Committee on Carcinogenicity 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 (http://www.iacoc.org.uk/).

During 2008 the Committee has considered a number of interesting items. We began our consideration of the complex problem of the assessment of mixtures of chemicals for carcinogenicity. This proved a difficult task due to the inevitable lack of data on carcinogenicity testing of mixtures and the need to attempt to draw conclusions from short-term studies and epidemiological findings. The Committee intends to produce a statement on this topic in 2009.

The committee was also asked to advise the UK National Coordinator for the Organisation for Economic Cooperation and Development (OECD) Test Guidelines on the planned revision of the guidelines for chronic toxicity and carcinogenicity studies and the associated Guidance Document. The Committee has agreed to draft a chapter on the investigations undertaken in studies of this type, which will include advice on histopathology.

I would like to thank the members and secretariat of the Committee for the work they have undertaken during the past year. We look forward to new challenges in 2009.

Professor David H Phillips
BA PhD DSc FRCPath

COC evaluations

Age as an independent risk factor for chemically-induced acute myelogenous leukaemia in children

3.1 In 2006 the COC discussed the question of whether there are age-related differences in susceptibility to carcinogenesis. At the November 2008 meeting, the Committee considered a recent review by Pyatt *et al* (2007; J Toxicol Env Health B, Volume 10(5): pp 379-400) which had tested the assumption that children are inherently up to 10-fold more sensitive than adults to genotoxic carcinogens. It had done this using data on the development of secondary or therapy-related acute myelogenous leukemia (t-AML) in children who had received treatment with high dose chemotherapy and/or radiation. This disease is well established as a potential long-term consequence of exposure to such treatment. The review had investigated the effect of age at treatment on a child's susceptibility to developing t-AML.

3.2 Members noted that there was little information, which had led the authors of the review to draw cautious conclusions. The Committee concluded the data presented did not give cause to think that children are more susceptible than adults, although the evidence was not strong enough to rule out such an effect.

3.3 Members also noted that the dose of chemotherapy administered to children is often scaled by body surface area, using an algorithm incorporating height and weight, whereas, in a risk assessment of chemicals which cause leukaemia, exposure would be scaled relative to metabolic rate (oxygen demand) on the basis of an exponent of body weight. It was acknowledged that, where susceptibility of the subpopulation is the result of increased exposure, this would normally be incorporated into the risk assessment by separate assessment of the exposure of the subpopulation, with emphasis on children's specific exposure assessment.

Betel Quid, Pan Masala and Areca Nut Chewing

3.4 Areca nut is an ingredient of betel quid or pan masala which is chewed as an aid to digestion and as a stimulant. Areca nut may have limited use as a food ingredient. The Committee reviewed the use of areca nut in betel quid and pan masala in 1993 and 1994 and advised that there was evidence of mutagenic and carcinogenic activity of areca nut extracts and derived compounds in experimental systems. Also, areca nut derived nitrosoamines, including the potent carcinogen MNPN, have been detected in the saliva of betel quid chewers. There were very limited data from epidemiological studies on the effect of betel or areca nut products without tobacco, but there was sufficient epidemiological evidence of a link between the chewing of betel quid containing tobacco and cancer in humans. The Committee concluded that the use of these products without tobacco was possibly carcinogenic in humans.

3.5 Following the publication of new information, the COC was asked to look at this subject again. Most of the epidemiological data available concerned the use of areca nut in betel quid or pan masala and the association with oral cancers and pre-cancerous lesions. Other epidemiological data associated the use of areca nut with other cancers such as liver cancers. There are also some limited animal studies and *in vitro* studies.

3.6 The Committee was informed at, in 2003, the International Agency for Research on Cancer (IARC) had categorised both the chewing of betel quid and of areca nut as carcinogenic to humans. It had also stated that there was sufficient evidence in humans to conclude that betel quid chewed without tobacco causes oral cancer.

3.7 The Committee considered the available data and concluded that there was sufficient epidemiological evidence to conclude that areca nut, when used in the form of betel quid or pan masala, is carcinogenic to humans. This relates primarily to an increased risk of oral cancers from retaining the areca nut or betel quid in the mouth for a significant length of time. Members also agreed that the use of areca nut as a food ingredient may result in an increased risk of cancer.

3.8 A statement is appended at the end of this report.

Carcinogen-DNA adducts as a biomarker for cancer risk

3.9 Researchers seeking to understand the mechanism by which a chemical causes cancer in a particular (target) tissue may measure the levels of adducts derived from the chemical which are bound to DNA. At the April meeting, the Committee considered a methodological paper by Rundle (2008; Mutation Research, Volume 600: pp 23-36) on the use of adducts as a biomarker for cancer risk. The paper suggests that epidemiological studies which seek to establish an association between carcinogen-DNA adduct levels and the risk of cancer often fail to incorporate fundamental epidemiological principles into their methods. The author described a number of studies which have investigated associations between DNA-carcinogen adduct levels and cancer, and he addressed a number of methodological issues common to these studies, such as the use of target tissue versus surrogate tissue and how this choice impacts on the selection of controls, the use of inappropriate statistical analyses, and small sample sizes. A number of suggestions were made to improve study designs to overcome these issues in the future.

