MUT/MIN/2022/02

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

Minutes of the meeting held at 10.30 on 9th June 2022 at UKHSA, RCE, Harwell Campus, Chilton, Didcot, Oxfordshire OX11 0RQ and via MS Teams.

Present:

Chairman:	Professor G Jenkins
Members:	Mr A Bhagwat Dr C Beevers Dr P Fowler Dr G Johnson Professor D Harrison (Ex officio) Professor S Doak Ms J Kenny Dr A Povey Mrs M Wang
Secretariat:	Dr O Sepai (UKHSA Scientific Secretary) Mr S Robjohns (UKHSA Secretariat) Ms B Gadeberg (UKHSA Secretariat) Ms C Mulholland (FSA Secretariat) Ms C Potter (FSA Secretariat) Ms C Tsoulli (FSA) Dr B Doer (FSA)
Secretariat Support:	Dr R Bevan (IEH Consulting)
Assessors:	Ms F Fernandez (VMD) Ms F Hill (BEIS) Ms Jo Little (HSE)
In attendance	Dr J O'Brien (Food Observatory)

52
53

ITEM 1: WELCOME AND APOLOGIES FOR ABSENCE

1. The Chair welcomed the COM members, assessors and secretariat. The Chair also welcomed Dr Ruth Bevan from IEH Consulting providing support to the COM secretariat. Apologies were received from Dr D Gott (FSA secretariat), Dr I Martin (Environment Agency), Jackie McElveny (?) and Liz Lawton (?).

ITEM 2: ANNOUNCEMENTS

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

3. The Chair informed the COM that Dr C Beevers and Dr A Povey had been reappointed as COM members for a further three years.

4. A difficulty in recruiting new members was noted. The Food Standards Agency suggested a longer-term solution might be the creation of associate members. Earlier career scientists could apply to become associate members and thereby gain experience in attending meetings and learn how the COM worked with a longer-term view of being a full member once greater experience had been gained. The introduction of associate members may also help improve the diversity of the COM. Members supported this suggestion and considered it would also help with succession planning and training and development.

5. Members were informed that the COM guidance statements on nanomaterial testing, 3D models and germ cell mutagens had been published on the COM website.

ITEM 3: MINUTES OF THE MEETING HELD ON 1st MARCH 2022 (MUT/MIN/2022/01)

6. The minutes of the COM meeting held on the 1st of March 2022 were agreed subject to minor typographical amendments.

ITEM 4: MINUTES OF THE JOINT COM/COC MEETING HELD ON 2ND MARCH 2022 (MUT/CC/MIN/2022/01)

7. The minutes of the joint COC and COM meeting held on the 2nd of March 2022 were also agreed subject to minor typographical amendments.

ITEM 5: MATTERS ARISING

8. The COM was informed that the development of a Guidance document on Quantitative Structure-Activity Relationship (QSAR) models had been paused for now. This may be combined with the development of advice on the assessment of the mutagenicity of mixtures and the impurities they may contain. Regarding toxicogenomics, members were also informed that an upcoming UKEMS meeting in July 2022 would include this topic and that there would likely be other meetings in the near future that would cover toxicogenomics, genomic

analysis and next generation sequencing. Attendance at such meetings by COM members would be a good way to help monitor this evolving field.

ITEM 6: DRAFT DOCUMENT ON HOW THE COMMITTEES EVALUATE THE RELEVANCE AND RELIABILITY OF DATA WHEN ASSESSING A CHEMICAL OF CONCERN (MUT/2022/04)

9. At the March 2022 meeting, COM considered a draft document outlining the Committee evaluation process focussing on the relevance and reliability of data written specifically to inform the lay person (MUT/2022/03). This document had evolved from a scoping paper on the topic of 'biological relevance and statistical significance', presented to the Joint COC/COM meeting in November 2020 (CC/MUT/2020/03) also attended by some COT members, which outlined some of the more relevant and significant work that has been published on this issue in recent years. During discussions it was agreed that two documents should be progressed. The first document should be aimed at the lay audience about the process used by the Committees to evaluate evidence and reach conclusions and a second document aimed at a more informed audience on statistical significance testing and consideration of biological relevance.

10. Paper MUT/2022/04 presented an updated version of the draft document, amended following comments from COM members at the March 2022 meeting. The draft document would also be discussed by COT and COC at their July 2022 meetings.

