MUT/2022/06

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

Scoping document for COM Guidance Statement (G0X): The Use of Biomarkers in Genotoxicity Risk Assessment

1. At the February 2022 meeting, COM considered the revised COC Guidance Statement G04 'The Use of Biomarkers in Carcinogenic Risk assessment', with a particular focus on the DNA adducts and genotoxicity biomarkers sections, both of which have been shortened in the current version.

2. Following discussions, it was considered that it would be helpful for COM to produce its own, more comprehensive, guidance on biomarkers relevant to its area of expertise. This document could then be referred to by the other Committees when needed and as appropriate.

3. The purpose of this scoping document is to provide an overview of the proposed content of the new COM guidance, for discussion and agreement by members. This is given at Annex A.

Questions for the Committee

1. Members are asked to consider the proposed guidance document outline, and, in particular, to:

   i. Comment on the suggested sections and whether additional themes need to be included.

   ii. Comment on the key themes that need to be covered under each section.

   iii. Consider next steps in progressing the document

IEH Consulting under contract supporting the UK HSA COC and COM Secretariat
May 2022

MUT/2022/06 – Annex A

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

COM Guidance Statement (G0X): The Use of Biomarkers in Genotoxicity Risk Assessment

Draft Scoping document

Secretariat

June 2022

Proposed guidance document outline

Introduction

- The focus of the guidance statement is biomarkers of genotoxic relevance for risk assessment purposes.

- Distinction between genotoxic and non-genotoxic carcinogens, to include consideration of mechanistic information - this is particularly relevant for risk assessment, with the assumption of the existence of no-effect concentrations (threshold levels) in case of the latter group. In contrast, genotoxic carcinogens, their metabolic precursors and DNA reactive metabolites are considered to represent risk factors at all concentrations since even one or a few DNA lesions may, in principle, result in mutations and, thus, increase tumour risk.

Biomarker types and their use in risk assessment

- Description of biomarkers of exposure, effect and susceptibility (as *per* COC current guidance).

- How are biomarkers used in the risk assessment of genotoxicity – to include an overview of the current COM guidance on a strategy for genotoxicity testing of chemicals and how biomarkers of genotoxicity are utilised within the individual components of the risk assessment process.

- Validation and characterisation of biomarkers (as *per* COC). In addition, it is important to highlight the importance of confirming biological significance e.g. by measuring DNA adducts and mutation in parallel. DNA adducts have an important role in the risk assessment process and in establishing a mode of carcinogenic action, although the association of an adduct with a disease does not automatically indicate causality.

Strategic uses of human biomonitoring

- Use of HBM has been developed in occupational settings where exposures to an identified chemical of particular concern might be relatively high. Subsequent application to population exposure has made progress but genotoxicity biomarkers are not applied extensively in large population studies.

- To focus on, with relevant examples, of exposure to genotoxic carcinogens and their application to risk assessment.

- Discuss the challenges in the use of genotoxicity biomarkers in risk assessment

Biomarkers of exposure

- Discussion of biomarkers of DNA damage – to include single-stand breaks, double-strand breaks, covalently bound chemical DNA adducts, oxidative-induced lesions and DNA–DNA or DNA–protein cross-links.

- Temporality considerations of biomarkers of DNA damage related to other critical events.

- Equivalent endogenous biomarkers of DNA damage and their effect on the dose-response curve of the exogenous biomarker.

Biomarkers of effect

- Discussion of biomarkers of genotoxic effect – to include cytogenetic endpoints such as micronuclei (MN) and chromosome aberrations (CA), which are considered to be biomarkers of early carcinogenic effects and are thought to be predictive for cancer risk in humans.

- Temporality considerations of biomarkers of genotoxic effect related to other critical biological events.

- Equivalent endogenous biomarkers of genotoxic effect and their influence on the dose-response curve of the exogenous biomarker.

Biomarkers of susceptibility

- Evidence suggests that genetic susceptibility plays a role in an individual's response to exogenous and environmental exposures. Provide relevant examples.

- Application of biomarkers of susceptibility to risk assessment, challenges for interpretation

Measurement of biomarkers of genotoxic exposure and effect

- Established quantitative *in vitro* and *in vivo* methods – to include omics (genomics, proteomics, metabolomics) and, potentially, transcriptomics and next generation sequencing.

- Developing methods - to include DNA adducts and mutational signatures (adductome analysis), epigenetic changes (DNA methylation, histone modifications, and miRNAs) and gene expression biomarkers.

Summary