Committee on CARCINOGENICITY

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC).

Scope of New Guidance Statement – Weight of evidence approach to assessing modification of cancer risk

Updated version for November 2020 meeting: This paper was first sent out for comment by correspondence. The comments provided have been captured in this updated paper and are presented to the Committee for full discussion of the contents of the new guidance statement.

1. The main sources of evidence used in the current risk assessment of potential carcinogens are human epidemiology studies and rodent long-term bioassays, with evidence from further studies being seen as supportive. The overall approach currently recommended by the COC for assessing carcinogenic risk of chemicals is outlined in guidance statement G01 (A strategy for the risk assessment of chemical carcinogens).

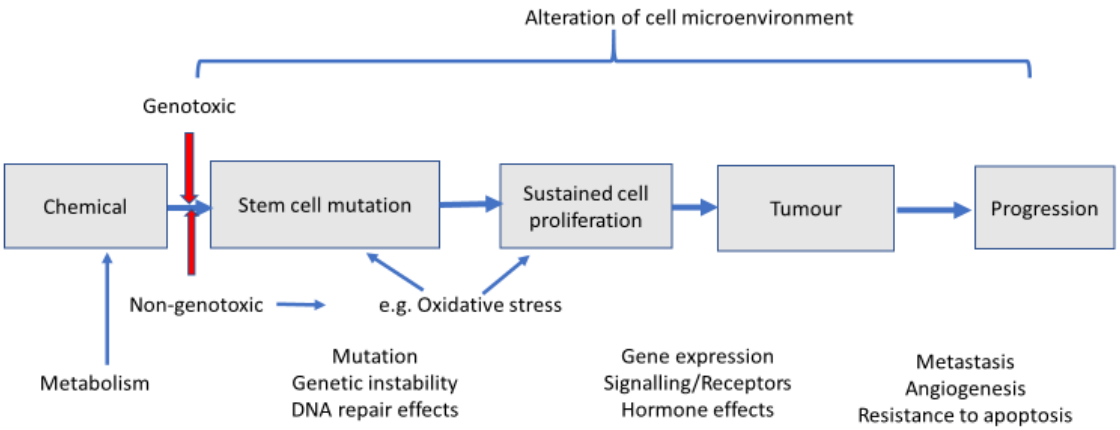
2. This strategy has proved to be a successful one when the substance under consideration has sufficient available information for evaluation. However, the approach can be limited as good epidemiology data is only available for a relatively small number of chemicals, usually where there is measurable occupational exposure over a long duration. In addition, the two-year rodent bioassay is primarily used to identify hazard rather than risk and the applicability of the findings in experimental species to humans is being increasingly called into question (Doe et al., 2019). Other pressures on the use of the rodent bioassay, which may make it unsustainable in the future, include ethical and financial considerations.

3. COC has been considering a new approach to the assessment of potential chemical carcinogens using a framework based on an increasing understanding of the carcinogenic process and the development of cancer. It incorporates new sources of emerging evidence regarding the influence of a number of different physiological and biochemical processes, such as those outlined in the Hallmarks of Cancer (Hanahan and Weinberg, 2000, 2011) on a dynamic carcinogenic process. It is hoped that such an approach will assist risk assessors when answering questions relating to potential impact on cancer risk following a specific chemical exposure.

4. In reviewing the current guidance statement series, the Committee agreed that two of the documents – Hazard Identification and Characterisation (G03) and Alternatives to the 2-year bioassay (G07) should be reviewed and the critical components from these reworked into a new document that considers all forms of evidence, including modifying factors, to assess the potential for a chemical exposure to influence cancer risk. It was agreed that the document would include aspects that work well from the current risk assessment process and build in new conceptual ways of considering information on the cancer process and how chemicals might influence it. A scope/outline structure of the document is suggested below for Members comments.

- Consideration would be given as to evidence of a chemical's ability to modify cancer risk rather than simply the need to identify a substance or industrial processes/exposures as carcinogenic/non-carcinogenic.
- The approach would be based on a Dynamic Cancer Risk (DCR) model (Figure 1) which considers the stages of cancer development, based on mutation, sustained cell proliferation, tumour progression and alteration of the cell microenvironment leading to tumour formation. In addition, such a model would also allow the impact of modifying factors on this process to be evaluated.

