Committee on MUTAGENICITY

MUT/MIN/2015/3

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

Minutes of the meeting held at 10.30 am on Thursday 15th October 2015 at the Department of Health in Room 125A Skipton House, Elephant and Castle, London, SE1 6LH.

Present:

Chairman:	Dr D Lovell
Members:	Dr C Beevers Dr G Clare Dr S Dean Professor S Doak Professor M O'Donovan Ms P Hardwick Professor G Jenkins Professor D Kirkland Dr A Lynch Professor F Martin Professor D Phillips
Secretariat:	Dr O Sepai (PHE Secretary) Mr B Maycock (FSA Secretariat) Dr K Burnett (PHE Tox Unit) Mr S Robjohns (PHE Secretariat)
Assessors:	Dr S Samuels (HSE) Dr H Stemplewski (MHRA)
In attendance:	Miss Helen Smith (PHE) Mrs Natalie Blowfield (PHE)

ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed Members, the secretariat and assessors. Mr B Maycock was attending for the FSA and Miss Helen Smith was attending as an observer (PHE). The Chair also welcomed Mrs Natalie Blowfield who had recently been appointed as the new administrator for the COM.

2. Apologies for absence were received from Dr D Benford (Secretariat FSA) and from the assessors Dr L Koshy (HSE), Dr S Fletcher (VMD) and Dr C Ramsay (Health Services Scotland).

3. Dr Michael Rennie had resigned due to ill health. The committee sent him its best wishes and the Chair thanked him for his work with the COM.

4. Members were reminded of the need to declare any interests before discussion of items.

ITEM 2: MINUTES OF MEETING ON 18th June 2015 (MUT/MIN/2015/2)

5. Members agreed the minutes subject to minor editorial changes.

ITEM 3: MATTERS ARISING

6. The committee was informed that following the consideration of cycloastragenol at the previous meeting in June and advice from members, an expert in telomere biology had been contacted by one COM member on behalf of the COC. The advice provided to the COC was copied to the COM for information. The expert on telomere biology was content with the information on telomeres and telomerase in the paper (MUT/2015/08). The expert on telomere biology was concerned about the consumption of this substance if it did what was claimed in the literature because it would then remove a key block to prevent clonal evolution and malignant progression of damaged/aging cells. Cycloastrogenol has been shown to remove this block via de-repression of human telomerase reverse transcriptase (hTERT) transcription, which would have the effect of stimulating telomere lengthening and thereby *in vivo* immortalisation of genetically damaged cells, which would otherwise undergo replicative senescence (and thus would not be able to proliferate indefinitely). Consequently, there would be particular concern over pre-malignant foci of cells, since these could go on to multiply and evolve further into cancer. Therefore, the expert on telomere biology considered that individuals consuming a product containing cyloastrogenol could be at an increased risk of cancer, particularly following long-term consumption.

7. The expert on telomere biology added that telomere regulation is a balance between preventing aging and preventing malignancy. Rodents do not have constitutively active telomerase and do not use telomere shortening as a cancer preventative mechanism. This suggests that a rodent carcinogenicity bioassay would not be biologically representative of humans and therefore would not be informative in assessing the potential carcinogenicity of cycloastragenol in humans. The expert on telomere biology

was also concerned that products containing cycloastragenol were available online, and noted that one of them recommended that it should not be taken for more than a year.

8. The COM was informed that this additional information and the concern expressed by the expert on telomere biology had been provided to the Advisory Committee on Novel Foods and Processes (ACNFP) by the COC.

9. The Chair informed members that the Annual report for 2014 had been completed.

10. Members were requested to keep their declarations of interests up to date.

ITEM 4: TRIENNIAL REVIEW (MUT2015/10)

11. The committee was informed that the triennial review of the COM had been undertaken and a draft report had been produced. The review had two main aims which were to evaluate whether the function of the committee was required and whether it was operating efficiently; and then to make any appropriate recommendations. The draft report would go further up through Government, before being agreed and published. Members commented on the draft report.

