Ongoing work - COM 2023

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COM guidance series update

Guidance statement the use of biomarkers in genotoxicity in risk assessment

2.1 At the request of the COC, the COM considered a revised version of the COC Guidance Statement G04 'The use of biomarkers in carcinogenic risk assessment' at the COM March 2022 meeting (MUT/2022/03). Particular focus was given to the 'DNA damage' and 'genotoxicity biomarkers' sections, both of which had had been shortened in the current version of G04 as part of a document revision process.

2.2 It was agreed that COM would produce a guidance statement that provided a more comprehensive overview of these areas, which could then be referred to by the other Committees. A draft scoping document outlining the proposed content of guidance statement was presented to the COM at its meeting in June 2022 (MUT/2022/06).

2.3 Several modifications to the scoping document were suggested by members and these were incorporated into a first draft document presented at the COM October 2022 meeting (MUT/2022/11). Members considered that the focus of the COM document should be *in vivo* biomarkers of DNA damage, with greater distinction from the COC Guidance Statement G04. Work is ongoing to progress a second draft document.

Non-expert summaries for COM website

2.4 At a previous COM meeting in June 2022, it was agreed that the general public could benefit from the addition of non-expert summaries to the start of each COM guideline document.

2.5 A draft non-expert summary for the overarching COM guideline, 'Guidance on a strategy for genotoxicity testing of chemicals (MUT/2022/13) was presented at the COM October 2022 meeting. Members considered that some text could be

removed, as this was available on the COM website, and a link provided to that website. In addition, it was recommended that links to the glossary should be utilised fully as this provided an immediate and understandable definition for readers. Specific comments on the paper were discussed at the February and June COM meetings so that the paper could be finalised.

Discussion paper on tetra-methyl bisphenol f diglycidyl ether (tmbpf-dge) in canned food packaging materials

2.6 This item was presented as a reserved item as the data are commercially confidential.

2.7 Members discussed the toxicological information provided to the Committee on TMBPF-DGE, a can coating, as well as the previous discussions of the Joint Expert Group on Food Contact Materials (FCMJEG). Following the COMs assessment, a discussion paper was presented to the FCMJEG and to the Committee on Toxicity, including the discussions of the COM. The work is ongoing, a final assessment is expected in 2024.

In vitro data / *in vivo* data review of titanium dioxide genotoxicity

2.8 Following the publication of the EFSA opinion on titanium dioxide in 2021, which concluded that titanium dioxide could no longer be considered to be ‘safe’ for use in food, the Food Standards Agency (FSA) initiated a review of the EFSA opinion.

2.9 The EFSA opinion was presented to the COM in June 2021 (MUT/2021/03) and to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in July 2021 (TOX/2021/36). The COM had a number of concerns over the EFSA opinion on the genotoxicity of titanium dioxide. Due to this and following the advice of the COT the FSA asked COM to initiate an independent evaluation of the safety of the use of titanium dioxide as a food additive.

2.10 In October 2021, paper MUT/2021/08 was presented to the COM, which summarised the available genotoxicity on titanium dioxide. Members considered that it was not possible to evaluate the genotoxicity of titanium dioxide at that stage. The COM suggested a sifting approach to the available genotoxicity should be adopted as a first step before evaluation. The Chair of the COM, a subgroup of the COM and the secretariat subsequently attended meetings to discuss and

agree the criteria and methodology for sifting to identify suitable papers for the evaluation of titanium dioxide.

2.11 At the COM June 2022 meeting, paper MUT/2022/05 provided information and papers on approaches relating to the sifting and evaluation of the quality genotoxicity studies and evaluating data on nanomaterials. As an update since that meeting, members were informed that a sub-group of the COM had met to discuss the process to select relevant and appropriate studies to be reviewed by the committee. A proforma had been produced, which would be shared with members. This considered two levels, namely, whether the characteristics of the test material had been sufficiently described (e.g., micro or nano sized particles) and the quality and reliability of how the genotoxicity studies had been conducted.

2.12 At the October 2023 meeting, the draft review on titanium dioxide was discussed in detail and members opinions were incorporated into the COM opinion and the subgroup aimed to get the final opinion ready for early 2024.

COM QSAR guidance – proposed workplan

2.13 The overarching COM guidance statement, “Guidance on a Strategy for Genotoxicity Testing of Chemical Substances” was revised in 2021. It recommends a tiered approach consisting of three stages: 0 (preliminary considerations including physico-chemical properties), 1 (*in vitro* genotoxicity tests), and 2 (*in vivo* genotoxicity tests), with the use of QSAR models being recommended for stage 0 only. During revision of the overarching guidance statement, COM agreed that a separate guidance statement on the development and use of QSARs was warranted as this was an impart field. Once developed, a more general narrative would be incorporated into the overarching guidance statement.

2.14 A sub-group of COM members are developing a guidance document for the use of QSARs both in the preliminary evaluation of a chemical (stage 0) and in the evaluation of impurities. This work is ongoing.

OECD Updates and COM input

2.15 COM members continue to input to OECD expert committees.

2.16 In 2022 there was an update to OECD Guidance on the *in vitro* micronucleus assay in terms of methodological adaptions that would allow

appropriate genotoxicity testing of nanomaterials. It was expected that there would be an interlaboratory trial with a view to updating the test guideline with a section on nanomaterials.

2.17 OECD project on the gamma H2AX *in vitro* assay this will progress with a Detailed Review Paper (DRP) moving toward a test guideline.

2.18 Update to OECD Test Guideline 489 on the *in vivo* comet assay to include germ cells. There had been a validation exercise in just one laboratory with five or six chemicals.