CC/2015/17

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

Horizon Scanning 2015

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 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 horizon scanning paper was not prepared for the Committee to discuss in 2014, due to the volume of work being considered by the Committee at the time. Therefore, this paper provides an update on topics completed and worked on during 2014 and 2015. The Committee completed a number of topics in 2014 and 2015:

3.1 Vitamin E and the risk of prostate cancer

The COC was asked by the Food Standards Agency to review the information available on vitamin E and prostate cancer, including epidemiological, animal and *in vitro* studies. The COC produced draft statements in 2013 and 2014, and the final statement was published on 10 July 2015.

3.2 The use of Zebrafish in biomedical research

A presentation was made at the July 2014 meeting on this topic.

3.3 Guidance statements on the risk assessment of carcinogens

G03, "Hazard assessment and characterisation – conduct and interpretation of animal carcinogenicity studies" was published in 2015.

G05, “Points of departure and potency estimates”, was published in 2014.

3.4 Consultation of the European Food Safety Authority (EFSA) on a draft Scientific Opinion on acrylamide in food

Comments were made by COC members at the July 2014 meeting, and were combined with comments made by the COT and then submitted to EFSA.

4. In addition there are a number of ongoing topics and guidance statements in preparation and/or discussion:

4.1 Alcohol and cancer risk Statement

A number of papers on this topic were discussed in 2013 and 2014. In July 2015, a first draft Statement was considered. A revised final draft of this statement is to be presented at the November 2015 meeting, with the aim of publishing the statement before the end of the year.

4.2 Guidance Statement G07: Alternatives to the 2-year Bioassay
A second draft of this statement was presented and discussed at the July 2015 meeting, covering two sections: Section A on alternative *in vivo* studies, and Section B on cell transformation assays. It is intended to publish these two sections in 2015.

4.3 Guidance Statement on assessing the risks of acute and short-term exposure to carcinogens

A paper discussing developments in approaches that could be used to assess risk following acute or short-term exposure to carcinogens was presented at the July 2015 meeting. A draft statement has been prepared for discussion at the November meeting.

4.4 Advice on the novel food ingredient cycloastragenol

In response to a request from the Advisory Committee on Novel Foods and Processes (ACNFP), a paper was presented at the April 2015 meeting concerning the potential carcinogenicity of a novel food application for cycloastragenol-TA65. The genotoxicity data were referred to the COM for review in June 2015. A verbal update on the COC and COM meetings was given at the last ACNFP meeting, and a short report on the expert opinion is due to be sent to ACNFP once this has been reviewed by COC and COM.

5. During the horizon scanning exercise in 2013, Members discussed and prioritised the following items (not included above) which are still outstanding:

High priority:

- Alternatives in risk assessment

Medium-high Priority

- Mode of action framework

Medium Priority

- Thresholds of Genotoxicity – keep informed of COM work
- Nanomaterials – presentation of research on inhalation of nanomaterials
- Dose response modelling in epidemiology studies - this will be covered as part of the Guidance Statement series G02 (Interpretation of Evidence of Carcinogenicity in Humans)
- *In vitro* cell lines - to be undertaken when resource allows
- ETS Exposure in Childhood and Cancer Risk - to be undertaken when resource allows

Alternatives in risk assessment

6. This continues the work on guidance statement G07 which provides an overview of approaches that have been proposed as alternatives to the 2-year rodent bioassay. G07 comprises four parts, two of which, Section A on alternative *in vivo* studies, and Section B on cell transformation assays, will be published in 2015. There remains Section C, on developing methodologies and strategies such as toxicogenomics, and Section D, which will cover alternative testing paradigms, such as evaluation using histopathology and proliferative markers, in sub-chronic rodent studies.

Question 1: An alternative strategy to the current carcinogenic risk assessment paradigm (Section D) was discussed as a new item in the 2013 horizon scanning, and several references were provided. Would Members like a more detailed review of this topic before a draft of the Section is produced?

Mode of Action and Human Relevance Framework

7. The Committee considered papers on the Mode of Action and Human Relevance Framework in 2005 and 2008. The papers refer to the US International Life Science Institute (ILSI) human relevance framework (HRF), and describe how to use the mode of action (MOA) for a chemical established as a carcinogen in experimental animals to evaluate the human relevance of the animal tumours.

8. A presentation was given at the November 2013 meeting describing the development of the HRF and a Key Events Dose-Response Framework (KEDRF). The KEDRF is largely based on MOA and on systematically examining key events that occur between the initial dose of an agent and the effect of concern. The WHO updated their guidance on the Framework in 2014 (Meek et al). Recently, OECD has developed guidance on Adverse Outcome Pathways (AOPs), which share many charactersitics of MOAs.

Question 2: Do Members still wish to consider this item?