3.10 The Committee considered that researchers are aware of the limitations of using surrogate tissues to measure DNA adducts. It also pointed out that, even if adduct levels were measured in samples of target tissue rather than in surrogate tissue, they may also lack relevance to the underlying pathological condition. This is because only certain cell types in the tissue will be targets, and only a limited number of adducts are causal, with the majority occurring at non-critical sites or in non-critical genes. The Committee considered that it was an over-simplification to argue that target tissue samples will overcome a major limitation of adduct determination and to dismiss the value of adducts in surrogate tissues.

3.11 The Committee noted that adducts measured at the time of diagnosis may not reflect exposure at the critical period and may be affected by the pathology of the condition suffered by the patient. It recommended that lymphocyte fractions of blood samples could be stored in biobanks and later used for biomarker analysis in outcome studies.

Chlorinated drinking water and cancer

3.12 Chlorination has long been an important part of water treatment, intended to ensure that drinking water contains no microbes hazardous to human health. Disinfection of drinking water is fundamental to preventing the spread of waterborne disease, such as cholera.

3.13 In the mid-1970s, refinements in techniques of chemical analysis resulted in the detection in drinking water of traces of chemicals formed when organic chemicals (such as those which may occur naturally in rivers, lakes, reservoirs and other water sources) are subjected to chlorination. In most supplies, the main chlorination byproducts (CBPs) are the four chlorinated and brominated trihalomethanes (THMs, ie chloroform, bromodichloromethane, chlorodibromomethane and bromoform). However, numerous other CBPs have been identified in drinking water, but many have yet to be characterised.

3.14 Some CBPs, including some of the THMs, are known to be carcinogenic in laboratory mammals and some are genotoxic in test systems. There have been many epidemiological investigations into the possible association between chlorination of drinking water and cancer in humans and experimental studies of the mutagenicity and carcinogenicity of CBPs. The COC reviewed the epidemiological studies in 1992 and 1999 and reviewed the animal carcinogenicity data in 1996. In 1996, it concluded that the levels of the four THMs considered by the Committee in drinking water in the UK were unlikely to provide a carcinogenic risk to humans and, in 1999, it concluded that the new epidemiological studies failed to provide persuasive evidence of a consistent relationship between chlorinated drinking water and cancer. The COC considered that efforts to minimise exposure to CBPs remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking water.

3.15 Thirteen further relevant epidemiological papers have been published since the 1999 review. The COC reviewed these at the July 2007 meeting and published the results of its review in 2008. The committee commented that problems remained in the interpretation of published studies on CBPs, particularly because adequate exposure assessment continued to be a major problem. It also noted that none of the studies reviewed were carried out in the UK and that it is possible that disinfection practices and constituents of the raw water may be different in other countries, in which case the study results may not be directly applicable to the UK. The committee concluded that the new studies on bladder cancer provided limited evidence for an association between bladder cancer and exposure to CBPs in men but that the evidence for an association in women is conflicting. In the 1999 review, the COC had commented that the studies of colorectal cancer gave inconsistent findings. In the current review, it noted that one well-conducted study provided some evidence for an association with colon cancer, but not rectal cancer, in men only. Also, a well-conducted study indicated an association with brain cancer in men but not in women. There were no consistent findings for other cancer sites. Overall, it concluded that the evidence for a causal association between cancer and exposure to CBPs is limited and any such association is unlikely to be strong. Efforts to minimise CBPs in drinking water should continue but must be balanced against the need for effective disinfection of drinking water.

3.16 A statement is appended at the end of this report.

Mode of Action/Human Relevance Framework

3.17 The International Programme on Chemical Safety (IPCS) Mode of Action (MOA) Framework is a conceptual framework for considering data on the mode of action of chemical carcinogens. The COC considered aspects of the MOA Framework in 1999 and, in 2004, considered a related topic, the Human Relevance Framework (HRF), which had been developed by a working group sponsored by the US Environmental Protection Agency and the International Life Sciences Institute (ILSI) Risk Science Institute (RSI). The HRF systematically considers the weight of evidence of hypothesized modes of action in animals and their potential human relevance for cancer.

3.18 In 2008, the Committee discussed recent developments made by the IPCS in the continuing evolution of HRFs. The IPCS HRF entails answering a series of three questions followed by a statement of confidence, analysis and implications. The COC considered 3 case studies which had used the IPCS HRF as an approach to determine the sufficiency of evidence and the relevance of an animal MOA for humans. These case studies entailed 3 different MOAs: 1) sustained cytotoxicity and regenerative proliferation leading to nasal tumours following exposure to formaldehyde, 2) direct alkylation of DNA leading to tumours in multiple sites following exposure to 4-aminobiphenyl, 3) increased hepatic clearance of thyroxin leading to thyroid tumours following exposure to thiazopyr.