ITEM 5: GERM CELL MUTAGENESIS

a. Aging and disease in offspring: a scoping paper (MUT/2015/11)

b. Transgenerational effect (MUT/2015/12)

12. This topic was discussed as part of the committee horizon scanning exercise in June 2015, where it was acknowledged that a large amount of data had become available. It was agreed that the committee should monitor developments in this area.

13. The committee was provided with two papers (paper ref: MUT/2015/11 and MUT/2015/12) in advance of the meeting. The first was a scoping paper, which outlined background information on: i) methods for investigating germ cell mutagenesis, ii) the germ cell genome, meiosis and mutagenesis, iii) the paternal age effect and iv) aneuploidy in germ cells. Available data on the links between (germ cell) mutagenicity and air pollution were also discussed as an area that could be explored further in the context of this topic. Relevant published papers were provided as an Annex.

14. The second paper was a Health Protection Agency (HPA) report (prepared by a sub-group of the Advisory Group on ionising Radiation) on transgenerational effects in human populations exposed to radiation (primarily as a result of radiotherapy). It also considered some groups that had undergone chemotherapy. This report was presented to the committee as a possible protocol/proof of principle that could be adopted to address this topic. It considered transgenerational effects that were not due to the inheritance of

a conventional DNA mutation or mutations arising in the next generation due to the transmission of damaged DNA through sperm (e.g. epigenetic effects).

15. The chair invited the committee to provide comments on the papers and suggestions on how this topic could be explored further.

16. Members noted that it was not known whether unique germ cell mutagens exist (i.e. chemicals that are germ cell mutagens but not somatic cell mutagens). This was mainly due to underutilisation of the currently accepted tests for assessing germ cell mutagenicity and a lack of investigations examining the possibility. Differences between mitosis and meiosis meant that it was possible that some chemicals may only be mutagenic in germ cells and raised some uncertainty over the relevance of somatic cell test endpoints to germ cells. It was noted that there was little relevant information publicly available. One member pointed out that there were some data relating to germ cell mutations and transgenic assays held by Health Canada in a database known as TRiAD. A form of this database was also available on the Swansea University website. However, one member noted that it may contain a number of corruption errors. It was suggested that Health Canada should be contacted to gain a better understanding of the available information and that the source of the errors on the Swansea University database be investigated.

17. Regarding test methods, it was acknowledged that the International Workshop on Genotoxicity Testing (IWGT) had evaluated approaches to measure germ cell mutagenesis in 2013. However, the committee suggested that consideration should be given to whether there had been any developments since then. This could include developments in molecular biology and tests that may be able to detect germ cell mutations even if they were not standard tests or OECD validated tests i.e. there was a need to explore new methods.

18. One member suggested that the committee should also explore other literatures (e.g. literature on assisted fertilisation and 3D tissue models for spermatogenesis), which may provide some insight into this topic. Members noted that DNA damage in germ cells can be associated with spontaneous abortions, infertility or heritable damage in the offspring/subsequent generations. Methotrexate was given as an example of a pharmaceutical that can cause teratogenicity through an indirect genotoxic mode of action. It was also acknowledged that the HPA report on transgenerational effects of radiation found some evidence for transgenerational effects in mice, but limited evidence in humans. This could be due to humans being less susceptible to such effects or due to transgenerational effects being limited to relatively short times post exposure (i.e. resultant changes or DNA damage may be repaired before conception). There could be species differences in responses to germ cell effects. One member noted that, if embryos with important chromosome damage were mainly aborted (as may be the case in humans) then adverse effects may occur mainly in terms of impaired fertility rather than as adverse effects in offspring. This may not occur in rats or mice. The committee agreed that toxicologists with expertise in other relevant areas should be invited to contribute to discussions on this topic (e.g. reproductive

toxicologists and germ cell expertise). It was agreed that the Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) should be contacted in the first instance to provide expertise on epigenetics and reproductive toxicity. It was acknowledged that other groups (e.g. the ENIGMA group and Genetic Toxicology Technical Committee/Developmental and Reproductive Toxicology) were also taking a similar approach by bringing together the expertise of reproductive toxicologists and genetic toxicologists.

