Committee on MUTAGENICITY

MUT/MIN/2020/1

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

Minutes of the meeting held at 10.30 am on 20th February 2020 at Department of Health, Skipton House, 80 London Road, London, SE1 6LH.

Present:

Chairman:	Dr D Lovell
Members:	Mr A Bhagwat Dr C Beevers Professor S Doak Dr M O'Donovan Dr S Dean Professor P Fowler Dr R Morse Dr A Povey
Secretariat:	Dr O Sepai (PHE Scientific Secretary) Mr S Robjohns (PHE Secretariat) Dr C Mulholland (FSA Secretariat)
Secretariat Support:	Dr R Bevan (WRc/IEH Consulting) Mr B Seery (WRc plc)
Assessors:	Dr L Koshy (HSE) Dr H Stempleski (MHRA) Mrs R Pearson (VMD)
Observers	Professor J O'Brien (FSA Scientific Council)

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	Dr G Stoddart (PETA International Consortium limited)
	Dr H Thurston-Smith (GW Pharmaceuticals)
In attendance:	Dr R Foster (Lhasa Ltd)

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ITEM 1: ANNOUNCEMENTS/APOLOGIES FOR ABSENCE

1. The Chair welcomed the COM members, assessors and secretariat. Dr C Mulholland attended for the Food Standards Agency. Professor J O'Brien (FSA Scientific Council); Dr H Thurston Smith (GW Pharmaceuticals); and Dr G Stoddart (PETA International Consortium limited) attended as observers. The Chair also welcomed Mr B Seery attending for WRc plc and Dr R Foster attending for Lhasa.

2. Apologies for absence were received from Professor D Harrison (Ex Officio), Dr R Morse, Dr D Gott (FSA), and Ms E Blenkinsop (DHSC).

3. The COM was informed that Dr D Gott is improving in health and hopefully will return to work in the next few months.

4. The Committee was informed that interviews would be conducted for the two vacant positions for expert members and one lay member. It was hoped that these vacancies would be filled in time for the next meeting in June.

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

ITEM 2: MINUTES OF MEETING ON 28th February 2019 (MUT/MIN/2019/1)

6. Members agreed the minutes subject to minor typographical changes. Item 10 on OECD updates was not complete. This would be added and sent out for agreement.

RESERVED SESSION

7. The draft minute on the reserved business item on the risk to human health from the use of azodicarbonamide (MUT/2019/07) was approved.

OPEN SESSION

ITEM 3: MATTERS ARISING

8. There were no matters arising not on the agenda.

ITEM 4: REVIEW OF THE GENOTOXICITY OF CANNABIDIOL UPDATE (MUT/2020/01)

CB – noted a potential conflict of interest in that she may have been involved in some of the contract studies but from the information provided could not say for certain whether she had been involved in these specific studies.

9. The Food Standards Agency (FSA) previously asked for an opinion from the COM on the genotoxicity of CBD. This was to assist the FSA in developing its advice relating to the increasing number of requests for a risk assessment

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of CBD in consumer products. The Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) evaluated the potential adverse health effects of CBD products in July 2019. It concluded that that genotoxicity data were conflicting and requested a COM view of the genotoxicity data. Subsequently, the COM considered genotoxicity data relating to CBD at its previous meeting in October 2019. The COM concluded that the *in vitro* and *in vivo* studies were inadequate. In January 2020, the COT received an update on available data, which included additional genotoxicity data. The COT therefore referred consideration of the new genotoxicity data to the COM.

10. Paper MUT/2020/01 provided details of additional genotoxicity studies submitted to the European Medicines Agency (EMA) (available online) in relation to a medicinal form of CBD known as Epidiolex (used to treat seizures in certain medical conditions e.g. Lennox-Gastaut syndrome and Dravet syndrome).

11. The *in vitro* data consisted of pure CBD tested in the Ames test conducted to GLP (in *Salmonella typhimurium* strains TA98, TA 100, TA 102, TA 1535, and TA 1537). Members had no concerns over the reported data and agreed with the conclusion of a negative result.

