

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

### **Horizon Scanning 2009**

#### **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 man at the request of Government departments and agencies; 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 and agencies.

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 2007/8 Horizon Scanning**

##### *Possible Carcinogenic Hazard from Dietary IGF-1*

3. The FSA Secretariat asked Members whether they wished to consider the possibility that dairy products from recombinant BST-treated cows might increase the risk of cancer in consumers due to elevated concentrations of the insulin-like growth factor IGF-1 in milk. This possibility was raised in a book written by Professor Jane Plant entitled “Your Life in Your Hands”.

4. Members suggested that the Secretariat should examine the evidence presented in Professor Plant's book. This was brought to the Committee at the July 2009 meeting and Members supported the proposal for a systematic review on the risk of cancer from dietary IGF-1, which will be brought to a subsequent meeting.

### *RNA Related Effects as Mechanism of Carcinogenicity*

5. The Committee was presented with a review by Scholzová *et al.* (2007, *Cancer Lett.* 246(1-2):12-23) on RNA regulation and cancer development. Members considered this to be an area of interest and highlighted research that suggests that microRNAs might play a part in interspecies differences in responses to peroxisome proliferators. Members considered there to be a substantial amount of emerging data. A discussion paper on this topic has been prepared for this meeting.

### *Carcinogenic Risk Posed by Carbon Nanotubes*

6. 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, *Nat Nanotechnol.* 3(7):423-8). Members were keen to hear a presentation on the subject, and this will be arranged in due course.

### *Red Meat and Cancer Risk*

7. This was an issue that had been identified by a Member during the 2008 horizon scanning exercise. This was discussed under the July 2008 item on the Scientific Advisory Committee on Nutrition (SACN) report on iron and health.

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

8. A Member had suggested that the COC might examine cancer risk following ETS exposure in childhood. Members considered that the available evidence be reviewed. The DH ongoing review of tobacco toxicology has focused on toxicity/carcinogenicity/mutagenicity approaches used to evaluate tobacco products and other areas, such as "Potentially Reduced Exposure Products (PREPs)", novel products etc. A review of childhood exposure to ETS and cancer in adulthood will be undertaken in due course.

### *Integrated Approaches to Carcinogenic Risk Assessment*

9. The COT held a one-day workshop on "21st Century Toxicology: emerging principles for refining toxicological safety assessments." The programme covered many topics including the US TOXCAST project, toxicogenomics, metabonomics, integrated approaches to carcinogenic risk assessment and quantitative structure activity relationship (QSAR) approaches. Several COC Members attended the meeting. The COT is in the process of drafting a Statement on this topic, which will be published in due course.

### *Proteomics*

10. This was identified in the 2007 horizon scanning exercise. It 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*

11. This was identified in the 2007 horizon scanning exercise. It was considered that this area should be subject to a joint review with the COM. It has been decided that, as an initial step, the COM will be asked to consider a paper on the general aspects of mutational spectrum analysis in due course.

## **2009 Horizon Scanning**

12. 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:

### *Fish as a tool for investigating chemical carcinogenicity*

13. Zebrafish (*Danio reio*) are increasingly being used as a model of toxicity, particularly for the study of developmental biology and embryogenesis (Kari *et al.* 2007) and zebrafish models have been developed which have the potential to be used in studies of carcinogenicity. For example, fish with mutant tumour suppressor gene tp53 develop malignant tumours after 8.5 months (Berghmans 2005a). Furthermore, transgenic models of leukaemia and melanomas have been developed in zebrafish.

14. The use of zebrafish as a cancer model has been reviewed by Feitsma and Cuppen (2008). As part of this review, a number of studies have been considered which assessed tumour development following exposure to mutagens; compounds examined include *N*-nitrosodiethylamine and 7,12-dimethylbenz[*a*]anthracene. Another aspect evaluated is the use of transgenic fish which express mammalian oncogenes, it is claimed that many zebrafish tumours resemble mammalian tumours.

15. The rainbow trout is another species of fish which is being utilized in toxicity testing, initially as a model in environmental carcinogenesis research (Bailey *et al.* 1996). Although it is accepted that it is not a perfect model for human carcinogenesis, it is claimed that it is adequate as far as biotransformation and the process of tumour development is concerned, and provides an alternative or adjunct species to rodents which can detect carcinogens. It has high sensitivity to a number of known human

carcinogens. Recently, this assay has been used in ultra-low dose carcinogenicity studies (Williams *et al.* 2009 [provided in Annex A], Bailey *et al.* 2009). Its usefulness for this kind of study is substantiated by the fact that extremely large studies can be conducted which significantly improves the statistical power to detect small increases in tumours above low background levels (e.g. ED<sub>001</sub> studies, prediction of 10 additional cancers in 10000). The principal study was conducted using 40800 trout and 8 dose levels of dibenzo[*a,h*]pyrene (in feed 0-225ppm). Data was modelled to extrapolate to a dose which could predict one excess tumour in a million individuals.