19. The scoping paper had focused on male germ cell mutagenesis. However, the relative susceptibility, stage of highest sensitivity and relative risk of germ cell mutagenesis could be different in male and female germ cells. For example, female germ cells are held in meiosis I, which increases the risk of aneuploidy. Female germ cell mutagenesis had previously been discussed in the context of Down's syndrome and maternal age in the COM guidance document on the significance of chemical-induced mutation in human health. However, it was considered that this could be developed by taking into account new tools to investigate female germ cell mutagenicity.

20. A paper by DeMarini (2012) had recently identified air pollution as a germ cell mutagen. The chair suggested that the committee could explore this further by adopting a similar approach to the HPA report on radiation and germ cell mutagenesis. However, it was noted that measurement of exposure to air pollution can be complex. The available data on air pollution and germ cell mutagenicity were discussed. In addition to the studies summarised in the scoping paper, it was noted there are ongoing in studies in China measuring the effect of air pollution on human sperm quality, gestational diabetes and epigenetic changes. The secretariat noted that Public Health England (PHE) also acts as secretariat for the UK Committee on the Medical Effects of Air Pollutants (COMEAP) and could facilitate discussion between the two committees on this topic. The COM also agreed to contact David DeMarini to discuss developments in this area and how the committee could contribute.

21. Overall, the committee agreed that this would be an interesting topic to investigate further and that future work could be separated into three key themes: i) test methods to identify hazard to germ cells ii) germ cell mutagenesis and ageing and iii) transgenerational effects.

ITEM 6: UDATE ON GLYPHOSATE (MUT/2015/13)

22. The assessor from the Health and Safety Executive (HSE) updated the COM on the current situation relating to glyphosate. The COM was informed that there were three key areas of ongoing work on glyphosate.

23. It was anticipated that the Joint Meeting on Pesticides Review (JMPR) would initiate a review of the toxicology of glyphosate, including carcinogenicity. A World Health Organization (WHO) working group was looking at the current differences between the glyphosate databases used by the recent International Agency for Research on Cancer (IARC) review and a

previous JMPR review. A draft paper had been produced for the European Chemicals Agency (ECHA) by Germany on the proposed classification for glyphosate. Recently, the European Food Safety Authority (EFSA) hosted a teleconference/web conference, which included participants from EU Member States, IARC, ECHA and the US Environmental Protection Agency. A consensus opinion on the carcinogenicity classification had been agreed and the minutes of the meeting would be available soon.

ITEM 7: OECD GENOTOXICTY TEST GUIDELINES UPDATE

24. The OECD is currently updating its Test Guidelines (TG) on genetic toxicology. Accordingly, the OECD has produced a draft accompanying Guidance document on revisions to Genetic Toxicology Test Guidelines (the previous version was produced in 1986). It is intended to give information on the revision process as well as an overview of the presently available TGs. It is not intended to provide in-depth guidance or assessment of genetic toxicology, nor of its evolving concepts. The OECD had requested comments on the draft guidance. The deadline for comments was the 16th of October 2015, but the COM and UK had been given an extension until the 19th of October for comments.

25. Members discussed the draft Guidance document and made a number of comments and suggestions. The COM would provide these comments and suggestions, via the UK OECD representative, to the OECD secretariat by the 19th October.

ITEM 8: ANY OTHER BUSINESS

26. The Committee was informed that Public Health England's Centre for Radiation, Chemical and Environmental Hazards (CRCE) was currently undergoing a review. The COM may be consulted as a stakeholder and this would be done through the Chair. The Chair would circulate the relevant information and questions to members.

ITEM 9: DATE OF NEXT MEETING

27. 25th February 2016.