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

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Foreward by Gareth Jenkins – Chair

I am pleased to present this report on the work of the Committee on Mutagenicity (COM) during 2021. I was honoured to be asked to take over the role of Chair of COM in May 2021 and I would like to begin by paying tribute to my predecessor (Dr David Lovell) for his stewardship of COM during the preceding years and Chairing the February 2021 meeting.

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 wider aspects of 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

In 2021, the updated COM guidance on genotoxicity testing strategy was published (MUT/2021/01). This update, begun in 2020, sets out the suggested strategy for genotoxicity testing of chemicals and updates our position to consider advances in the field of safety testing. COM also updated guidance on testing of germ cell mutagens (MUT/2021/02) and the use of 3D tissue models as alternative approaches to animals in testing (MUT/2021/03). The documents will be published on the COM website. The 3D tissue strategy responds to the growing focus on animal alternatives driven by the

production of novel sophisticated tissue models which can recapitulate aspects of human biology.
In 2021, COM discussed the safety testing of impurities (MUT/2021/04) and the use of QSAR and toxicogenomics in testing (MUT/2021/05 and MUT/2021/06).
In 2021, COM started a discussion of the genotoxicity of titanium dioxide (MUT/2021/07 and MUT/2021/12), following the updated opinion published by EFSA in 2021. This review of titanium dioxide will be continued and concluded in 2022.
In 2021, COM further discussed the use of toxicogenomics in safety testing (MUT/2021/08), separating out the transcriptomics aspect from the next generation sequencing (NGS) approaches. Given the advances in NGS in general, it is likely that over the coming years, NGS approaches may replace some traditional mutation testing platforms. COM also published guidance on a testing approach for nanomaterials, with a focus on considerations of the fact that key physico-chemical aspects of nanomaterials render some traditional genotoxicity tests not suitable (MUT/2021/09).
COM also discussed the potential genotoxicity of specific compounds as requested by Government departments and agencies. For example, COM reviewed the genotoxicity of Hydroxyanthracene Derivatives (MUT/2021/12) and associated human health risks.

The Committee carried out its annual Horizon scanning exercise, identifying potential topics for future work. The COM continues to be interested in hearing from Government Departments and Agencies on how its advice is acted upon.
The COM maintained its awareness of the implications of EU EXIT on its work and remained alert to the continuing uncertainty as to how the UK's regulatory environment and its relationships with international organisations will develop in 2022 and onwards.

I would specifically like to thank the COM secretariat for their exceptional support to the COM and to the WRc/IEH team for the excellent work they delivered in 2021. As always, I am grateful for the support of the individual members of the committee for their expert advice, the effort and time they put in and their support throughout the year.

Professor Gareth Jenkins

ONGOING WORK

COM GUIDANCE SERIES UPDATE

The updating of the overarching COM Guidance document on a strategy for the genotoxicity testing of chemicals was finalised in 2021. Amendments to the overarching COM Guidance document had previously been considered at Committee meetings in July 2018 (paper MUT/2018/09), October 2018 (paper MUT/2018/13), February 2019 (MUT/2019/01), October 2019 (MUT/2019/12), February 2020 (MUT/2020/03), June 2020 (MUT/2020/09) and November 2020 (MUT/2020/16). An additional sub-group meeting was held in January 2021 to complete review of comments left outstanding following the November 2020 meeting. This was attended by Dr David Lovell (Chair), Dr Carol Beevers, Dr Paul Fowler, Dr Ovnair Sepai (Scientific Secretary) and Dr Ruth Bevan (Secretariat support).

Following consideration of paper MUT/2021/01 the update of the overarching COM Guidance document on a strategy for the genotoxicity testing of chemicals was agreed by members, signed off by Chair action and published on the COM website. It was intended that this would be updated in the future as part of a rolling revision.

GUIDANCE STATEMENT – GERM CELL MUTAGENS

Drafts of a stand-alone guidance statement on genotoxicity testing strategies for germ cell mutagens were considered at the Committee meeting in February 2019 (MUT/2019/05), in October 2019 (MUT/2019/12), in June 2020 (MUT/2020/11) and November (MUT/2020/17). In 2021, members considered paper MUT/2021/02, which presented changes suggested following the November 2020 meeting. Following agreed amendments, the finalised document was signed off by Chair's action and published on the COM website.

