# Completed Work

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26. 2024 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
27. Declaration of members interests during the period of this report - COC 2024

## Review of genotoxicity of titanium dioxide – summary of *in vitro* and *in vivo* data

2.1 In 2021, the European Food Safety Authority (EFSA) published an opinion concluding that food additive titanium dioxide (E171) could no longer be considered to be safe for use in food. The Food Standard Agency (FSA) initiated a review of the EFSA Opinion. Identifying a number of concerns, it was decided that the Opinion should be referred to the UK's Scientific Advisory Committees for independent expert review. The EFSA opinion was presented to the COM and COT (MUT/2021/03 and TOX/2021/36), and the committees considered that the conclusions were not robust, and it was decided that the UK should undertake an independent evaluation.

2.2 FSA asked COM to initiate an independent evaluation of the genotoxicity data of titanium dioxide specifically as a food additive.

2.3 In October 2021, paper MUT/2021/12 was presented to COM, summarizing the available studies on the genotoxicity of titanium dioxide. However, members concluded that it was not possible to evaluate its genotoxicity at that stage. As a preliminary step, the COM recommended a sifting approach to identify high-quality studies before conducting a full evaluation. A subgroup of COM was tasked with evaluating the evidence. The subgroup established criteria and methodology for the selection of studies.

2.4 In June 2022 meeting, paper MUT/2022/05 introduced the agreed methodology for systematically sifting the papers and evaluation of the quality of the genotoxicity studies and evaluating data on nanomaterials. A subgroup of the COM later refined this approach, developing a proforma which considered two levels, namely, whether the characteristics of the test material had been sufficiently described (e.g., micro or nano sized particles) and the quality and reliability of how the genotoxicity studies had been conducted.

2.5 By October 2023, a 3-tiered screening and selection approach was presented by the subgroup to evaluate the publicly available literatures and assigned a quality rating based on its robustness (MUT/2023/07 and

MUT/2023/08). It was agreed that revised draft papers would be prepared by incorporating members opinions and the subgroup aimed to finalize the opinion by early 2024.

2.6 At the February 2024 meeting, the final assessment of *in vitro* and *in vivo* data was reviewed (MUT/2024/01 and MUT/2024/02).

2.7 Regarding the in vitro studies, the COM concluded that overall, there is little evidence that titanium dioxide nanoparticles are genotoxic in vitro, with the limited number of positive studies all reporting no dose-response effects. There was also a lack of replication of study outcomes using the same nanoparticle in different labs. With regards to the titanium dioxide food grade additive E171 specifically, COM commented that: ‘currently a definitive assessment of the safety of E171 is difficult when there are no high-quality OECD-compliant studies that adequately incorporate the study design considerations and characterisation of the nanoparticulate fraction present in E171. The studies identified in this report were not representative of E171, where the fraction of nanoparticulate is <50% and according to the recent "Guidance on the implementation of the Commission Recommendation 2022/C 229/01 on the definition of nanomaterial" ( https://data.europa.eu/doi/10.2760/143118), E171 would not fall under the definition of a NM, hence GLP studies with E171 would be required to definitively assess the hazard.

2.8 Regarding the in vivo studies, the COM concluded that overall, there is little evidence in the literature to suggest that there is a health concern related to genotoxicity induction by titanium dioxide, particularly via the oral route of exposure and especially the micro sized titanium dioxide fraction (most studies used the nano-sized material). With regards to E171 specifically, COM comments that: ‘currently a definitive assessment of the safety of food grade E171 is difficult when there are no high-quality OECD-compliant studies that adequately incorporate the study design considerations and characterisation of the nanoparticulate fraction present in E171. COM also noted that there is a dearth of high-quality data sets that are OECD compliant, and this has led to a lot of conflicting data and uncertainty in the risk assessment for titanium dioxide.

2.9 In October 2024, the COT published a statement on the safety of titanium dioxide (E171) as a food additive, included the conclusions on genotoxicity from COM. The COM concluded that there was a little evidence in the literature to suggest that titanium dioxide posed a genotoxicity risk, especially via the oral route. Notably, most studies analysed focused on nano-sized titanium dioxide, whereas food-grade titanium dioxide (E171) is primarily micro-sized.

Hence, any genotoxicity risk from dietary food grade titanium dioxide (E171) was considered to be low.