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

Horizon Scanning 2016

Introduction

1. The Committee's Terms of Reference indicate that the primary role of the Committee is to advise on the carcinogenic risk of substances to humans at the request of Government departments and agencies. The Code of Practice for Scientific Advisory Committees (Office of Science and Technology, December 2001), specifies that:

"Committees should ensure that they have mechanisms in place that allow them to consider on a regular basis whether new issues in their particular areas of responsibility are likely to emerge for which scientific advice or research might be needed".

2. Since 2001, members have undertaken a regular Horizon Scanning exercise in which the Secretariat and/or Members have suggested areas/topics that may need consideration in the light of new and emerging evidence relating to cancer risk assessment. This paper presents a brief update on work agreed at previous meetings and presents some new suggestions for discussion provided by the Secretariat and Assessors.

Update on previous Horizon Scanning and Committee activity

3. A number of topics have been completed since the last horizon scanning paper presented to the Committee in November 2015. These are:-

Alcohol and cancer risk

4. The third draft of this statement was updated following the November 2015 meeting, and the statement was published on 8th January 2016, in co-ordination with the publishing of the CMO's new guidelines on alcohol consumption. The COM statement on the mutagenicity of alcohol was published at the same time.

Guidance statement G07: Alternatives to the 2-year bioassay, parts A and B

5. Parts A "*In vivo* assays" and B "Cell transformation assays" of this guidance statement were published on the COC website on 2nd February 2016.

Mode of Action/Human Relevance Framework

6. A paper was presented to the Committee at the July 2016 meeting providing an update on recent developments in the Mode of Action and Human Relevance Framework and related activities. Based on this discussion a few minor changes were suggested for the guidance statements, which will be actioned when the documents are reviewed.

Industrial exposure leading to cancer

7. A paper on frailty and cancer was discussed at the July 2016 meeting. The discussion paper included a commentary paper which had been raised under Horizon Scanning in 2015 and an associated review, as well as other commentary papers and author's response. A number of aspects were brought out in discussion, and it was recommended that frailty could be borne in mind for the planned joint COM, COC and COT meeting on epigenetics.

Cycloastragenol

8. The COC and COM gave advice in 2015 to the Advisory Committee on Novel Foods and Processes (ACNFP) on the potential carcinogenicity of a novel food application for cycloastragenol-TA65. The ACNFP continued to have concerns about the product after receiving this advice, with the result that the company withdrew their application. Thus the product is not approved as a novel food, and cannot be sold in the EU, although it may still be available elsewhere (e.g. in the USA). The ACNFP was grateful for the advice of the COC and the COM in undertaking this work.

Presentation of IATA for non-genotoxic carcinogens

9. In the context of the guidance on alternative testing strategies incorporating results from short-term tests (G07 part D, described below), a presentation was made at the July 2016 meeting by PHE on the ongoing work for the Organisation for Economic Co-operation and Development (OECD) to develop an Integrated Approach to Testing and Assessment (IATA) for non-genotoxic carcinogens. Members of COC were invited to join the expert group either to participate in the work, or to review the work as appropriate as it progresses.

Ongoing topics

10. In addition there are several ongoing topics and guidance statements in preparation and/or discussion. These are:-

Possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-I) in the diet, Part 3: The potential association of IGF-I with colorectal cancer risk and with lung cancer risk

11. A paper was presented at the March 2016 meeting covering Part 3 of the evaluation of the possible carcinogenic hazard to consumers from IGF-1 in the diet.

Parts 1 and 2 had been considered at COC meetings in March and November 2012, covering human physiological levels of IGF-1, its use as a human medicine, and association between blood levels of IGF-1 and breast and prostate cancer. This third part of the evaluation considers data on potential associations between blood levels of IGF-1 and colorectal and lung cancer. It was agreed at the March 2016 meeting that two Members of COC would consider further the meta-analyses and review the studies selected and the data that was included from the studies, with the aim of obtaining a clearer view of the possible size of any effect and the range of the available estimates. A further paper on this topic is being presented at the current meeting (November 2016).