Thresholds of genotoxicity

9. At the last horizon scanning in 2013, Members decided that they wished to be kept informed of COM work on this topic. The COM are awaiting a special issue of the journal Mutagenesis which will report on this topic following an ILSI/HESI session

at the 43rd Annual Meeting of the EEMS (European Environmental Mutagen Society) at Lancaster University in July 2014.

Question 3: Are Members satisfied with this coverage of the topic?

Nanomaterials

10. The topic of nanomaterials has been discussed on a number of occasions: in 2005 the Joint Statement of COT, COC and COM was published on nanomaterial toxicology; in 2007 the COT made an addendum to the joint statement concerning a toxicity testing strategy for nanomaterials; in 2012 COM published a statement on genotoxicity assessment of nanomaterials and experimental considerations. The COC has discussed carbon nanotubes, along with some other nanomaterials, in 2010 and again in 2011.

11. The topic was raised during the 2012 horizon scanning, and has also been raised by assessors as a topic on which it would be timely to update the Committee's opinion. At the 2013 horizon scanning, Members considered that there was little change in the evidence on carcinogenicity of nanomaterials since the last review. Members suggested that a presentation of research on the inhalation of nanomaterials and the implications for health would be useful.

Question 4: How do the Committee wish to take forward consideration of nanomaterials? Are Members agreed that a presentation of research on inhalation of nanomaterials would be useful?

Dose response modelling in epidemiology studies

12. This topic, the Interpretation of Evidence of Carcinogenicity in Humans, will be covered as part of the Guidance Statement series as Statement G02. The statement will provide advice on how epidemiological studies and case reports can be used to inform carcinogen risk assessment. This statement is awaiting the outcome of a joint COC/COM subgroup on synthesising epidemiological evidence.

In vitro cell lines

13. Members noted at the 2013 horizon scanning exercise that, with reducing use of animals, there is likely to be an increased reliance on results from *in vitro* studies in the future. The point was made that not all cell lines are alike, and it is not clear to what extent they are human relevant. Members suggested that it would be helpful to assess cell lines with a view to identifying which ones are useful for which purpose. The comment was made that some cell lines are used simply because they are easy to use, or because the research group has experience with that line, but it may not be most appropriate for the specific purpose for which it is being used.

14. It was suggested that papers on different cell lines should be reviewed, and the quality of evidence should be assessed. It was also suggested that a review of

various cell lines would be informative, especially highlighting the validation status of each specific cell line for the assays performed.

Question 5: Could Members suggest which particular cell lines it might be most valuable to review, and/or which assays they think should be considered?

ETS exposure in childhood and cancer risk

15. The association between exposure to environmental tobacco smoke (ETS) in childhood and incidence of cancer in adulthood is a controversial issue. A number of studies have examined this topic. For example, Chuang et al. (2011) looked at exposure to environmental tobacco smoke in childhood and incidence of cancer in adulthood in never smokers, in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. They found no association between ETS and overall cancer risks. With regard to specific sites, they found no association with most common sites, apart from pancreatic cancer. This is in agreement with the findings of Vrieling et al. (2010), who also worked with the EPIC cohort and found that pancreatic cancer risk was increased among never smokers exposed daily to ETS (for many hours) during childhood (HR 2.61, 95% CI 0.96–7.10), or who were exposed to ETS at home and/or work (HR 1.54, 95% CI 1.00–2.39).

16. Findings regarding lung cancer also vary. For example, Janerich et al. (1990) found that household exposure to 25 or more smoker-years during childhood and adolescence doubled the risk of lung cancer (OR 2.07, 95% CI 1.16-3.68). On the other hand, Boffetta et al. (1998) found no association between childhood exposure to ETS and lung cancer risk (OR for ever exposure 0.78; 95% CI 0.64–0.96).

17. Exposure to tobacco smoke by non-smokers is also considered in IARC monograph 100E (2012), entitled “Second-hand tobacco smoke”. The monograph includes consideration of children’s exposure to second-hand tobacco smoke in their home or outside the home. Reference is made to emerging evidence that suggests exposure to second-hand tobacco smoke among children significantly enhances the risk of lung cancer in adulthood, but the monograph focuses on association of parental smoking with childhood cancers, rather than on cancer in adulthood. Overall, the evidence for an association between parental smoking and childhood cancer (all sites combined) remains inconsistent and may be subject to bias, but a fairly consistent association of paternal tobacco smoking with childhood cancers is beginning to emerge.

Question 6: Could Members clarify whether they wish to consider the effects of exposure to ETS in children on childhood cancers, or on cancer in adulthood?

Question 7: How do Members wish to take forward the consideration of this topic?

