Fifth draft statement on the safety of Titanium Dioxide (E171) as a Food Additive- Methodology of the COT review

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Methodology of the COT review

20. The EFSA updated opinion (2021) papers and the EFSA opinion on the papers that were considered most relevant were reviewed by the COT with an additional literature search undertaken for the COT to consider relevant literature and opinions published between 2021 and 2023, including the Health Canada report on Titanium Dioxide.

21. A literature search was undertaken. The database Lit-fetch was used to search the following search terms between the dates 2021-01-01 to 2023-04-28. For the first 2 search strings, the numbers in brackets denote (number of hits; number of relevant hits), the 3rd search string just denotes number of hits. An updated search was also carried out for the first 2 search strings for 2023-04-28 to 2024-03-01, but only for in vivo studies. The search terms can be found in Annex B.

22. Paper titles and abstracts were manually sorted, and papers deemed not relevant were disregarded.

23. A summary table of all the studies considered by the COT is available in Annex D

This section will be updated.

Titanium Dioxide

General information

24. Titanium dioxide (TiO_2) is an inorganic compound which exists in nature in different crystalline forms. The anatase and rutile being the two most important for its use as a food additive.

25. The Chemical Abstracts Service (CAS) Registry number for TiO_2 is 13463-67-7 and the European Inventory of Existing Commercial Chemical Substances (EINECS) number is 236-675-5. The Colour Index (C.I.) number is 77891.

26. TiO_2 was an authorised Food Additive (E171) in the EU in accordance with Annex II to Regulation (EC) No 1333/2008 in both anatase and rutile forms (Commission Regulation (EU) No 231/2012) and is currently authorised under GB Food Law (retained EU Regulation No 1333/2008 on food additives).

27. The uses of TiO_2 as a food additive include:

- As a colour to make food more visually appealing
- To give colour to food that would otherwise be colourless
- To restore the original appearance of food.

28. It is found in a wide variety of food items such as pastries, chocolate and sweets, sauces and chewing gum. It is also widely used in cosmetics and medicines (EFSA, 2016).

29. The current assessment of the safety of TiO_2 (E171) as a food additive is being considered at the request of the Food Standards Agency following the recent (2021) review of TiO_2 (E171) by EFSA. This assessment is being conducted jointly by the COT and the COM. The COM have assessed the available data on the genotoxicity of TiO_2 and the full COM statement will be available on their website. The COT previously considered and commented on the EFSA 2016 Opinion on TiO_2, whilst the UK was part of the EU.

30. For the purposes of this evaluation, the COT mainly considered the updated evidence provided in the 2021 EFSA opinion with a focus on the EOGRT study commissioned after the 2016 EFSA review. In this statement, references to ‘The Committee’ will be the COT unless otherwise stated. The COT considered updated evidence including the results of the EOGRT study reviewed by EFSA, and several additional studies from 2015 to 2020.

31. A report by Health Canada, “State of the Science of Titanium Dioxide (TiO_2) as a Food Additive” (2022) had previously been reviewed and commented on by COT Members prior to its publication. Therefore, some of the discussion and conclusions from this document have also been included in the endpoints discussed below.

32. Food Standards Australia New Zealand (FSANZ) have also published a report “Titanium Dioxide as a Food Additive”. Some of the discussions and conclusions from this repot have also been included in the sections discussed below.

Physicochemical Characterisation of food grade TiO_2

33. The characterisation of TiO_2 has been described in detail in EFSA (2016) and in the Health Canada State of the Science Report (2022). This section provides a summary of the TiO_2 characterisation to provide background information for the better understanding of this statement on the safety of TiO_2 as a food additive.

34. TiO_2 is a white powder used as a pigment in various industries and is valued for its high refractive index. Specifically in food, the primary function of TiO_2 is as an opacifier and white pigment. To achieve this function, it is critical that food grade TiO_2 exists as an aggregate of smaller primary particles with a median particle size of 200 – 300 nm, which corresponds to roughly half the wavelength of visible light and provides optimal light scattering, thus producing the desired whitening effect (Winkler et al. 2018).

