Committee on MUTAGENICITY

MUT/MIN/2019/1

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

Minutes of the meeting held at 10.30 am on 28th February 2019 at Public Health England, Wellington House, 133 – 155 Waterloo Road, London, SE1 8UG.

Present:

Chairman:	Dr D Lovell
Members:	Mr A Bhagwat Dr C Beevers Dr G Clare Professor S Doak Dr M O'Donovan Dr S Dean Mrs P Hardwick Professor D Harrison (Ex Officio) Professor G Jenkins Professor D Kirkland Dr R Morse Dr A Povey
Secretariat:	Dr O Sepai (PHE Scientific Secretary) Dr B Maycock (FSA Secretariat) Mr S Robjohns (PHE Secretariat)
Secretariat Support:	Dr R Bevan (WRc/IEH Consulting) Dr S Bull (WRc/IEH Consulting)
Assessors:	Mrs R Pearson (VMD) Dr L Koshy (HSE) Dr H Stemplewski (MHRA) Ms S Geerts (DHSC)

		Paragraph
1.	Announcements/Apologies for absence	1
2.	Minutes of the meeting held on 26th June 2018 (MUT/MIN/2018/2)	4
3.	Matters Arising	5
4.	Update of the COM guidance series (MUT/2019/01)	7
5.	Test strategies for manufactured nanomaterials (MUT/2019/02)	10
6.	Guidance statement on the use of QSAR models to predict genotoxicity (MUT/2019/03)	15
7.	3D Models for genotoxicity testing (MUT/2019/04)	19
8.	Test strategies for germ cell mutagens (MUT/2019/05)	21
9.	OECD Updates	24
10.	Horizon Scanning	25
11.	Annual Report (MUT/2019/06)	29
12.	Any other business	30
13.	Date of next meeting – COM Workshop – 12 and 13 June 2019	31

ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed the COM members, assessors and secretariat. Dr B Maycock (FSA) was attending instead of Dr D Gott (FSA).

2. Apologies for absence were received from Dr D Gott (FSA), Ms H Nakeeb (PHE secretariat), Ms B Gadeberg (PHE PHE secretariat) Dr C Ramsay (Health Protection Scotland), Dr I Martin (EA assessor), Dr J McElhiney (FSS Assessor) and Dr W Munro (FSS Assessor), Dr L Dearsly (HSE Assessor), Mr S Fletcher (VMD Assessor) and Ms T Netherwood (DHSC).

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

ITEM 2: MINUTES OF MEETING ON 18th October 2018 (MUT/MIN/2018/3)

4. Members agreed the minutes subject to minor typographical changes.

ITEM 3: MATTERS ARISING

5. The COM was informed that initial enquiries into the availability of representatives from National and International regulatory organisations, such as the European Chemicals Agency (ECHA), the European Food Standards Agency (EFSA) and the European Medicines Agency (EMA), to attend a workshop organised by the COM to explore the harmonisation of the approach to strategies for *in vivo* genotoxicity testing had been positive. The practicalities, such as the date and venue had yet to be confirmed, but June 2019 was suggested as a potential month to hold the meeting.

6. This was the last meeting for the COM members Professor Gareth Jenkins, Professor David Kirkland and the lay member Mrs Philippa Hardwick. The Chair thanked them for all their hard work. Submissions had been made to reappoint the members Dr Gill Clare, Professor Shareen Doak and Dr Mike O'Donovan, but the secretariat were waiting for confirmation and sign off from Ministerial approval.

ITEM 4: UPDATE OF THE COM GUIDANCE SERIES (MUT/2019/01)

7. Amendments to the COM Guidance document as a whole, up to Annex 1, had been previously considered at Committee meetings in July 2018 (paper MUT/2018/09) and October 2018 (paper MUT/2018/13). It was agreed at the October 2018 meeting that comments would be sought on the first draft of the amended document from a limited number of Members. These changes were subsequently collated by the Secretariat into an updated version of the Guidance document.

8. The paper presented (MUT/2019/01) contained all amendments made to date. The Chair addressed each page of the document in turn, inviting suggested comments and/or amendments from Members. For those pages not discussed during the meeting due to time constraints (pages 72 to Annex 1), Members were asked to annotate a copy of the document and forward to the Secretariat for collation. All changes received would then be incorporated into a new version of the guidance document to be reviewed at the next COM Committee meeting in June 2019.

