Committee on Mutagenicity

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

Guidance on the use of 3D Tissue Models for genotoxicity testing.[RB1][RB2]

Continued consideration and comments of the updated COM Guidance document on the use of 3D Tissue Models for genotoxicity testing.

This paper has been amended according to comments received from members of COM following the meeting in November 2020. Members are asked to complete review of this latest draft as attached and consider the following :

1. Please provide advice where this is indicated in the text.
2. Following any changes that are discussed, this statement will now be published following Chairs action- do the members agree?

Secretariat

February 2021

Background

1. The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) has a remit to provide UK Government Departments and Agencies with advice on the most suitable approaches to testing chemical substances for genotoxicity. The COM views regarding the most appropriate strategy for genotoxicity testing are outlined in full in the COM (202x) "*Guidance On A Strategy For Genotoxicity Testing Of Chemical Substances*".

2. In brief, the COM recommend a staged approach to genotoxicity testing. **Stage 0**, in the absence of test data from adequately designed and conducted genotoxicity tests, consists of preliminary considerations of the test chemical substance, including, physicochemical properties, Structure Activity Relationships (SAR), and information from screening tests. **Stage 1** consists of *in vitro* genotoxicity tests that provide information on three types of genetic damage (namely, gene mutation, chromosomal damage and aneuploidy) and gives appropriate sensitivity to detect chemical genotoxins. **Stage 2** consists of *in vivo* genotoxicity tests which are chosen on a case-by-case basis to address any genotoxic endpoints identified in Stage1; investigate genotoxicity in tumour target tissue(s) and/or site of contact tissues; investigate potential for germ cell genotoxicity; and investigate potential genotoxicity for chemicals where high/moderate and prolonged exposure is anticipated, even if negative in Stage 1.

3. The use of 3D models for genotoxicity testing has not previously been discussed in the full COM guidance document (COM, 202x). However, as the development of 3D models is a rapidly evolving field, members considered it appropriate to prepare guidance in this area, that can be updated at regular intervals. As such, a brief summary of this area is provided in the full guidance document, while this document outlines in more detail the 3D models currently used for genotoxicity testing and those under development and/or validation.

Application of 3D models for genotoxicity testing

4. The main drivers for the development/use of 3D models were the Cosmetics Directive, which prevented the use of *in vivo* testing for cosmetics, and the 3Rs principle that requires the reduction, replacement and refinement of the use of animals in toxicity testing. 3D models have also been developed to undertake testing for which there is no robust in vivo system, such as site of contact studies, and have shown a utility that is now being assessed for genotoxicity testing.

5. Although currently used *in vitro* genotoxicity testing batteries can reliably identify *in vivo* genotoxicants, there are a number of positives which, when tested *in*

vivo, are non-genotoxic i.e. these are misleading positive findings, commonly referred to as 'false positives'. As a consequence, animal usage, testing time and costs can be unnecessarily increased which go against current initiatives that attempt to reduce the number of misleading positives from in vitro testing.

6. Such misleading positive findings are considered to occur for a number of reasons, including the use of cell lines of rodent origin (V79, CHO or CL) that partially lack normal cell cycle control, have limited metabolic capacity (even with the addition of rat liver S9) and do not mimic site-specific metabolic capacity (Reus et al., 2013). However, the impact of these factors has become increasingly recognised and has led to the development of models which more closely reflect tissue structure and tissue metabolic activity.

7. A number of types of 3D model, ranging from single cell microtissues to multi cell types grown within scaffolds have been developed. It is hoped the use of such models will improve the accuracy of predictions due to their improved metabolic capacity and the proximity [RB3]to *in vivo* gene expression and protein function (Andres et al., 2012; Barcham et al., 2018).

8. The International Workshop on Genotoxicity Testing (IWGT) concluded that '3D tissue models offer a more 'in-vivo-like' behaviour for key parameters like cell viability, proliferation, differentiation, morphology, gene and protein expression, and function and therefore provide a valuable complement to the classical '2D' cell culture-based assays' (Pfuhler et al., 2020a).

3D models of skin

9. 3D models have, to date, mainly been developed for the skin. These models mimic the architectural features and behaviour of normal human skin and the changes that occur during early skin cancer progression and wound re-epithelialisation. Reconstructed 3D human epidermal skin models are used in OECD TG 431 (*in vitro* skin corrosion: Reconstituted human epidermis (RHE) test) (Kandárová et al., 2006; Kidd et al., 2007; OECD, 2016a) , which can be used in addition to the acute dermal irritation/corrosion test in rats (OECD TG 404). OECD TG 439 *(in vitro* skin irritation: Reconstituted human epidermis test) also utilises reconstructed 3D epidermal skin models (Alépée et al., 2010; Kandarova et al., 2009; OECD, 2015). Assessment of phototoxic properties (Jírová et al., 2005; Lelièvre et al., 2007) and sensitisation potential (dos Santos et al., 2011; Teunis et al., 2013) are also being explored using reconstructed 3D skin models and are considered to have a high potential to be accepted as OECD TGs (Reus et al., 2013)[RB4].

