MUT/MIN/2023/03

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

Minutes of the meeting held at 10.30 on 12th October 2023 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 Mr P Rawlinson Mrs M Wang
Secretariat:	Dr O Sepai (UKHSA Scientific Secretary) Mr S Robjohns (UKHSA Secretariat) Ms B Gadeberg (UKHSA Secretariat) Dr C Mulholland (FSA Secretariat) Dr C Potter (FSA Secretariat) Mr T Fraser (UKHSA)
Secretariat Support:	Dr R Bevan (IEH Consulting)
Assessors:	Ann Baker (VMD) Fay Conry (HSE) Ms Jo Little (HSE) Krystle Boss (FSS)

	Dr Sarah Bull (IEH)
	Dr Autumn Bernal (IEH)
	Dr Jason Weeks (IEH)
Observers:	Paula (PETA)
	Max Ellington (UKHSA)
	Mousumi Chatterjee (UKHSA)
	Helen Hunt (UKHSA)
	Nive Raja (UKHSA)
	Henry Mayes (UKHSA)
	Robert Foster (Lhasa science)

		Paragraph
1.	Welcome and Apologies for absence	1
2.	Announcements	2
3.	Minutes of the meeting held on15th June 2023 (MUT/MIN/2023/02)	4
4.	Matters Arising	5
5.	Review of genotoxicity of titanium dioxide A) Summary of in vitro data (MUT/2023/07) B) Summary of in vivo data (MUT/2023/08)	6
6.	Review of COM QSAR guidance – Presentation and propsed work plan (MUT/2023/09)	12
7.	Lay summaries of COM Guidance statements (MUT/2023/10)	15
8.	OECD Updates	18
9.	AOB	20
10.	Date of next meeting	22

96
97

ITEM 1: WELCOME AND APOLOGIES FOR ABSENCE

1. The Chair welcomed the COM members, assessors, and secretariat. Tom Fraser was welcomed as a new member of the UKHSA support team for the COM. The Chair also welcomed Dr Ruth Bevan, Dr Sarah Bull, and Dr Autumn Bernal from IEH Consulting providing support to the COM secretariat. Apologies were received from the assessors Dr Lata Koshy (HSE), Ms Natalie Hough (HSE) and Ms Liz Lawton (Defra).

ITEM 2: ANNOUNCEMENTS

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

3. The Chair informed the COM that interviews had been conducted for new COM members. Official appointments needed to wait for sign off by ministers.

ITEM 3: MINUTES OF THE MEETING HELD ON 15th JUNE 2023 (MUT/MIN/2022/02)

4. The minutes of the COM meeting held on the 15th of June 2023 were agreed subject to a minor amendment.

ITEM 4: MATTERS ARISING

5. There were no matters arising not already on the agenda.

ITEM 5: REVIEW OF GENOTOXICITY OF TITANIUM DIOXIDE

A) SUMMARY OF IN VITRO DATA (MUT/2023/07) AND B) SUMMARY OF THE IN VIVO DATA (MUT/2023/08)

6. Dr Paul Fowler and Dr Carol Beevers declared that they had been paid by the Titanium Dioxide Manufacturers Association (TDMA). Dr C Beevers was no longer paid by the TDMA but did provide voluntary advice to the TDMA. Both cases were considered to a specific interest. Dr Fowler and Dr Beevers were not permitted to take part in the COM discussion of this item but could be asked a question for the purposes of clarity on a certain point. Dr Fowler and Dr C Beevers had had no direct involvement in the drafting of the COM paper (MUT/2023/07) on titanium dioxide. Dr George Johnson Chaired a Health and Environmental Sciences Institute (HESI) subgroup on titanium dioxide and Professor Shareen Doak was also a member of this subgroup discussing the mode of genotoxic action of titanium dioxide. This was not considered to be a conflict of interest. Dr Nathan Goldsmith declared that his employer Exponent undertook paid work for the TDMA. However, as an associate member he did not take part in the COM discussion of this item.

7. Following the publication of an opinion on the genotoxicity of titanium dioxide (TiO2) by the European Food Safety Authority (EFSA) entitled ‘Safety

assessment of titanium dioxide (E171) as a food additive' (EFSA, 2021), the UK Food Standards Agency asked the COM to provide an opinion on the genotoxicity of TiO2. Papers assessed included those cited in the EFSA 2021 evaluation and additional papers identified in a literature search conducted to collate more recent papers.

8. A subgroup of four members of the COM was formed to help with the COM evaluation of TiO2. The role of the subgroup was to outline a screening and selection process involving inclusion/exclusion criteria against which all identified papers were to be assessed. Only papers presenting data on assays with an OECD test guideline, such as the micronucleus and chromosomal aberration assay were considered. Papers were screened for reliability and relevance using a tiered approach, by first assessing in tier 1 the nanomaterials used in the studies and generic study design, followed by a tier 2 assessment of the generic genotoxicity design and lastly in tier 3 a more detailed assessment of genotoxicity study design and results. In tier 3, the subgroup also critically evaluated all papers and collectively, assigned a red, amber and green (RAG) quality rating. Green indicated good robust studies without major deficiencies; amber indicated studies considered sufficient for assessment; and red indicated studies with significant deficiencies in procedural descriptions or protocols meaning that they were not of sufficient quality for use in the assessment of the genotoxicity of TiO2. This screening and selection approach was intended to be applied to both *in vitro* studies, as described in Paper MUT/2023/07, and *in vivo* studies, as described in Paper MUT/2023/08.

9. The COM requested clarification on the scope of the genotoxicity evaluation of TiO2 e.g., whether it was to be solely on TiO2 as the food additive E171 or whether there would be a wider focus, such as use in pharmaceuticals, toothpaste and sunscreen. It was agreed that the focus would be on the oral exposure, but other routes of exposure could also be included.