9. Members also commented that as more frequent updates of the main document and associated stand-alone guidance documents were likely to occur, it was important to put version control in place. Additionally, it was felt that access to previous versions of the Guidance and stand-alone documents was needed.

ITEM 5: TEST STRATEGIES FOR MANUFACTURED NANOMATERIALS (MUT/2019/02)

10. The Committee previously discussed the update of the "*Guidance On A Strategy For Genotoxicity Testing Of Chemical Substances*". As part of the update, information on methodologies to test the mutagenicity of nanomaterials was requested. Therefore, a scoping paper was presented that evaluated the suitability of test methodologies currently used in genotoxicity testing for assessing the mutagenicity of nanomaterials, with the ultimate goal of updating or amending the COM guidance.

11. A number of initiatives were included in the scoping paper, including OECD projects (Working Party on Manufactured Nanomaterials), and the associated Testing Programme and various EU projects (NanoSafety programme, NANOGENTOX Joint Action, NanoReg project, Prosafe project). Members discussed that conclusions could not be made from some of the projects as some of the data were difficult to interpret and queried the inclusion of some of the projects in the paper.

12. Members agreed that the summary of initiatives was comprehensive and well described, although a recent review by the Genetic Toxicology Technical Committee (GTTC) was not included in the paper. It was noted that the GTTC review only covered projects up to 2014. The Committee recommended including the GTTC paper when updating the Guidance Statement on nanoparticles (MUT/2012/04). This Guidance Statement would sit alongside the COM Guidance Strategy for Genotoxicity Testing of chemical Substances. It was agreed that the GTTC paper would be provided to the Secretariat.

13. Overall, the Committee recommended a number of topics that should be included in the updated Guidance Statement (MUT/2012/04), including an opinion about the use of the Ames test in the testing of manufactured nanoparticles, and the use of cytochalasin B in the micronucleus assay. Members noted that these topics were being discussed by the OECD for inclusion in the test guidelines.

14. The draft Guidance Statement, would be discussed at the next COM meeting.

ITEM 6: GUIDANCE STATEMENT ON THE USE OF QSAR MODELS TO PREDICT GENOTOXITY (MUT/2019/03)

15. The COM had previously agreed that when no genotoxicity data were available an initial assessment of potential genotoxicity could be based on publicly available Structure Activity Relationships (SAR) and Quantitative Structure Activity Relationships (Q)SAR models. Members previously considered a scoping paper (MUT/2018/2) on the use of QSARs to predict genotoxicity in February 2018, which formed the basis of the draft Guidance Statement (MUT/2019/03).

16. During discussions on the draft Guidance Statement, Members asked whether the OECD QSAR principles were given the same weight when validating the QSAR. It was also noted that the OECD Toolbox is not a model per se as it is a collection of models, hence this should be discussed separately. Discussions were also held over the availability of data, such as the algorithms behind the QSAR prediction that is in the public domain. Members noted that for some commercial models, such information is available to licence holders.

17. The Chair requested comments on the Guidance Statement and Members provided various editorial amendments. It was suggested that the document should indicate that although QSAR models should not be used to overrule test results that QSAR predictions may aid interpretation of test data, for example, by identifying structural alerts or by helping to explain test results. Members also recommended that a summary table be included in the Discussion and Conclusion section that summarises how each model complies with the OECD principles, although it was noted that the table should not be used to validate the QSAR model or select a model to use for predictions.

18. The next draft of the Guidance Statement, would be discussed at the next COM meeting.

ITEM 7: 3D MODELS FOR GENTOXICITY TESTING (MUT/2019/04)

19. During discussions of the updated COM Guidance at the Committee meeting in October 2018 (paper MUT/2018/13), Members agreed that the area of 3D models for genotoxicity testing should be included in the updated Guidance document. However, as this was a fast-moving field, meaning that frequent updates to the COM Guidance document would need to be made, it was agreed to produce a stand-alone document which would support the main Guidance, but which could be updated as frequently as required.

