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

COC Annual Report for 2013

Members are invited to comment on the draft text for the COC 2013 Annual Report attached in Annex A.

Secretariat
February 2014

CC/2014/05 – Annex A

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COC Annual Report for 2013

Draft COC Annual report for 2013

Secretariat
February 2014

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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 (http://www.iacoc.org.uk/).

The COC held three meetings in 2013. After extensive review of the evidence, we provided advice to the Department of Education on the relative vulnerability of children to asbestos. We considered the role of epigenetics in carcinogenesis and the influence of vitamin E on risk of prostate cancer. We discussed a study on the interpretation of margins of exposure for genotoxic carcinogens. We began to consider the current evidence on alcohol and cancer risk. Finally, we continued our review of guidance statements on carcinogen risk assessment and published one on biomarkers.

As always, I am grateful to members of the committee for the invaluable advice and expertise they have provided during the year and to the secretariat for their support. I look forward to working with them on more topics and challenges in 2014.

Professor David H Phillips
BA PhD DSc FRCPath

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COC Evaluations

Relative Vulnerability of Children to Asbestos

Asbestos is a well known carcinogen that can cause both mesothelioma and lung cancer. Asbestos was used in the past in the building of homes, schools and other buildings and hence there is a potential for individuals to be exposed to asbestos from this historical use. An independent advisory group called the “Asbestos in Schools Steering Group” aims to promote effective management of asbestos in schools and to contribute to the development of guidance on such management. The group reports to the Department for Education (DfE). Following discussions in this Group, the DfE had asked the Department of Health for a study of the risk of asbestos to children and the Department had facilitated a DfE request for advice from the COC on the relative vulnerability of children to asbestos. In July 2011, COC members agreed an appropriate strategy to take forward a consideration of this issue.

The Committee had considered a number of relevant papers in 2012 and 2013, including the review of an additional epidemiology study published in early 2013 which had examined the cancer incidence and all-cause mortality of people exposed as children to crocidolite (blue) asbestos, which was mined and milled at Wittenoom Gorge, Western Australia. This study involved the same cohort as had been reviewed previously by members. It was noted that there was probably more data on this cohort yet to be published, which could provide good evidence on exposure in childhood and risk of mesothelioma in later life, but it was unclear what the timescales for any further analysis or publications might be.

In March 2013, a drafting group meeting was convened to discuss revisions to a previous draft of the statement. During discussions at this meeting, it was considered necessary for the COC to obtain values on the comparative risk of developing mesothelioma as a result of first exposure in childhood compared to first exposure in adult life. The Secretariat requested the assistance of HSE in obtaining this information and asked whether analysis of data from the deliberations of the Working Group on Action to Control Chemicals could be used to determine the effect of age at first exposure to asbestos on mesothelioma risk. There was some discussion in the correspondence received from HSE as to whether 25 or 30 should be used as the age of first exposure to compare with that of people first exposed at the age of 5 years. While different approaches had been used, the risk values obtained were broadly similar for first exposure at age 5 and that at age 30. It was agreed that the statement would include comparison of first exposure at age 5 with that at both age 25 and age 30.

The COC statement was completed in 2013 and the Committee agreed the following conclusions:

a) Asbestos is classified by IARC as a group 1 carcinogen, i.e. it is carcinogenic to humans. Asbestos causes mesothelioma, and cancer of the lung, larynx, and ovary. In their recent evaluation, IARC also considered that there is evidence (in some cases limited) in humans for positive associations between exposure to asbestos and cancer of the pharynx, stomach and colorectum.

b) In general terms, the levels of respirable asbestos fibres in air range from lowest to highest in the following order:

- background outdoor ambient levels (lowest levels)
- background indoor ambient levels in buildings not built with asbestos
- levels in buildings built with asbestos where the asbestos is in good condition
- levels in buildings built with asbestos where the asbestos has been disturbed or damaged and/or is in bad condition (highest levels)

c) The data in general suggest that the levels of asbestos found in schools with no asbestos in their construction are of the same order of magnitude as indoor asbestos levels in other buildings. When asbestos is present and is disturbed or damaged, the data indicate that exposure to asbestos fibres can increase. However, the information on levels found in schools is largely historical and there is a lack of contemporary data on asbestos in schools. In view of the importance of this issue, there would be a benefit in generating new exposure data.

