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CC/2022/03

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COC Annual report 2021 - draft

1. The draft COC Annual Report 2021 is attached at Annex A.

2. Members are asked whether they have any comments or suggested changes for the draft.

Secretariat
February 2022

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CC/2022/03 Annex A

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COC Annual report 2021 - draft

Draft report

Secretariat
February 2022

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Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their potential to cause cancer in humans at the request of UK Government Departments and Agencies.

The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc).

[To be updated]

Professor David Harrison
MD DSc FRCPath FRCPEd FRCSEd

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COC Evaluations

Human Biomonitoring for EU and Development of Human Biomonitoring Guidance Values in the HBM4EU project

A presentation was given by Dr Sepai, Public Health England (PHE), at the COC meeting on 11th March 2021 and the COT meeting on March 23rd 2021, with a supporting paper 'Development of Human Biomonitoring Guidance Values in the HBM4EU biomonitoring project'.

Human biomonitoring (HBM) programmes can provide essential information for identifying population exposures to chemicals of concern that can be assessed with regards to potential health risks against derived guidance values (GVs) in specific population subgroups or areas. These can be important complements to the conventional sources of information for regulatory chemical risk assessments and for supporting public and occupational health protection policies.

There is currently a diversity in the derivation of health-based guidance values for both the general population and for occupational exposures. Dr Sepai outlined the methodology for the derivation of human biomonitoring guidance values (HBM-GVs) by the European Human Biomonitoring Initiative, referred to as HBM4EU. This is a project involving 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The UK has been involved in the project with PHE leading the UK input. The initiative is designed to develop a harmonised and systematic strategy for the derivation of HBM-GVs.

Importantly, the HBM4EU strategy is based on current practices for deriving health-based assessment values based on internal exposure, which will supplement those already derived relating to external exposure measurements. The key schemes on which the HBM-GV derivation methodology is based are those already existing from the German Human Biomonitoring Commission, Summit Toxicology and the French Agency for Food, Environmental and Occupational Health & Safety. Members of the COC and COT were asked to consider whether the derived HBM-GVs could be used for risk assessment purposes and if the HBM-GVs would be accepted by the UK.

It was agreed, in principle, by members of both Committees that the framework was a robust and scientifically valid way to determine HBM-GVs but offered suggestions to make some components of the process more explicitly stated, including the impact of data availability (for example, toxicokinetic data) on the estimated level of confidence associated with each HBM-GV. It was accepted that the estimated level of confidence would vary on a case-by-case basis, depending on available data, which should be reflected in the use of the HBM-GV in different tiers for risk assessment purposes. As the values are able to be applied to any population, the absence of UK-specific population data was not considered an issue for derivation, with the caveat that the critical endpoint on which the HM-GV was derived is appropriate for the UK population. However, members considered that UK-specific data would be required before the HBM-GVs could be used for risk assessment purposes in the UK.

The COT commented that the HBM-GV's would need to be validated from a toxicological perspective. It was also suggested that refinements in exposure assessment could be achieved through the collection of environmental data (in collaboration with the Environment Agency or Defra) and through the inclusion of all routes of exposure, including dermal. Members agreed that going forward, the use of HBM-GVs in risk assessment could be particularly helpful to the FSA and that the Committee was happy to look at future case studies and offer their perspective. If endorsement of individual values was needed, the Committee would have to perform a detailed evaluation to offer their opinion.

Modification of Cancer Risk

COC had expressed aspiration in the preceding years to move away from traditional risk assessment approaches for potential carcinogens, to a more holistic approach encompassing consideration of the effects of chemicals on all stages of cancer development. This has been reinforced by increasing concern over the reliability and applicability of the rodent two-year bioassay in predicting chemical carcinogenicity. In addition, consideration had also been made of combining two guidance statements covering hazard identification and characterisation (G03), and alternatives to the two year bioassay (G07) to a combined document on considering modification of cancer risk using a weight of evidence based approach.

The COC discussed this further in 2021, in the main Committee and as a sub-group discussion. It was agreed that there was currently insufficient information available on all aspects of cancer development and the potential modification of these events by chemicals to facilitate its use by risk assessors. Therefore, COC guidance should not be developed at this point, and two guidance statements G03 and G07 should be updated (see below). The option of a position paper was considered but in the meantime a paper was published in Toxicology Research, (Harrison & Doe (2021) The modification of cancer risk by chemicals. Toxicology Research, 10(4), 800-809). This paper covered many of the aspects discussed by the Committee and it was agreed the topic would not be progressed to a published COC document at this time.

FSA Science Council Draft Principles and Guidelines on Third Party Evidence

The COC was presented the draft set of principles and guidelines on third party and uncommissioned evidence that had been prepared by the FSA Science Council to support consideration of such evidence, and provide transparency on the ways in which evidence submitted in a non-standard way would be assessed.

The COC made some suggestions for clarity in terms of the audience for the principles and guidelines and to be clear on the meaning of the wording on data cleaning.

The document has subsequently been finalised by the FSA Science Council.

Terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

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The terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS) was presented to the COC for awareness of this group. The COC fed back the suggestion of having lay representation on the group in the future.