GUIDANCE STATEMENT - 3D MODELS

Drafts of a stand-alone guidance statement on the use of 3D models for genotoxicity testing were considered at the Committee meetings in February 2019 (MUT/2019/04), October 2019 (MUT/2019/12), June 2020 (MUT/2020/11) and November (MUT/2020/18). In 2021, members considered paper MUT/2021/03, which included suggested changes following the meeting in November 2020. Following agreed amendments, the finalised document was signed off by Chair's action and published on the COM website.

GUIDANCE ON GENOTOXICITY TESTING STRATEGIES FOR NANOMATERIALS

Genotoxicity testing of nanomaterials (NMs) was recognised by the Committee as a rapidly developing area. Paper MUT/2021/09 presented a draft COM Guidance on the genotoxicity testing strategy for NMs. This was prepared to a format previously agreed by COM at the meeting in November 2020 (MUT/2020/19). Members considered that it was important to add a note to clarify that 'Stage 0' of the COM recommended approach for genotoxicity testing would not apply to NMs. A question was raised regarding whether COM should recommend a positive control for NM testing. This was not considered feasible at present as this would probably need to be both assay and cell line specific, due to differing sensitivities. Members requested that this information be added to the document. It was also agreed that a note should be added to consider the most appropriate dispersion technique for a specific NM. Following these amendments, members agreed that a final version of the document could be signed off by Chair's Action and published on the COM website. It is recognised by the Committee that this is a rapidly developing area and updates will be carried out as new information becomes available.

GUIDANCE STATEMENT ON TESTING FOR IMPURITIES – UPDATE

The COM published a guidance statement in 2012 on a strategy for genotoxicity testing and mutagenic hazard assessment of impurities in chemical substances. Since 2012, there have been a number of initiatives in this area and as part of the ongoing update of the COM Guidance Statement series, members agreed that the Guidance document should be updated. A draft revised document was presented at the Committee meeting in November 2020 (MUT/2020/21) and following comments and suggestions from members a revised draft statement was produced (MUT/2021/04) and presented at the February 2021 meeting. During review it was suggested that the impurities guidance statement and QSAR guidance statement could be merged as there was overlap between the two areas. Members discussed this possibility but agreed to keep the two as separate documents.

Following revision of the draft Guidance document on impurities to include suggested amendments, members agreed that a second revised interim draft would be presented for discussion at a later meeting.

COM GUIDANCE STATEMENT ON THE USE OF QSAR MODELS

A range of Quantitative Structure-Activity Relationship (QSAR) models have been developed to predict genotoxicity. The COM has previously agreed that where no genotoxicity data are available, the intrinsic chemical and toxicological properties of a chemical must be considered prior to developing a genotoxicity testing programme, as reported in "*Guidance On A Strategy For Genotoxicity Testing Of Chemical Substances*" (COM, 2011) and as updated in 2021. This guidance describes a staged approach to testing consisting of stages 0 (preliminary considerations including physico-chemical properties), 1 (*in vitro* genotoxicity

tests) and 2 (*in vivo* genotoxicity tests). QSARs are incorporated into Stage 0 of the COM guidance.

Alternatives to animal testing and the usefulness of computational methods in the prediction of genotoxicity are areas of increasing research. QSAR models and their predictions currently cannot replace the need to undertake the *in vitro* and *in vivo* genotoxicity tests required to derive conclusions on mutagenic hazard except in specific regulatory settings. As the development and use of QSAR is a rapidly developing field, it was agreed that the current text in the COM overarching guidance document should be reduced and a larger 'stand-alone' guidance statement be prepared which could be updated as needed.

A draft document - 'Guidance Statement on the use of QSAR models to predict genotoxicity' was prepared and discussed by COM in February 2019 (MUT/2019/03). Following amendments, a revised paper was discussed in February 2020 (MUT/2020/02) and November 2020 (MUT/2020/20). No agreement was reached as to whether the draft guidance statement was 'fit-for-purpose' and it was also suggested that QSARs could be incorporated into the COM guidance on impurities, as this is where it is likely to be used.

