MUT/2018/05

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

FORWARD PLAN AND HORZON SCANNING

1. The COM is a joint DH/FSA committee which provides independent advice to government departments and agencies on the potential mutagenicity and genotoxicity of chemicals (whether they are likely to cause mutation in cells), from natural products to new synthetic chemicals used in pesticides or pharmaceuticals. It also advises on strategies and research for genotoxicity testing. advises on the risk of cancer from chemicals in food, consumer products and the environment. The COM has a joint PHE/FSA secretariat, which is led by PHE.
2. Each year the COM carryout a Horizon scanning exercise which feeds into its forward work plan.
3. This paper summarises the current issues and some of the issues which have been suggested by members of the committee, government department and agency assessors and through the joint discussions held in October 2017 at the joint meeting of COM and its sister committees on toxicity (COT and carcinogenicity (COC)
4. The members are asked to review the paper in light of developing a work programme for 2018.

Secretariat/PHE Toxicology Unit

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1. The current list of topics:

	Topic	Status
1.	OECD Guidance document for Genotoxicity test methods COM keeps a watching brief on methods proposed through OECD	Complete
2.	Ames II or Ames MPF	*subject of a new OECD project* – updates from the UK representative
3.	Epigenetics and public health – was the topic of the joint meeting in October 2017.	*Emma Marczylo presented to COM in June 2016, this is now the subject of a joint COM/COC and COT meeting*
4.	Updates from OECD Test Guidelines	*This is a standing item*
5.	Germcell mutagens	*Statement written in 2016*
6.	Review current practices of incorporating genotoxicity testing into existing toxicity tests for example, integration of the micronucleus test and the comet assay into repeat dose toxicity testing to reduce the overall numbers of animals tested and the use of transgenic animals in 28 day toxicity studies to evaluate transgenic mutations.	
7.	How high the maximum tested dose should be and	

what constituted a biologically significant response, for example a fold increase above background.	
8. Further, the use of genotoxicity data in an approach to risk assessment similar to that used with toxicological risk assessments was considered important.	*Draft statement*
9. Watching brief on how nanoparticle will be addressed in OECD Genotoxicity test methods.	
10. Genotoxicity of E-Cigarettes; one published paper reports that E-cigarettes "… induce DNA damage in mouse lung, bladder, and heart and reduces DNA-repair functions and proteins in lung. Nicotine and its nitrosation product 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone can cause the same effects as ECS and enhance mutations and tumorigenic cell transformation in cultured human lung and bladder cells." (Annex 1) May form the basis for discussion on the investigation/ assessment of genotoxcity using systems other than the standard OECD test methods.	For consideration may be referred to COM during the review being carried out by COT.
11. Expanded simple tandem repeat (ESTR) mutation induction in male germline	

2. For discussion and forward planning:

In October 2017 a Joint COC, COM and COT Horizon scanning discussion highlighted the following as noted in the minutes of the meeting (Annex 2).

- For the COM it was noted that other topics of interest included genotoxicity associated with non-cancer endpoints, CRISPR technology and quantification of the dose response relationships for genotoxicity studies.

- Regarding epigenetics, it was noted that for the COM the relevant interests were in epigenetic changes in the germ line and epigenetic changes that were transmissible to the next generation. The COM would keep a watching brief on this. Regarding the suggestion of updating some aspect of the COM Guidance on mutagenicity testing and interpretation, members considered that other authoritative organisations needed to update similar Guidance documents before this should be undertaken. A lack of clarity over an appropriate *in vivo* follow up study for a positive gene mutation test result was highlighted, however, it was noted that an International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI) working group was already addressing this.

- Members expressed concern over publication bias in that a positive finding was more likely to be published than a negative result and that some journals were very reluctant to publish negative results. There was also concern over the increase in number of 'predatory' journals, which was resulting in an increase in the publication of poorer quality studies. One member noted that that some agencies appeared to give greater emphasis to positive results in non-validated test systems using non-standard protocols, compared to negative results from regulatory studies conducted in accordance to OECD test guidelines and good laboratory practice (GLP). It was suggested that the Committees needed to consider how to address this problem. There was a need to emphasise the importance of being cautious of studies using methods that are not validated and to promote the value of standard OECD/GLP studies. It was suggested that perhaps this could be addressed by the Committees writing to authoritative organisations, such as ECHA and EFSA, or to a high profile journal.

- In terms of priorities for joint Committee consideration, it was suggested one important area was how to evaluate the biological or toxicological relevance of a reported response or perturbation, especially where this may be an atypical endpoint and how statistics can, and should, be used to help determine this. This should encompass how the Committees could judge whether the statistics used were appropriate. Consideration of sufficient levels of health protection and dealing with uncertainty could also be useful, for example, the degree of confidence over a non-significant result in relation to health protection. Another area of importance was how to deal with different sources of evidence considered by the Committees (e.g. predatory journals and poor quality non-standard tests), which could be a follow up to the SEES group work. In addition, a watching brief should be maintained on nanomaterials, especially as size distribution is of relevance for e-cigarettes and also heat-not-burn tobacco products.

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Forward Plan and Horizon Scanning

Published paper - E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. PNAS.ORG (2017)
Available from http://www.pnas.org/content/early/2018/01/25/1718185115

MUT/2018/05 Annex 2

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

Joint Committee Workshop – 9 October 2018 – Draft Horizon Scan Minutes

ITEM 2: Joint COC, COM and COT Horizon Scanning (Paper 2)

1. Professor Alan Boobis declared an interest as a member of the Risk21 consortium, which was on the COT horizon scan. Dr Phil Botham declared an interest as he works for Syngenta and is aware of some of the issues raised due to the effect they have on products produced by the company.