Guidance statement G07: Alternatives to the 2-year bioassay, part D, Alternative testing strategies incorporating results from short-term tests

12. A strategy for discussing alternative approaches to assessing carcinogenic risk was considered at the March 2016 meeting, and followed up with a paper presenting an overview of testing strategies that incorporate results from short-term tests and/or *in silico* data at the July 2016 meeting. A draft version of this statement is being discussed at the current meeting (November 2016).

Guidance statement G09: Assessing the risk of acute and short-term/less-than-lifetime exposure to carcinogens

13. An updated first draft of this guidance statement was discussed at the March 2016 meeting, when it was proposed that the term “less-than-lifetime” exposure should replace “short-term”, to avoid the problem of having to define “short-term” exposure. A second draft statement was presented to the Committee in July 2016. A further paper on this topic will be presented in due course.

Outstanding items

14. At the horizon scanning exercise in November 2015 Members also discussed and prioritised the following items (not included above), which are still outstanding:-

Medium priority

Applicability of Margins of Exposure for exposure of young children

Thresholds of genotoxicity – keep informed of COM work

Nanomaterials – presentation on research on inhalation of nanomaterials

Dose-response modelling in epidemiology studies – this will be covered as part of the Guidance series G2 (Interpretation of Evidence of Genotoxicity in Humans)

In vitro systems – to be undertaken when resource allows

Studying cancer genomics through next generation DNA sequencing – as relevant papers are published

Effect of immunomodulation on cancer susceptibility

Low priority

Environmental tobacco smoke exposure in childhood and cancer risk

Applicability of Margins of Exposure for exposure of young children

15. An item for discussion in the Horizon Scanning paper in November 2015 was the question of risk characterisation for exposure of young children to genotoxic carcinogens. The Committee felt that the interpretation of margins of exposure (MOE) for children was of interest, but that examples or a case study were required to aid discussion (possibilities include arsenic and acrylamide in the infant diet). This issue was also of concern to the COT and the advice of COC would be appreciated. The COC has developed an MOE banding system for genotoxic carcinogens with the aim of assisting risk management and risk communication, although risk management is outside the remit of the Committee. The role of COC is seen as helping to explain risks. It was noted that there is a new EFSA working group on applicability of acceptable daily intakes to infant exposure, and that the findings of this group might be informative. It was also suggested that consideration of animal data on *in utero* and lifetime exposure might be helpful to investigate differences in susceptibility.

Question 1: Are Members content to keep this topic on the list of priorities?

Thresholds of genotoxicity

16. At the horizon scanning in November 2015 it was noted that the COM was awaiting publication of a series of papers on thresholds of genotoxicity and would then consider this topic. It had previously been agreed that the COC would await the outcomes of the COM's deliberations before addressing this topic.

17. A scoping paper was presented at the October 2016 COM meeting and further discussions will be taking place in 2017. It is likely that some of these discussions will also link it to carcinogenicity and a COC discussion or support from COC Members at a COM discussion may also be required. In due course the COM and COC Secretariats will discuss the best approach for this in liaison with the Committee Chairs.

Question 2: Are Members satisfied with this approach?

Nanomaterials – presentation on research on inhalation of nanomaterials

18. The COC guidance statement on nanomaterials (G10) was published over 10 years ago as a joint statement by COM, COT and COC. The COT produced an addendum in 2007 concerning a toxicity testing strategy for nanomaterials, and in 2012 the COM published a statement on genotoxicity assessment of nanomaterials. At the July 2016 meeting of COC it was stated that a presentation on nanomaterials and the inhalation aspects being researched by PHE has been arranged for a future

COC meeting. It was also suggested at the November 2015 COC meeting that biopersistent fibres could be considered separately to other nanomaterials.

Question 3: Are Members satisfied with the proposals to address this topic? Are there any particular aspects the Committee would like to be included in the presentation?

