CC/2019/06

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

COC Annual report 2018 - draft

1. The draft COC Annual Report 2018 is attached at Annex A.

2. Members are asked whether they have any comments or suggested changes for the draft.

Secretariat
March 2019

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

COC Annual report 2018 - draft

Draft report

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

Preface

To be drafted

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COC Evaluations

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes) – overview of available data on carcinogenicity

The COC assessed the available data with respect to carcinogenicity as part of the COT assessment of the relative and absolute toxicological risks from E(N)NDS compared to conventional cigarettes, and where feasible heated tobacco products.

The Committee raised concern around the use of flavourings in E(N)NDS products and queried whether there was an 'approved' list for use in such products. The extent of carcinogenicity testing of the flavourings via the inhalation route was considered to be a potential issue, with most testing presumed to be by the oral route. In addition, thermal decomposition of flavourings and other materials was a potential risk, though it was difficult to draw any conclusions on relative risks compared to conventional cigarettes based on the available evidence.

It was noted that the risk to new users taking up the use of E(N)NDS products had not been considered. One paper had compared the risk associated with using conventional cigarettes, heated tobacco products and E(N)NDS products. The Committee considered that the risk for tobacco-containing products was implicit to the user as tobacco doesn't need to be heated to be carcinogenic. For E(N)NDS products, the available evidence suggested that nicotine itself was not a carcinogen.

There was some discussion on the potential risks to bystanders from exhaled aerosols and whether there was a difference between second hand smoke from conventional cigarettes when compared to E(N)NDS products. It was noted that only limited data were available on this topic.

The COC concluded that relative risk of E(N)NDS compared to conventional cigarettes appeared to be lower, but there was still some risk associated with the chemicals and particles in the emissions from E(N)NDS. This risk should be emphasised to new users. In addition. Members concluded that the possibility of bystander effects should also be considered.

Presentation on Immunological and stromal cell modulations relevant to cancer risk by Professor Nigel Gooderham

The COC is currently considering the wider role of immunomodulation in cancer development. As an initial step in these considerations, Professor Nigel Gooderham from Imperial College, London, presented his research in the area of metabolism and its interaction with the inflammatory system in cancer to the COC in November 2018.

In a presentation entitled 'Immunological and stromal cell modulations relevant to cancer risk', Professor Gooderham outlined his early research investigating a possible link between the exposure of humans to heterocyclic amines (HAs) from cooked meat in the diet and colon cancer, outlining the hypothesis that the genotoxicity of the

metabolites of HAs absorbed from cooked meat in the diet was a major driver for colorectal cancer. However, this hypothesis was not supported by the findings of a study of 500 incident colon cancer cases in which patients showed depressed hepatic cytochrome P450 activity (involved in HA metabolism), probably as a result of systemic infection and inflammation.

The abovementioned finding led to further investigations of the 500 incident colon cancer cases and the effects of HAs on the immune system. Increased expression of CYP1B1 and 2E1 was demonstrated, both of which are involved in carcinogen metabolism, in tumour tissue, and a distinct inflammatory microenvironment, with a number of pro-inflammatory cytokines (COX-2, IL-1β, IL-6, NF-kB-p65) being elevated. One of these, IL-6, was known to induce tumour CYP2E1 via the activation of JAK2 and STAT3 and mediated tumour CYP1B1 induction by reducing the expression of miR27b, an inhibitor of CYP1B1, to relieve its inhibition. Within the tumour microenvironment, IL-6 mediated immune and epithelial cancer cell cross-talk via miRNA and cytokines to sustain chronic inflammation and promote pro-metastatic cancer cell behaviour. In addition, miRNAs were indicative of a tissue-specific response making them good biomarkers. Looking forwards, it was suggested that CYP1B1, 2E1, IL-6, the JAK/STAT pathway and IL-6-mediated miRNAs could be therapeutic opportunities for colorectal cancer.

The Committee considered that there could be further investigation of whether miRNAs could be utilised for the diagnosis of early stages of disease, for example as part of ongoing epidemiology studies or by the screening of samples collated as part of the BioBank initiative. In addition, it was questioned whether elevated levels of miRNAs in pre-tumour tissue could indicate a causal mechanism in tumour development and provide therapeutic opportunities. It was recognised that the gut microbiome may have some effect on the miRNA profile in patients as the gut microbiome had its own miRNAs; however, the function of gut microbiome miRNAs had not yet been established.

In conclusion, it was agreed that the presentation had been and excellent introduction and that the COC would investigate further aspects of the role of immunomodulation in cancer in due course.

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 2018, the Committee considered the list of topics of interest from 2017, and discussed potential new topics on the microbiome and follow up to the Synthesising Epidemiological Evidence subgroup of the COT and COC on integrating epidemiological and toxicological evidence. Additional interest was also noted in unusually potent non-genotoxic carcinogens, for which BRAF inhibitors and pioglitazone could be examples.

Following this discussion, the list of COC priority topics (in no specific order) was:

- Immunological and stromal cell modulations relevant to cancer risk – to continue discussion from November 2018
- Presentation to provide background on the microbiome
- Unusually potent non-genotoxic carcinogens
- Integrating toxicological and epidemiological evidence, with COT as follow up to SEES subgroup
- Nanomaterials
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- Effect of early life exposure to cigarettes, depending on COT deliberations on developmental effects of nicotine
- *In vitro* systems - to be undertaken when resource allows

The Committee continues to have a standing agenda item for each meeting on horizon scanning topics and to update the COC on upcoming topics for IARC and the EU Scientific Committees.

Working Groups

COT/COC Subgroup on synthesising epidemiological evidence

Following the COC consideration of the draft report from the subgroup in 2017, the report was published in 2018 and its conclusions presented at EUROTOX. More information can be found in the COT section of this report (para X.XX).

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Guidance statements

The Committee continued to develop the guidance statement series during 2018. Updates were agreed for five papers in the series: Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies (G03), The use of biomarkers in carcinogenic risk assessment (G04), Defining a point of departure and potency estimates in carcinogenic dose response (G05), Risk characterisation methods (G06), and Alternatives to the 2-year bioassay (G07). In addition, a non-technical introduction to the series of statements was agreed.

Further discussion papers on developing a framework for consideration of risk due to less than lifetime exposures were discussed. Two papers on effects of combined exposures to chemical carcinogens were also considered. Both these are expected to become guidance in 2019.

These developments, updates and revisions to the guidance statements will continue to be addressed in 2019.

2018 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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