MUT/2018/11

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

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

This is a preliminary paper for discussion. It does not represent the views of the Committee and must not be quoted, cited or reproduced.

Preface

Forward by David Lovell – Chair

I am pleased to present this report on the work of the Committee on Mutagenicity (COM) during 2017. As always, the COM would be happy to receive any feedback from readers of this report.

The Committee on Mutagenicity (COM) provides advice on potential mutagenic activity of specific chemicals at the request of UK Government Departments and Agencies. Such requests generally relate to chemicals for which there are incomplete, non-standard or controversial data sets for which independent authoritative advice on potential mutagenic hazards and risks is required. Recommendations for further studies are, on occasions, made.

The Committee also advises on important general principles and on new scientific work related to the assessment of mutagenic risk and makes recommendations on mutagenicity testing. The membership of the Committee, declarations of their interests, agendas and minutes of meetings, and statements are all published on the internet. https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment

Field Code Changed

During the course of 2017, the Committee worked on a number of topics. The COM reviewed the genotoxicity evidence on novel heat-not-burn tobacco products as part of Committee on Toxicity's (COT) toxicological evaluation. It discussed quantitative approaches to the assessment of genotoxicity data and a document related to this will be published early in 2018. It consolidated discussions on issues related to germ cell mutations and considered, in the context of epigenetics', the transgenerational effects of Vinclozolin. The committee joined with its sister committees: the COT and the Committee on Carcinogenicity (COC) for a one-day symposium on "Whether epigenetics should be used in chemical risk assessment" at Public Health England (PHE), Chilton in September 2017.

Comment [SR1]: I'm not sure this is correct, unless this is referring to consideration at the Joint Committee meeting on epigenetics in October 2017? A discussion paper on vinclozolin was provided at the Joint Committee meeting and the statement on the joint meeting referred to vinclozolin. The COM considered vinclozolin in June 2016.

The Committee also carried out its annual Horizon scanning exercise, identifying a number of potential topics for future work. The COM is interested in obtaining information from Government Departments on how its advice is acted upon.

Throughout 2017 the COM continued to take an active interest in the work of the OECD (Organisation for Economic Cooperation and Development) on test guidelines. It commented on the OECD's reviews of old test guidelines (TGs) and the development of new TG's.

The COM also maintained an awareness of the possible implications of Brexit on its work and was aware that there remained uncertainty in how this may affect the regulatory environment and the UK's relationship with international organisations.

I want to thank the secretariat for their work and the members of the Department of Health's Toxicology Unit who maintained their usual high standard of work up until the end of the Unit's contract. We look forward to working with WRC/IeH in the future. I am again grateful for the support of the individual members of the committee for their expert advice, the time they put in and their support throughout the year.

Dr D Lovell Chair
PhD BSc (Hons) FBS CStat CBiol CSci

ONGOING WORK

Joint committee workshop – Use of epigenetics in chemical risk assessment

The field of epigenetics research and the potential role of epigenetic changes in toxicology has been considered previously by COC, COM and COT, and all have recently recommended maintaining a watching brief on developments in their respective Horizon Scanning exercises. To fulfil this brief, a workshop for Members of all three Committees was organised in October 2017 with the aim of considering the overarching question; 'Whether epigenetics should be used in chemical risk assessment'.
A joint statement on the discussion of the topic is in draft and will be finalised in 2018.

COM EVALUATIONS

MUT/2017/01 and MUT/2017/05 Toxicological evaluation of novel heat-not-burn commercial products: Overview of genotoxicity data submitted (Confidential)

As part of the COT assessment of the toxicological risks from novel heat-not-burn tobacco products, the COM assessed the available genotoxicity data. The COM participated in a joint discussion with COT and COC where the two manufacturers of products notified in the UK before November 2016 presented the relevant toxicity data held.
More information on the assessment and a link to the COT statement is available in the COT section of this report (paragraph 1.9 **[DN – FSA to check paragraph numbering]**).