d) There is also potential for children to be exposed to asbestos in their home environment in homes where asbestos-containing products (ACPs) were used in their construction. In general, the reported levels of asbestos found in traditionally built houses and flats are of the same order of magnitude as ambient indoor levels. However, activities such as maintenance can disturb asbestos and increase exposure both at home and at school.

e) From an epidemiological perspective, there is good evidence that childhood exposure to asbestos can cause mesothelioma in later life. However, the epidemiological data are too limited to assess differential susceptibility between children and adults. We recognise the effect of increased life expectancy of children compared to adults and the increased likelihood of mesothelioma as a result of the long latency period for this cancer. Because of differences in life expectancy, for a given dose of asbestos, the lifetime risk of developing mesothelioma is predicted to be about 3.5 times greater for a child first exposed to asbestos at age 5 compared to an adult first exposed at age 25 and about 5 times greater when compared to an adult first exposed at age 30.

f) There are respiratory and immunological differences between adults and children but their impact on the susceptibility of children to asbestos-induced cancer is unclear. We were informed that the juvenile lung is particularly susceptible to injury and that any lung damage received in the first 4 years of life, in terms of air flow obstruction, would remain for life. However, it is not possible to determine what effect fibre inhalation before the age of 5 would have on lung function, and whether any effect would persist. Some physiological differences (e.g. respiratory rates, total volume, and airway dimension) have the potential to modify the susceptibility of children compared to adults to asbestos. However, modelling of fibre deposition in children has indicated that children are unlikely to inhale more fibres than adults.

g) While the available relevant animal study provides data on age-related susceptibility to asbestos in rodents, it does not offer any significant insight into the relative vulnerability of children compared to adults to asbestos.

h) From the available data, it is not possible to say that children are intrinsically more susceptible to asbestos-related injury. However, it is well recognised by this Committee that, due to the increased life expectancy of children compared to adults, there is an increased lifetime risk of mesothelioma as a result of the long latency period of the disease. In reaching our conclusion and taking into consideration that there are a number of uncertainties and data gaps, we conclude that exposure of children to asbestos is likely to render them more vulnerable to developing mesothelioma than exposure of adults to an equivalent asbestos dose.

The COC's statement on the Relative Vulnerability of Children to Asbestos is available at: http://www.iacoc.org.uk/statements/index.htm.

Epigenetics in Carcinogenesis

Epigenetics is the modification of gene expression or cell phenotype caused by mechanisms other than a direct change in the DNA sequence. It is known to be involved with many regulatory processes in the cell, including cell growth and transformation. Epigenetics and its role in carcinogenesis was first considered by the Committee at the Horizon Scanning meeting in November 2010, and in 2013 the COC considered two papers and a presentation by Professor Tim Gant which provided a background and introduction to epigenetics.

One key question raised was whether epigenetic changes were the cause or consequence of the carcinogenic process. Changes in the methylation status of gene promoter regions during tumour formation had been identified, however it was noted that it was the resultant change in gene expression which could progress to tumour formation. The importance of looking at the gene level rather than global methylation state was highlighted.

The COC considered evidence of epigenetic effects following exposure to arsenic or benzene. There was also a brief discussion of the impact of endocrine disruptors on epigenetics but it was noted there was little information on cancer. Any assessment of epigenetic changes and cancer associated with endocrine disruptors would need to be based on a systematic review of the literature rather than undertaking an evaluation on a study by study basis.

It was noted that there were data gaps in the published epigenetic studies. This included a lack of study replication, that the human relevance of animal studies was not clear, and often epidemiological evidence was not available. It was queried whether methylation of DNA would be preserved during sample storage as this would enable investigation of epigenetics using some of the large cohort studies collecting and storing relevant biological samples.

Overall, the Committee considered that it was possible that epigenetic changes contribute to the carcinogenic action of arsenic and benzene but much more work would be required to assess this. It was agreed that epigenetic changes could be considered on a case-by-case basis when undertaking a carcinogen risk assessment, though it was noted that epigenetic changes could be causal for tumour development or an effect of tumour development.

It was agreed that the Committee would be kept up to date with developments in the epigenetics field, particularly where relevant to carcinogenicity. The role of epigenetics in at the carcinogenic effects of alcohol and smoking may also be considered.