10. For genotoxicity testing purposes, 3D skin models have been linked to the standard genotoxicity endpoints of the micronucleus test and Comet assay. Two endpoints are utilised to reflect different types of genetic damage, namely

clastogenicity and aneugenicity and DNA strand breaks, incomplete repair sites [RB5][RB6]and alkali labile sites, respectively. The 3D Skin Comet assay and Reconstituted Skin Micronucleus (RSMN) test are described in paragraphs 11 to 17 below. These assays allow the *in vitro* assessment of DNA damage following dermal exposure, which has only previously been possible using *in vivo* assays; this is despite dermal exposure being a common route for a number of compounds found in household products, cosmetics, and industrial chemicals (Reisinger et al., 2018).

3D Comet assay[RB7][RB8]

11. The Comet assay has been adapted for use with two reconstructed full thickness human skin models: the EpiDerm™- and Phenion® FullThickness Skin Models. Both skin models are comprised of primary and p53 competent cells of human origin. These models have a number of advantages over current monolayer-type assays including: species specificity, with a phenotype close to native human skin; normal cell cycle control; DNA-repair competence; similar gene and protein expression patterns; and the mimicking of conditions of use for dermally applied substances/products (Reisinger et al., 2018).

12. As the Comet assay does not rely on proliferating cells and can be used with a wide range of cell types, it is particularly suitable for application to skin tissue models. The assay also detects a wide range of DNA damage including double-stranded and single-strand breaks from direct interaction of the test chemical or related to incomplete excision repair as well as alkali labile sites (OECD, 2016b). This ensures that both clastogenic DNA damage and lesions that may give rise to gene mutation are detected.

13. The 3D Skin Comet assay has undergone inter-laboratory validation using the Phenion® Full-Thickness Skin Model to assess its potential use as a new *in vitro* tool for following up positive findings from the standard *in vitro* genotoxicity test battery for dermally applied chemicals. The authors reported that the skin model has similar metabolic competency to natural human skin. Further, for the 32 substances tested, there was a high predictive capacity with a sensitivity of 80%, a specificity of 97% and an overall accuracy of 92% when compared to *in vivo* animal genotoxicity test outcomes. Improved predictability of the assay [AP9][RB10]was seen when combined with the RSMN assay in a testing battery, with the sensitivity increasing to 90% and specificity remaining high (Reisinger et al., 2018; Pfuhler et al., 2020b).

14. A number of 3D human airway models (also called lung models) have been established that [RB11][RB12]closely resemble the lining of the human airway (discussed in paragraphs 21 – 23). As such, their utility for the genotoxicity testing of inhaled chemicals is being evaluated. The IWGT reported that 'initial data show that the comet assay can be applied to the 3D airway models and the WG encourages further development of this assay'. It was emphasised that 'the lack of 3D airway assays that can detect aneugenicity is considered a gap and the development of such an assay is strongly encouraged'.

15. ~~Use~~ The IWGT also suggested that use of the MN assay with the current 3D airway models ~~was thought to~~ may be restricted by the limited proliferation rate of the cells in the models (Pfuhler et al., 2020a)[DS13][RB14]. However, developments are being made in this area and a recent publication has described the use of the cytokinesis-block micronucleus assay (CBMN) to detect secondary toxicity of nanomaterials in a dual cell co-culture model of the bronchial cell line, 16HBE14o- and differentiated THP-1 (dTHP-1) macrophages (Evans et al., 2019).

3D human reconstituted skin micronucleus assay

~~14.~~16. The RSMN assay has been developed to assess the genotoxicity of dermally applied compounds incorporated into cosmetics, utilising a highly differentiated *in vitro* model of the human epidermis (EpiDerm™) with automated micronucleus detection using the standard cytokinesis block micronucleus assay (Barcham et al., 2018). The RSMN offers a close approximation of natural human skin due to the origin of the cells used and its physiological properties for cosmetic testing. The model also allows topical administration which ensures that all parts of the model are exposed, regardless of the lipophilic nature of the test substance. The assay has been successfully expanded to the Episkin LM™ model (Chen et al., 2020) which has previously been shown to have a similar metabolic capacity to that of native human skin (Eilstein et al., 2014) allowing the assessment of genotoxic potential by metabolic activation as an intrinsic feature.

~~15.~~17. A global validation of the assay has been carried out with the blinded testing of over 40 coded chemicals using the EpiDerm™ model Findings showed an overall accuracy of 84%, a sensitivity of 80% and specificity of 87% when compared to in vivo genotoxicity outcomes (Pfuhler et al., 2020). IWGT noted that the sensitivity of the 72 h protocol was superior to that of the 48 h and that the assay was now suitable for OECD TG development. A submission has now been made to the OECD to include this assay into the Test Guideline programme. Further the WG concluded that the 'RSMN assay was an acceptable alternative to the in vivo test for cosmetic testing and that the high predictivity also demonstrates that the test complies with all requirements to be accepted as a 2nd tier test' (Pfuhler et al., 2020a).

