmental toxicity up to a dose of 1,000 mg/kg bw per day, the highest dose tested, were observed in the EOGRT study with E 171. No other reliable studies were found in the literature addressing these effects with E 171;
- some findings regarding immunotoxicity and inflammation with E 171 as well as neurotoxicity with TiO₂ NPs may be indicative of adverse effects;
- there are indications of the induction of aberrant crypt foci in the colon with E 171;
- no studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO₂ nanoparticles were available;
- combining the available lines of evidence on genotoxicity, TiO₂ particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. No clear
correlation was observed between the physico-chemical properties of TiO₂ particles – such as crystalline form, size of constituent particles, shape and agglomeration state – and the outcome of either in vitro or in vivo genotoxicity assays;

- a concern for genotoxicity of TiO₂ particles that may be present in E171 could not be ruled out;
- several modes of action for the genotoxicity may operate in parallel. The relative contributions of different molecular mechanisms elicited by TiO₂ particles are unknown and there is uncertainty whether a threshold mode of action could be assumed;
- A cut-off value for TiO₂ particle size with respect to genotoxicity could not be identified.

Overall, on the basis of all currently available evidence along with all the uncertainties, in particular the fact that genotoxicity concern could not be ruled out, the Panel concluded that E171 can no longer be considered as safe when used as a food additive.

This conclusion applies to E171 as described in Commission Regulation (EU) No 231/2012 as well as to E171 specified in the EFSA FAF Panel (2019).

The FEEDAP Panel endorses the above conclusions reached by the FAF Panel and considers that they apply to the TiO₂ under assessment as a feed additive.

### 3.2.1.1. Safety for the target species

No studies have been submitted by the applicant to support the safety of TiO₂ for the target species. Considering that (i) the additive is intended to be used in all animal species/categories, (ii) no specific studies are available designed to assess the safety for the target species and (iii) the genotoxicity of the compound cannot be ruled out, the FEEDAP Panel cannot conclude on the safety of TiO₂ for the target species. The assessment of the newly submitted 14-day palatability study in rats does not add any new information that would lead the Panel to reconsider the conclusions above.

### 3.2.1.2. Safety for the consumer

Although it is estimated that the absorption of TiO₂ is limited (EFSA FAF Panel, 2021) (as this compound is used as an inert marker in digestibility studies in animals), the FAF opinion highlighted that particles of TiO₂ can accumulate in the body due to their long half-life. No data on the absorption, distribution, metabolism and excretion of TiO₂ in the target animals is available. In addition, no residue studies in relevant food-producing target animals were submitted by the applicant.

Considering the concerns and the limitations with regard to the toxicity of TiO₂ expressed by the FAF Panel, particularly concerning the genotoxicity potential of the additive and the fact that no information on the potential exposure of consumers to TiO₂ particles in food products from animals fed the additive is available, the FEEDAP Panel cannot conclude on the safety of TiO₂ for the consumer.

### 3.2.1.3. Safety for the user

No studies performed with TiO₂ were provided. The applicant submitted review assessments performed by IUCLID4 in 2000, an opinion of the Scientific Committee on Cosmetic products and non-food products intended for consumers (SSNFP, 2000), and a study from the literature (Boffetta et al., 2004) conducted to assess the risk of lung cancer mortality associated with occupational exposure to TiO₂ (reviewed by the International Agency for Research on Cancer (IARC/WHO, 2010)). The original studies mentioned in the review assessments were not provided. The FEEDAP Panel assessed the information available and summarised the outcome in the following chapters.

**Effect on respiratory system**

One form of the additive showed a high dusting potential (150 g/kg), indicating that exposure of users by inhalation is very likely to occur.

The IUCLID database reports numerous studies on the inhalation toxicity of TiO₂ in rats and a few studies in mice and guinea pigs using air concentrations of up to 1,900 mg/m³ and exposure periods of up to 1 year. In rats, adverse effects (increased lung weight and increased rate of alveolar clearance) were seen at concentrations as low as 10 mg/m³. At higher concentrations, effects included hyperplasia of type-2 pneumocytes, desquamation, bronchiectasis and emphysema. Concentration-
dependent increased numbers of particle-laden macrophages were found in the lung and lymph nodes, and particles were also detected in the liver and the spleen.