2015 Horizon Scanning – New items

18. As experts in their field, Members are encouraged to identify emerging and developing issues that affect carcinogenic risk assessment. These will be discussed within the Committee and taken forward if considered appropriate. The Secretariat has identified using next-generation DNA sequencing to study cancer genomics as

one potential emerging and developing issue that the Committee might wish to consider. The Food Standards Agency (FSA) has also proposed the topic of risk characterisation for exposure of young children to genotoxic carcinogens as an issue to consider.

Studying cancer genomics through next-generation DNA sequencing

19. Recent advances in the technology of sequencing have made it possible to analyse a whole cancer genome. There are usually multiple mutations within cancer cells, which can include single-nucleotide substitutions, insertions, deletions, copy number alterations, and structural rearrangements. A patient's cancer can contain a combination of these aberrations, and the ability to generate a comprehensive genetic profile has recently become possible (Doyle et al., 2014). Next-generation sequencing (NGS) has become the tool to uncover multiple cancer mutations in a single tumour. It is a rapid high-throughput technology, which allows millions of short DNA sequences to be generated from a single sample, and makes cancer sequencing studies less costly and easier to perform.

20. Several collaborations for cancer sequencing have been set up, such as The Cancer Genome Atlas (TCGA), funded through the National Institutes of Health in the US, and the International Cancer Genome Consortium (ICGC), a voluntary organisation that provides a forum for collaboration among cancer and genomic researchers. The ICGC was launched in 2008 to coordinate large-scale cancer genome studies in tumours from 50 cancer types and/or subtypes that are of major importance across the world.

21. Genomic studies involve a number of techniques besides whole-genome sequencing, such as genome-wide association studies, whole-exome (protein coding genes) sequencing, array-based comparative genomic hybridisation, global DNA methylome (methylation patterns) mapping, and gene or non-coding RNA expression profiling. As an example, such procedures have recently been applied to hepatocellular carcinoma (HCC) patients with different clinical features, to uncover the genetic risk factors and underlying molecular mechanisms involved in this cancer's initiation and progression, as described in a review by Han (2012). Genome-wide detection of somatic copy number aberrations and mutations, as well as whole-genome and whole-exome sequencing, have revealed a variety of genetic aberrations that indicate marked heterogeneity among HCCs, consistent with multiple risk factors for HCC and a long period of chronic inflammatory disease. The new techniques have also showed, however, that genomic instability seems to be more remarkable in hepatitis B-related HCC than in hepatitis C-related HCC. It is thought that genomic studies on liver cancer will further contribute to an understanding of the complexity and heterogeneity of HCC in the future, as well as to a better understanding of the pathogenesis and molecular classification of liver cancer, and to the identification of new diagnostic biomarkers and therapeutic targets.

Question 8: Do Members think that this is a topic which should be considered in depth by the COC?

Risk characterisation for exposure of young children to genotoxic carcinogens

22. The Committee on Toxicity (COT) is undertaking a series of evaluations of risks associated with chemicals in the diet of young children, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of dietary recommendations for infants and young children. The COT evaluations will include a number of genotoxic carcinogens, such as acrylamide and polycyclic aromatic hydrocarbons that are unavoidably present as contaminants in food. Exposure to food contaminants, expressed on a body weight basis is generally higher in young children than in adults, due to their relatively higher food consumption. It would be helpful for the COT and the Food Standards Agency to have a generic view from COC on the risks to young children incurred by such exposures.

23. The COC has endorsed the margin of exposure (MOE) as an approach to prioritising and assisting with the communication of the risks associated with unavoidable exposure to genotoxic carcinogens[1] . The MOE is the numerical value obtained by dividing a point of departure on the dose response curve by estimated human exposure to the chemical. The preferred point of departure is the lower 95% confidence limit of the benchmark dose (BMDL). When using dose response data from a rodent carcinogenicity assay, a benchmark response of 10% is commonly used, and hence the point of departure is known as a $BMDL_{10}$.

24. The Committee has proposed the system in Table 1 for banding MOE values, when based on the $BMDL_{10}$ from an animal study. This expands on proposals for the interpretation of the magnitude of the MOE, made by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA), that a MOE greater than 10,000 indicated low concern.

Table 1: Banding of MOE values based on a $BMDL_{10}$ from an animal study to aid risk communication	**Interpretation**
<10,000	May be a concern
10,000-1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be a concern

25. The interpretation of MOEs for children has not been explicitly discussed by COC, JECFA or EFSA. Publications in the literature generally refer to the MOEs of greater than 10,000 as being a low concern for all age groups. However, it might be argued either that a higher MOE value should be used to allow for potential greater vulnerability of young children, or that a smaller MOE could be a low concern in young children provided that the MOE is greater than 10,000 over a longer period.