Following a further draft COM Guidance on QSARs (MUT/2021/05) considered at the February 2021 meeting, a sub-group discussion with some COM members was held in September 2021 to plan a way forward. It was suggested that, based on current acceptance and use of QSARs, incorporation of examples of use and reporting of data should be included in the updated impurities guidance document, with a link to the OECD portal provided to give the most current perspective/tools etc. A more general description (taken from the current draft document) would then be re-introduced into the COM overarching guidance document to support the Stage 0 testing text.

Members agreed that it was important for any COM guidance to highlight applications of QSAR, as for the assessment of impurities, rather than proving a list of QSAR models and approaches. As such the proposed approach was accepted with a draft statement to be considered at the COM meeting in June 2022.

It was also agreed that a sub-group of interested members would be convened to facilitate updating of the impurities guidance statement. A timeline for this was not discussed.

TOXICOGENOMICS AND RISK ASSESSMENT: APPLICATION OF TRANSCRIPTOMICS AND NEXT GENERATION SEQUENCING TO GENOTOXICITY AND CARCINOGENICITY ASSESSMENT

At the COM meeting in February 2021, during discussions of some preliminary literature on 'toxicogenomics and risk assessment' (MUT/2021/06), members

noted that this field could at present be considered to comprise two different major elements; the more highly established field of transcriptomics, and the newer area of next-generation sequencing technologies. It was felt that it would be useful for a document to be prepared providing a preliminary overview of these two areas and their potential applications to risk assessment in the fields of mutagenicity and carcinogenicity. Discussion paper MUT/2021/08 provided an overview of these two areas, summarising narrative from three recently published review articles.

Members noted that overall, this was a very fast-developing area. For this reason, it may be difficult for the COM to establish a specific guidance document, as this would rapidly become out of date. However, members also considered that this is a very important area in the development in genotoxicity assessment and should be kept under evaluation by the Committee.

Some major areas of work in this field were highlighted. These included: Current efforts to obtain mutational signatures and match these to environmental exposures, which was noted as an area that the COM would probably wish to focus on further; Progression of work on TGx-DDI (a transcriptomic biomarker for genotoxicity), noting that data is being passed to regulators with the aim to be able to provide guidance; Development of duplex sequencing at Health Canada, which is starting to be useful for investigations of germ-cell mutagenesis and for dose-response analysis; Use of cancer-driver mutations via the 'CarcSeq' method at FDA.

In terms of document progression, a more detailed paper could be envisaged, noting techniques and methodologies that are becoming available, and describing some examples of how these techniques may be becoming applicable to investigation of genotoxicity. It was agreed that further development of any paper from COM concerning the use of toxicogenomics for risk assessment purposes would be discussed by a small sub-group of interested members.

PRESENTATION BY PROFESSOR MICHAEL K SKINNER – WASHINGTON STATE UNIVERSITY, USA – ENVIRONMENTAL TOXICANT INDUCED EPIGENETIC TRANSGENERATIONAL INHERITANCE OF DISEASE. GENERATIONAL TOXICOLOGY – OPEN TO COC AND COT MEMBERS

At the February 2021 meeting, Professor Skinner from Washington State University (Washington, USA) presented a talk entitled 'Environmental Toxicant Induced Epigenetic Transgenerational Inheritance of Disease: Generational Toxicology'. This was also open to COC and COT members.

As an introduction, Professor Mike Skinner highlighted that it is difficult to explain all disease based solely on the genome and that that environmental factors also play a role on the occurrence of disease. What is observed is not completely

explained by the paradigm of the genome affecting gene expression, which in turn affects physiology and the development of disease. For example, the development of disease in identical twins is reported to vary when identical twins live in different regions. This indicates that other factors are involved in addition to individual DNA sequence.

Professor Mike Skinner summarised animal studies that showed adverse effects in future generations (i.e. F2 and later generations, where the germline was not directly exposed to the initial test chemical) arising from an initial chemical exposure in pregnant females. The observed adverse effects arose from epigenetic changes. Epigenetic effects could arise from chemical induced changes in DNA methylation, histone modifications and effects on RNA (i.e. not involving a change in the DNA sequence). Such chemical induced epigenetic changes can result in modification of gene expression.