3.19 The COC considered that the IPCS HRF was a valuable evolution of the work on this concept and proposed that the IPCS HRF approach should be used on a case-by-case basis in its future evaluations of chemicals.

3.20 The Committee also reviewed a paper by Sielken *et al* (2005; Scand J Work Environ Health, Volume 31, Suppl 1: pp151-5). This paper described a dose-response modelling approach to provide statistical insight into the relative likelihood of different mechanisms of action in cancer dose-response studies. The paper provided two examples based on time-to-tumour data for mammary fibroadenoma and adenocarcinoma in female Sprague-Dawley rats exposed to a pesticide in the diet. The examples considered how 34 different dose metrics (i.e. a measure of exposure to the pesticide or a measure of the biological activity potentially generated by the exposure if a specific mechanism of action applies) related to the incidence of fibroadenoma and adenocarcinoma and demonstrated how maximum likelihood statistical methodology could be used to provide an indication of the mechanism of action of the pesticide.

3.21 The Committee considered that it was unclear how the dose metrics and the different variables were identified and chosen for inclusion as no references were cited in the paper. It questioned the statistical robustness of the approach and considered that, although the most likely mechanism of action for the unidentified pesticide in the above examples was found to be hormonal, no other data were provided to show that it acted through a hormonal mechanism and therefore the assumption made in the paper was unwarranted. Moreover, no data were provided on the other dose metrics used. The Committee concluded that there may well be potential value in the approach suggested, but that more work was required. Before applying this approach to a specific example, it would be necessary to have alternative endpoints linked to a MOA.

3.22 The Committee also heard a short presentation by a PhD student at Imperial College London on the weight of evidence in framework approaches to cancer hazard identification.

Preliminary report by the EU Scientific Committees on Consumer Products, on Health and Environmental Risks, and on Emerging and Newly-Identified Health Risks on "Risk assessment methodologies and appproaches for mutagenic and carcinogenic substances"

3.23 The Committee was invited to comment on a preliminary report by the EU Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR).

3.24 The Committee considered the report to be well considered and up-to-date. However, it expressed concern about the discussion of the T25 method, which has been proposed for use in risk assessment. Several organisations no longer support this methodology due to its reliance on the lowest tested dose and lack of consideration of dose response which makes the methodology inherently more variable than the Benchmark Dose Modelling (BMD) approach. Also, the T25 method does not incorporate uncertainty in the analysis of the data. Committee members were concerned that the report suggests that the T25 and BMDL10 are equivalent. Most organisations considered that the BMDL10 was considerably superior to the T25 and that, where it was not possible to determine a BMDL10, it would not be possible to derive an informative T25 . The Committee also criticised the fact that the *post hoc* justification of the uncertainty factor of 10,000 commonly used in the Margin of Exposure (MoE) approach. This justification had never been adopted by the European Food Safety Authority (EFSA) and it was not clear that there was any reference to this specific derivation.

3.25 The Committee considered that the report should refer to the International Programme on Chemical Safety (IPCS) mode of action (MoA) framework since it is critical to understand whether there is likely to be a genotoxic MoA underlying the carcinogenicity of a chemical. It also noted that the text does not reflect the more refined framework for application of the Threshold of Toxicological Concern (TTC) by Kroes *et al* (2004; Food and Chemical Toxicology, Volume 42: pp 65–83). This methodology should not be used indiscriminately and consideration should be given to whether the chemicals under consideration are adequately represented by the database used to develop the TTC approach.

Pyrrolizidine alkaloids in food

3.26 The COC was asked by the COT for advice on the carcinogenicity of pyrrolizidine alkaloids (see paragraphs 1.44 to 1.47). The COC considered data on the mutagenicity and carcinogenicity of seven pyrrolizidine alkaloids (riddelliine, lasiocarpine, clivorine, petastitenine, senkirkine, symphytine and monocrotaline) and on the chemicals dehydroheliotridine and dehydroretronecine, which are the metabolites of many pyrrolizidine alkaloids. The Committee assessed whether the evidence was sufficient to conclude that each of the pyrrolizidine alkaloids had carcinogenic activity. As a general comment, the Committee noted that some of the data was rather old.

