This is a draft paper for discussion. It does not necessarily represent the views of the Committee.

CC/2008/17

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

Horizon Scanning 2008

Introduction

1. The Committee Terms of Reference indicate that the primary role of the Committee is to advise on the carcinogenic risk of substances to man at the request of Government departments; particularly, but not exclusively, the Food Standards Agency and the Health Protection Agency. Therefore, the work of the Committee is primarily reactive and the agendas are set by the Secretariat based upon the need for advice from Government departments.

2. 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."*

Therefore, in 2001, Members agreed that it would be useful to have an annual agenda item where Members suggest areas/topics that needed further consideration in the light of new and emerging evidence relating to cancer risk assessment.

Update on 2007 Horizon Scanning

Mechanisms of transgenerational carcinogenesis

3. The FSA arranged a one-day workshop[1] on transgenerational epigenetics in February 2008. Some COC Members attended the meeting. The COT has published a statement summarising the workshop and the subsequent discussion amongst COT Members (COT, 2008).

Mode of Action Human Relevance Framework

The Committee discussed developments in this area at the April 2008 meeting (CC/08/3) and heard a presentation by Ms Idahosa of Imperial

[1] http://cot.food.gov.uk/cotmtgs/cotmtsem/cotwrkshoptransepigfeb08

College London, about her project on the weight of evidence framework in approaches to cancer hazard identification.

Carcinogenicity of mixtures

4. This work is currently being taken forward. The Committee has been presented with a proposed strategy for reviewing carcinogen-carcinogen mixtures (CC/08/14) together with a case study on mechanisms contributing to the synergism of alcohol and tobacco in human cancers (CC/08/10). Further papers are presented for discussion at this meeting.

Proteomics

5. This work is being taken forward as part of the update of the COT/COC/COM statement on toxicogenomics. COM discussions are underway and papers for COT and COC will be drafted when Secretariat resources permit.

Mutational spectra

6. It was considered that this area should be subject to a joint review with the COM. It is interesting to note that studies investigating mutational spectra are being considered as part of the COM's systematic review of acrylamide genotoxicity. The Secretariat will draft a COM paper on the general aspects of mutational spectrum analysis in the first instance when Secretariat resources and COM agenda permit.

2008 Horizon Scanning

7. 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 where this is considered appropriate. The Secretariat and some Members have identified some potential emerging and developing issues that the Committee might wish to consider:

Possible Carcinogenic Hazard from Dietary IGF-1

8. A member of the public has contacted the Food Standards Agency (FSA) and the Veterinary Medicines Directorate (VMD) to express concern that import of dairy products from countries that allow the use of recombinant bovine somatotropin (rBST) in dairy cows in USA and Mexico could cause an increased risk of certain cancers in UK consumers. The concern had been prompted by issues raised in the book "Your Life in Your Hands" by Professor Jane Plant. In the book the author describes her personal experience of having breast cancer and suggests that eating dairy produce could result in an increased risk of breast cancer (and possibly also prostate cancer).

Elevated concentrations of the insulin-like growth factor IGF-1 in milk from IGF-1-treated cows is highlighted as the causative agent.

9. At its meeting in July 2008, the Veterinary Products Committee (VPC) discussed the allegation that milk from rBST-treated cows could increase the risk of cancer in consumers. It was noted that, in 1999, a VPC Working Group on the Safety of rBST concluded that:

- The administration of rBST to dairy cows does not substantially increase the level of BST in milk.
- The likely increase of IGF-1 in the gut lumen from milk from rBST-treated cows raises concern about enhanced cell proliferation of gut mucosa and therefore increased prevalence of carcinoma in the large bowel.
- Treatment with rBST causes welfare problems, notably increased levels of mastitis, lameness and injection site lesions.

10. After hearing this advice, in 1999, the VPC turned down an application to allow the marketing of rBST in the UK to increase the milk production of cows. As use of rBST is not permitted in the UK, it was concluded that the question about the safety of imported dairy produce from rBST-treated cows was outside of the remit of the VPC and the matter fell to the FSA to address.

11. The FSA notes that IGF-1 is present in a wide range of animal-derived foods, often at concentrations in excess of those found in milk. If it were to be demonstrated that dietary IGF-1 caused an increased carcinogenic risk to consumers there could be concern about the safety of many foods.

12. Members may wish to consider whether there is a need for the COC to assess the possible carcinogenicity of the IGF-1 that is present in animal-derived foods. The FSA is obtaining copies of the articles cited by Professor Plant in relation to her claims about the carcinogenic hazard from dietary IGF-1. If the COC considers that there is value in investigating this subject more deeply, the FSA could also look more widely at the scientific literature on this subject, taking particular note of articles that were not available to the VPC Working Group on the Safety of rBST. Then, the FSA could bring a paper to the COC seeking advice on the hazard and/or risk to consumers from IGF-1 in foods.

RNA Related Effects as Mechanism of Carcinogenicity

13. A Member has highlighted a publication by Scholzová *et al.* (2007), which reviews the potential for RNA related effects as mechanisms of carcinogenicity. This publication highlights the scope for effects during post transcriptional modification of mRNA (splicing, capping, nonsense mediated decay, etc.), mRNA turnover, and RNA interference by microRNAs and non coding RNA (ncRNAs).

