Committee on MUTAGENICITY

MUT/MIN/2017/1

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

Minutes of the meeting held at 10.30 am on Thursday 23rd February 2017 at St George's University of London in Room J1 – J13, Jenner Wing, Cranmer Terrace, London, SW17 0RE.

Present:

Chairman:	Dr D Lovell
Members:	Dr C Beevers Dr G Clare Professor S Doak Dr S Dean Professor H Drummond Professor D Harrison Professor G Jenkins Professor D Kirkland Dr A Povey
Secretariat:	Dr O Sepai (PHE Secretary) Mr B Maycock (FSA Secretariat) Dr K Burnett (PHE Tox Unit) Mr K Okona-Mensah (PHE Tox Unit) Mr S Robjohns (PHE Secretariat) Miss H Smith (PHE Secretariat)
Assessors:	Dr L Dearly (HSE) Dr S Fletcher (VMD)
In attendance:	Miss B Gadeberg (PHE COC & COT Secretariat)

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ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed members, the secretariat and assessors. Mr B Maycock was substituting for Dr D Benford as secretariat for the Food Standards Agency (FSA) and Miss B Gadeberg (PHE) was attending for the COC and COT Secretariat. Professor D Harrison, the chair of the COC, was attending as an ex-officio member. The Chair also welcomed Dr Andrew Povey as a new expert member from the University of Manchester and Professor Helga Drummond as a new Lay member from the University of Liverpool.

2. Apologies for absence were received from Dr D Benford (Secretariat FSA), Professor F Martin (member), Dr M O'Donovan (member), Ms P Hardwick (member), Dr H Stemplewski (MHRA) and Dr Colin Ramsay (Health Protection Scotland).

3. The members were asked to review their declarations of interest for inclusion in the 2016 Annual Report.

ITEM 2: MINUTES OF MEETING ON 16 JUNE 2016 (MUT/MIN/2016/2)

4. Members agreed the minutes subject to minor changes.

ITEM 3: MATTERS ARISING

5. The assessor for HSE gave an update on the EU review on the harmonised classification of glyphosate. The European Chemicals Agency's (ECHA) Committee for Risk Assessment (RAC) held its first preparatory discussion on the harmonised classification and labelling of glyphosate in December 2016. To provide a balanced overview of a wide range of scientific views already published on glyphosate, a number of organisations were invited to give presentations to RAC. This included presentations from the German Federal Institute for Occupational Safety and Health (BAuA) as the dossier submitter, the European Food Safety Authority (EFSA), the International Agency for Research on Cancer (IARC), the joint FAO/WHO meeting on pesticide residues (JMPR), industry's glyphosate task force (GTF) and a representative of civil society (Health and Environmental Alliance, HEAL). All of the presentations are now available on ECHA's website. RAC will continue discussing the harmonised classification and labelling of glyphosate at its next meeting in March 2017. The legal deadline for RAC to adopt its opinion on glyphosate is November 2017. The meeting minutes, harmonised classification and labelling report and a YouTube video outlining ECHA's work on glyphosate are available on ECHA's website.

6. PHE secretariat and chairs of the Department of Heath's (DH) expert committees met with Jill Meara (Interim Director of PHE's Centre for Radiation, Chemicals and Environmental Hazards (CRCE)) and the Food Standards Agency (FSA). At both meetings, the resources available to provide support to

the committees were discussed as the contract with Imperial College London, who currently provides secretarial support to the COM, is up for renewal. It was noted that Brexit will have an impact on the role of the government's scientific committees. The chairs requested that the committees receive formal feedback on committee advice given to Ministers, which could be documented. The DH has asked the committees to provide annual forward plans, which should include a balance between short-term advice and long-term strategies (e.g. guidance and testing).

RESERVED BUSINESS

ITEM 4: DRAFT SCOPING PAPER – TOXICOLOGICAL EVALUATION OF NOVEL HEAT – NOT BURN COMMERCIAL TOBACCO PRODUCTS: OVERVIEW SUMMARY OF SUBMITTED GENOTOXICITY DATA (MUT/2017/01)

OPEN SESSION

ITEM 5: QUANTITATIVE APPROCHES TO THE ASSESSMENT OF GENOTOXICITY DATA II (MUT/2017/02) AND ITEM 6: QUANTITATIVE APPROACHES TO THE ASSESSMENT OF GENOTOXICITY DATA II – EVALUATION OF BENCHMARK DOSE SOFTWARE (MUT/2017/03)

16 At the COM meeting in October 2016, Dr George Johnson from Swansea University gave a presentation on quantitative analysis of genotoxicity data including work undertaken by the Quantitative Analysis working group (QAW) of the Genetic Toxicology Technical Committee. Members also considered a paper (MUT/2016/07), which outlined various aspects of quantitative analysis of genotoxicity data. This included; points of departure; threshold dose response relationships; risk assessment approaches; comparisons of genotoxic and carcinogenic potencies and some publications on the developments of quantitative approaches in the analysis of genotoxicity data.

17. There had been some preliminary discussion of this topic at the October 2016 COM meeting and members had agreed that this subject should be discussed further with the aim of producing a COM statement on the topic. Aspects considered at the current meeting included: the most suitable test system and endpoints (e.g. gene mutations or micronuclei); appropriate tissues for analysis; appropriate critical effect size (CES) or suitable benchmark response (BMR) values; and the potential for using genotoxicity data in a margin of exposure (MOE) approach to carcinogenicity risk assessment.