Dose-response modelling in epidemiology studies – to be covered as part of the Guidance series, G02 (Interpretation of Evidence of Genotoxicity in Humans)

19. The guidance statement on "Interpretation of evidence of carcinogenicity in humans: epidemiology and case reports", G02, is awaiting the report of a joint COT/COC subgroup on synthesising epidemiological evidence. Progress on the work of this subgroup is continuing and a further update is likely to be available in time for the November 2016 meeting. COC Members recognised that the subgroup report would not necessarily cover all of the aspects required for the guidance statement, but that it would be wise to wait for the draft report of the subgroup before deciding which other aspects to cover.

Question 4: Are Members satisfied with the current position on this topic?

In vitro systems

20. In discussion at the November 2015 meeting it was agreed that the work on *in vitro* cell lines should be expanded to encompass *in vitro* cell systems such as microphysiological models. These are more complex systems using human cells to test the effects of drugs and other substances, and they have the potential to improve toxicity testing beyond currently available tools, so that toxicity may be identified earlier in product development (Andersen et al., 2014). It was suggested that the presentation on 3D models given to COM at the June 2015 meeting (MUT/2015/06) could also be provided to COC.

Question 5: Would Members wish to hear the presentation on 3D models?

Studying cancer genomics through next generation DNA sequencing

21. A literature search of the PubMed database concerning the topic of next generation human DNA sequencing covering the years 2015-16 brought up over 1,600 hits ((next generation human DNA sequencing) AND (2015 OR 2016), performed 10 October 2016). A range of different aspects are covered in the recent literature, including the continuing evolution of new techniques, such as the use of circulating tumour DNA for sequencing, whole genome sequencing, massive parallel sequencing, and nanopores in next generation sequencing.

22. Of more specific interest to the Committee might be the finding and interpretation of patterns of sequence changes, a topic covered by a recent review (Hollstein et al., 2016). The paper refers to some well-known examples of

environmental impacts on tumour mutation patterns, such as UV light causing C to T transitions at dipyrimidines observed in skin tumours, and G to T transversions caused by tobacco smoking observed in lung tumours. The authors further state that there are now precise definitions of at least 30 distinct patterns of sequence change found in mutation databases, and that at least half of these can be assigned to known human carcinogenic exposures or endogenous mechanisms of mutagenesis. They provide an example of two representative cases of upper urinary tract urothelial tumours from regions of either low or high risk of exposure to the carcinogen aristolochic acid, which were analysed using whole-exome sequencing (Castells et al., 2015). Three distinct mutational signatures could be identified, and the absence of one of the signatures from one of the tumours suggested that the two tumours had distinct aetiologies.

23. Another review of interest covers the subject of targeting the cancer epigenome for therapy. Jones et al. (2016) is an up-to-date and comprehensive overview of the current situation concerning epigenetics in human cancer. Changes in the epigenome are detected by sequencing, and the authors comment that there are a large number of chromatin-controlling genes that have been found to be mutated in cancer, and that research is currently focused on determining how these mutations directly or indirectly alter the functioning of the epigenome. It is known that environmental exposure to carcinogens can directly alter the epigenome in a somatically heritable fashion. Furthermore, the authors highlight the potential role for nutrition in altering the epigenome, as suggested by a recent discovery that vitamin C is an essential cofactor for TET (Ten-eleven Translocation) enzymes which act as erasers of marks on DNA – TET genes are often mutated in human cancer, so that vitamin C deficiency could be contributing to increased DNA methylation and therefore aberrant gene expression. Evidence is also increasing that epigenetic abnormalities may occur because of cell stress, present during chronic inflammation or during the ageing process, and tumour initiation and progression are associated with chronic DNA damage.

Question 6: Do Members wish to carry forward the topic of next generation DNA sequencing on the list of priorities? If so, would Members wish to provide direction on what aspects should be focused on which would of most relevance to the Committee?

