Fifth draft statement on the safety of Titanium Dioxide (E171) as a Food Additive- Executive Summary

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Executive Summary

Introduction

Prior to August 7th 2022, titanium dioxide (TiO2) was an authorised Food Additive (E171) in the EU. It currently remains authorised in the UK. It is used in food as a colour (white pigment) to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food. It is commonly used in products such as bakery products, soups, broths, sauces, salad dressings, savoury based sandwich spreads, processed nuts, confectionary, chewing gum, food supplements and cake icing.

Titanium dioxide has been the subject of multiple safety evaluations including three recent evaluations by the European Food Safety Authority (EFSA) in 2016, 2019 and 2021.

In their most recent Opinion (2021), EFSA considered that some findings regarding immunotoxicity, inflammation and neurotoxicity with respect to TiO2 nanoparticles may be indicative of adverse effects. On the basis of the currently available evidence and the uncertainties, in particular a concern regarding genotoxicity which could not be resolved, the EFSA Panel concluded that E171 could no longer be considered as safe when used as a food additive.

Following this, in 2021 the COT published an interim position on titanium dioxide (COT, 2021) capturing the outcomes of discussions and outlining the next steps. A review has now been undertaken by the COT, which includes the conclusions on mutagenicity from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), to assess the safety of TiO2 as a food additive. This review is summarised below.

Since the EFSA and COT publications in 2021, reviews of TiO2 have also been carried out by Health Canada (2022), Food Standards Australia New Zealand (FSANZ) (2022) and most recently by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO/WHO, 2023).

Characterisation and ADME considerations

Specifically in food, the primary function of TiO2 is as an opacifier and white pigment. To achieve this function, it is critical that food grade TiO2 (E171) exists as an aggregate of smaller primary particles with a median particle size of 200 – 300 nm. Engineered nano-TiO2 have all (100%) of their particles less than 100 nm in diameter and are colourless and would therefore be unsuitable for use as a pigment in food applications.

The COT concluded that the physical form of TiO2 will affect the absorption and distribution of TiO2. The wide variance of test materials used (nano, micro and mixtures of nano and micro) was noted. Due to this large variability, as well as the potential impact of the matrix of administration, the Committee could not ascribe a percentage for the absorption of TiO2. **However, the Committee considered that absorption of food grade TiO2 (E171) is low, based on the available evidence.**

The COT has reviewed toxicological studies which have been conducted using any form of TiO2, including nanoparticles, but its conclusions are primarily based on those which have used food grade TiO2 (E171).

Review of the Extended One Generation Reproductive Toxicity (EOGRT)

The COT reviewed the EOGRT provided to the Food Standards Agency (FSA) by the Titanium Dioxide Manufacturers Association (TDMA) (LPT, 2020) as part of their safety assessment of TiO2. This study was carried out in response to a conclusion by EFSA regarding the uncertainty around TiO2 (E171) and reproductive and developmental toxicity. The COT agreed that the EOGRT study was well conducted.

Overall, there was no evidence of reproductive or developmental toxicity up to and including the highest dose tested (1000 mg/kg/day).

Review of toxicity for endpoints identified by the COT

The following endpoints were reviewed initially by the COT and then in more detail by a sub-group of COT Members: Aberrant crypt foci (ACF) (as a potential marker for carcinogenicity), inflammation and immunotoxicity, reproductive and developmental toxicity and neurotoxicity. The COM reviewed the genotoxicity data.

The Committee gave greater weight to studies in which TiO2 was administered orally, particularly in the diet, as they were considered to be the most relevant for human exposure to TiO2 through consumption of food.

Aberrant Crypt Foci (ACF)

The Committee considered that although small numbers of ACF were observed in some animals exposed to TiO2 alone, these could not necessarily be attributed to TiO2, as ACF were also present in control groups without exposure to TiO2 in other studies (e.g. the EOGRT). Additionally, none of the studies distinguished between hyperplastic or dysplastic ACF in any groups of control or treated animals. The Committee concluded that there was no conclusive evidence that TiO2 induced ACF and no evidence to support progression to proliferative lesions in the colon.

Inflammation and immunotoxicity

The COT sub-group noted that only three studies, including the EOGRT, (Riedle et al., 2020; Blevins et al., 2019; and LPT, 2020) used E171 TiO2 administered in the diet. These studies showed no adverse effects resulting in inflammation or immunotoxicity.

Five studies using food grade TiO2 administered to rats or mice in water (Talamini et al., 2019; Pinget et al., 2020; Bettini et al., 2017; Han et al., 2020; and Mortensen et al., 2021) were considered by the COT. In several studies, differential cytokine and host defence gene expression was observed but was neither consistent across studies, nor ubiquitous in terms of pathway activation, making interpretation or formulation of conclusive statements challenging.