3.27 The most data were available for riddelline and lasiocarpine. Riddelliine is positive in a range of *in vitro* and *in vivo* assays for genotoxicity. In a carcinogenicity study conducted by the US National Toxicology Programme (NTP), it induced an increased incidence of liver haemangiosarcomas in both rats and mice, and of alveolar and bronchiolar neoplasms in female mice. The COC concluded that there was good evidence that riddelliine was genotoxic and carcinogenic and that it would be prudent to assume that at least part of its carcinogenic effect was due to a genotoxic mechanism. Lasiocarpine is positive in *in vitro* assays for genotoxicity but has not been tested in *in vivo* studies. In an NTP carcinogenicity study in rats, it induced an increased incidence of liver angiosarcoma in both sexes. In more limited studies in rats by either dietary or parenteral administration, treatment-related angiosarcomas of the liver and liver cell carcinomas were seen. The Committee decided that the database was less extensive than that for riddelliine but, due to the similarities in tumour profiles, concluded that it was also carcinogenic and likely to have a genotoxic mechanism

3.28 Clivorine shows conflicting results in *in vitro* assays for genotoxicity and has not been tested in *in vivo* assays. In a limited rat study in which clivorine was administered in drinking water, it induced an increased incidence of haemangioendothelial sarcoma of the liver. The COC considered that there were not enough *in vivo* data to reach a definite conclusion but clivorine was likely to have carcinogenic properties, based on its structure and limited evidence that it induced the same tumour type as riddelliine and lasiocarpine. Petasitenine is positive in *in vitro* assays for genotoxicity but has not been tested in *in vivo* studies. In a limited rat study in which petasitenine was administered in drinking water, there was a treatment-related increased incidence of liver haemangioendothelial sarcomas and liver cell adenomas. The Committee concluded that petasitenine would be likely to have carcinogenic properties, based on the structure and tumour type induced in the rat study.

3.29 Senkirkine has shown largely positive results in *in vitro* assays for genotoxicity but has not been tested in standard *in vivo* studies. In a limited study in male rats using parenteral administration, there was a treatment-related increased incidence of liver cell adenomas. The Committee concluded that there was insufficient evidence to conclude that senkirkine had carcinogenic activity. No genotoxicity data have been found on symphytine. In a limited study in male rats using parenteral administration, there was a treatment-related increase in liver haemangioendothelial sarcoma and a small treatment-related increase in liver cell adenomas. The COC concluded that it was probable that symphytine had carcinogenic activity based on the structure and the limited evidence that it induced angiosarcomas.

3.30 Monocrotaline has shown conflicting results in *in vitro* assays for genotoxicity and a positive result in one *in vivo* assay. In a limited study in male rats using parenteral administration, there were treatment-related increases in a number of tumours, principally liver cell carcinomas and pulmonary adenocarcinoma. From the available evidence and commonality of structure, the Committee concluded that the data were sufficient to conclude that monocrotaline had carcinogenic activity but with a different tumour profile to the other pyrrolizidine alkaloids. The mode of action was unclear. The metabolite dehydroretronecine has shown positive results in *in vitro* assays for mutagenicity but no genotoxicity data were found for dehydroheliotridine. The Committee found no convincing evidence of carcinogenicity for these metabolites.

3.31 The Committee decided that benchmark dose modelling on riddelliine and lasiocarpine, which had been carried out by the Secretariat, could be used as a basis for a Margin of Exposure approach to the risk assessment of pyrrolizidine alkaloids. A $BMDL_{10}$[7] of 0.073 mg/kg bw/day for lasiocarpine, based on the angiosarcoma incidence in the NTP study, should be used for any Margin of Exposure approach to the risk assessment. The Committee further agreed that a "Cumulative Assessment Group" approach, as described in the opinion of an EFSA Scientific Panel on methodologies for the assessment of cumulative and synergistic risks from pesticides, would be appropriate for pyrrolizidine alkaloids in view of the evidence for a common tumour pattern for several of these comounds.

Revision of OECD Test Guidelines for carcinogenicity studies

3.32 The Organisation for Economic Cooperation and Development (OECD) is currently revising its Test Guidelines for carcinogenicity studies and chronic toxicity studies. The purpose of these guidelines is to enable mutual acceptance of data by different regulatory authorities around the world and hence to reduce costs and use of animals. The OECD is also preparing a Guidance Document to accompany the revised guidelines. The first chapter, on dose selection, was discussed by the Committee at the April meeting when it was also asked whether the UK should offer to draft any of the other planned chapters. Members considered that, although much guidance already exists on histopathology, it would be important to bring it into an OECD context, and recommended that the UK should propose leading on this chapter.

3.33 The COC was also asked for advice on the guidelines in July, when it was informed that one of the principal issues under consideration for the revision of the Test Guideline for carcinogenicity testing (no. 451) is the required duration of the studies, in particular, how to deal with high levels of mortality before scheduled termination of the study. Specifically:

- if there is excess mortality in the high dose group and other treated groups. The Committee commented that this scenario would indicate a seriously flawed study and would recommend abandoning it at that point.

- if there is excess mortality in treated groups other than the high dose group. The Committee advised that there would be concern about study design and technical handling since the deaths would probably not be compound related. They considered that, on balance, it would be better to run the study to completion

- if there is excess mortality in the controls only, or in controls and one or more treated groups. It was noted that what action was taken would depend on how much survival is reduced. The COC recommended the continuation of the study only if the number of surviving animals is similar across the groups. It would be important to establish that the study still had sufficient power to detect effects at the level of concern.