The development of new screening levels for contaminants in soil

At the September 2013 meeting, the COC was asked by Defra to consider a revised toxicological framework for aiding the development of new screening levels for contaminated land risk assessment. The project had been assessed by the COT and further information is provided in paragraphs 1.36-1.49. The COT had recommended that the COC could provide further advice on whether it was appropriate to use an Excess Lifetime Cancer Risk higher than 1 in 100,000 to define low risk.

The COC made a number of comments on the report and the contaminated land regime as a whole, including comparing the revised framework with the existing approach of using Health Criteria Values to define Soil Guideline Values.

In the context of contaminated land, the Committee discussed whether the use of an Excess Lifetime Cancer Risk (ELCR) higher than 1 in 100,000 (e.g. 1 in 10,000 to 1 in 50,000) was appropriate to define an intake dose that would represent 'low risk' when defining a C4SL. Given the uncertainties involved, it was difficult to make a generic judgement and factors such as cancer site, data quality and animal versus human data would need to be considered. It was noted that the specific data for each of the six contaminants analysed in the project would have been helpful to the Committee's consideration. In general, the COC favours a minimal risk approach and would not like to see the threshold go higher than 1 in 100,000 ELCR. It was emphasised that the Committee already had a banding system for Margins of Exposure to aid risk communication and the derivation of the descriptors for each band had involved in depth discussion by the Committee in 2007. The term "Low Risk" was not used in the COC MOE banding.

The Committee noted that consideration was not currently given to exposures to mixtures of contaminants, except in the case of PAHs. Another potential approach could be to sum up the agreed level of risk for each of the contaminants present in the soil sample in question to get an indication whether there is a risk present.

The Committee discussed the need for transparency and consistency between Local Authorities and other stakeholders using the framework to identify C4SLs. It was advised that in the final reports to Defra for each contaminant, a number of different possible C4SLs had been presented for each exposure scenario, so Defra could determine how precautionary or conservative the values should be, and the Committee noted the need for risk management in such a decision. The Committee was advised that Local Authorities have to produce a risk summary document stating how land was categorised and the implications for landowners. The COC considered it important to have guidance to go with the C4SLs explaining the levels of risk. It was noted that the complex nature of the methodology could lead to uncertainty.

The decisions taken by Local Authorities were on record but no central database was available. The COC suggested that a national register of land classifications should be made publicly available.

Overall, the Committee concluded that there was no scientific basis for using a default margin smaller than those recommended by COC to derive an LLTC and advised the consortium to refer to the current COC bandings for the appropriate communication of the margin.

In addition, the COC noted that there were no plans to update the current SGVs but that the SGV for lead had been withdrawn by EA in light of the scientific data which had been published recently. Therefore, Local Authorities would not have any basis on which to assess the health risks from lead in land that may be contaminated. This could result in difficulties in determining the land as contaminated land. The Chair subsequently wrote to Defra expressing this concern and requesting feedback on the support being provided to Local Authorities.

Food Standards Agency funded research project on Interpretation of Margins of Exposure for Genotoxic Carcinogens (T01051)

Also at the September 2013 meeting, the COC was asked to review the final report of a research project funded by the FSA on “Interpretation of Margins of Exposure for Genotoxic Carcinogens”.

The general approach to genotoxic carcinogens has been to reduce exposure to levels that are "as low as reasonably practicable" (ALARP) or "as low as reasonably achievable" (ALARA), but this does not provide a clear basis for deciding on the urgency or extent of risk management actions. To address this, a series of international initiatives have recommended adopting a "Margin of Exposure" approach (MOE), for assessing risks from chemical substances in food that are genotoxic and carcinogenic. In this approach, a point of departure is generated by modelling the dose response data from an animal carcinogenicity study. The point of departure used is usually the lower 95% confidence limit of the BMD for a 10% response over control levels ($BMDL_{10}$). The margins between this value and estimates of exposure to the chemical are then calculated. A judgement can be made on the basis of the magnitude of these MOE.

The COC has previously concluded that the MOE approach could be useful for risk management action and communicating relative levels of concern. MOEs less than 10,000 were considered to be of possible concern, those between 10,000 – 1,000,000 were considered unlikely to be of concern and those above 1,000,000 were considered highly unlikely to be of concern.

In view of the lack of international consensus on interpreting the level of concern for an MOE on the basis of uncertainty factors related to species differences, the Food Standards Agency (FSA) commissioned a research project (T01051) to support the establishment of levels of concern for the MOE or assist the development of alternative approaches. The project approach focussed on systematic review of evidence and elicitation of expert opinion on dose-response

relationships for genotoxic carcinogens, development of a statistical framework to inform the definition of levels of concern, and comparison of the results with data on a number of known or potential human carcinogens. The draft final report was provided to COC as part of the review process.