Other potential immunotoxic effects have been reported that are distinct from the induction or modulation of inflammation. These include, but are not limited to: induction of immune cell mediated inflammation in the gut, including in Peyer’s patches, as well as in the spleen and via peripheral blood mononuclear cells; effects on broader host defence mechanisms, including antimicrobial peptides; effects in the gut microbiota; effects on dendritic cell populations in the gut;

effects on T cell subpopulations and macrophage populations in the gut; effects on plasma lymphocyte counts and proportions; and disruption of the mucus layer in the gut.

Overall, however, there is insufficient evidence of sufficient quality to conclude that food grade TiO2 is of concern with regards to immunotoxicity and inflammation.

Reproductive and Developmental Toxicity

The COT considered the EOGRT report to be detailed and that the study was carried out according to the relevant scientific guidelines with no obvious deficiencies. It was noted that there were some minor effects observed in the study including focal effects of the testes and epididymides and a difference in weight of the right testes. However, the COT agreed with the authors' conclusions that these changes were spontaneous and not of toxicological relevance.

Overall, therefore, no adverse effects on reproductive and developmental toxicity were observed, up to the highest dose tested. The COT noted that the low absorption of TiO2 may have contributed to the NOAEL (1,000 mg/kg bw per day) established in the EOGRT study.

Data from peer reviewed literature were inconclusive. The best overall quality additional studies were determined by the COT to be the studies by Warheit, Boatman and Brown, 2015, and & Lee et al., 2019. The COT concluded that there was no strong evidence that TiO2 is reprotoxic and that the NOAELs in these additional studies are consistent with that from the EOGRT study.

Neurotoxicity

Overall, there is no new evidence on neurotoxicity to justify a change to the COT position on this endpoint as stated in its 2021 interim position paper. The findings of the studies on neurotoxicity were considered inconsistent by the COT. It was noted that the EOGRT study did not report any effects and that most of the other studies on this endpoint used nanomaterials.

It was noted that in the EOGRT study the routine regulatory histopathology tests would have been less sensitive than the specific neuro-histopathology tests performed in some other studies. It should be recognised that this qualified COT opinion on neurotoxicity is more conservative than that of Health Canada who considered the EOGRT to be sufficiently sensitive and relevant to conclude on the

lack of neurotoxicity potential of food grade TiO2.

Impact of Nanoparticles

The Committee concluded that there is uncertainty over the effect that TiO2 nanoparticles have on toxicity. The Committee therefore considered that if animals and/or humans are exposed to test substances which contain higher levels of nanoparticles than normally found in food-grade TiO2, that could change the toxicological profile and potentially the risk, but it is unclear by how much or in what way.

The COT considered that the data from the relevant studies available indicated that TiO2 did not induce ACF, nor were there significant effects from studies that assessed inflammation and immunotoxicity, reproductive and developmental toxicity, and neurotoxicity. On balance, the Committee considered that the NOAEL of 1,000 mg/kg bw per day was robust.

Genotoxicity review of TiO2 review by the COM

The COM reviewed a number of studies to assess the genotoxicity of TiO2.

The COM stated that a definitive assessment of the safety of food grade E171 was difficult when there were no high-quality OECD-compliant studies that adequately incorporate the study design considerations and characterisation of the nanoparticulate fraction present in E171. It was also noted that there is a lack of high-quality data sets that are OECD compliant, and this led to conflicting data and uncertainty in the risk assessment for TiO2. (COM, 2024b. Not yet published).

The COM opinion is that there is little evidence that TiO2 micro-sized or nanoparticles are genotoxic in vitro or in vivo based on data from well conducted studies. There is also a lack of replication of study outcomes using the same nanoparticle in different labs. (COM, 2024a. Not yet published).

Overall, however, the COM concluded that there was little evidence in the literature to suggest that there was a health concern related to genotoxicity induction by TiO2, particularly via the oral route and especially the micro sized TiO2 fraction (most studies in the literature used nano-sized material) (COM 2024b. Not yet published).

The COT agreed with the conclusions of the COM.

Derivation of a Health-Based Guidance Value (HBGV)

The Committee concluded that on the basis of the available evidence, 1,000 mg/kg bw/day was a robust Point of Departure (POD). This was based on the EOGRT study findings as well as studies by Warheit et al., 2015b and Lee et al., 2019 that reported no effects up to the same dose. There was variability noted in the other studies, but nothing which would alter the proposed POD for food grade TiO2 (E171).

A standard uncertainty factor of 100 (10 for inter species variability and 10 for individual variability) was agreed by Members and applied to the POD which results in a HBGV of 10 mg/kg bw/day. There is likely to be additional conservatism in the application of this uncertainty factor to the NOAEL of E171 due to the low absorption of TiO2 and because there is no metabolism of TiO2 particles.