[7] The lower 95% confidence limit on the benchmark dose associated with a 10% response.

3.34 The COC was also asked for comments on a paper by Roth *et al* (2007; Toxicologic Pathology, Volume 35: pp 1040-1043) which discussed excess mortality in two-year rodent carcinogenicity studies. The committee considered that the paper was suited more to testing of pharmaceuticals, where a risk/benefit analysis was required, than to other chemicals for which a hazard identification is needed. The paper was a reasonable qualitative description of potential strategies but failed to justify the details and included many "rules of thumb" of unknown origin. Many relevant issues had not been discussed in the paper.

3.35 The COC also considered whether the wording in the "Duration of Study" section of the 1981 Test Guideline 451 should be revised, and if so, how. The current text states that overall survival should be 50% for a negative study to be acceptable. The COC advised that the wording should be revised but the proposals set out in the Roth paper were not acceptable. The Committee also agreed with the proposal that the normal duration of carcinogenicity studies in mice should be revised to 2 years.

3.36 The Committee considered that the method of analysis to be used should be explicit at the outset and both data analysis and study design should be clearly linked to the primary objective of the study. Therefore, it was important that the key requirements for study design and data analysis were included in the Test Guideline, so that they become obligatory under the Mutual Acceptance of Data agreement and thus avoided rejection of completed studies or the need for duplication.

Horizon scanning

3.37 The COC undertakes "horizon scanning" exercises at regular intervals to identify new and emerging issues which have the potential to impact on public health. A number of topics were identified by the secretariat for consideration by the Committee at the 2008 exercise. From these and Committee members' own proposals, the COC considered that the following topics should be taken forward:

- RNA related effects as mechanism of carcinogenicity
- Endogenous DNA adducts
- Carcinogenic risk of carbon nanotubes
- Carcinogenic risk of exposure to environmental tobacco smoke in childhood
- Possible carcinogenic hazard from dietary insulin-like growth factor 1 (IGF-1)

Ongoing topics

Carcinogenicity of mixtures

3.38 The COC is discussing current developments in the assessment of chemical mixtures with regard to carcinogens and their modes of action. A statement is expected in 2009.

Chemical aetiology of Non-Hodgkin's lymphoma

3.39 Non-Hodgkin's lymphoma is the seventh most common cancer in men and the sixth most common cancer in women in the UK and statistics indicate that the incidence has increased since the 1970s. The COC is reviewing the scientific literature to assess whether there is any convincing evidence that environmental chemicals are responsible for the reported increase in the incidence of Non-Hodgkin's lymphoma.

3.40 A statement is expected in early 2009.

Update review of epidemiological studies on cancer incidence near municipal solid waste incinerators

3.41 The COC published a statement on municipal solid waste incinerators and cancer in 2000. In 2008, the Committee reviewed the results of new epidemiological studies published in the scientific literature since that date.

3.42 A statement will be published in 2009.

Statements of the COC

Second Statement on Chlorinated Drinking Water and Cancer

Introduction

1. In the United Kingdom, North America, and many other places, chlorination has long been an important part of water treatment, intended to ensure that drinking water contains no microbes hazardous to human health. Disinfection of drinking water is fundamental to preventing the spread of waterborne disease, such as cholera.

2. In the mid-1970s, refinements in techniques of chemical analysis resulted in the detection in drinking water of traces of chemicals formed when organic chemicals (such as those which may occur naturally in rivers, lakes, reservoirs and other water sources) are subjected to chlorination. Each of these chlorination byproducts (CBPs) is typically present in drinking water at a concentration below 1 microgram per litre (µg/l). In most supplies, the main CBPs are the four chlorinated and brominated trihalomethanes (THMs, ie chloroform, bromodichloromethane, chlorodibromomethane and bromoform), which may be present at concentrations up to 100 µg/l. However, numerous other CBPs have been identified in drinking water, but many have yet to be characterised.

3. Some CBPs, including some of the THMs, are known to be carcinogenic in laboratory mammals and some are genotoxic in test systems. There have been many epidemiological investigations into the possible association between chlorination of drinking water and cancer in humans and experimental studies of the mutagenicity and carcinogenicity of CBPs. In 1986, the Department of Health Committee on Medical Aspects of Contamination of Air, Soil and Water (CASW) reviewed the data which were then available and concluded that there was no sound reason to conclude that the consumption of the byproducts of chlorination, in drinking water that has been treated and chlorinated according to current practices, increases the risk of cancer in humans. The COC considered further epidemiological studies in 1992 and 1999 and reviewed the animal carcinogenicity data in 1996. In 1996 it concluded that "The ratio between the lowest dose level giving rise to a carcinogenic effect in animals and the likely human exposure level from drinking water for each of the four THMs considered by the Committee was in excess of 10,000. Thus the levels of these THMs in drinking water in the UK are unlikely to provide a carcinogenic risk to humans." In 1999, it concluded that the new epidemiological studies failed to provide persuasive evidence of a consistent relationship between chlorinated drinking water and cancer. The Committee stated: "It remains possible that there may be an association between chlorinated drinking water and cancer which is obscured by problems such as the difficulty of obtaining an adequate estimate of exposure to chlorination by-products, misclassification of source of drinking water (including the use of bottled water), failure to take adequate account of confounding factors (such as smoking status), and errors arising from non-participation of subjects" (1). The COC considered that efforts to minimise exposure to CBPs remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking water.

