CC/2016/05

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

Annual Report 2015

Attached is a draft of the COC's Annual Report for 2015, which will be published as part of the 2015 COT/COM/COC annual report on the Committees' websites. Members are asked whether they have any comments or suggested changes to this draft?

Secretariat
March 2016

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

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their carcinogenic potential 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).

The COC held three meetings in 2015. The major item of work this year was the ongoing review of the risk of cancer from consuming alcohol. The statement on this was finalised at the end of the year and published very early in 2016. The year also saw the publication of our statement on Vitamin E and the risk of prostate cancer which we have been considering for some time.

2015 saw a referral from the Advisory Committee on Novel Foods and Processes for advice on the novel food ingredient cycloastragenol. The COC reviewed the carcinogenicity data and advised further referral to the COM for consideration of the mutagenicity data.

There was also continued discussion of the guidance statement series, with publication of the statement on hazard identification and characterization. There will be a couple of further statements published in 2016.

As 2015 was my last full year as Chair, I wish to extend my gratitude to all the members of the committee I have worked with for the invaluable advice they have provided and to the secretariat for its support. I wish my successor all the best for the future.

Professor David H Phillips
BA PhD DSc FRCPath

COC Evaluations

Alcohol and Cancer - Statement 2015/02 – Statement on consumption of alcoholic beverages and risk of cancer.

Since 2013, the Committee has undertaken a programme of work considering the new evidence on alcohol and cancer risk.

The Committee has considered the new papers published since the most recent IARC review of alcohol conducted in 2009 (IARC, 2012). New cohort and case-control studies were considered as well as meta-and pooled analyses. The review focussed on upper aerodigestive tract (combined), oral cavity and pharynx, larynx, oesophagus, female breast, liver and colorectum cancers as IARC considered consumption of alcohol to be causally related to these sites. In addition, the Committee considered the new evidence on pancreatic cancer and alcohol consumption for which an association had been identified by IARC.

The COC also considered the available evidence on the effect of binge drinking on cancer risk as this was identified as an emerging area of concern, the interaction of alcohol consumption and genotype in cancer risk, the burden of alcohol on cancer, the effect of cessation of alcohol consumption on cancer risk and the potential mechanisms by which alcohol may increase the risk of cancer. Some individual meta-analyses reporting potential inverse effects for some cancer types were also discussed.

Overall the findings supported the IARC conclusions and suggest that all types of alcoholic beverage can cause cancer with risk increasing the more alcohol a person consumes. Using the two most appropriate available studies investigating the burden of cancer attributable to alcohol, produces estimates that 4-6% of all new cancers in the UK in 2013 were caused by alcohol consumption.

The new publications show:

- At **low, medium and high alcohol intakes**, a statistically significant increased risk at the following cancer sites:
    - oral cavity and pharynx (combined)
    - oesophagus (squamous cell carcinoma)
    - female breast
- At **medium and high alcohol intakes** (i.e. generally at intakes >12.5 g ethanol/day, or > approximately 1.5 UK units/day), a statistically significant increased cancer risk at the following cancer sites:
    - larynx
    - colorectum
- At **high levels of alcohol intake** (i.e. generally at intakes >50 g ethanol/day, or > approximately 6 UK units/day), a statistically significant increased cancer risk for the following cancer sites:
    - liver
    - pancreas.

The risk of getting some alcohol-related cancers gradually decreases over time in people who stop drinking alcohol, but it can take many years for the risk to fall to levels similar to those in people who have never drunk alcohol. It is logical to assume that reducing alcohol consumption would also lead to a reduction in cancer risk.

The full statement, and supporting discussion papers, are available here: https://www.gov.uk/government/publications/consumption-of-alcoholic-beverages-and-risk-of-cancer

Statement CC/2015/S1 – Statement on vitamin E and the risk of prostate cancer.

In 2011, analysis of results from the selenium and vitamin E cancer prevention trial (SELECT), which investigated the chemoprotective effects of selenium and vitamin E, suggested that vitamin E supplementation in healthy men significantly increased the risk of prostate cancer; the results of this study contrasted with the findings of other authors, who have reported both a protective effect and no effect.

The Food Standards Agency asked the Committee to review the information available on vitamin E and prostate cancer, including epidemiological, animal and in vitro studies on this topic as well as to peer-review the SELECT study. The Committee highlighted a number of shortcomings in the SELECT trial and these are outlined in their statement which was published in 2015. This can be found here:
https://www.gov.uk/government/publications/vitamin-e-and-the-risk-of-prostate-cancer

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.

In 2015, the Committee considered the items still outstanding from the last horizon scan in 2013, as no horizon scanning was undertaken in 2014 due to the ongoing volume of work. In addition, some new suggestions of topics were made by the Secretariat as well as Members. Following discussion of these items, the list of priority topics was agreed as:

High priority:
- Alternatives in Risk assessment

Medium-high Priority
- Mode of action framework

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 Carcinogenicity in Humans)
- In vitro systems - to be undertaken when resource allows
- Studying cancer genomics through next generation DNA sequencing – as relevant papers are published
- Cancer genetics and cancer advancement by industrial exposure
- Effect of immunomodulation on cancer susceptibility

Low Priority
- ETS Exposure in Childhood and Cancer Risk

Ongoing work

Cycloastragenol

Cycloastragenol is a novel compound extracted from the root of plants of the genus *Astralagus* (including *Astralagus membranaceus*) and intended for use in food supplements. It is reported in the scientific literature that cycloastragenol increases the activity of the enzyme telomerase and thus reduces the number of critically short telomeres but it does not increase mean telomere length. This finding has been reported both in mouse embryonic fibroblasts *in vitro* and in five different types of tissue in mice supplemented with cycloastragenol, as well as in the lymphocytes of human volunteers supplemented with cycloastragenol.

