MUT/MIN/2024/01

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Minutes of the meeting held at 10.30 on 29th February 2024 at UKHSA, 10 South Colonnade, London, E14 and via MS Teams.

Present:

Chairman:	Professor G Jenkins
Members:	Mr A Bhagwat Dr C Beevers Dr A Doherty (Co-opted member) Dr P Fowler Dr N Goldsmith (Associate member) Dr G Johnson Professor D Harrison (Ex officio) Professor S Doak (Co-opted member) Ms J Kenny Dr A Povey Mrs M Wang
Secretariat:	Dr O Sepai (UKHSA Scientific Secretary) Mr S Robjohns (UKHSA Secretariat) Dr N Raja (UKHSA Secretariat) Dr C Mulholland (FSA Secretariat) Dr C Potter (FSA Secretariat) Mr T Fraser (UKHSA)
Secretariat Support:	Dr R Bevan (IEH Consulting) Dr Sarah Bull (IEH) Dr A Bell (IEH)
Assessors:	Krystle Boss (FSS)
Observers:	Kerrie Webster (HSE) Gopika Chettuvatty (UKHSA) Robert Foster (Lhasa science)

ITEM 1: WELCOME AND APOLOGIES FOR ABSENCE

1. The Chair welcomed the COM members, assessors and secretariat. Three new members have been appointed to the committee. Dr Ann Doherty, formerly serving as a co-opted member has now been appointed as a new member. The other two new members would be, Dr Robert Foster (Lhasa) and Dr Rob Smith (LabCorp) following the expected finalisation of relevant paperwork. Apologies were received from Mr Paul Rawlison, Dr Ian Martin and Dr Lata Koshy.

ITEM 2: ANNOUNCEMENTS

2. Members were requested to declare any interests before the discussion of any items.

3. The Chair informed the COM that there is a vacancy for associate member position. All the members and secretariat were requested to use their networks to inform people who are interested in this opportunity. Individuals who work in fields related to genetic toxicology and DNA mutation are preferred. There are no strict criteria regarding age or years post-PhD. The associate member position offers young scientists an opportunity to gain experience by attending meetings and understanding the workings of the COM, with a long-term goal of potentially becoming full members once they have gained sufficient experience. Interested individuals can submit their curriculum vitae to the committee within the next couple of months. The committee will review the applications and conduct interviews, if necessary, with the aim of finalizing the selection by 22nd June 2024.

4. The Chair informed that this was Professor Shareen Doak's last meeting, after 10 years on COM, and thanked her for all her contributions over the years.

ITEM 3: MINUTES OF THE MEETING HELD ON 12th OCTOBER 2023 (MUT/MIN/2023/03)

5. The minutes of the COM meeting held on the 12th of October 2023 were agreed.

ITEM 4: MATTERS ARISING

6. The Chair highlighted the establishment of the new COM QSAR subgroup, chaired by Dr Paul Fowler. Dr Fowler provided an overview of the subgroup's first meeting, emphasizing the evolving scope of their work. In the upcoming COM meeting agenda, there would be a discussion expected on this subgroup and its progress.

7. The FSA provided an update regarding the ongoing COT review of titanium dioxide. The current draft version was undergoing review. Based on the COM's conclusion on the genotoxic potential of titanium dioxide, the characterization section would be drafted. The next COT meeting was scheduled for the 26th of March, where the aim was to finalize the papers and

characterization details. The FSA emphasized that the meeting was anticipated to serve as a sign-off stage, with minimal changes expected thereafter.

ITEM 5: REVIEW OF GENOTOXICITY OF TITANIUM DIOXIDE

A) SUMMARY OF *IN VITRO* DATA (MUT/2024/01)

8. Interests were declared by Dr Carol Beevers (Corteva), Dr Paul Fowler (Fstox Consulting) and Dr George Johnson (Swansea University Medical School) for this item. Dr Fowler and Dr Beevers declared that they had been paid by the Titanium Dioxide Manufacturers Association (TDMA) and whilst Dr Beevers was no longer paid by the TDMA she did provide voluntary advice to them. Both cases were considered to be a specific interest. Dr Fowler and Dr Beevers were permitted to take part in the COM discussion of this item as they had had no direct involvement in the selection of studies and drafting of the COM papers (MUT/2024/01 and MUT/2024/02) on titanium dioxide. Dr George Johnson also declared that he had chaired a Health and Environmental Sciences Institute (HESI) subgroup on titanium dioxide and partially involved in the GTTC, this was not considered to be a conflict. It was also considered that although titanium dioxide is present in many products, such as pharmaceuticals, this did not exclude members associated with manufacturers of such products from taking part in the discussion.

9. Following the publication of the opinion on titanium dioxide (TiO2) by the European Food Safety Authority (EFSA) entitled ‘Safety assessment of titanium dioxide (E171) as a food additive’ (EFSA, 2021), the COM has been asked by the COT to provide an opinion on its genotoxicity. A subgroup of COM members was formed to evaluate publicly available literature using a 3-tiered screening and selection approach, developed by the subgroup for the process, which was discussed at the COM meeting in October 2023 (MUT/2023/07 for *in vitro* studies and MUT/2023/08 for *in vivo* studies).