4. Thirteen further relevant epidemiological papers have been published since the 1999 review. At our July 2007 meeting, we were asked to review these and to advise whether revision of the 1999 statement was required.

New epidemiological studies

5. The 13 new studies were on a range of cancers:

Type of cancer	Reference
Bladder cancer	3, 9, 10, 11, 12, 13
Colorectal cancer	8
Childhood acute lymphoblastic leukaemia (ALL)	5, 6
Adult leukaemia	7
Brain cancer	2
Pancreatic cancer	4

One study (14) examined mortality from a wide range of cancers.

6. Of the original studies, most were either hospital-based or population-based case-control studies. One was a prospective cohort study (9) and one a retrospective ecological study (14). There were one meta-analysis and two pooled analyses of overlapping sets of papers on bladder cancer. Four of the 13 studies were from Canada, with others from the US, France, Italy, Spain and Australia. None was from the UK. We recognise that the levels of and, therefore, exposure to, CBPs may not be the same in other countries as in the UK. Nevertheless, it is important to review these studies to determine whether there is a carcinogenic hazard from CBPs in drinking water.

7. As the Committee noted in 1999, those animal carcinogenicity studies which have been performed on CBPs do not identify any CBP, or group of CBPs, which appears likely to cause cancer at these sites at the concentrations found in drinking water. A number of different surrogates of exposure have been employed in epidemiological studies. In the recent studies, they include:

- Duration of time exposed to chlorinated water
- THM levels (usually total THMs)
- Chlorinated vs. non-chlorinated water source
- Source of water

n some papers, several exposure measures were used, resulting in multiple comparisons, which can influence the number of positive associations reported. Frequently, no historical measurements of THMs were available and estimates had to be made, for example, from information on water sources and history of chlorination treatment. There is also uncertainty about the lifetime estimates of water consumption made in some studies. Different exposure ranges were used, rendering comparisons between studies difficult. Overall, adequate exposure assessment continues to be a major problem with these studies.

8. Most of the new studies have attempted to control for known or suspected risk factors although the extent of control varied from study to study and was in part dependent on the degree to which there are known or suspected risk factors for the cancer under study. Nevertheless, as noted in 1999, where there are positive associations between cancer risk and measures of exposure, they are usually weak and the elevated risks may be within the range of uncertainty arising from possible confounding factors.

Bladder cancer

9. Previous epidemiological studies have suggested associations between bladder cancer and CBPs although the studies reviewed in 1999 were not considered to show any consistent dose-response relationship with estimated exposures to CBPs or THMs. Of the 6 new papers concerning bladder cancer, 3 were pooled analyses or meta-analyses of overlapping sets of papers, most of which we have already considered. The meta-analysis compared individual consumption of chlorinated drinking water and bladder cancer and reported small but statistically significantly elevated combined odds ratios (ORs) for men but not for women (10) [combined OR for ever consumption in men = 1.4, 95% confidence interval (CI) 1.1-1.9; OR for women = 1.2, 95% CI 0.7-1.8]. In the first pooled analysis of 6 case-control studies (3 of which were included in the meta-analysis), the adjusted OR for bladder cancer in men exposed to an average of more than 1 μg/l THM compared to those who had lower or no exposure was 1.24 (95% CI 1.09-1.41). Estimated ORs in men increased with increasing exposure up to 1.50 (95% CI 1.22-1.85) (11). No association was found among women. Additional results from the pooled analysis using different measures of exposure to THMs (total fluid consumption and intake of tap water) found that total fluid consumption was associated with a slightly increased risk of bladder cancer [adjusted OR = 1.08, 95% CI 1.03-1.13 overall for men and women] (12). Tap water consumption was also associated with a slightly increased risk of bladder cancer [adjusted OR/l/day increase overall = 1.10, 95% CI 1.04-1.17], with higher ORs reported in men than women.