2. The Code of Practice for Scientific Advisory Committees (Office of Science and Technology, December 2001), states that: “Committees should ensure that they have the mechanisms in place that allow them to consider on a regular basis whether new issues in their particular areas of responsibility are likely to emerge for which scientific advice or research might be needed”.

3. The Committees have undertaken regular Horizon Scanning exercises in which the Secretariat, Members and/or assessors have suggested areas/topics that may need consideration in the light of new and emerging evidence relating to chemical risk assessment.

4. Due to overlapping interests in horizon scanning items and a recommendation from the last COM triennial review for flexible and coordinated approaches to work of intersecting interest, it was considered timely for the Committees to have a joint horizon scanning session.

5. Paper 2 outlined current horizon scanning topics on the list for each of the three Committees and a number of suggested new topics for each Committee. Members were invited to comment on the topic areas mentioned in Paper 2, consider areas of overlap between the Committees and how these could be addressed, and suggest priorities.

6. The three Committees were introduced to the WRc and IEH Consultancy team who have been contracted to PHE to provide Secretariat support.

7. For the COT, the topics on the current horizon scan were as outlined in the discussion paper, and it was noted that in addition the Committee would be taking forward work on e-cigarettes.

8. For the COM in addition to the aspects highlighted in the discussion paper, it was noted that other topics of interest included genotoxicity associated with non-cancer endpoints, CRISPR technology and quantification of the dose response relationships for genotoxicity studies.

9. The COC items of interest were also outlined and it was noted that there were areas where the Committees had overlap in interest which it would be good to discuss.

10. Members of the Committees made a number of suggestions for horizon scanning topics in addition to those already described in the paper.

11. Members expressed concern over publication bias in that a positive finding was more likely to be published than a negative result and that some journals were very reluctant to publish negative results. There was also concern over the increase in number of ‘predatory’ journals, which was resulting in an increase in the

publication of poorer quality studies. One member noted that that some agencies appeared to give greater emphasis to positive results in non-validated test systems using non-standard protocols, compared to negative results from regulatory studies conducted in accordance to OECD test guidelines and good laboratory practice (GLP). It was suggested that the Committees needed to consider how to address this problem. There was a need to emphasise the importance of being cautious of studies using methods that are not validated and to promote the value of standard OECD/GLP studies. It was suggested that perhaps this could be addressed by the Committees writing to authoritative organisations, such as ECHA and EFSA, or to a high profile journal.

12. Other areas of potential common horizon scanning interest were outlined, such as, uncertainty in risk assessment (including modelling approaches and toxico-kinetics); extrapolation from lifetime animal studies to early human less than lifetime exposure; balance between environmental exposure and food exposure; by-products of various drinking water disinfection treatments.

13. Regarding epigenetics, it was noted that for the COM the relevant interests were in epigenetic changes in the germ line and epigenetic changes that were transmissible to the next generation. The COM would keep a watching brief on this. Regarding the suggestion of updating some aspect of the COM Guidance on mutagenicity testing and interpretation, members considered that other authoritative organisations needed to update similar Guidance documents before this should be undertaken. A lack of clarity over an appropriate *in vivo* follow up study for a positive gene mutation test result was highlighted, however, it was noted that an International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI) working group was already addressing this.

14. It was suggested that a case study of the RISK21 framework could be undertaken using the data presented during the recent COT consideration of heat not burn tobacco products. This could help illustrate how far the RISK21 approach could be used, and may provide a basis on which quantification of any effects could be better estimated.

15. Potential concern over natural products and ‘new’ natural foods was raised. The Committees were informed that this was a complex area with a lack of clarity in terms of regulation, which needed to be considered on a case by case basis. Some natural products or supplements were classified as novel foods. Natural products were treated differently in terms of regulation depending on whether there was a claim for a medicinal benefit or not. There appeared to be no overall framework or systematic approach to natural product in general. It was suggested that it would be worthwhile to determine whether there was a potential health risk from natural product before taking this further, and that a brief survey involving the National Poisons Information Service could be undertaken in the first instance.

16. The use of epidemiological information in a chemical health risk assessment was discussed. It was noted that a sub group of the COT and COC was finalising a document on synthesising epidemiological evidence and how this could be used by Committees. The question of how to deal with poor published studies was raised. Members noted that such studies could cause difficulties for various expert Committees, where poor studies were used to question Committee opinions in some

cases. It was noted that EFSA currently required scoring of individual papers and used a weight of evidence approach in its evaluations using its PROMETHEUS approach.

17. In terms of priorities for joint Committee consideration, it was suggested one important area was how to evaluate the biological or toxicological relevance of a reported response or perturbation, especially where this may be an atypical endpoint and how statistics can, and should, be used to help determine this. This should encompass how the Committees could judge whether the statistics used were appropriate. Consideration of sufficient levels of health protection and dealing with uncertainty could also be useful, for example, the degree of confidence over a non-significant result in relation to health protection. Another area of importance was how to deal with different sources of evidence considered by the Committees (e.g. predatory journals and poor quality non-standard tests), which could be a follow up to the SEES group work. In addition, a watching brief should be maintained on nanomaterials, especially as size distribution is of relevance for e-cigarettes and also heat-not-burn tobacco products.

18. It was agreed that a joint horizon scanning activity should be undertaken again in the future.