Professor Skinner noted that If a gestating F0 female animal is exposed to a particular chemical, then the F3 generation would be first generation that did not receive a direct test chemical germline exposure. Chemical induced effects seen in the F3 generation and subsequent generation could be due do epigenetic effects or inherited changes in gene expression arising from the initial gestating exposure of the F0 female. This would be an example of transgenerational inheritance. If a non-pregnant female or a male animal was exposed to the test chemical, then the F2 generation would be the first generation that did not receive direct germline chemical exposure. Chemical induced effects in this generation could arise from inherited epigenetic changes (this would be an example of transgenerational inheritance).

A number of examples of results of chemical exposure in animals were reported where 90% of treated animals showed adverse effects in the F3 generation resulting from an initial F0 gestating female exposure. For example, vinclozolin (agricultural fungicide), TCDD/Dioxin, DDT, bisphenol A and diethyl hexyl phthalate produced adverse effects in the F1 generation and in the F3 generation. Flutamide (anti-androgenic pharmaceutical) produced adverse effects in F1, but not in F3 generation. However, atrazine (agricultural herbicide) and glyphosate (herbicide) did not induce adverse effects in F1 but did in F3 (transgenerational effect). Examples of chemically induced transgenerational disease effects included spermatogenic defects, male infertility, prostate disease, premature ovarian failure, ovarian polycystic ovarian disease, birth defects, kidney disease, obesity, behavioural effects and immune effects.

Other types of exposures can also induce epigenetic and transgenerational effects, such as extreme temperature, drought, high fat diet or caloric restriction, smoking and alcohol. Studies were described where various transgenerational epimutations and clusters were detected in the sperm genome in the F3 generation following initial chemical exposure, such as with vinclozolin and DDT.

One of the most sensitive periods of exposure is during fetal gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation occurs. The suggestion that environmental toxicants can re-programme the germ line to induce epigenetic transgenerational inheritance of disease, is a new paradigm in disease aetiology, and indicates the need to assess generational toxicology in the future.

Key take home messages from the presentation included: the germline (eggs and sperm) are where epigenetic changes are critical because they get passed on in a transgenerational manner; this epigenetic transgenerational inheritance does not involve an inherited change in the DNA sequence; and a recommendation that adverse transgenerational effects need to be investigated in chemical health risk assessment. It was suggested that animal studies would be required to do this because current *in vitro* studies would not be suitable.

In discussions following the presentation, clarification was sought by members around how assessment of intragenerational effects may be included in current testing regimes. At the present time this can only be achieved through laboratory animal studies where the third generation needs to be evaluated, with minimum study length of between 1 and 1.5 years. It is not feasible to assess the germ cells of affected individuals because the shifts in developmental programming need to be established before the effects of the exposure are seen. A large proportion of the changes seen in earlier generations are due to direct exposure.

At present, transgenerational effects have been shown for many toxic compounds and so such testing is likely to be needed on a routine basis. There are no *in vitro* approaches that are effective to replace *in vivo* assays. It was considered possible that thresholds existed for the level of DNA methylation sites, below which long-term disease was avoided.

Diet was discussed as a major factor that had previously been linked with epigenetic changes. For a generational impact to occur the dietary influences have to be quite severe (for example, calorific restriction or high fat diets), with small shifts in diet not having an impact. Timing of exposure was also found to be key, with exposure during the early fetal life period being critical. Environmental toxicants were considered to have an effect at similar levels to calorific restriction. The importance of epidemiology studies in supporting animal data and showing causality was also discussed. Epigenetic biomarkers are needed for use in epidemiological studies and these have not been developed.

The Chair thanked the speaker on behalf of the Committee for an interesting and informative presentation. In conclusion, it was agreed that the COM would keep an active watching brief on developments in the area, particularly in relation to inclusion in toxicity testing regimes.