Following concerns that the available data was not robust enough to demonstrate the safety of cycloastragenol in relation to its carcinogenic potential, cycloastragenol was referred to the COC by the Advisory Committee on Novel Foods and Processes (ACNFP).

Cycloastragenol was submitted to the ACNFP for authorisation as a novel food. The submitted data indicated that cycloastragenol has low oral bioavailability and was metabolised to a number of oxidised and hydroxylated compounds. A number of genotoxicity studies were also submitted that were considered by the manufacturers to be either equivocal or negative. Although some information on carcinogenicity was supplied, no standard carcinogenicity studies were submitted. The ACNFP had noted that there was a suggestion of a non-statistically significant increase in liver cancer incidence in treated mice in a study by Bernardes de Jesus *et al*. (2011) which was cited by the applicant. However, the study was limited by small numbers and a relatively short duration of exposure as well as having a relatively high background rate of tumours. This prevented any clear conclusions being drawn from the study. Given the available data and the reported effects on telomeres, the ACNFP requested advice from the Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC).

The COC considered that there were notable differences in metabolism between rats and humans. Although the compound was stated to have low bioavailability, there was little parent compound present after ingestion, due to rapid absorption and metabolism by hydrolysis and/or oxidation; no data on metabolite concentrations or longevity were presented.

The Committee had a number of concerns about the study by Bernardes de Jesus *et al*. (2011)[1]. These included the following; the age of death of the animals was not known; the tissues had not been studied; all tumour types had been summed, and; it was not clear whether other organs of relevance had been examined to ascertain that the liver tumours were secondary tumours as they were reported to be. The study was also too small to have sufficient power to show statistical significance, and since the cycloastragenol was only administered for 4 months it was not considered to be an adequate carcinogenicity study.

The 13 week study repeat dose feeding study was considered to be well conducted. Although outside the remit of the COC, the Committee were concerned that the increase in heart weight observed in that study had been dismissed by the applicant, despite a cardiotonic effect being claimed for the compound.

[1] Bernardes de Jesus B, Schneeberger K, Vera E, Tejera A, Harley CB and Blasco M (2011) The Telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. Aging Cell, 10, 604-621.

The mode of action of telomerase is to produce genetic changes by increasing repeats at the ends of DNA and it was not known whether this effect might also occur elsewhere in the DNA. It was noted that the in vivo genotoxicity tests undertaken would not necessarily pick up such effects. The genotoxicity experiments had been done to standard and were well reported but the results seemed to be equivocal and the COC recommended that cycloastragenol be referred to the COM.

The possibility of increasing telomere length or stopping telomeres shortening was of concern as these factors could increase cancer risk by allowing the proliferation of damaged cells which might otherwise undergo apoptosis. The Committee were concerned about the effects of cycloastragenol in younger people taking it compared to those who are older. Since the precise mode of action was uncertain it was unclear if it might be different in older animals and if other effects could also be occurring. There might also be the potential for differences in the effect(s) of cycloastragenol in people with tumour precursors and those without.

COC conclusions

The Committee has scientifically reviewed the data submitted and agrees that there remains general concern about the use of cycloastragenol. The Committee made the following recommendations:

a) Cycloastragenol should be considered by the COM. In particular, the raw data from the genotoxicity tests should be further examined, and consideration given as to whether another Ames test using a pre-incubation protocol would provide enough weight to establish whether or not a full 2 year bioassay would be required.

b) In the absence of additional appropriate negative mutagenicity data, the Committee would recommend a two year bioassay, or other suitable study to show a lack of effect in a strain prone to tumourigenicity. The aim should be to identify an observable effect in older animals, but also to check whether any effects are likely to occur in younger people taking cycloastragenol.

IGF-1 and cancer risk

Interleukin Growth Factor 1 (IGF-1) is a growth factor which has a variety of biological effects including the promotion of cell division and growth. It has been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers.

The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-1 in food and the association between blood levels of IGF-1 and the risk of certain types of cancer. The review is ongoing, though it was not possible to progress work on it in the period 2014-5. It is hoped that it will be progressed in 2016.

Guidance statements

In 2010, the COC adopted a proposal to change the way in which technical guidance on the risk assessment of carcinogens is presented on the COC website. At present, guidance is presented in a stand-alone booklet and is also spread throughout minutes and certain statements. This has several drawbacks. The proposed changes aim to improve accessibility of up-to-date advice, ease timely review, and make it easier to reference specific parts of COC guidance. The new system comprises an overarching statement G01 (which provides an ‘executive summary’ of the

advice, and a series of guidance statements on specific aspects of the risk assessment of carcinogens. The overarching statement will undergo regular updates as each detailed guidance statement is revised to reflect the best available scientific practice as it evolves.

During 2015, the COC published guidance statement G03 - Hazard Identification and Characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies.

Guidance statement G07 – Alternatives to the 2 year Bioassay was also discussed. The Introduction, parts A (*in vivo* assays) and B (cell transformation assays) was circulated for final comment from Members towards the end of the year and is expected to be published in early 2016.

A discussion paper on assessing the risk of acute and short-term exposure to carcinogens which will form the basis of guidance statement G09 was considered and this topic will be discussed further in 2016.