12. Two *in vivo* studies were reported, a bone marrow micronucleus test and a comet assay for chromosome damage. Pure CBD was evaluated for its potential to increase the incidence of micronucleated polychromatic erythrocytes (MNPCEs) in rat bone marrow cells. Male rats received two oral gavage doses of 0 (sesame oil), 125, 250 and 500 milligrams per kilogram of body weight per day (mg/kg bw/day. The positive control group was dosed once with cyclophosamide (CPA 20 mg/kg) on the second day of dosing. In addition to animals tested for micronucleus formation, two groups of satellite animals were dosed with vehicle and pure CBD (500 mg/kg/day) for confirmation of exposure (this did not include toxicokinetic data). Clinical signs of exposure (e.g. lethargy, ataxia, piloerection, anogenital soiling and unkempt appearance) were observed on day 3. CBD treated rats showed mean MNPCE frequencies similar to those of the vehicle control group and fell within the laboratory's historical vehicle control range. Members noted that they could not see any information provided on whether the target tissue had been exposed (e.g. toxicokinetic or plasma levels) but assumed that bone marrow exposure would occur when a medicinal product is used. The COM agreed that from the information provided that the study appeared to be robustly conducted and gave a negative result.

13. In a rat alkaline comet assay, rats were given single oral gavage doses of 0 (sesame oil), 125, 250 or 500 mg/kg/day CBD oral solution. Liver samples were taken 24 hours after the initial dose. No clinical signs of toxicity were observed at any dose. Members agreed that from the information provided the study appeared to be robustly conducted and gave a negative result.

14. Overall, the COM concluded that from the information provided, the studies appeared to be well conducted and gave negative results. However, the COM asked whether it could see all the relevant data for the *in vivo* studies to confirm that there was sufficient target tissue exposure and to evaluate whether there was any important species difference in metabolism (i.e. between humans

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and rats) because the potential for this this was mentioned in the summary information provided.

ITEM 5. GUIDANCE STATEMENT ON QSAR MODELS TO PREDICT GENOTOXICITY (MUT/2020/02)

Presentation by Dr Robert Foster from Lhasa Ltd

15. Dr Robert Foster from Lhasa Ltd provided a presentation from Lhasa on its views on the COM scoping document and draft statement on QSAR models to predict genotoxicity. Lhasa had been asked to discuss the transparency of the data used to develop structural alerts.

[To be provided by Benjamin Seery from WRc?]

ITEM 6. COM Guidance Series update (MUT/2020/03)

Amendments to the COM Guidance document as a whole have been ongoing and previously considered at Committee meetings in July 2018 (paper MUT/2018/09), October 2018 (paper MUT/2018/13), February 2019 (MUT/2019/01) and October 2019 (MUT/2019/12). At the last consideration, the Committee completed their review and suggested amendments to the main text.

The paper presented (MUT/2020/03) contained all amendments made to date to the main text. Members were asked to separately consider the content of Table 1 and Annexes 1, 2 and 3 and outstanding questions regarding the main text. The Chair addressed each page of the document in turn, inviting suggested amendments to outstanding questions. The author of Annex 1 had been consulted by the Secretariat and had recommended removing the text as the information was now historical in nature. This was agreed by the Committee with the suggestion that reference was made in the latest version of the Guidance to older versions with this information, as it provided valuable background. A decision was also taken to apply this approach to Annex 3.

With regards to Table 1 and Annex 2, the Committee agreed that these should remain. Members were also asked to provide updated references for a number of sections and it was agreed that the specific areas needed would be identified by the Secretariat and sent to members.

All changes received would be incorporated into a new version of the Guidance Document to be reviewed at the next COM Committee meeting in June 2020.

ITEM 7: TWO DAY WORKSHOP IN BIRMINGHAM ON THE INTREPRETATION OF GENOTOXICITY DATA

At the previous COM meeting in October 2019 members were presented with two draft papers following the two-day workshop held in Birmingham in June 2019 on the interpretation of genotoxicity data in a regulatory environment. The first paper (MUT/2019/09) provided notes of the presentations and discussions. The second paper (MUT2019/09) provided an assimilated summary of the

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workshop. Following comments from members at the October 2019 meeting the two draft papers were sent out for comments to two ex-COM members who had been present at the workshop, external attendees from industry and participants from EFSA. Following the received comments the two papers were updated. The amended papers (i.e. draft notes (MUT/2020/04) and summary document (MUT/2020/05)) were presented to the COM for any further comments.

Members considered that the various questions and the outstanding matters that needed to be resolved could better be addressed by a summary of the relevant questions being sent to the members by email. Regarding a future publication, it was suggested that this could be drafted by using the greater detail contained in the draft notes combined with some of the useful introduction and 'setting the scene' descriptions contained in the draft summary paper. The secretariat agreed to summarise the outstanding questions and circulate to members via email.