26. Dietary exposure to widespread food contaminants is typically highest in the toddler age group (1-3 years), at which time it is 2-3 times that of adults (see for example table 8 of EFSA 2015). As a result it would be possible for an MOE to be

[1] COC Guidance Statement G06: Risk characterisation methods

5000 in a young child, and 15,000 when that child becomes an adult, if the levels of contaminant in food remain unchanged.

27. Carcinogenicity studies involving administration of a chemical in the diet or drinking water commonly use a fixed concentration of the test material throughout the dosing period. Since younger animals eat and drink more, the actual received doses decrease over the study duration. The dose response data used in calculation of the $BMDL_{10}$ are average dose levels. Thus it might be argued that the $BMDL_{10}$ should be divided by averaged lifetime dietary exposure of humans in calculating the MOE. Juvenile animals are not routinely included in rodent bioassays. However analysis of consumption data throughout chronic rat studies demonstrates that the food consumption in the early weeks is 2-3 times higher than the average over the study duration (EFSA, 2012), which is comparable to the difference between human toddlers and adults.

28. The US Environmental Protection Agency (US EPA) conducted a comparison of tumour incidence following early life exposure to chemical carcinogens with incidence in standard rat and mouse bioassays in which exposure begins at six to eight weeks old. They concluded that the cancer risk for carcinogens with a mutagenic mode of action was higher for a given exposure occurring early in life when compared with the same exposure during adulthood. As a result, they recommended applying adjustment factors in cancer risk estimates. In the absence of chemical specific data, default adjustment factors of 10 for age 0 to ≤ 2 years and 3 for age 2 to ≤ 16 years were proposed. The distinction between these age groups was on the basis that 0 to 16 years encompasses the periods of rapid development, including puberty, and that in addition toxicokinetic differences from adults are greatest in the first year (US EPA, 2005).

29. When taking into account the proportions of a 70-year lifespan of these age groups, assumed to be at 10-fold and 3-fold greater risk, respectively, and the proportion of the remaining lifespan as an adult, the overall estimates of lifetime risk from lifetime exposure generated by the EPA's quantitative risk assessments will be in the order of a little over two times higher than under the previous EPA approach before the introduction of these adjustment factors for children.

30. For example, a quick calculation assuming that dietary intake is 3 times higher by 0-≤2 year olds than adults and 1.7 times higher by 2 to ≤16 year olds than adults (approximate figures based on typical results from total diet studies of chemicals, although there is variability from chemical to chemical), and taking into account proportions of lifespan spent in the different age groups of 2/70 years, 13/70 years and 55/70 years, respectively, the estimated lifetime risk would be 2.2 times higher using the adjustment factors than not using the adjustment factors. Given that dietary intakes of chemicals in the diet by young children are up to around three times higher than in adults, and are typically around 2.5-times higher than exposure averaged over a 70 year lifespan, it could be argued that if the MOE bandings are applied to the intakes of young children, e.g. an MOE of 10,000 considered of low concern (with the MOE of adults being three-fold higher still and an MOE for lifetime exposure being around 2.5-fold higher), then this already allows for potential increased susceptibility of young children when considering the overall lifetime risk, without a higher MOE being required for the young children.

31. The subject of early life exposure to carcinogens has been discussed previously by the Committee in 2003 and 2006. In 2003 the COC discussed the EPA guidance which developed the adjustment factors given above, using a limited number of studies which had compared tumour incidence after dosing with a chemical at different life stages. In 2006, the Committee discussed further work on this by Hattis et al (2004, 2005). Members queried whether the default assumption used by Hattis, that juvenile rodents and humans would always be at a higher risk of cancer following exposure to genotoxic carcinogens than adults, would always be appropriate. It was considered that this was theoretically possible for direct acting genotoxic carcinogens but not for those requiring metabolic activation. In addition, for non-genotoxic carcinogens, it was likely that the accumulation of mutations with age could influence the subsequent response to tumour promoting agents. Although several studies have been published containing data on the effect of age at starting smoking on the risk of tobacco-induced cancer, it is difficult to disentangle the effect of age at start from the effect of duration. Members considered that there was insufficient evidence at that stage to adopt adjustment factors for genotoxic carcinogens for different life stages. Members did not support the conclusion that most of the lifetime risk associated with genotoxic carcinogens arose from pre-adult exposure. However, they agreed to continue to keep this subject under review.

Question 9: Are Members able to comment on whether the MOE banding in Table 1 should also be applied to young children?

Question 10: If Members are not able to comment, do they consider that a COC review of this topic should be conducted, and if so could they give suggestions on how this should be approached.

Further questions for Members:

1. Do Members have any further suggestions for topics, in relation to chemicals and cancer risk assessment, that they would like to see examined by the Committee?

2. How would Members prioritise the topics and any new suggestions which they have agreed should be considered?

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