18. Members agreed that there have been changes in the available quantitative modelling approaches and methods that meant that genotoxicity data could now be evaluated quantitatively rather than just qualitatively. For example, the shape of the dose-response curve could be analysed and that this could be done with as little as 3 doses. The COM noted that the calculated benchmark dose (BMD) consistently produced a lower and more conservative value than the other available options for determining the point of departure (POD) (e.g. the no observed genotoxic effect level (NOGEL) and the breakpoint dose (BPD)) . This indicated that the lower confidence limit of the benchmark dose (BMDL) would be the most health protective of the available genotoxic PODs.

19. However, the COM had concerns about using quantitative dose response analysis of genotoxicity data for carcinogenicity risk assessment. Members agreed that there were many uncertainties and methodological aspects that required addressing before BMDLs for genotoxicity endpoints and BMDLs for carcinogenicity data could be usefully compared. For example, differences in responses between species or sex; the shorter durations of exposure in *in vivo* genotoxicity studies compared to carcinogenicity studies; and differences in tissues evaluated. Furthermore, genotoxicity endpoints were considered to consist of continuous data (e.g. mutation frequency and micronucleus frequency) whilst carcinogenicity endpoints were considered to consist of dichotomous data (i.e. a yes or no event). Also, it was not clear which benchmark response (BMR) value should be used for each endpoint (e.g. 5% or 10% or 1SD etc.). Members noted that because of the different stages and complex events that occur following an initial mutation to the development of cancer (e.g. DNA repair and organ specific metabolism), a direct correlation between genotoxicity and cancer would not be expected (e.g. a 10% increase in mutation frequency above controls is very different to a 10% increase in tumour bearing animals above controls). Whilst it was considered that a potent mutagen is likely to be a potent carcinogen, the correlation for weaker mutagens was not as clear. Members noted that various events or stages leading to cancer did appear to occur at increasing doses, for example, adduct formation, mutations, pre-neoplastic lesions and tumours. However, currently, with the various uncertainties and lack of supporting quantitative analytical data on a large number of chemicals and different chemical classes, it was unclear how genotoxicity could be used in carcinogenicity risk assessment. Overall, it was concluded that that there was some potential for the use of a BMDL from genotoxicity data in a MOE approach similar to that used in the risk assessment of genotoxic carcinogens, but further evaluation of the relationship between mutagenicity and carcinogenicity, using a greater number and range of chemicals, was required to enable a more reliable comparison to be made.

20. The COM also discussed the various dose response modelling methods utilised in BMD analysis e.g. the Hill or the exponential model. The main differences in the US EPA and RIVM software approaches (called BMDS and PROAST respectively) related to the use of log transformed data or not, and the use of one standard deviation or a percentage increase (e.g. 5 or 10%) as the BMR/CES. It was noted that the use of 10% as the CES was small

compared to the currently used 2-fold increase, for example, in the frequency of micronuclei in a micronucleus study. Members agreed that more clarification of each model's basic assumptions and uncertainties was required before the COM could come to any conclusions or make any recommendations.

21. The COM also considered the importance of study design and data quality in BMD modelling. It was noted that data quality will be reflected in the confidence intervals, which will also be affected by the number of dose groups and numbers of animals per group. Members commented that it would be useful to have some guidance on the degree of uncertainty in the data and, for example, guidance on what ratio of the upper confidence limit to lower confidence limit would be considered unacceptable. The COM agreed that if the quality of the dose-response data were not sufficient or there was a lot of variability in the data, then it may not be appropriate to fit a model to the dose-response data. Members believed that the current OECD guidelines for design of genotoxicity studies were suitable for quantitative analysis, but agreed that flexibility on study design should be considered (e.g. a larger number of doses and fewer animals per dose could be used if required). The COM agreed that it was very important to consider the quality of the available data before conducting or interpreting quantitative analysis of genotoxicity data.

22. The COM considered that currently, it was not able to draw firm conclusions or make any recommendations on the use of an appropriate critical effect size for the various genotoxic endpoints or on the most appropriate genotoxic endpoint to use. More data and further explanations were needed before the COM would be in a position to do this. It was agreed that a statement would be drafted on the current research and the COM's views on the topic.

ITEM 7: ANY OTHER BUSINESS

i) Annual Report

23. Members were asked to provide comments on the first draft of the annual report, which would be circulated shortly. It was suggested that the annual report could have more impact if it contained an overview of the committees work given in layman's terms.

ii) Statements from EU Regulatory Agencies

24. One member provided an update on the ongoing work regarding concerns expressed at a previous meeting on four statements from regulatory reviews by ECHA/EFSA. The first three statements were being addressed by the ILSI Health and Environmental Sciences Institute (HESI) Genetic Toxicology Committee (GTTC). However, one member had drafted a white paper on the fourth statement from the ECHA's Member State Committee

(MSC) which requested that the glandular stomach (in addition to the liver and duodenum) should be sampled for site of contact assays to help account for tissue variables; such as tissue structure/function, pH conditions, absorption rates and differences in breakdown products. The paper contained information available in the public domain on studies that had used both the duodenum and glandular stomach and was circulated to members for comments. The paper had also been shared with the United Kingdom Environmental Mutagen Society (UKEMS) Industrial Genotoxicology Group (IGG) to see if any additional data using both tissues was available. One member agreed to share a number of studies for inclusion in the paper, which would be presented at the next meeting. The assessor for HSE agreed to identify contacts in EFSA and ECHA for which the outcome of this work could be shared with.

iii) Horizon scanning

25. The chair invited the committee to contribute to a horizon scanning exercise. One member was invited to give a presentation on the 'development of chronic and passive *in vitro* dosing systems for genotoxicity assessment', which had recently been covered at the joint National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs) and Unilever Workshop on 'applying exposure science to increase the utility of non-animal data in efficacy and safety testing'. It was also suggested that a presentation could be given on the US Environmental Protection Agencies (EPA) Benchmark Dose Software (BMDS).

ITEM 8: DATE OF NEXT MEETING

26. 22nd June 2017