11. During discussions COM members asked for a small number of additional changes to be made prior to the document being evaluated by COC and COT. This included emphasising the public-facing role of the document. It was agreed that any changes made would be copied to COM members at the same time as the paper was being distributed to COT and COC members, to allow any further comments to be made.

ITEM 7: REVIEW OF TITANIUM DIOXIDE GENOTOXICITY (MUT/2022/05)

12. Following the publication of the European Food Safety Authority (EFSA) opinion on titanium dioxide in 2021, which concluded that titanium dioxide could no longer be considered to be 'safe' for use in food, the Food Standards Agency (FSA) initiated a review of the EFSA opinion.

13. The EFSA opinion was presented to the COM in June 2021 (MUT/2021/03) and to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in July 2021 (TOX/2021/36). The COM had a number of concerns over the EFSA opinion on the genotoxicity of titanium dioxide. Due to this and following the advice of the COT the FSA initiated an independent evaluation of the safety of the use of titanium dioxide as a food additive.

14. In October 2021, paper MUT/2021/08 was presented to the COM, which summarised the available genotoxicity on titanium dioxide. Members considered that it was not possible to evaluate the genotoxicity of titanium dioxide at that stage. The COM suggested a sifting approach to the available genotoxicity

should be adopted as a first step before evaluation. The Chair of the COM, a subgroup of the COM and the secretariat subsequently attended meetings to discuss and agree the criteria and methodology for sifting to identify suitable papers for the evaluation of titanium dioxide.

15. Paper MUT/2022/05 provided information and papers on approaches relating to the sifting and evaluation of the quality genotoxicity studies and evaluating data on nanomaterials. Members were asked to consider the information provided and for any comments.

16. The papers that formed the discussions of the subgroup meeting were presented in Annexes A-D of MUT/2022/05.

- Annex A - presented a paper by Fernández-Cruz et al.,2017 on the use of GUIDEnano approach on the quality evaluation of human and environmental toxicity studies performed with nanomaterials.
- Annex B - contained information from an unpublished study that offered a case study of the pragmatic use of the GUIDEnano approach in evaluating available data.
- Annex C - contained recommendations on alterations of existing methodologies and the best practices as proposed by Elespuru et al.,2018 with regards to the standard battery of genotoxicity tests.
- Annex D - presented an example table as an illustration of the genotoxicity assay specific criteria for quality control of available databases.

17. The paper at Annex A, provided a guide to scoring papers on nanomaterials for reliability and assessing how well a test nanomaterial had been characterised. Annex B provided an unpublished case study on how the GUIDEnano approach could be applied. Annex C made recommendations on alterations to existing methods for a standard battery of genotoxicity tests and Annex D provided a table to illustrate how to capture information on criteria and quality control.

18. Dr C Beevers and Dr P Fowler informed the Chair of a potential conflict of interest as they had both been working with a Titanium dioxide manufacturers association on a review of its genotoxicity. Although, this is a specific non-personal conflict, the chair considered that this did not prevent them from taking part in the COM discussion because this agenda item involved a discussion of the method of how the COM would proceed with its evaluation of the genotoxicity of titanium dioxide.

19. Members agreed that sifting and exclusion criteria could be based on those suggested in the highlighted papers. It was greed that the approach described in the Fernández-Cruz et al.,2017 paper could also be applied to non-nanomaterials. However, it was noted that if exclusion criteria were applied too strictly there was the potential to have very little remaining data to evaluate and therefore a balance was needed, and some expert judgement would therefore also need to be applied. Additionally, members agreed that although the characterisation of the test material was important, many of studies did not do

this well. If studies with poor characterisation were used in the final evaluation (i.e., where the focus was on hazard), then this poor or no characterisation would need to be noted.

20. The FSA would use the presented papers and the suggestions by COM members to produce a paper summarising the approach to sifting and selecting the papers to be included in the evaluation.

ITEM 8: SCOPING DOCUMENT – THE USE OF BIOMARKERS IN GENOTOXICITY RISK ASSESSMENT (MUT/2022/06)

21. At the March 2022 meeting, COM considered the revised COC Guidance Statement G04 'The Use of Biomarkers in Carcinogenic Risk assessment', with a particular focus on the DNA adducts and genotoxicity biomarkers sections, both of which have been shortened in the current version. Following discussions, it was considered that it would be helpful for COM to produce its own, more comprehensive, guidance on biomarkers relevant to its area of expertise- that could be referred to by the other Committees when needed or as appropriate.