Other 3D tissue models

3D liver microtissue model

~~16.~~18. Conventional *in vitro* monolayer assays using hepatic cell lines may not be the most relevant assays to carry out functional and metabolic studies as the cells loose key liver specific functions, in particular cytochrome P450 activity (Godoy et al., 2013; Kim et al., 2011; Mingoia et al., 2007; Pfuhler et al., 2020a). In addition, non-parenchymal cells are absent which play an important role in clearance and in the initiation of an immune response. Due to the limited lifespan of the conventional assays, repeated exposures are not possible (Kermanizadeh et al., 2014).

~~17.~~19. A 3D liver microtissue model has been described (Messner et al., 2013; Kermanizadeh et al., 2014; Kratschmar DV, 2013) which has a number of advantages over conventional hepatic assays. These include: the use of primary human hepatic cells; viability of cells for long periods which allows multiple exposures to be assessed; maintenance of a high level of metabolic activity across the lifespan of cells.

~~18.~~20. A 3D liver model utilising HepG2 cells grown using a 'hanging-drop' technique has been assessed for genotoxicity testing, with micronucleus detection in the 3D spheroid models. Micronucleus induction was seen to be greater in the 3D structures than in the 2D format (Shah et al., 2018). The IWGT concluded that for 3D liver spheroids 'initial data show that the MN assay can be applied to 3D liver spheroids and the WG encourages further development of this assay'. It is also recognised by the WG that this technique is being investigated within the EU Horizon 2020 project PATROLS which includes characterisation of their metabolic competence (Llewellyn et al., 2020; Pfuhler et al., 2020a). A recent study has shown adaptation of the 3D HepG2 model for the assessment of genotoxicity following longer term low dose exposure (Conway et al., 2020).

3D tissue models of the airway epithelium

~~19.~~21. In conventional monolayer (2D) cultures of basal cells, only maintenance and expansion of cells is possible. However, in 3D airway tissue models, basal cells can differentiate into a mucociliary pseudostratified epithelium containing ciliated, goblet and basal cells. Other properties similar to the native human airway epithelium include beating cilia, mucus secretion, barrier properties and remodelling and restoration properties (Rock et al., 2009).

~~20.~~22. The two most widely used models of the airway epithelium are 3D microtissue models and co-cultures of multiple cell types, both of which can be grown at the air-liquid interface (ALI) (Evans et al., 2017; Evans et al., 2019; Barosova et al., 2020; Pfuhler et al., 2020a).

~~21.~~23. ALI cultures reflect physiological conditions *in vivo*, with the respiratory epithelium being exposed to the air. These cultures are currently used to study cell biology and infection, culture patient-derived cells to model diseases, and test the effects of aerosolised particles (including drug formulations and cigarette smoke) on the respiratory epithelium (for example (Azzopardi et al., 2015)). IWGT considered that these models may enable a more realistic (geno)toxicity assessment of inhaled compounds, and subsequent developments have been reported using the CBMNassay to detect secondary toxicity in a dual cell co-culture of 16HBE14o-bronchial cells and dTHP-1 macrophages (paragraph 14). .In addition, as the models can be kept in culture for months, IGWT considered that this presented the possibility of assessing subchronic exposures, and this has subsequently been demonstrated for 3D HepG2 model (paragraph 19).

Regulatory challenges

~~22.~~24. There is a requirement within OECD TGs to show proliferative index and viability when undertaking in vitro assays for genotoxicity. This is challenging to do with 3D models and requires further consideration.

~~23.~~25. The cosmetics industry is more accepting of the findings of 3D models as no *in vivo* testing can be carried out. However, the application and acceptance of data to other areas of chemical genotoxicity testing is currently not known. In both cases though, data from such models would be considered as part of an overall weight of evidence.

Conclusion

~~24.~~26. 3D human tissue models may offer an alternative testing strategy to *in vivo* assays for substances that are found to be positive using the traditional *in vitro* genotoxicity battery of tests. Extensive progress has been made on the development and validation of 3D genotoxicity models and models are available for the major routes of exposure in humans.

~~25.~~27. The most advanced of such models, the 3D Skin models, have undergone inter-laboratory validation and been shown to comply with all requirements to be accepted as a 2nd tier test for cosmetic ingredients testing.

~~26.~~28. The 3D RSMN assay is currently moving into OECD TG development. For the 3D airway model, measurement of clastogenicity and gene mutation are possible, and detection of aneuploidy has been demonstrated. A test for gene mutation is required for the 3D liver models, with both models also requiring validation.

~~27.~~29. Using historic data, chemicals that are positive for genotoxic activity *in vivo* have been shown to be positive in either the 3D-micronucleus or 3D-Comet assay skin models. In the main, chemicals that are negative for genotoxic activity *in vivo* are also negative in the two 3D models (Kirkland et al., 2014).

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Abbreviations used in the document (not present in main glosssary)

3D Tissue Model	Artificially created environment in which biological cells are permitted to grow or interact with their surroundings in all three dimensions.
2D	Two dimensional
RSMN	Reconstituted Skin Micronucleus
ECVAM	European Center for Validation of Alternative Methods
HepG2 cells	Immortalised cell line consisting of human liver carcinoma cells

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