10. With regards to the *in vitro* studies identified, five were assessed to be acceptable quality (labelled as ‘green’) and eight were considered to have some suboptimal aspects (labelled as ‘amber’). Members discussed the green papers presented in MUT/2024/01 and a number of points of clarification were suggested to be added. It was recommended that the green studies by Di Bucchianico *et al.* (2017) and Li *et al.* (2017) be re-evaluated by the subgroup as potential amber papers before finalising the paper, however it was considered that this would not change the overall COM opinion. Members were asked to forward any further comments on the amber papers to the Secretariat.

11. Overall, based on findings from both green and amber studies, the COM opinion was proposed as: ‘overall, there is little evidence that TiO_2 nanoparticles are genotoxic *in vitro*, with the limited number of positive studies all reporting no dose-response effects with significant effects being observed at the lowest doses used. There was also a lack of replication of study outcomes using the same nanoparticle in different labs.

12. 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. The studies identified in this report are 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 we need GLP studies with E171 to definitively assess the hazard.

13. The final COM opinion would be drafted as a summary statement, including the clarifications identified during discussions, and sent for comment to members.

ITEM 6: REVIEW OF GENOTOXICITY OF TITANIUM DIOXIDE (MUT/2023/02)

A) SUMMARY OF *IN VIVO* DATA (MUT/2023/02)

14. Interests were declared for this item as for paper MUT/2024/01.

15. Methodological aspects for the *in vivo* data were as described for the in vitro studies (MUT/2024/01). The 3-tiered screening and selection approach identified two green and three amber rated studies, as detailed in the paper (MUT/2024/02). Members discussed the green studies presented and a number of points of clarification were suggested to be added.

16. Overall, based on findings from both green and amber studies, the COM opinion was proposed as: ‘overall, we conclude that there is little evidence in the literature to suggest that there is a health concern related to genotoxicity induction by TiO2, particularly via the oral route and especially the micro sized TiO2 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. We also note 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 TiO2’.

17. Members asked for some editorial changes to be made to the opinion wording in the final COM summary statement, based on the clarifications identified during discussions, and sent for comment to members.

18. In light of the very small number of *in vivo* studies identified in the initial search and the knowledge that an OECD-compliant *in vivo* study had been recently published, which may contradict the later part of the COM opinion, it was agreed that a new literature search be carried out to cover the period from the end of the previous search to the present date. It was anticipated that the number of *in vivo* studies identified was likely to be minimal but should be used to update paper MUT/2024/02.

ITEM 7: OECD UPDATES

19. Members were informed that United Kingdom, along with several other countries, would submit a Standard Project Submission Form (SPSF) to the OECD to propose adaptations to the test guideline TG487 (*in vitro* micronucleus assay). These adaptations would aim to include updates to the considerations necessary for evaluating nanomaterials. An independent interlaboratory trial is required to achieve this, which is the primary focus of the SPSF project. The trial would aim to provide the necessary data and evidence to facilitate the adaptation of TG487 for nanomaterials. The proposal is scheduled to be presented at the April OECD meeting, primarily for sign-off. The project is anticipated to commence in early summer.

ITEM 8: AOB

20. The FSA informed the COM that the Joint Expert Group for Additives, Enzymes, and Other Regulated Products (AEJEG) had concluded the second round of evaluation for the smoke flavourings dossiers submitted. However, it was noted that certain systemic toxicity studies were still pending. Following the completion of AEJEG's evaluation, the COM would likely be requested to comment on the genotoxicity aspects associated with smoke flavourings. One member offered to provide an update from the upcoming joint meeting of the Committee on Toxicity (COT), Committee on Mutagenicity (COM), and the Joint Expert Group for Additives, Enzymes, and Other Regulated Products (JEG) on smoke flavourings.

21. The COM was also informed of upcoming vacancies for five members for Committee on Carcinogenicity (COC), and COM members were encouraged to spread the word to anyone interested in applying.

22. Updates were provided on recent discussions regarding genotoxicity assessments, including the possibility of an OECD document defining approaches for genotoxicity weight of evidence assessments. EFSA's response to questions posed by Professor David Kirkland could be shared following the publication of the technical report titled “Harmonised approach for reporting reliability and relevance of genotoxicity studies”. Discrepancies between OECD guidance and EFSA's approach were noted, particularly regarding the relevance of *in vivo* and *in vitro* assays. Differences in EFSA's approach were highlighted, leading to discussion on the need for a harmonized approach to genotoxicity weight of evidence assessments.

23. Updates were also provided on various discussions held at the recent German Federal Institute for Risk Assessment (BfR) meeting, which included representatives from regulatory bodies such as EFSA, ECHA, the EU, Health Canada, as well as scientists, industry professionals, and academics. Topics covered included cancer data in the presence of genotoxicity, genotoxicity data in the absence of cancer data, and the potential development of an OECD-defined approach to move beyond hazard characterization towards a risk assessment framework. Other discussions centered around *in vitro* data, new approaches, and the formation of a new group to assess food contact materials. Further updates could be shared with the COM as they become available.

ITEM 9: DATE OF NEXT MEETING

24. Date of next meeting – 20th June 2024.