16. Although there are limited data available at the moment, it is believed that the greater power of this model of carcinogenicity is useful for the prediction of environmental risks at low doses and that the ability to generate more detailed dose -responses will be useful in the evaluation of the responses of chemical mixtures.

17. Does the Committee think that the use of fish in carcinogenicity research and assessment merits a more detailed evaluation?

#### *Gene Environment Studies*

18. In 2001 the Committee reviewed in detail a number of papers prepared on the subject of interaction between genotype and exposure to chemicals in the environment, and the induction of cancer. The following papers were presented and evaluated, and subsequently a statement prepared.

- [CC/01/3](#) - Criteria for the design of gene-environment epidemiology studies
- [CC/01/4](#) - A review of potential target genes for susceptibility to carcinogenesis
- [CC/01/5](#) - A review of how gene-environment studies should be used in risk assessment process

19. The review considered 'low-penetrance' genes, genes which may have a high prevalence in the population but alone are not a substantial contributor to the increase in cancer risk. Key elements of this review looked at epidemiological studies of candidate susceptibility genes and genetic association studies of the category of genes. The greatest number of examples retrieved were for genes associated with metabolic activation and / or reduced detoxification (e.g. CYP genes, GSTM1, GSTT1, NAT1&2). Very few studies were retrieved when other categories of genes which had been identified as having potential impact on carcinogenesis were addressed (e.g. DNA repair capacity, immune surveillance).

20. Criteria for how to assess interactions between genotype and environmental chemical exposure were also discussed. These included study design optimization, and the significance of these interactions for public health. The model of lung cancer and GSTM1 polymorphisms was selected as an example. In the statement, one of the recommendations from the committee was to keep the subject under review, particularly in light of the

expected developments from the Environmental Genome Project and other initiatives.

21. A preliminary search of the literature for articles on the genetic epidemiology of cancer revealed over 200 reviews, many systematic or meta-analyses, that had been published between 2001-2009. Many of these have focussed on specific cancer types (a wide variety have been examined), the impact of specific classes of genes on cancer risk and the impact of particular gene single nucleotide polymorphisms on specific cancer types. Examples include an examination of the role of cell proliferation associated gene polymorphisms on gastric cancer (Gao *et al.* 2009), GST1 gene and bladder cancer risk (Zeng *et al.* 2009), an examination of CYP1SA1 and GSTM1 polymorphisms and oesophageal cancer (Zhou *et al.* 2009) and a polymorphism in GSTM1 in breast cancer (Yu *et al.* 2009). It is noteworthy that many of the studies published are still preliminary or inconclusive, although many causal associations are suggested.

22. The NIEHS Environmental Genome Project is a multi-disciplinary, collaborative effort focused on examining the relationships between environmental exposures, inter-individual sequence variation in human genes and disease risk. There is an aim to identify and genotype single nucleotide polymorphisms (SNPs) in environmental response genes. The first phase of the effort is focused on finding SNPs in human genes involved in DNA repair and cell cycle pathways. Although the entire project is still in its infancy, it has prompted detailed explorations of interactions in genetic and environmental factors, cancer being one significant endpoint under review (e.g Chen and Hunter 2005, Hemminki *et al.* 2006 [provided in Annex A], Savas and Liu 2009).

23. It is noted that the quantity of data generated in this area is substantial. It is not immediately evident whether all studies provide useful information.

24. Does the Committee want to receive an update of this topic? If so, are there any particular areas that need to be considered (particular gene classes, particular cancers) and what should the goals of the review be?

#### *Joint COM / COC meeting on Thresholds of Genotoxicity*

The COM is in the process of preparing a guidance statement on the assessment of the thresholds associated with certain mutagenic modes of action and the implications for risk assessment. Would COC Members be interested in attending a joint meeting to discuss this topic and the broader implications for carcinogenic risk assessment?

#### *Further suggestions*

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

**Secretariat  
November 2009**

*References for: Fish as a tool for investigating chemical carcinogenicity*

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*References for: Gene Environment Studies*

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for GSTM1 in breast cancer. *FASEB J.* 23(7):2274-87.

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### References

[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.]

Hemminki K, Lorenzo Bermejo J, Försti A.(2006) The balance between heritable and environmental aetiology of human disease. *Nat Rev Genet.*;7(12):958-65.

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