ITEM 8: HORIZON SCANNING

It was noted that the previous item on the two-day workshop on the interpretation of genotoxicity data contributed to horizon scanning. For example, there was a proposal to form a working group to develop a framework or guidance (perhaps, similar to that of the Bradford-Hill criteria) on how to evaluate genotoxicity data from different sources (e.g. unpublished GLP studies conducted to OECD test guidelines and non-GLP studies published in the scientific literature). A few members expressed an interest in contributing to this. It was also noted that an additional COM led workshop could be organised in the future to further discuss unresolved questions that came out of the Birmingham meeting.

The committee was informed of an email from the DHSC assessor that said the UK would start formal negotiations with the EU in March 2020. It was anticipated that the UK would publish its mandate for negotiations with the EU next week. This would include UK objectives for the chemical sector and rules/regulations relating to future trade. It was also anticipated that formal negotiations with the EU would start in March and that Defra would be developing a new chemical strategy. Additionally, it was expected that there would be a call for evidence in Spring relating to human health and chemicals in the environment.

The COM assessors considered that it was currently difficult to predict how the various government departments/agencies may require COM input in the future.

Members noted a few topics that the COM may need to consider in the future and these included the baseline for spontaneous inherited mutations; environmental DNA (eDNA) collected from environmental samples (e.g. soil, water or air), which could be informative for monitoring various aspects, such as biodiversity (via DNA sequencing without having to collect individual living organisms); and new techniques for evaluating DNA damage. Additionally, it was noted that horizon scanning needed to be targeted with a need to avoid duplication or unnecessary work (e.g. in terms of regulatory response to technological changes). The COM was also informed that the COT was holding a workshop on exploring dose-response analysis at Manchester on the 11th March 2020.

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ITEM 9: OECD PIG-a UPDATE

The COM was provided with paper MUT/2020/06 relating to the PIG-a gene mutation assay, mainly for information. This included UK comments that had been submitted to the OECD on the development of its test guideline. Member were asked if they had any additional comments.

The Chair declared an interest in that he had been involved with an OECD working group on a development for a Test Guideline for the PIG-a assay.

The COM agreed this did not contain anything controversial and was generally content. It was noted that although there was nothing wrong with the assay, it did not appear to fill any useful gaps i.e. it did not enable anything to be investigated that couldn't already be done with existing methods. It would be useful if it could be developed further to examine other tissues in addition to peripheral blood.

Additionally, an update on the development of OECD Test Guideline 488 on transgenic rodent somatic and germ cell mutation assays was circulated to the COM (just a day before the meeting). Members were aware that there had been some disagreement between some countries over the text for sampling time in relation to rat germ cells. Members were also aware of reported evidence and modelling of rat spermatogenesis that suggested that a 28 day + 28-day (i.e. sampling 28 days later, after 28 days of dosing) designs was a better germ cell design than 28-day + 3-day (i.e. sampling 3 days later, after 28 days of dosing) for both the mouse and rat. The UK had previously commented that the data on appropriate sample times were not as good for the rat as the mouse. The relevant paragraph had been reworded to create a 'quick fix' for TG 488.The COM was content with the new wording that had been circulated (e.g. regarding sample times).

ITEM 10: WHO JECFA RESPONSE TO CONSULTATION (MUT/2020/07)

The Committee was provided with comments from COM members that had already been sent to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) secretariat on its draft revision of EHC 240 chapter on genotoxicity. Members were asked whether they wished to submit any additional comments. JECFA were expected produce a final version and provide responses to any not taken into consideration. The COM had no further comments.

ITEM 11: DRAFT ANNUAL REPORT (MUT/2020/08)

An initial incomplete version of the draft report was circulated for information. It was incomplete because items from the previous COM meeting in October 2019 could not be incorporated until the minutes had been approved. The items in the approved minutes from today's meeting would be inserted into the draft annual report.

Members noted that the wording on Toxtracker needed to be amended to reflect that it detects two different responses to DNA damage rather than two different types of DNA damage (i.e. there are more than two types of DNA damage).

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Members were requested to send any further comments on the draft annual report to the secretariat via email.

ITEM 12: ANY OTHER BUSINESS

There was no other business.

ITEM 13: DATE OF NEXT MEETING

9 June 2020 – venue to be arranged.

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