Figure 1. Dynamic Cancer Risk Model – Potential Risk Modification Points



- A DCR model would be developed for the chemical being evaluated, incorporating a potential carcinogenic pathway for both chemical (e.g. metabolism) and biological events (similar to Mode of Action and Adverse Outcome Pathways [some details of these approaches are outlined in G03, (Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies) and would be carried across]. This may be

driven by a chemical directly reacting with DNA (i.e. genotoxic) or by non-genotoxic mechanisms such as the induction of oxidative stress.

- A tiered approach might be appropriate based on the DCR with data on mutation and proliferation being considered primary 'initiating' effects in cancer with subsequent effects on cancer development being considered secondary ('promoting').
- On this pathway, other evidence would be superimposed of effects known to influence the development of cancer such as DNA repair, immunosuppression, gene expression and cell signalling, hormonal influence and the tumour microenvironment. [This would link to the Committee discussion in the Watching brief on the possible role of the tumour microenvironment in carcinogenicity].
- Consideration can also be given to other potential effects at the stage of tumour progression such as metastasis and angiogenesis.
- Assessment of the influence of factors/modifiers, such as different patterns of exposure (discussed in G09, COC set of principles for consideration of risk due to less than lifetime exposure), interactions with other chemicals either simultaneously or in the future (discussed in G08, Risk assessment of effects of combined exposures to chemicals on carcinogenicity), or lifestyle factors such as obesity can also be superimposed on the pathway.

5. It is envisaged that the following sources of evidence could be utilised. Consideration would need to be given to the priority of information and whether a tiered approach is possible giving some indication of the weight of evidence derived from the following types of data sources:

- Epidemiology – precancer, cancer, other relevant effects. Further information on this is discussed in the Synthesising Epidemiology Evidence Subgroup (SEES) Report.
- *In silico* models – structural knowledge and structural alerts.
- *In vitro* studies – genotoxicity assays, mode of action studies, relevance and validation.
  Note to members: Information on in vitro and in silico models are included in G07 and could be integrated into the new document – see Part c) Omics, high-throughput screening technologies, and bioinformatics. However, G07 is aimed at assessing these methods as potential alternatives to the 2-year bioassay rather than possible stand-alone information on the effects of a chemical on the modification of cancer risk.
- Animal studies – shorter-term studies with relevant endpoints and mode of action. This has been considered for pharmaceuticals by ICH (Van der Laan et al., 2016[P1]).
  Note to members: Some information on these is given in G07, and this could be integrated into the new document – see Part a) In vivo assays; Part b) Cell transformation assays; Part d) Alternative testing strategies for carcinogens incorporating results from short-term tests.
- Animal studies – 2-year bioassay and other chronic studies.
  Note to members: Information on the conduct and assessment of the results of the bioassay is given in G03, and this could be transferred to the new document.

6. Following the formulation of such a new approach and production of associated guidance, it is recognised that some additional points of clarification will likely be required in the future across the other COC guidance documents. Such aspects could include:

- How the evidence be quantified for risk assessment and how should they be communicated?[RB2]
- If qualitative,[RB3] how can this be expressed and communicated; for example, if there were differences in primary cancer effects (such as mutation and proliferation) rather than later effects on progression and/or the tumour microenvironment.
- Possible interactions with other factors such as chemicals or lifestyle.
- Concepts such as 'as low as reasonably practicable (ALARP)' and 'margins of exposure (MOE)' can continue be used for risk management and risk communication respectively but, the magnitude of the MOE may affect the confidence in the assessment and inform the evidence base required; but can other modifying effects on the carcinogenic process also be effectively expressed and communicated.

Questions for the Committee

7. Members are asked to

i. Comment and discuss the scope of the new guidance document outlined in paragraphs 4 & 5, including the updates following Members comments by correspondence.

ii. Inform the Secretariat of any relevant publications to reference in the new document.

References

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