The FEEDAP Panel noted that TiO$_2$ has been tested for possible carcinogenicity by inhalation exposure in rats and female mice, by intratracheal administration in hamsters and female rats and mice. These studies have been reviewed by IARC in 2010 (IARC/WHO, 2010). IARC categorised titanium dioxide as possibly carcinogenic to humans (Group 2B), noting that ‘there is sufficient evidence in experimental animals for the carcinogenicity of titanium dioxide’, but that ‘there is inadequate evidence in humans for the carcinogenicity of titanium dioxide’. In 2017, the Committee for Risk Assessment (RAC) of the European Chemical Agency (ECHA) adopted an opinion proposing harmonised classification and labelling (CLH) at EU level of titanium dioxide. In this opinion, it was concluded as follows: ‘Generally, classification for carcinogenicity does not specify a route of exposure. However, the profile of lung carcinogenicity described for TiO$_2$ is specifically linked to the inhalation route of application. Currently, there is no experimental evidence for TiO$_2$ carcinogenicity for the oral or dermal route of application. TiO$_2$ lung carcinogenicity is associated with inhalation of respirable TiO$_2$ particles. Based on the data available today RAC considers it conclusively proven that no other route of exposure causes the carcinogenicity hazard. Correspondingly, RAC proposes to classify TiO$_2$ as a Category 2 carcinogen, with the hazard statement H351 (inhalation)’. These provisions have been put in place by Commission Delegated Regulation (EU) 2020/21735.

**Effect on eyes and skin**

The applicant provided toxicological reviews including summaries of studies performed to demonstrate the effects on eyes and skin of TiO$_2$ (SSNIP, 2000$^{34}$; IUCLID, 2000$^{27,33}$).

The limited information provided on skin irritancy tests in rabbits and humans and of eye irritancy tests in rabbits, and skin sensitisation potential in guinea pigs and humans, would indicate that TiO$_2$ should be considered to be moderately irritant to skin and eyes and unlikely to cause skin sensitisation.

The FEEDAP Panel notes that full reports were not available, and the identity of the test items used in the experiments was not always clearly specified (e.g. TiO$_2$ natural colour, TiO$_2$ solid, TiO$_2$ powder, TiO$_2$ in petrolatum solution), which precludes the direct extrapolation of these conclusions to the additive under assessment.

**Conclusions on safety for the user**

In the absence of studies with the additive under assessment, the Panel cannot conclude on the assessment of the effects of the additive on eyes and skin. TiO$_2$ is potentially carcinogenic to workers if inhaled; the dusting potential of one form of the additive under assessment is very high; therefore, the inhalation of the dust represents a risk for the user.

Since the concern for genotoxicity of TiO$_2$ particles cannot be ruled out, this should be considered as an additional potential concern to users handling the additive.

**3.2.1.4. Safety for the environment**

The applicant submitted a report of the EPA (2005) to support the safety of the additive for the environment. However, the Panel considers that this cannot be used as it does not fulfil the requirements for the assessment of the safety of feed additives for the environment (EFSA, 2008). In addition, the FAF opinion raised concerns on the presence of nanoparticles in the additive (EFSA FAF Panel, 2021), which should be properly addressed when assessing the safety of TiO$_2$ for the environment.

In the absence of adequate data to evaluate the safety of TiO$_2$ for the environment, including the impact of the presence of nanoparticles, the FEEDAP Panel cannot conclude on the safety of TiO$_2$ used as a feed additive for all animal species for the environment.

**3.3. Efficacy**

Where the function requested for feed is the same as that used in food, no further demonstration of efficacy might be necessary (Regulation (EC) No 429/2008)$^{36}$. However, considering the wide variety of feedingstuffs used in complete and complementary feed for all animal species and the uncertainty

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$^{35}$ Commission delegated regulation (EU) 2020/217 of 4 October 2019 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures and correcting that Regulation. OJ L 44 18.2.2020, p. 1.

$^{36}$ OJ L 133, 22.5.2006, p. 1.
which concentration of titanium dioxide would result in a visible effect, a demonstration of dose-effect in a typical complementary feedingstuff was requested.

Samples of standard biscuits were prepared containing wholemeal flour, milk powder and vegetable oil. TiO₂ was added at 0.1% and 1%. The biscuits were baked at 300°C for 1 h and the colour of the samples was measured by reflectance spectrophotometry. By the addition of TiO₂, the ‘L’ value (lightness) increased (from 56.9 to 61.2 and 73.1, respectively). No changes were observed in the ‘b’ value (yellowness) of samples with the addition of 0.1% (from 26.1 to 26.1); the ‘b’ value decreased in samples added with 1% TiO₂ (from 26.1 to 16.8).³⁷

The analytical data already indicate that the colouring effect of supplementing 0.1% TiO₂ to a cereal based biscuit would be marginal, which is confirmed by visual appraisal. There is clear evidence that 1% TiO₂ visibly colours feedstuffs and biscuits of different composition.

The FEEDAP Panel concluded that TiO₂ is efficacious when used at a minimum concentration of 1% in feedstuffs for cats and dogs.

For use in all animal species other than cats and dogs, the applicant proposed it use as by-product of the food industry and not as direct use to colour the feed. As the scope of this use is not the direct use of the additive in feed but a secondary use, the FEEDAP Panel does not consider the need to demonstrate efficacy in feed for all animal species other than cats and dogs.