Carcinogenic Risk Posed by Carbon Nanotubes

14. A pilot study has shown carbon nanotubes to cause asbestos like (length dependent) pathology in the mesothelium when injected into the abdominal cavity of mice (Poland *et al.*, 2008). Prof Ken Donaldson of Edinburgh University, the senior author, is an expert in particle-related lung and respiratory disease and inhalation toxicology relating to nanoparticles.

15. Would members be interested to hear a presentation on this area of work from Prof Ken Donaldson during 2009?

Endogenous DNA Adducts

16. There has been some debate about the implications of endogenous DNA adducts for risk assessment at the European Environmental Mutagen Society (EEMS) and European Societies of Toxicology (Eurotox) meetings. When assessing exogenous genotoxic carcinogens, there is normally a difference between biomarkers of exposure (DNA adducts), which often extrapolate down to zero, and biomarkers of effect which can only be interpolated to a background mutation rate. However, in some instances, the adduct formed by the exogenous genotoxin is the same as an adduct formed by an endogenous chemical. In these instances, biomarkers of both exposure and effect may be interpolated to a background level. Some argue that this may have implications for risk assessment.

Cupric Gluconate

17. Cupric gluconate is a permitted nutrient source in the EU. A Member has highlighted a recent publication by Abe *et al.* (2008) which presents a medium-term liver carcinogenicity bioassay showing promotion at a Cu dose of about 60mg/kg bw/day and has asked whether the COC should review copper gluconate. It is not clear from the paper whether they have tested cupric (Cu II) or cuprous (Cu I) gluconate.

18. The Food Standards Agency's (FSA) Expert Group on Vitamins and Minerals (EVM) set a Safe Upper Level for copper of 0.16 mg/kg bw per day, the European Food Safety Authority (EFSA) upper level is 5 mg/day, equivalent to 0.08 mg/kg bw/day in a 60kg adult. Maximum levels for dietary supplements and fortified food use are under discussion, but current UK intakes are 2 mg/day from supplements and 3 mg/day from food excluding supplements. Therefore, there is a large margin of safety between the effects seen in this study and the level showing effects in this study; 375 based on the EVM guidance and 750 based on the EFSA guidance.

19. Would Members like to review the paper by Abe *et al* (2008)?

Red Meat and Cancer Risk

20. A Member has highlighted red meat and cancer risk as a developing issue. The FSA's Scientific Advisory Committee on Nutrition (SACN) is nearing completion of a draft report on iron, which addresses beneficial and adverse effects of increasing iron intakes. Potential adverse effects to be considered include free radical damage and the risk of cancer. The Secretariat is also aware of active research in this area. It is anticipated that COC will be consulted in due course.

Hair Dyes and Bladder Cancer

21. A Member suggested hair dye and bladder cancer as a topic for horizon scanning. This is being dealt with at the European level as part of the on-going review of hair dyes by Scientific Committee on Consumer Products (SCCP), formerly the Scientific Committee on Cosmetic Products and Non-food products intended for Consumers (SCCNFP); COC opinion would normally only be sought if new data suggests that a UK specific risk assessment is required.

Environmental Tobacco Smoke (ETS) Exposure in Childhood and Cancer Risk

22. A Member suggested that the COC might examine cancer risk following ETS exposure in childhood. A recent publication by the United States' Surgeon General (USDHHS, 2007) discusses this issue.

23. The COC conducted a major review of ETS and lung cancer in 1997. The Committee concluded that passive smoking in non-smokers exposed over a substantial part of their life is associated with a 10-30% increase in the risk of lung cancer (COT, COM & COC Annual Report, 1997). However, there were insufficient data to characterise the risk from ETS exposure in childhood alone. Would Members consider a review of this topic to be worthwhile, if sufficient new data were now available?

Integrated Approaches to Carcinogenic Risk Assessment

24. The COT Secretariat is arranging a one-day workshop on "21st Century Toxicology: emerging principles for refining toxicological safety assessments." The programme has yet to be finalised, but is currently expected to cover toxicogenomics, metabonomics, integrated approaches to carcinogenic risk assessment and quantitative structure activity relationship (QSAR) approaches. This programme aims to be relevant for all three sister committees; therefore, COC Members are encouraged to attend. The workshop will be held on 11th February 2009 and a programme will be circulated in due course.

Further suggestions

25. Do Members have any further suggestions for future work on chemicals and cancer risk assessment?

Secretariat
November 2008

For References see Annex A

This is a draft paper for discussion. It does not necessarily represent the views of the Committee.

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

Horizon Scanning 2008

References

Abe M, Usuda K, Hayashi S, Ogawa I, Furukawa S, Igarashi M, Nakae D (2009) Carcinogenic risk of copper gluconate evaluated by a rat medium-term liver carcinogenicity bioassay protocol. Arch Toxicol. 82(8):563-71

COT (2008) Statement on the COT workshop on transgenerational epigenetics (http://cot.food.gov.uk/pdfs/cotstatementtransepi200803.pdf)

Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A, Stone V, Brown S, Macnee W, Donaldson K. (2008) Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol. 3(7):423-8.

Scholzová E, Malík R, Sevcík J, Kleibl Z. (2007) RNA regulation and cancer development. Cancer Lett. 246(1-2):12-23.

United States Department of Health and Human Sciences; USDHHS (2007) The health consequences of involuntary exposure to tobacco smoke : a report of the Surgeon General. – [Atlanta, Ga.] : Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, [2006]

[Note: For copyright reasons the papers in the Annexes are not included in the published version. The bibliographic details of the annexed material are listed above. The documents are all in the public domain and individuals can obtain them by application to appropriate sources.]