10. Using data from a case-control study whose main objective was to assess the carcinogenic risk of ozonation of drinking water, no statistically significant association of bladder cancer was found with various measures of THM exposure (3). When adjusted for duration of exposure to ozonated water, a statistically significant association was found at the highest average levels of THM concentration [OR = 2.99, 95% CI 1.1-8.5] and with cumulative exposure to THM [OR = 3.39, 95% CI 1.2-9.6] but there was no statistically significant trend with exposure levels. A large case-control study reported a statistically significantly increased risk of bladder cancer in men associated with various estimates of CBP exposure including average residential THM level [adjusted OR up to 2.53, 95% CI 1.23-5.20], ingestion of THMs [adjusted OR up to 1.61, 95% CI 1.06-2.44], exposure from showering and bathing [adjusted OR up to 2.01, 95% CI 1.23-3.28] and swimming in pools [ever swimming vs. never swimming: OR =1.62, 95% CI 1.20-2.19] (13). In women, there were no statistically significantly raised risks from showering and bathing [2.26, 95% CI 0.58-8.90] nor from swimming in pools [ever swimming vs. never swimming: OR=1.19, 95% CI 0.30-4.72].

11. Conflicting results were found in two studies which examined the association between frequency of micronuclei in either urinary bladder epithelial cells (9) or exfoliated urothelial cells (13) and measures of THM exposure.

12. We consider that the additional studies provide limited evidence for an association between bladder cancer and exposure to CBPs.

Colon and rectal cancers

13. A number of studies have examined the association between cancer of the colon or rectum and exposure to chlorinated drinking water. A new, well conducted case-control study has been published on these endpoints (8). It found increased risks of colon cancer among males with a number of measures of exposure to THMs. The highest adjusted OR was 2.10 (95% CI 1.21-3.66) for >35 years exposure to >75 µg THM/l compared to <10 years. No significantly increased risks were found for colon cancer in females nor for rectal cancer.

Other sites

14. A study of exposure to drinking water contaminants and childhood ALL found no statistically significant increases in risk with a number of measures of exposure to THMs (5). However, an additional study of a subset of cases found significant interactions between pre- and post-natal exposure to THMs and polymorphisms in the *GSTT1* and *CYP2E1* genes (6). The OR for children with the GSTT1 null genotype exposed to an average total THM level in the postnatal period above 95th percentile was 9.13 (95% CI 1.44-57.82), and that for children with one or more CYP2E*1 alleles and average total THM level in the prenatal period at or above the 75th percentile was 9.75 (95% CI 1.10-86.01). We note that there were only 12 children with one or more CYP2E*1 alleles, most of whom would probably have been heterozygotes, and question the plausibility of such an association being causal. Nevertheless, the finding is of interest. A large case-control study of adult leukaemia cases found an increased risk of chronic myelocytic leukaemia (CML) with increasing years of exposure to several CBP indices but the risk of other leukaemia subtypes was found to decrease with increasing years of exposure to CBP (7).

15. A well-conducted case-control study found a positive, dose-related association in men between measures of exposure to CBPs and brain cancer (glioma) with a significant trend with estimated lifetime average THM concentration [OR for exposure to chlorinated surface water of >40 years = 2.5 (95% CI 1.2-5.0] (2). In contrast, no significant trend was found in women [OR for exposure to chlorinated surface water of >40 years = 0.7 (95% CI 0.3-1.6)].

16. No association was found between pancreatic cancer and increasing CBP levels in a population-based case-control study [OR for the highest THM concentration = 0.90 for men and women combined, 95% CI 0.62-1.33] (4).

17. In a retrospective ecological study which compared the mortality from a wide range of cancers in an area supplied with tap water with high THM levels with rates in an area with low THM levels, overall cancer mortality rates were slightly raised in the high THM area [men: SMR[8] = 1.2, 95% CI 1.1-1.4; women: SMR = 1.1, 95% CI 1.0-1.3] (14). In men, there were raised SMRs for cancers of the stomach [1.7 (1.2-2.5)], lung [1.3 (1.0-1.6)], melanoma [3.8 (1.0-10.5)] and breast [18.4 (1.0- 98.6)]. No individual cancer showed a raised rate in women.

[8] Standardised Mortality Ratio.

Conclusion

18. We have reviewed the new epidemiological studies on chlorinated drinking water and cancer published since 1999. In 1999, the COC concluded that the studies which were reviewed on bladder cancer did not show any consistent dose-response relationship with estimated exposures to CBPs or THMs. We consider that the new studies on bladder cancer, which include a meta-analysis and two pooled analyses by the same group, provide limited evidence for an association between bladder cancer and exposure to CBPs in men. The evidence for an association in women is conflicting.

19. In the 1999 review, the COC commented that the studies of colorectal cancer gave inconsistent findings. In the current review, one well-conducted study provides some evidence for an association with colon cancer, but not rectal cancer, in men only. In 1999, the COC did not consider the studies of other sites to be of good quality or to produce consistent associations. One new, well-conducted study has indicated an association with brain cancer in men but not in women.

