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MUT/2023/03

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

Draft non expert summaries for COM statements

1. It was agreed at the COM meeting in June 2022 that the general public could benefit from the addition of non-expert summaries at the start of each COM guideline statement.

2. The paper provided at Annex A is a second draft non-expert summary for the overarching COM guideline entitled 'Guidance on a strategy for genotoxicity testing of chemicals', which has been amended following comments from Members when presented at the meeting in October 2022 (MUT/2022/13).

3. The paper provided at Annex B is a first draft non-expert summary for the COM guidance statement on quantitative assessment of genotoxicity data.

4. The paper provided at Annex C is a first draft non-expert summary for the COM guidance statement on the use of mutation spectra in genetic toxicology.

Questions for the Committee

5. Members are asked to consider the draft non-expert summaries presented in Annex A, B and C and, in particular, to:

   i. Comment on whether the language used is consistent with that for a lay person.

   ii. Consider whether the draft non-expert summary provides an accurate overview of the respective COM statements.

IEH Consulting under contract supporting the UK HSA COC and COM Secretariat
February 2023

Committee on Mutagenicity

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MUT/2023/03 – Annex A

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

Second draft non-expert summary for COM document: Guidance on a strategy for genotoxicity testing of chemicals

Second draft non-expert summary for COM overarching guidance document.

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February 2023

Committee on Mutagenicity

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The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) is an independent expert advisory committee with specific interest in the inherent genotoxic properties of chemicals. More detailed information on the COM can be accessed via the website.

This document outlines the strategy that COM considers to be the most scientifically appropriate for the genotoxicity testing of chemicals. It takes into account currently available methods and the need to avoid the use of live animals (in vivo studies) where practical and validated alternative methods (for example, in vitro studies) exist.

A staged testing approach is recommended by COM, as follows.

Stage 0 considers any available information regarding the physical and chemical properties of the chemical under investigation, the identification of any relationship between chemical structure and biological activity (structure activity relationships (SAR)) and the data from scaled down in vitro genotoxicity assays used for screening large numbers of test chemicals.

Stage 1 consists of in vitro genotoxicity assays that allow identification of three types of genetic damage: to genes, chromosome structure (clastogenicity), and/or the number of chromosomes (aneuploidy). Core tests comprising the 'Ames test' and the 'in vitro micronucleus test' are advised by COM to be sufficient to detect genotoxic chemicals.

Stage 2 consists of three core in vivo genotoxicity assays that allow identification of two types of genetic damage. tests: The 'rodent micronucleus/ chromosome aberration assay' (aneuploidy and clastogenicity), and the 'transgenic rodent gene mutation assay' and the 'rodent alkaline comet assay' (DNA damage).

For most chemicals, the core in vivo tests are sufficient to evaluate whether a chemical can cause genotoxicity in the human body, which is a primary concern in the development of some cancers. However, in some cases further in vivo studies may need to be carried out to provide more detailed information on the genotoxic response or to determine the mechanism by which the chemical causes genotoxicity (genotoxic mode of action).

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MUT/2023/03 – Annex B

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

First draft non-expert summary for COM guidance statement on quantitative assessment of genotoxicity data.

First draft non-expert summary for the COM guidance statement on approaches to apply quantitative evaluation to genotoxicity data.

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

February 2023

Committee on Mutagenicity

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The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) is an independent expert advisory committee with specific interest in the inherent genotoxic properties of chemicals. More detailed information on COM can be accessed via the website.

This document considers whether, based on current literature, a change can be made to the way that genotoxicity data are evaluated.

The risk to health following exposure to substances that are toxic, including non-genotoxic carcinogens, is currently assessed in a quantitative (numerical) way to identify a level of exposure in people that does not cause an effect, i.e., a non-toxic level. This can then be used to derive guidance values that aim to protect human health.

On the other hand, data from in vitro and in vivo assays that are used to detect damage to DNA, and/or other components within a cell, are currently most commonly evaluated in a qualitative (non-numerical) way, providing a yes/no decision regarding the genotoxicity of the substance being evaluated. For substances that are genotoxic carcinogens, it is assumed that a non-toxic level of exposure does not exist and any exposure may result in an effect. Such information is used to protect the general public by restricting exposure that may occur from the environment or through the ingestion of food. However, this qualitative approach is generally thought to be overly cautious in nature, meaning that the use of substances may be restricted even if exposure and the risk to health may actually be very low.

It is generally considered that evaluation of genotoxicity data in a quantitative rather than qualitative way would improve their interpretation, and might reduce the need for long-term animal assays to assess carcinogenic potential.

Following their evaluation of literature, COM was broadly in agreement with the principle of quantitatively evaluating genetic toxicology data. The importance of the continued development of models that facilitate such quantitative evaluations were recognised, but as such models vary widely, no conclusion could be made on the suitability of the models for the quantitative assessment of genotoxicity data.

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MUT/2023/03 – Annex C

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

First draft non-expert summary for COM guidance statement on the use of mutation spectra in genetic toxicology.

First draft non-expert summary for the COM guidance statement on how mutation spectra may be used to evaluate chemical carcinogenesis.

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

February 2023

Committee on Mutagenicity

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The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) is an independent expert advisory committee with an interest in the inherent genotoxic properties of chemicals. More detailed information on the COM can be accessed via the website.

The subject of this document is 'mutation spectra', referring to the total number and types of mutations in a given gene that are induced by exposure to a chemical. Some chemicals that are carcinogenic through a genotoxic mechanism generate unique mutation spectra in both *in vitro* and *in vivo* experimental systems, and these can be used to determine the mechanism by which carcinogenesis occurs. Some mutation spectra have been shown in genes that are related to specific tumours, which can help with diagnosis.

Here, COM considers the currently available literature to assess whether mutation spectra can be used to evaluate the carcinogenic potential of chemicals. Some traditional mutation assays, based on neutral (non-selectable) genes, are considered suitable for identifying mutation spectra. Whilst COM sees value in using mutation spectra data to help identify DNA damage caused by specific chemicals, caution is expressed around the interpretation of such data, as only a few examples are known where specific mutation spectra are positively linked to a chemical exposure with subsequent tumour induction in humans. These examples are further discussed.

Looking forward, COM anticipates that advances in sequencing technology, referred to as 'next generation' sequencing, in combination with advanced data analysis methods, will provide better insight into the evaluation and interpretation of chemically-induced mutation spectra. This technology has currently been used to examine changes in gene expression in a wide variety of cancers and it is envisaged that correlating these changes with mutation spectra from known chemical exposures in defined in vitro and in vivo experimental systems will advance the understanding of cancer aetiology.