4. Conclusions

The EFSA FAF Panel concluded that E171 can no longer be considered as safe when used as a food additive. The FEEDAP Panel endorses the conclusions reached by EFSA FAF Panel on the safety of TiO₂ and considers that they also apply to TiO₂ as a feed additive for all animal species.

TiO₂ is absorbed to a low extent; however, particles of TiO₂ can accumulate in the body due to their long half-life. The genotoxicity of TiO₂ particles cannot be ruled out raising potential concerns on the safety of the additive for the target species (especially for long-living animals and reproductive animals), consumers and users. Considering this fact and the absence of specific data related to its use as a feed additive, the Panel cannot conclude on the safety of TiO₂ for the target species, consumers and the environment. Regarding user safety, in the absence of studies with the additive under assessment, the Panel cannot conclude on the assessment of the effects of the additive on eyes and skin. TiO₂ is potentially carcinogenic to workers if inhaled. The concern for genotoxicity of TiO₂ particles cannot be ruled out, this should be considered as an additional potential concern to users handling the additive.

TiO₂ is efficacious in colouring the food for cats and dogs at a minimum content of 1%. The Panel does not consider the need to demonstrate efficacy in feed for all animal species other than cats and dogs.

5. Documentation provided to EFSA/Chronology

| Date       | Event                                                                 |
|------------|-----------------------------------------------------------------------|
| 05/11/2010 | Dossier received by EFSA. Titanium dioxide (rutile and anatase) for all animal species. Submitted by Kronos International, Inc |
| 24/11/2010 | Reception mandate from the European Commission                         |
| 13/04/2011 | Application validated by EFSA – Start of the scientific assessment     |
| 04/07/2011 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: characterisation and efficacy |
| 13/07/2011 | Comments received from Member States                                  |
| 18/08/2011 | Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives |
| 12/10/2011 | Request of supplementary information from the applicant - Scientific assessment re-started |
| 23/11/2011 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: characterisation and safety |
| 10/02/2012 | Reception of supplementary information from the applicant - Scientific assessment re-started |

³⁷ Colour quantification standardised by the Commission International de l’Eclairage. L (lightness, black to white reflectance, 0-100), a (red = positive, green = negative), b (yellow, blue).
Titanium dioxide for all animal species

| Date       | Event                                                                 |
|------------|----------------------------------------------------------------------|
| 17/02/2012 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. **Issues: characterisation and safety** |
| 26/04/2012 | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 18/11/2016 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. **Issue: safety** |
| 07/04/2021 | Reception of supplementary information from the applicant - Scientific assessment re-started |
| 06/05/2021 | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment |

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**Abbreviations**

ACF Aberrant Crypt Foci  
ADI acceptable daily intake  
AFC EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food  
ANS EPSA Scientific Panel on Additives and Nutrient Sources added to Food  
ANSES French Agency for Food, Environmental and Occupational Health & safety  
BW body weight  
CAS Chemical Abstracts Service  
EC European Commission  
ECHA European Chemicals Agency  
EINECS European Inventory of Existing Chemical Substances  
EOGRT extended one-generation reproductive toxicity  
EURL European Union Reference Laboratory  
FAD Food Additive and Flavourings  
FAO Food Agricultural Organization  
FEEDAP EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed  
HBGV health-based guidance value  
JECFA The Joint FAO/WHO Expert Committee on Food Additives  
LOQ limit of quantification  
OECD Organisation for Economic Co-operation and Development  
RAC Committee for Risk Assessment  
SCAN Scientific Committee on Animal Nutrition
SCF  Scientific Committee on Food
WHO  World Health Organization
Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of the Analysis for titanium dioxide

In the current application, authorisation is sought under articles 4(1) and 10(2) for Titanium dioxide in anatase and rutile structure, under the 'sensory additives', functional group 2(a) 'colours', according to the classification system of Annex I of Regulation (EC) No 1831/2003. Authorisation is sought for the use of the feed additive for all animal species and categories. The feed additive is intended to be incorporated directly in feedingstuffs, with no recommended minimum or maximum levels.

The Applicant used X-Ray Diffraction (XRD) to identify the anatase and rutile structure in the feed additive. Furthermore, the Applicant proposed the internationally recognised European Pharmacopoeia method, based on a redox titration with ammonium and cerium nitrate for the determination of Titanium dioxide in the feed additive. Even though no performance characteristics are provided, the EURL recommends for official control the European Pharmacopoeia method (Ph. Eur. 7.0, method 01/2011:0150), for the identification and quantification of Titanium dioxide in the feed additive.

The Applicant did not provide any experimental method or data for the determination of Titanium dioxide in premixtures and feedingstuffs. However, EURL identified several analytical methods to determine Titanium in food and feed, based on sample digestion followed by spectrophotometry or by multi-elemental techniques, such as Inductively Couple Plasma Optical Emission Spectrometry (ICP-OES) or Mass Spectrometry (ICP-MS). The EURL considers these methods suitable for quantification of Titanium in premixtures and feedingstuffs.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.