MUT/2017/02 Quantitative approaches to the assessment of genotoxicity data II and MUT/2017/03 First Draft Quantitative risk assessment statement

At the COM meetings in October 2016 and March 2017, members considered papers on recent developments in Quantitative approaches to the risk assessment of genotoxicity data. This included overviews of reports from the International Workshops on Genotoxicity Testing (IWGT) working group on quantitative approaches to genetic toxicology risk assessment (the QWG); publications arising from a workshop organised by HESI; and publications in a recent edition of Mutagenesis on this topic. Aspects, such as, the development of different benchmark dose (BMD) software (PROAST[1] and US EPA BMDS), point of departure metrics, and application in carcinogenicity risk assessment were considered.

[1] This includes the EFSA-PROAST platform

A first draft had been produced (MUT/2017/03) for consideration and comment by members. Overall, the COM considered that quantitative dose-response analysis of genotoxicity data was work in progress and that further work was required. It was important to address a number of the points referred to above such as, the most suitable BMD software; documentation and explanation of the various versions of the BMD software; clearer explanation of the analytical quantitative approaches; difference between quantal and continuous data; suitable sampling time; a cut-off point for poor quality data; suitable genotoxic endpoint and tissues; biological relevance of critical effect size (CES) or benchmark response (BMR); and analysis of a larger number of chemicals and classes with different modes of genotoxic action.
A final statement has been published in 2018.

MUT/2017/04 Consolidated Summary of germ cell mutation discussions

The COM considered germ cell mutation at a meeting in June 2013, October 2015 and in February 2016.

COM discussed appropriate sampling times to detect mutations in sperm and the potential implications for current guidance on germ cell gene mutation assays (e.g. OECD Test Guideline 488). Members were aware of suggestions that a sampling time of 28 days post dosing in *in vivo* studies may be more appropriate than the current recommendation of a 3 day post dosing sampling time to detect DNA effects in sperm. It was agreed that this should be addressed in the draft COM summary document.

The COM noted that there was evidence that the number of mutations in sperm increased as paternal age increased. It was not clear whether this increase in mutations was due to an individual being older per se (i.e. due to the aging process) or whether it was a consequence of a longer duration of exposure to environmental mutagens.

Regarding the suggestion that air pollution was a germ cell mutagen, the COM considered that the sperm assays used in providing evidence for this assertion had not been sufficiently validated for detecting germ cell mutations. Members had previously agreed that the SCSA and the TUNEL assays were difficult to interpret in terms of germ cell mutagenicity and had not been sufficiently validated for detecting mutation.

MUT/2017/05 Epigenetics: the transgenerational effects of Vinclozolin

Comment [SR2]: I don't think this should be a heading. I don't think that vinclozolin was considered by COM at the February and June 2017 meetings. It was considered at the COM June 2016 meeting. It was considered at the Joint Committee meeting in October 2017 and referred to in the Joint statement from the meeting.

HORIZON SCANNING

The COM undertakes an annual 'Horizon Scanning' exercise, which provides an opportunity for Members and assessors from Government Departments/Agencies to discuss and suggest topics for further work.

COM considered statements by ECHA/EFSA which have caused concern. The first statement was that for *in vivo* genotoxicity assays the intraperitoneal (IP) route of administration should be preferred over oral and inhalation as it leads to a by-pass of some first pass metabolism in the liver, and therefore, produces a more sensitive test. The second statement was that for the *in vivo* mouse micronucleus test, even if a test compound is detected in the plasma, it does not necessarily indicate that the target tissue in the bone marrow had been sufficiently exposed to the test compound. The third statement was that even if it can be demonstrated that a test chemical has reached the bone marrow at a concentration that exceeds anticipated human exposure, it may not be considered adequate, as higher exposure could have been achieved in an *in vivo* site-of-contact comet assay. The fourth statement was 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. These statements were discussed as part of the horizon scanning exercise.

A joint horizon scan exercise was carried out at the Joint COM/COC and COT meeting in October 2017.

The committee keeps up to date with discussion at OECD with regard to genotoxicity test guidelines.

Comment [SR3]: Or kept?

GUIDANCE STATEMENTS

None