10. Members supported the general methodology used in the screening approach described in the papers MUT/2023/07 and MUT/2023/08 but requested further details on the description of the screening and selection process to be provided in the relevant papers. This included further details on aspects such as, the size of the TiO2 particles, test system, appropriate number of cells, exposure time, dose, route of exposure where relevant, and mechanism of genotoxic action. It was also requested to add authors opinions into the narrative for all papers and a statement on whether the COM agreed with the authors opinions.

11. It was agreed that revised draft papers would be prepared for further consideration by the COM at its next meeting in February 2024, with interim subgroup meetings taking place as needed.

ITEM 6: REVIEW OF COM QSAR GUIDANCE – PROPSED WORK PLAN AND PRESENTATION (MUT/2023/09)

12. The COM member Dr Paul Fowler provided a presentation on a proposed plan of work for a COM Guidance document on the use of QSARs. During

revision of the COM overarching Guidance Document (A strategy for testing of chemicals for genotoxicity) members requested that a separate Guidance document be prepared on the use of QSAR models to evaluate the potential mutagenicity of chemicals and that this document would allow more frequent updates to be incorporated in the fast-moving area. An initial Guidance statement was drafted in 2018 with amended versions being presented to the COM on several occasions. The most recent presentation was given at the COM meeting in February 2021 (MUT/2021/05).

13. At the meeting in February 2021, it was agreed that a subgroup of interested COM members would facilitate the progress of the COM Guidance. It was also noted that a likely use of the Guidance would be to evaluate the mutagenic potential of impurities. Paper MUT/2023/09 provided a summary of the first meeting of the COM QSAR subgroup, held on the 7th of September 2023, concerning further development of the draft Guidance on the use of QSARs to predict the mutagenic potential of chemicals.

14. During the discussion of this item, it was suggested that the QSAR Guidance would be useful to the COC and that it would be beneficial for a member of the COC to join the COM QSAR subgroup to provide input from a COC perspective. Members supported the proposed steps in paper MUT/2023/09 such as, collating a list of current guidance on the use of QSARs; highlighting how/which type of QSAR models should be used; inclusion of a 'real-life' case study example of use i.e., for an impurity; some consideration of signals for clastogenicity in addition to Ames data; support the COM overarching Guidance Statement referring to the use of QSARs in stage 0; discussion of the use of the TTC approach; use of read-across; justification for the QSAR models used and how to use 'out of domain' predictions. It was noted that inclusion of alerts for clastogenicity would likely generate a large number of alerts and there would be a need to consider how to deal with this. Furthermore, it was suggested that members of Government Departments/Agencies provide information on how they used QSARs, which would help identify suitable case studies in the Guidance document. A draft QSAR document would be prepared for the COM meeting in June 2024, with interim subgroup meetings to take place as needed.

ITEM 7: DRAFT NON-EXPERT SUMMARIES FOR COM STATEMENTS (MUT/2023/10)

15. At the COM meeting in June 2022, it was agreed that the general public could benefit from the addition of non-expert summaries at the start of each COM Guidance statement. The format and style of the non-expert summaries were previously agreed by COM members for the overarching guidance statement at the meeting in June 2023 (MUT/2023/05).

16. Paper MUT/2023/10 provided the first draft non-expert summaries for the COM Guidance document on testing strategies to evaluate the potential for manufactured nanomaterials to cause genotoxicity (Annex A) and the COM guidance document on testing strategies to evaluate the potential of chemicals to cause germ cell mutations (Annex B).

17. Some amendments to specific scientific terms were suggested to the non-expert summaries for clarification, such as preference for the use of the generic

term ‘damage to DNA’ rather than various terms relating to genotoxicity. Once amended, it was agreed that these could be published on the COM website.

ITEM 8: OECD UPDATES

18. Members were informed that last year there was an update to OECD Guidance on the *in vitro* micronucleus assay in terms of methodological adaptions that would allow appropriate genotoxicity testing of nanomaterials. It was expected that there would be an interlaboratory trial with a view to updating the test guideline with a section on nanomaterials. Germany was leading on drafting a standard submission form (SPF) to go to the Working Group of National Co-ordinators of the OEC Test Guideline programme (WNT) WNT.

19. One member highlighted that an OECD SPF on the gamma H2AX *in vitro* assay will progress with a Detailed Review Paper (DRP) moving toward a test guideline. Also, there would be an update to OECD Test Guideline 489 on the *in vivo* comet assay to include germ cells. There had been a validation exercise in just one laboratory with five or six chemicals. The next steps were to include additional compounds and recruit further laboratories. The aim was to use tail intensity and only focus on developing germ cells. Members were also informed that it was expected that an SPF for next generation sequencing would be submitted in November, and this was expected to be supported by a trial with the Health and Environmental Sciences Institute (HESI). The SPF would mainly focus on error corrected next generation sequencing *in vivo*, although it had been recommended to expand to other versions to also include *in vitro* and human data.

ITEM 11: AOB

20. The COM heard that the European Food Safety Authority (EFSA) had recently published a document on how to use a weight of evidence approach to assessing genotoxicity data. It was agreed that it would be useful for the COM to review this document.

21. Members were also informed that a joint COC/COM meeting had been held on the 9th of October 2023, which involved some consideration of the paper by Hill W. et al., 2023 that suggested that air pollution, such as particulate matter, had a role in the promotion of cancer rather than damge to DNA. This paper was of interest to the COC and it was suggested that this paper would be considered at the next COM meeting in February 2024.

ITEM 12: DATE OF NEXT MEETING

22. Date of next meeting – 29th February 2024.