Committee on MUTAGENICITY

MUT/2020/19

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

Guidance on Genotoxicity Testing Strategies for Manufactured Nanomaterials

Consideration and comments of the updated structure of COM Guidance document 'Guidance on genotoxicity testing strategies for manufactured nanomaterials'.

Members are asked to complete review of this proposed restructuring as attached and consider the following questions:

1. Do members agree with the proposed structure presented?
2. Are there any other aspects which should be included within the guidance document?

Secretariat

November 2020

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

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, physico-chemical 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. As part of an update of the overarching COM guidance, specific topics have been added dealing with areas that require a more detailed discussion. One such area addresses genotoxic testing strategies for manufactured nanomaterials. A brief summary of this area is provided in the full guidance document, while this document outlines in more detail the initiatives that have been carried out in the area. It is recognised by the Committee that this is an area that is rapidly developing. As such, COM will keep a watching brief and update this guidance document with new information as it becomes available.

Evaluation of genotoxicity testing methodologies

4. A number of projects and initiatives have been conducted over recent years to evaluate and harmonise methodologies to assess the genotoxicity of nanomaterials. These include the OECD WPMN, NANOGENTOX, NANoREG and ProSafe that have evaluated test methodologies for genotoxicity testing and their applicability for nanomaterials.

Brief description and references for each project. Should project limitations be highlighted?

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Applicability of in vitro assays for genotoxicity testing to nanomaterials

- *Bacterial (Ames) Genotoxicity Assays*
- *In vitro MN Assay*
- *In Vitro Chromosomal Aberration Assay*
- *In Vitro Comet Assay*
- *In Vitro Mammalian Gene Mutation Assays*

For each assay discuss: ILSI/HESI/GTTC conclusion; any updates since Elespuru paper; state COM opinion including any remaining limitations. Should the assays listed be restricted to those that are part of the hazard characterisation framework?

Applicability of in vivo assays for genotoxicity testing to nanomaterials

- In Vivo Bone Marrow MN assay and Chromosomal Aberration Assay
- In Vivo Comet Assay
- In Vivo Gene Mutation Assays in Transgenic Rodents

For each assay discuss: ILSI/HESI/GTTC conclusion; any updates since Elespuru paper; state COM opinion including any remaining limitations.

Special Considerations for the genotoxicity testing of nanomaterials

- Physical characterisation of the nanomaterials
- Understanding the mode of action and the importance of secondary toxicity (e.g. Evans et al., 2019; Evan et al., 2017; Pfuhler et al., 2020; Pfuhler et al., 2017).

Future directions

Horizon2020 initiatives (to include RiskGONE; NanosolveIT; PATROLS; any others?)

Summary