Effect of immunomodulation on cancer susceptibility

24. A PubMed search of ((human immunomodulation) AND cancer susceptibility) AND (2015 OR 2016)), performed 10 October 2016, produced 55 hits, of which only a small number were of possible relevance. Two papers cover the importance of killer T cell activity in controlling tumour cells – Pietra (2016) describes the importance of harnessing natural killer (NK) cell-based immunotherapies against solid tumours, and Bommarito et al. (2016) describe how inhibition of the PI3K pathway can make tumour cells more susceptible to NK cell activity. Lei et al. (2016) put forward the view that immunosuppression plays a pivotal role in assisting

tumours to evade immune destruction and promotes tumour development. They conducted a pooled analysis of over 42,000 cases of European ancestry from the Breast Cancer Association Consortium, and suggest that genetic variation in immunosuppression pathway genes may be implicated in breast cancer tumorigenesis. Finally Dzutsev et al. (2015) consider the role of microbiota in cancer development, and review the part played by microbial imbalance in the development, progression, and immune evasion of cancer. They discuss mechanisms of microbiota-mediated regulation of innate and adaptive immune responses to tumours, the consequences of these on cancer progression, and whether microbiota affect the ability of tumours to become resistant or susceptible to different anticancer therapeutic regimens.

Question 7: Are Members content for this topic to remain on the list of priorities? If so, could Members provide direction on what aspects of this topic might be most relevant to the Committee?

Environmental tobacco smoke exposure in childhood and cancer risk

25. In November 2015, this topic was considered to be of low priority as no specific question was being asked of the COC. It was suggested, however, that questions such as whether adult cancer occurring in the present day could be affected by smoke exposure in the home in childhood, could be considered.

Question 8: Are Members satisfied with the coverage of this topic?

New topics

Novel tobacco products

26. The Department of Health has asked COT to review novel tobacco products that are being evaluated under the EU Tobacco Products Directive which came into force in March 2016. COC and COM will be consulted and asked to review carcinogenicity and mutagenicity data as part of this request.

Electronic cigarettes

27. COT has started a review of e-Cigarettes, focusing on specific aspects such as additives, nitrosamines produced by these devices, and secondary exposure to exhaled products. Some carcinogenicity data has been published, some of these aspects may be referred to COC and/or COM.

Further question for the Committee

Are there any new items that Members would like to suggest for the Committee's consideration?

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References

Andersen ME, Betts K, Dragan Y, Fitzpatrick S, Goodman JL, Hartung T, Himmelfarb J, Ingber DE, Jacobs A, Kavlock R, Kolaja K, Stevens JL, Tagle D, Lansing Taylor D and Throckmorton D (2014). Developing microphysiological systems for use as regulatory tools – challenges and opportunities, ALTEX 31(3): 364–367

Bommarito D, Martin A, Forcade E, Nastke M-D, Ritz J, Bellucci R. (2016). Enhancement of tumour cell susceptibility to natural killer cell activity through inhibition of the PI3K signalling pathway, Cancer Immunol Immunother 65: 355–366

Castells X, Karanovic S, Ardin M, Tomic K, Xylinas E, Durand G et al.(2015). Low-coverage exome sequencing screen in formalin-fixed paraffin-embedded tumors reveals evidence of exposure to carcinogenic aristolochic acid, Cancer Epidemiol Biomarkers Prev 24: 1873–1881

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (2015), 3D Tissue models, MUT/2015/06

Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L and Trinchieri G (2015). The role of the microbiota in inflammation,carcinogenesis, and cancer therapy, Eur J Immunol 45: 17–31

Hollstein M, Alexandrov LB, Wild CP, Ardin M and Zavadil J (2016). Base changes in tumour DNA have the power to reveal the causes and evolution of cancer, Oncogene advance online publication 6 June 2016: 1-10

Jones *PA*, Issa *J-P J* and Baylin S (2016). Targeting the cancer epigenome for therapy, Nat Rev Genet 17: 630-41

Lei J, Rudolph A et al. (2016). Genetic variation in the immunosuppression pathway genes and breast cancer susceptibility: a pooled analysis of 42,510 cases and 40,577 controls from the Breast Cancer Association Consortium, Hum Genet 135: 137–154

Pietra G, Vitale C, Pende D, Bertaina A, Moretta F, Falco M, Vacca P, Montaldo E, Cantoni C,Mingari MC, Moretta A, Locatelli F, Moretta L (2016). Human natural killer cells: news in the therapy of solid tumours and high‐risk leukemias, Cancer Immunol Immunother 65: 465–476