35. TiO_2 can also be in the form of engineered nano-TiO_2. One form of nano-TiO_2 that is generally sold for catalytic applications and is also widely used in toxicity studies is P25. Food-grade and P25 TiO_2 are engineered products, frequently synthesized from purified titanium precursors, and not milled from bulk scale minerals (Yang et al., 2014). Engineered nano-TiO_2 (e.g., P25, NM-101, NM-102, NM-103, NM-104 and NM-105) has 100% particles less than 100 nm in diameter, they are colourless and therefore would be unsuitable for use as a pigment/opacifier in food and pharmaceutical applications (Farrell and Magnuson, 2017).

36. Pure TiO2 assembles in several crystal structures although only anatase, rutile or a mixture of the two are used in foods. For many applications, including cosmetics and some therapeutic products, surface coatings are applied to TiO2 particles that alter their physicochemical properties. Therefore, toxicity and ADME studies using these materials may not be relevant to TiO2 used as a food additive, which normally undergoes no surface treatment and is uncoated (EFSA 2016). Due to differences in the manufacturing processes food-grade TiO2 differs in surface composition compared to other TiO2 materials, such as TiO2-NPs. The surface of food-grade TiO2 particles is covered by superficial phosphate groups, while materials manufactured with alternative methods may have different surface functional groups (e.g., hydroxyl groups) (Dudefoi, et al., 2017a; Yang et al., 2014). The surface properties of TiO2 materials have a significant impact on their behaviour in various environments, including biological media. Therefore, TiO2 materials with surface properties that differ from food-grade TiO2 may not be considered relevant models when studying the fate of dietary TiO2 (Dudefoi et al. 2017a).

37. Suspended TiO2 particles tend to aggregate/agglomerate to form larger clusters, although a majority of the individual particles may display a primary diameter 100 nm. The term “aggregate” designates an assembly of particles held together by covalent or metallic bonds. Instead, “agglomerates” result from weak forces like van der Waals interactions, hydrogen bonding, electrostatic attractions or adhesion by surface tensions. Due to this aggregation and agglomeration it is important not to equate the nanoparticle fraction measured by number with the same value by mass (Winkler et al., 2018).

38. However, despite having a mean particle size in the desired range (200 - 300 nm), primary particles in food-grade TiO2 form a broad size distribution that invariably contains particles below 100 nm, i.e. nanomaterial. A number of studies have measured particle size in food grade TiO2 or E171 and found a range of 17 – 36% of TiO2 NPs with a diameter less than 100 nm (Verleysen et al. 2020 and 2021; Yang et al, 2014; Dudefoi et al. 2017; Weir et al., 2012). The percentage by number of particles with a diameter less than 30 nm is on the order of 1% or less (EFSA 2021a).

39. When calculating exposure to TiO2 NPs the equivalent mass of NPs is more relevant than particle number. Several studies reviewed by Ropers et al estimated the mass (weight %) of nanoparticles present in E171 across a range from 0.31 to 12.5% (EFSA, 2016; Bachler et al., 2014; Rompleberg et al., 2016; and Dudefoi et al., 2017). This variation explains some differences in the

estimated exposures to TiO2 nanoparticles in the literature including between the study by Rompelberg et al. who used a value of 0.31% of NPs and the evaluation of EFSA who used a weight ratio of 3.2%. (Ropers et al., 2017).

40. Since E171 is a particulate material containing a fraction of nanoparticles, and toxicology studies mainly focus on the systemic absorption of this nanofraction after ingestion, EFSA noted the need for more data; for example, information related to the particle size distribution of the titanium dioxide, when used as a food additive. Moreover, it was noted that the EU specifications for E171 should also include full characterisation of the particle size distribution of the materials as well as indication on the percentage (in number and by mass) of the particles in the nanoscale together with the information on the analytical methods/techniques used for detection and quantification of the nanosized particles. In this respect, the European Commission called in early 2017 for data addressing those EFSA recommendations. (Verleysen et al., 2020; Geiss et al., 2020).