22. Paper MUT/2022/06 was presented to the COM as a draft scoping document designed to provide an overview of the proposed content of the new COM guidance, for discussion and agreement by members.

23. During discussion, the importance of including the current COM Guidance was emphasised. In addition, members noted that care needed to be taken when defining biomarkers of effect due to the temporary nature of some changes which may not be taken through to the development of cancer. Additional areas for inclusion were suggested, for example, the exploration of dose-metrics in Human Biomonitoring studies, hazard and risk assessment applications, correlation vs causation, influence of DNA repair and linking to the key characteristics of carcinogens. Members were requested to send any comments or suggestions for inclusion in the document to the Secretariat by mid-July 2022 for incorporation in an amended outline, which would be presented at the COM October 2022 meeting.

ITEM 9: EFSA ASSESSMENT OF THE GENOTOXICITY OF ACRYLAMIDE (MUT/2022/07)

24. Following a request from the European Commission (EC), the European Food Safety Authority (EFSA) published a statement in 2022 on the assessment of recent publications on the genotoxicity of acrylamide. The request from the EC was due to a publication of a review by Eisenbrand (2020a) and its erratum (2020b). However, as EFSA did not consider the review and its erratum to be comprehensive, it conducted a literature search of the recent data on the genotoxicity and mode of action of acrylamide.

25. Paper MUT/2022/07 summarised the key points from the EFSA 2015 opinion on acrylamide and the main considerations from the EFSA 2022 evaluation. A brief overview of the Eisenbrand review was also provided along

with a link to the full paper at Annex A. EFSA did not change its earlier 2015 conclusions following its 2022 evaluation. Members were asked to consider the EFSA 2022 opinion and the following questions:

1. Do Members consider that the weight of evidence supports EFSA's conclusion that genotoxicity and non-genotoxic effects may contribute to the carcinogenicity of acrylamide?
2. Do Members agree with EFSA's conclusion that the new data do not alter the previous conclusions on the risk of acrylamide and that a Margin of Exposure (MOE) approach to its risk assessment is still appropriate?
3. Do Members have any other comments on the EFSA statement?
4. Do Members have any comment on the paper by Eisenbrand?

26. Members agreed with the EFSA decision to not change its earlier conclusions on acrylamide in the light of new evidence. Members agreed that exposure to acrylamide induced gene mutation and was clastogenic in mammalian cells. The genotoxic mode of action appears to occur via CYP2E1 metabolism to the mutagenic and clastogenic metabolite glycidamide. The role of acrylamide itself was unclear. Members considered that the genotoxicity arising from acrylamide exposure may also involve the generation of reactive oxygen species (ROS) and oxidative damage. The COM also agreed with EFSA in not deriving a health-based guidance value for acrylamide and with the adoption of a MOE approach to the risk assessment of acrylamide.

27. The review paper by Eisenbrand 2020 argued against a genotoxic mode of action for the carcinogenicity of acrylamide and that genotoxic effects were only seen above normal physiological levels of exposure. Members had reservations about the paper by Eisenbrand and considered that it had limitations. The review appeared to ignore some of the evidence that did not support its conclusions. It focused on N7 DNA adducts and ignored N3 DNA adducts that were consistent with mutation spectra reported in other studies.[SR1][OS2]

ITEM 10: COM ANNUAL REPORT 2021 (MUT/2022/08)

28. The COM 2021 annual report had been drafted. When finalised this would be merged with the annual reports of the COT and COC. Members were asked for any comments on the draft document.

29. Members provided some editorial comments and suggested some typographical amendments. Aside from these the document was approved.

ITEM 11: AOB

30. Members were informed that OECD Test Guideline 488 on the Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays and the OECD Test Guideline 470 on the Mammalian Erythrocyte Pig-a Gene Mutation Assay had been agreed and updated and would soon be published. The OECD Test Guideline 489 on the In Vivo Mammalian Alkaline Comet Assay would be reconsidered with a view to integrate germ cell assessment using new data. Additionally, a preliminary Guidance document had been produced on the

adaptation of the OECD Test Guideline for the in vitro Mammalian Cell Micronucleus Test for nanomaterials.

31. Regarding meetings, the UK Environmental Mutagen Society (UKEMS) would be holding a meeting in July in Harrogate and the Industrial Genotoxicity Group (IGG) would be holding workshops on basic assays and interpretation.

ITEM 12: DATE OF NEXT MEETING

32. 13th October 2022.