PRESENTATION ON TOXICOGENOMICS IN TOXICOLOGY TESTING BY DR SCOTT AUERBACH, DIVISION OF THE NATIONAL TOXICOLOGY PROGRAM, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, USA

At the June 2021 COM meeting, Dr Scott Auerbach provided a presentation on toxicogenomics in toxicology testing. Dr Auerbach noted that functional omics technologies are a powerful tool for the characterisation of chemical effects in biological systems. Historically the primary use of omics technologies, transcriptomics in particular, has been to characterise chemical mode of action to understand toxicological mechanisms and human relevance. More recently effort has been put into use of transcriptomics as a means to identify a biological effect point of departure that roughly approximates a point of departure derived from much more resource intensive studies such as the two-year cancer bioassay.

The presentation discussed how transcriptomics has been used for qualitative characterisation of chemical effects and how it is being modelled to derive a genomic-based point of departure. In addition, some of the current scientific challenges that need to be addressed to facilitate more widespread use of genomic point of departure values for health-based guidance value determination were also discussed.

Following the presentation, the sensitivity of the methodology was queried as some genotoxic compounds may not have a strong genotoxicity signal over the shorter exposure time. This is addressed by the inclusion of doses of test substance up to the maximum tolerated dose during screening which should produce a signal if it is genotoxic. The limitation of precision of toxicogenomics in its ability to determine what proportion of cells are affected to produce the measured 'fold' change was highlighted. This was anticipated to be a chemical specific issue as those only affecting a small number of focal points (e.g. nitrosamines) would take longer to produce a signal than chemicals affecting multiple sites (e.g. 3,3',4,4'-Tetrachloroazobenzene; TCAB) and should be taken into account to avoid inaccuracies. The use of gene-set dose response data (as a point of departure) with benchmark dose modelling was also discussed. There is no standard model to use with such data as the adverse effect size (BMR) for a particular gene is not known for many chemicals. It is also not possible at this time to take into account the effect of co-variables, which is an important consideration for human data, however this is being actively addressed by a number of groups.

Presentation on OECD development of the Mini-Ames
Dr Robert Smith, Covance

This was a reserved item, so I have not inserted any text.

Dr Robert Smith, the UK representative on the OECD expert group developing the mini-Ames test, gave a presentation and summary of the activities of the OECD expert group on the miniaturised bacterial mutation assay.

New approaches to the or Ames test (OECD TG 471) are being explored, such as minaturised assays, as they offer higher throughput with a significant reduction in the amount of test material required, resources and cost.

Several miniaturised versions have been developed and are already extensively used for screening purposes during product development/candidate selection or for impurity assessment/qualification. These have some differences when compared to the standard Ames assay and are not described in any existing OECD TG. Differences include the use of multi-well plates, use of liquid media rather than agar plates, the number of bacterial strains used, and the use of reduced numbers of bacterial cells (and volumes, etc.).

Following the presentation, members considered the possibility that data obtained from Ames II™ assays run by inexperienced laboratories may have influenced the findings of the DRP. However, there had been a requirement for laboratories to show proficiency prior to submitting data for inclusion. Although there was good concordance between the 4 assays evaluated (6 and 24-well agar plates, micro-fluctuation and Ames II™ assays) there was some remaining discussion around comparison of top doses, as the microfluctuation assay expressed doses as µg/ml and the Ames assay as µg/plate. It was also considered that exposure might be enhanced for the fluctuation assay, as fewer cells are present. The effect of pre-incubation in the fluctuation assay was queried and had been associated with a small increase in sensitivity and specificity. The maximum limit on concentration per well/plate was considered by members to be a critical factor for take-up of the assays once finalised. [SR1]The OECD had produced a Detailed Review Paper (DRP) on the evaluation of various mini-Ames assays cited in the literature compared with the standard Ames test. The OECD DRP was circulated to COM members for comment.

COM EVALUATIONS

REVIEW OF THE OPINION ON TITANIUM DIOXIDE (E171) PRESENTED BY THE FOOD STANDARDS AGENCY

The Food Standards Agency requested advice from the COM on the genotoxicity of Titanium Dioxide, following a re-evaluation by the European Food Safety Authority (EFSA) published in 2021.

