Review of EFSA Opinion on the Reproductive Toxicity of Titanium Dioxide as a Food Additive

Introduction - Review of EFSA Opinion

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This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

1. Titanium dioxide is an authorised Food Additive (E171) in the EU and under UK Food Law it is used in food as a colour to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food. Titanium dioxide has been the subject of multiple safety evaluations.

2016 EFSA evaluation

2. In 2016, EFSA evaluated the safety of E171 and determined that it consisted mainly of micro-sized titanium dioxide particles, with a nano-sized (< 100 nm) fraction less than 3.2% by mass. Uncertainties around the identity and characterisation of E171 were highlighted, noting that no limits for the particle size of E171 were set. Similarly, with regard to toxicity, uncertainties around the identity and characterisation of E171 were also highlighted.

2019 EFSA re-evaluation

3. Specifications of E171 titanium dioxide were reviewed again in 2019. Based on the fraction of nanoparticles present in E171, it was determined that the food additive fell under the scope of the EFSA guidance on nanotechnology for “a material that is not engineered as nanomaterial but contains a fraction of particles, less than 50% in the number–size distribution, with one or more external dimensions in the size range 1–100 nm”. Thus, a recommendation for re-assessment of the safety of titanium dioxide was proposed and as a result a new EFSA Opinion was published in May 2021.

4. In this opinion, the EFSA Panel considered that some findings regarding immunotoxicity and inflammation with E171 as well as neurotoxicity with TiO2 nanoparticles may be indicative of adverse effects. They also considered that there are indications of the induction of aberrant crypt foci (ACF) with E171 and that no studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO2 nanoparticles were available. Overall, on the basis of the currently available evidence along with all the uncertainties, in particular the fact that the concern regarding genotoxicity could not be resolved, the EFSA Panel concluded that E171 can no longer be considered as safe when used as a food additive.

COT and COM comments on the EFSA re-evaluation

5. Following the publication of the EFSA Opinion, the UK’s COT and Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) considered the EFSA findings, and an interim position paper was published (COT, 2022). Overall, it was observed that the percentage of absorption was reported to be higher in the 2021 opinion than in the previous evaluation (EFSA, 2016), based on the same dataset. Additionally, the COT also questioned the conclusions with regards to the ability of TiO2 to induce ACF.

Furthermore, the findings of the studies on neurotoxicity were considered inconsistent by the COT. It was noted that the Extended One Generation Reproduction Toxicity (EOGRT) study did not report any effects and that most of the other studies on this endpoint were of nanomaterials. They considered that had the test material in the EOGRT study been dispersed and stabilised in the nano form, some effects could possibly have been observed. The COT, as previously, questioned the relevance of such dispersion to real world use. Members noted that the histopathology tests performed for the EOGRT study were standard and were not sensitive enough in comparison to other studies on this endpoint that performed specific neuro-histopathology testing.

6. With regards to genotoxicity, the COT were in agreement with the COM's view and further noted the large discrepancy between the underlying dataset and the conclusions drawn by EFSA. They further highlighted the inconsistencies between the outcomes of the 2020 SCCS Opinion discussed in detail in paragraph 45, where it was determined that the genotoxic effects of titanium dioxide manifest either via a thresholded or secondary mechanism, and the outcomes of the 2021 EFSA evaluation, where the EFSA Food Additives and Flavourings (FAF) Panel concluded that it was unclear if a threshold mode of action could be assumed. Regarding the genotoxicity of the nanoparticles, the COT considered that this could either be a concentration effect leading to oxidative damage or a stress effect, however, it was unclear as the results in different cell lines were equivocal and inconsistent. It was also noted that in some tests titanium dioxide had shown less reactivity.

7. On balance, the Committee considered that the weight of evidence did not support the conclusions drawn by EFSA. The COT also agreed with the comments of the COM with regards to risk communication that "As it stands the conclusion is highly risk adverse based on the weak evidence available, and it might create unnecessary concern to the public." The COT suggested that the COM should independently review the database on genotoxicity and apply their Guidance on determining thresholds. When considering whether they agreed with EFSA's conclusion that no differentiation could be made with regards to size/form of titanium dioxide and different aspects of toxicity, the COT took the opinion that nanoparticles were driving the toxicity. COM are currently in the pre-draft stages of re-assessing the genotoxicity of TiO2.

8. The full TiO2 interim position paper is available on the committees website. Considering the outputs of the discussions from the COT and the COM, the FSA has decided to launch their own review of the safety of titanium dioxide

as a food additive.

Aim of this paper

9. The current paper presents the data from the EOGRT study as well as information from the literature; a second paper will be presented to the Committee at a future meeting. The aim of these papers is to present the data underlying the main changes in the 2021 Opinion, conclusions on toxicokinetic and absorption data, reproductive toxicity and ACF, developmental immunotoxicity and neurotoxicity from the recent EOGRT study and a revised literature search covering the period from 2015-2021, which the COT questioned in their review of the newest EFSA Opinion and enable the COT to independently assess the safety of titanium dioxide.