20. The discussion paper presented (MUT/2019/04) provided a summary of 3D models currently used for genotoxicity testing and those under development and/or validation. Members were requested to provide any comments. It was noted that the end-point for the comet assay was currently

described differently across many COM documents and needed to be harmonised throughout. Members also noted that co-cultures and 3D models were useful because they could detect inflammation that may lead to DNA damage that was not picked up by conventional 2D or single cell cultures. These 3D models may also be useful for assessing inhalation exposure, for example of particulates/nanomaterials, in providing mechanistic information. The COM agreed that the most up-to-date information had not been included for the skin micronucleus assay and the skin comet assay. However, the information relating to the updated assays were awaiting publication and were not publicly available. It was decided that as this information was needed before the discussion document could be completed, that this document would be revisited.

ITEM 8: TEST STRATEGIES FOR GERM CELL MUTAGENS (MUT/2019/05)

21. During discussions of the updated COM Guidance at the meeting in October 2018 (paper MUT/2018/13), Members agreed that the area of germ cell mutagen testing should also form a stand-alone document which would be used to support the main Guidance document and updated as frequently as required.

22. The discussion paper presented (MUT/2019/05) provided a brief summary of test methodologies that are currently used or under development and/or validation, to assess germ cell mutagenicity. It was asked whether the IWGT had updated information that should also be included, as some of the references used in the discussion document were relatively old. It was confirmed by another member that the latest IWGT information had been included. The possibility that the GTTC working group may also publish something of relevance in the near future was also raised, although it was considered that the focus of this and other groups was now on gaps in testing, such as female germ cell mutagenicity testing strategies. Members also suggested key references for inclusion that were currently being used to drive changes in OECD Guidelines.

23. The Chair asked for any additional comments to be sent to the Secretariat for collation and an updated version, presented as a draft Guidance Document, would be discussed at the next COM meeting. It was noted that when the COM germ cell mutagen testing document had been finalised that it would be useful to send this to the HSE as it would aid HSE in its role of chemical regulation (e.g. biocides and pesticides). The HSE could then also bring this document to the attention of ECHA.

ITEM 9: OECD TEST GUIDELINES

24. OECD Test Guidelines were not considered at this meeting.

ITEM 10: HORIZON SCANNING

25. As part of the COM horizon scanning exercise members were requested to make suggestions for potential future topics of importance for consideration by the committee.

It was suggested that *in vitro* multi-endpoint test systems were likely to become more important, including high-throughput test systems, imaging systems and 3D cell cultures. These could be used to evaluate a number of endpoints in addition to mutation that are relevant to cancer e.g. cell division rates and suppression of apoptosis. It was suggested that the COM could consider other such endpoints rather than focusing solely on mutation to give a clearer overall picture in terms of genotoxicity and cancer.

26. Another suggestion was for the COM to consider a weight of evidence approach to evaluating genotoxicity data and mutation potential. This could involve bringing various aspects together (e.g. mode of action, non-linear dose response relationships, quantitative genotoxicity analysis etc.) to aid consistency in the interpretation of data. The multi-endpoint test systems (e.g. MultiFlow and Toxtracker) could also help with this.

27. The Pig-a *in vivo* assay was highlighted as a test that had the potential to be used to a greater extent in the future. Currently it is only used in blood cells. However, it was suggested that it could be conducted in other tissues and that this would provide a further option in addition to the *in vivo* transgenic rodent (TGR) gene mutation test, which was currently the only option for an *in vivo* gene mutation test.

28. A further suggestion was that the COM should consider a more holistic approach when considering potential harms to the public (e.g. disinfection by-product mixtures in swimming pools) rather than focussing on just the mutation aspect (i.e. consider the overall public health concern).

ITEM 11: ANNUAL REPORT 2018

29. Then 2018 annual report was not considered at this meeting.

ITEM 12: ANY OTHER BUSINESS

30. The Chair thanked the members Professor David Kirkland, Professor Gareth Jenkins and Phillipa Hardwick for all their hard work over the years as it was their last meeting

ITEM 13: DATE OF NEXT MEETING

31. Date of next meeting – 12 and 13 June 2019 – COM Workshop