Members acknowledged the final draft report was well-structured and reflected a large amount of work by contractors. However, the small number of carcinogens for which both animal and human quantitative data were available limited the analyses that could be undertaken. Members commented that studies based on the mechanism of action (MOA) could have provided information on the shape of the dose-response relationship at low doses in animal and human cells *in vitro*, to aid low dose extrapolation from carcinogenicity studies. Despite this limitation, Members agreed the research project adequately addressed its objectives.

Members agreed on the good quality of the report and that it fulfilled the objectives set in the research project. The overall conclusion of the research project was that it was not possible to establish with certainty the level of concern for a MOE of 10,000. Some of the case studies indicated that an MOE of 10,000 is a low concern, whereas for others the uncertainties in the assessments were such that conclusions could not be drawn. The Committee agreed that on the basis of the outcomes of this project there was no need to alter the previous conclusions on the MOE approach. It encouraged further studies addressing the MOA in order to determine the shape of the dose response relationship at low doses which might support developments in the MOE approach.

Horizon Scanning 2013

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

In 2013, the Committee considered the outstanding items from previous years, and one new discussion topic. Following these discussions, the list of priority topics was agreed as:

High priority:

- Alternatives in Carcinogenic Risk assessment
- Thresholds of Genotoxicity – to take forward as topic of interest in a joint COT/COC/COM horizon scanning meeting
- Alcohol and cancer - this work is ongoing

Medium Priority

- Mode of action framework
- ETS Exposure in Childhood and Cancer Risk - to be undertaken when resource allows
- 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* cell lines - to be undertaken when resource allows

Low Priority

- Mechanistic studies in Zebrafish

Ongoing work

Vitamin E and risk of prostate cancer – 1st Draft Statement

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 has asked the Committee to review the information available on vitamin E and prostate cancer, including epidemiological, animal and *in vitro* studies on this topic. In 2013, the Committee considered further information on the placebo used in the SELECT study published by the study authors. The review is ongoing and it is hoped it will be completed in 2014.

Alcohol and Cancer Risk

The need for an updated review of alcohol and cancer was identified by the Committee during the Horizon Scanning exercise at its meeting in November 2012 and it was considered that a statement generated from such a review would provide useful information for both Public Health England (PHE) and the Department of Health (DH).

In 2013, the COC considered a strategy to take forward a review of alcohol and cancer risk and agreed that the principal outcome of the review should be to inform risk reduction strategies. Investigations of dose-responses and patterns of intake (e.g. binge drinking) were considered essential to the review as this information could be directly related to the public's drinking habits, in difference to reviews by the International Agency for Research on Cancer (IARC) which are more focused on cumulative exposure. It was agreed the COC should review of the epidemiological data and assess the overall burden of alcohol on cancer incidence in the UK. The COC would also consider interactions of alcohol and smoking. Two other interactions 1) caffeine and alcohol and 2) obesity and alcohol were also suggested.

It was noted that an evidence-based review on alcohol was ongoing by the UK's Chief Medical Officiers (CMOs) and due to be published in 2014. The Committee discussed a pre-publication report relating to this work, and further liaison with the groups undertaking the CMOs' review will take place in 2014.

The COC was also provided with a paper on alcohol consumption and trends. The Committee found the information on the proportion of adults drinking above government guidelines helpful. It was also noted that data from the survey of children indicated an overall reduction in the numbers of 11-15 year olds drinking alcohol and the amount they consumed in recent years. Overall, the information was considered useful for the Committee to move forward and consider the impact of alcohol consumption on cancer burden in the UK.

The review of alcohol and cancer risk is ongoing, with a number of further papers expected in 2014.

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-1in 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 2013. It is hoped that it will be progressed in 2014.

Guidance statements

During 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, which 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 will comprise an overarching statement which will provide 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 2013, the COC published guidance statement G 4: The Use of Biomarkers in Carcinogenic Risk Assessment. This discusses biomarkers of effect and their use to assess mode of action of a carcinogen, and the application and value of different biomarkers of exposure

Guidance statements G 5: Points of Departure and Potency Estimates, and G 7: Alternatives to the 2-Year Bioassay, were discussed in November 2013 and are expected to be published in 2014.

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