Presentation by Dr Steve Dean "In vitro high content screening using patient-derived cell models"

The presentation by Dr Steve Dean, Imagen, described a personalised treatment for cancer that evaluates potential drug therapies using patient derived cell models. The PredictRx assay utilises a biopsy from patients to derive cells that are screened against 60 drugs to determine sensitivity of the tumour cells. There is a good prediction of clinical response with an 89% positive predictive value and 99% negative predictive value for those currently tested. Due to the low number and heterogeneous nature of the tumours, between 3 and 5 needle biopsies are usually taken which are pooled. The results therefore represent an average of the responses of the different tumour cells.

Since 2019, with informed consent, the patient-derived cells have been stored in a biobank and a searchable database has been established. The biobank has a range of solid tumour types and is being expanded to include haematological tumours. As with primary cell lines, patient-derived cell models generally have a limited life span, and to ensure that the cell models do not diverge from the original, a limited number of passages are allowed. The biobank and database are a key resource for the evaluation of new drug candidates at all stages of development, including the potential to enhance Phase I II and III clinical trials.

The biobank and database are also seen as a potentially interesting resource for cancer research to help gain an understanding of carcinogenicity and mutagenicity. Advantages include high throughput analysis of a range of endpoints including cytotoxicity and apoptosis, cell cycle, DNA damage & repair, morphological and phenotypic changes, cell stress and inflammation, cell signalling and transcription factors and drug internalisation. Importantly, the cell models are reliable pre-clinical models with a traceable origin and are accompanied by patient histories.

Following the presentation, the COC noted that this was potentially a good example of how in vitro methodology may allow risk assessors to steer away from the use of traditional in vivo study data and allow better understanding of mechanisms in humans. The stability of the cell models was questioned as this was seen as crucial to ensure that the models continued to represent the patient. As this could be different for each model, whilst this is being evaluated, the models are currently limited to 15-20 passages. It was recognised that validation will be key to getting clinical acceptance as a diagnostic tool and acceptance of findings within regulatory submissions.

The translatability of the approach, particularly the data, to establish mechanistic rather than response data was also raised. This had been attempted successfully for a metabolic syndrome and was believed to be applicable more widely to non-cancer endpoints. Artificial Intelligence platforms may play a key role in interpreting mechanistic

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data. Benefits of the use of the approach to assess risk included the high throughput nature, availability of detailed genotypic and phenotypic parameters and a response pathway analysis.

Joint ongoing topics

Relevance and Reliability of Evidence

The topic of 'biological relevance and statistical significance' has been raised as an area of interest during Committee horizon scanning activities for a number of years. A scoping paper was presented at the Joint COC/COM meeting in November 2020 also attended by some COT members, which outlined some of the more relevant and significant work that has been published on this issue in recent years. It was agreed that the general public would benefit from guidance that provided clarity on how the expert Committees evaluate data with respect to consideration of biological relevance and statistical significance.

A document providing a brief outline of the Committee evaluation process focussing on the relevance and reliability of data was drafted and discussed by COC and COT in 2021. During the COC and COT discussions it was proposed that two documents be developed. One aimed at the lay audience about the process used by the Committees to evaluate evidence and reach conclusions, which could possibly be presented on the website rather than formally as a statement. A second document aimed at a more informed audience on statistical significance testing and consideration of biological relevance, for which the current draft would be the basis.

This topic will be discussed further, including by COM, in 2022.

Horizon scanning

The COC undertakes horizon scanning exercises at regular intervals with the aim of identifying new and emerging issues which have potential to impact on public health.

At the end of discussion in 2021, it was agreed that the priority topics were:

- Maintain a watching brief on factors affecting cancer susceptibility including shift work, stress and other lifestyle factors and how that might affect assessment of chemicals and carcinogenicity
- Consider an update to guidance on assessment of nanomaterials, possibly as a joint activity across COC, COM and COT
- Gain awareness of the potential effects of antibiotics and antivirals on the microbiome

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- Consider a joint discussion with COM on thresholds for in vivo mutagens and whether there is new information subsequent to the 2010 COM opinion
- Endocrine disruption and the link with carcinogenicity, acknowledging that endocrine disruption is also a COT remit
- Impact of chemicals on potential for metastasis or progression of cancer, in particular with respect to the Hallmarks of Cancer and linking to the tumour microenvironment topic
- Communication of cancer risk and how COC should be involved with this, especially with the move away from a yes/no decision on whether a substance is a carcinogen, and ensuring consistency in describing risks, possibly starting with a landscape review of terminology across a number of Committees (FSA and UKHSA) and led by Lay Members
- Ensuring appropriate considerations are made to acknowledging diversity in the population especially where there might be differences in risk between different groups

The Committee continues to have a standing agenda item for each meeting on horizon scanning topics and to update the COC on upcoming topics for UK and international scientific advisory groups.

Working Groups

COT/COC subgroup on the synthesis and integration of epidemiological and toxicological evidence in risk assessment

The COT and COC set up a subgroup to review the approaches to synthesising epidemiological and toxicological evidence that are used in chemical risk assessments. More information is provided in the COT section 1.XX-1.XX

Guidance statements

The Committee continued to develop the guidance statement series during 2021. This included finalising revisions to the cancer risk characterisation methods (G06) statement.

Updates to the guidance on hazard identification and characterisation (G03), the use of biomarkers in carcinogenic risk assessment (G04) and alternatives to the two-year bioassay (G07) are ongoing and these are expected to be finalised in 2022.

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