Titanium dioxide is an authorised Food Additive in the EU and under GB Food Law (retained EU law Regulation No 1333/2008 on food additives). It is used in food as a colour to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food.

Titanium dioxide has been the subject of multiple safety evaluations. Following a review of Titanium dioxide specifications in 2019, and based on the fraction of nanoparticles present in E171, it was considered that the food additive fell under the scope of the EFSA guidance on nanotechnology and a recommendation for re-assessment of the safety of Titanium dioxide was proposed.

In the most recent evaluation published in 2021, data evaluated was for the food additive Titanium dioxide E171 as well as titanium dioxide other than E171 containing a fraction of nanoparticles <100nm or nano titanium dioxide. Concerning the genotoxicity studies, combining the available lines of evidence, the EFSA Panel on Food Additives and Flavourings (FAF) concluded that Titanium dioxide particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. No clear correlation was observed between the physico-chemical properties of Titanium dioxide particles – such as crystalline form, size of constituent particles, shape and agglomeration state – and the outcome of *in vitro* or *in vivo* genotoxicity assays (*i.e.* a cut-off value for Titanium dioxide particle size with respect to genotoxicity could not be identified). The EFSA FAF Panel concluded that several modes of action (MOA) may operate in parallel and the relative contributions of the different molecular mechanisms resulting in the genotoxicity of Titanium dioxide particles are unknown. Based on the available data, no conclusion could be drawn as to whether the genotoxicity of Titanium dioxide particles is mediated by a mode (s) of action with a threshold(s). Therefore, the EFSA FAF Panel concluded that a concern for genotoxicity of Titanium dioxide particles cannot be ruled out.

The COM were requested to consider paper MUT/2021/03, which summarised the EFSA 2021 evaluation and included a number of questions that the COM were requested to consider.

The COM had concerns over the quality and robustness of some of the studies considered by EFSA to draw its conclusions and noted that the overall data considered by EFSA was heterogenous (e.g. the range of particles evaluated was diverse; different types of approach and assays; different doses; different cell models; some studies were published in obscure or non-genotoxicity journals and the inclusion of non-GLP studies, which all contributed to the difficulty in making comparisons and an overall evaluation). Members were also concerned over the potential for publication bias in the studies evaluated by EFSA (i.e. where negative studies were less likely to be published). It was also noted that until relatively recently, the specification of E171 was poorly defined, which contributed to uncertainty and difficulty in evaluation.

Regarding mode of genotoxic action, the COM agreed that the evidence indicated an indirect interaction with DNA with a threshold for genotoxicity. Some positive results were found with a mixture of nano and micro particles. It was impossible to interpret which fraction was responsible, although pure micro sized particles generally were negative. The *in vivo* studies tended to be of better quality and negative. The nano-fraction in E171 is thought to be low but the fraction of nanoparticles (<100nm) can be over 50%. The percentage of the nano-fraction and its bioavailability are important factors when considering risk assessment.

Members considered that the lack of quality in the evidence (e.g. mixed particle sizes (micro and nanoparticles) and a wide variety of testing approaches) did not allow definitive conclusions to be drawn and therefore did not agree with the EFSA overall conclusions on the genotoxicity of E171 Titanium dioxide. A review of more reliable and robust dataset may be required before conclusion could be drawn on the mutagenicity of titanium dioxide particles. Members noted that EFSA made no clear distinction between the genotoxicity of nano-sized and micro-sized titanium dioxide particles. EFSA seemed to have put a lot of emphasis on the evidence from nano-sized particle studies when nanoparticles made up only a small fraction of E171. The COM suggested that if practicable, restricting the amount of nanoparticles in the specification for E171 may reduce any potential genotoxicity risk. Additionally, the COM considered that the wording of EFSA's conclusion was not helpful from a risk communication perspective. Due to the heterogenous data and equivocality of the evidence further refinement of the data evaluated may be needed before definitive conclusions on the genotoxicity and safety of titanium oxide could be made. Currently, the EFSA conclusions were not justifiable based on the available evidence and this may create unnecessary concern for the public.[SR2][SR3]

HYDROXYANTHRACENE DERIVATIVES

This item was classified as reserved business. The minutes will be published at a later date.[SR4]

HORIZON SCANNING

Forward look from the Chair

The Chair suggested two main areas of potential interest to the COM, which were genomics and next generation sequencing, and the use of genotoxicity markers in human biomonitoring. It was anticipated that in the next few years genomics and sequencing would be seen more in genotoxicity, including Duplex sequencing. There was a potential for this to support or even replace genotoxicity testing, particularly testing for gene mutation or point mutation. Developments in these areas may also provide an opportunity to gain more information from biomonitoring, occupational exposure or environmental exposure.

Presentation by Health and Safety Executive

Dr Lata Koshy gave a presentation on the work of the Health and Safety Executive (HSE) post the UK exit from the EU. HSE are involved in a number of activities within UK REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), which includes identifying hazards, such as mutagenicity, and identifying substances of Very High Concern (SVHC). Most of the HSE work on Classification, Labelling and Packaging regulation relates to hazard identification for industrial chemicals. The HSE is also involved in the regulation of biocides and pesticides. Additionally, the HSE produces summaries for ministers and HSE opinions on the mandatory classification of substances and whether to align with EU opinion. The future work programme of the HSE is still being worked out post EU Exit and will be limited by resource and recruitment. HSE anticipated that it would complete the evaluation of two to three active substances per year. Evaluation of mutagenicity is a key part in determining whether an active substance will be given approval. Mutagenicity is also a key factor in the UK review of new and existing substances and import tolerance for pesticides. Due to the short timeline, it may be difficult consulting with COM, which has three meetings per year.

Some key differences for HSE since the UK exit from the EU is that the HSE has to act in isolation from EFSA and ECHA and from that peer review process. Its independence meant that it had to improve its own individual peer review process and has set up various expert groups and developed links with various other expert advisory groups. HSE may consult the COM in the future in relation

to complex genotoxicity data sets and for advice in reviewing GHS for germ cell mutation category 1 and 2. The COM guidance documents and expert advice will be useful to the HSE and its advice on specific areas, for example, on mode of action/threshold mode of genotoxic action and the use of QSARs.

Government assessors

Assessors from other Government Departments and agencies were asked for any horizon scanning topics they wished to highlight. VMD had an interest in biopharmaceutical molecules and their potential for mutagenicity. VMD were not aware of any guidance on how to assess the mutagenic potential, for example, of modified stem cells or monoclonal antibodies, particularly those sourced from different species (e.g. xenogeneic stem cells). VMD may seek the view of the COM of this area in the future. BEIS noted that it had set up its own expert scientific advisory groups following UK exit from the EU and that it would be seeking to develop links with secretariats for other expert advisory groups, such as the COM.

Members of the COM were asked to send in any thoughts on horizon scanning topics to the COM secretariat.

OECD

The COM was sent a consultation on a new draft Test Guideline on the mammalian erythrocyte Pig-a gene mutation assay. Members were requested to send any comments to the secretariat so that these could be collated and sent to the OECD.

OECD Draft Detailed Review Paper on the Miniaturised Versions of the Bacterial Reverse Gene Mutation Test.

Members were requested to provide comments on an OECD Draft Detailed Review Paper (DRP) on the miniaturised Ames test (bacterial reverse gene mutation test) for collation by the National Coordinator at UK HSA. Assessors were requested to also send any comments which would be submitted separately.

It was noted that the DRP will not lead to a revision of the TG (TG471), but the aim of the review was to provide recommendations on the use of each of the mini-Ames tests proposed. From a UK perspective it was considered important to highlight and record any controversial points that were not in line with UK practice.

There was general agreement with the recommendations of the DRP. It was felt that until a robust validation process of the mini-Ames assays had been carried out, no further progress could be made in implementing the assays for regulatory testing. Further justification was requested, including better definition of what the assay is for, e.g. increasing output and reducing costs, incorporation of information relating to how laboratories were chosen to take part and whether there is a clear

benefit of using mini-Ames assays above TG471. It was intended that a short written summary of the text submitted to OECD would be provided to COM members at the meeting in March 2022.