20. Problems remain in the interpretation of published studies on CBPs. These include the small relative risks recorded, the possibility of residual confounding, and the problems with exposure assessment described above. There is no obvious reason why positive associations should be seen so frequently in men but not in women. There is always concern that publication may be biased in favour of positive results, as it may in any field of science. Moreover, as previously stated, none of the studies we have reviewed were carried out in the UK and it is possible that disinfection practices and constituents of the raw water may be different in other countries, in which case the study results may not be directly applicable to the UK.

21. We conclude that the evidence for a causal association between cancer and exposure to CBPs is limited and any such association is unlikely to be strong. Efforts to minimise CBPs in drinking water should continue but must be balanced against the need for effective disinfection of drinking water.

COC/08/S1
May 2008

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Statement on Betel Quid, Pan Masala and Areca Nut Chewing

Introduction

1. Areca nut is an ingredient of betel quid or pan masala which is chewed as an aid to digestion and as a stimulant. Areca nut may have limited use as a food ingredient. The COC first considered the carcinogenicity of areca nut in 1993 and 1994. Following the publication of a number of new, relevant papers, the COC was asked to look at this subject again in November 2006.

Background

2. Areca nut is widely used in Asian immigrant populations in the UK and other countries in Europe (Warnakulasuriya, 2002). Areca nut is primarily used as an ingredient of betel quid, which is made up of areca nut mixed with slaked lime (calcium hydroxide) and catechu[9], wrapped in a betel leaf (Piper betel). The betel quid is usually chewed for between five minutes and an hour or maybe more. Traditional use varies between countries; sometimes tobacco is added to the quid and sometimes spices such as cardamom or ginger. Recently, pan masala has become a popular alternative to betel quid. This is a pre-prepared mixture containing the same ingredients as the betel quid, but is not wrapped in a betel leaf. Betel quid and pan masala are chewed to aid digestion and for their stimulatory effects. The juice is often spat out but sometimes it is swallowed. Once chewed, the fibrous remains of the quid are also normally spat out (Zain *et al*, 1999).

3. Whole areca nuts can be bought in some supermarkets in the UK but more commonly they are bought in shops stocking traditional Asian foods. It is thought that these are generally used to prepare betel quid at home, but it has also been suggested that they may be used to add flavour when cooking by adding grated or sliced nut to food. However, it has not been possible to substantiate this use.

4. Under the terms of The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977 part 1, Areca catechu (the botanical source of areca nut) is considered to be a medicinal plant and any substance derived from it should only be sold on licensed premises (a registered pharmacy or where a pharmacist is present) (HMSO, 1977). However betel quid is not considered medicinal by the Medicines and Healthcare Products Regulatory Agency (MHRA) and is therefore covered by food law.

Constituents and metabolism of betel quid ingredients

5. Areca nuts may be used ripe or unripe and may be processed by being sun-dried and/or cured. Uncured areca nut is reported to contain 11.4- 26% tannins and among the polyphenols identified are leucocyanadins, catechins, 3,4-flavandiols and hexahydroxyflavan. The main pharmacological action of areca nuts is attributed to the alkaloids arecoline, arecaidine, guvacine, guvacoline and arecolidine, which make up 0.15-0.67% of uncured nuts (Awang, 1986). *in vitro* experiments suggest that nitrosation of arecoline occurs readily, giving rise to at least four N-nitrosocompounds: N-nitrosoguvacoline

[9] An extract of wood from a variety of acacia species but can also be obtained from the leaves and bark of other plants.

(NGCO), N-nitrosoguvacine (NGCI), 3-(methylnitrosamino)proprionitrile (MNPN) and 3-(methylnitrosamino)proprionaldehyde (MNPA). Several of these N-nitroso compounds have been detected in the saliva of betel quid chewers (Wenke and Hoffmann, (1983), Nair *et al*, (1985), Nair *et al* (1987)).

6. Among their other components, the mature green leaves of Piper betel contain volatile oils including eugenol, chavicol, terpenes, and tannins.

7. Catechu is the residue of a hot water-extraction of the heartwood of Acacia catechu (also see note 1). It contains mainly tannin and polyphenols, including catechutannic acid, catechin, catechu red, quercetin, kaempferol, dihydroxycaempferol, taxifolin, isorhamnetin, (+) afzechin and dimeric procyanidin (IARC, 1985).

8. Metabolic studies suggest that arecoline is de-esterified in the liver and both arecoline and arecaidine are excreted in the urine as the mercapturic acid N-acetyl-S-(3-carboxyl-1-methylpiperid-4-yl)-L-cysteine. NGCO and NGCI are metabolised in the liver to N-nitrosonipectoic acid. This is largely excreted in the urine, though faecal excretion also occurs (IARC, 1985).

Previous COC advice

9. The Committee reviewed the use of areca nut in betel quid and pan masala in 1993 and 1994 and considered a range of human epidemiology studies, animal carcinogenicity studies and *in vivo* and *in vitro* mutagenicity studies[10]. On the basis of this evidence, the COC concluded the following:

   - There was evidence of mutagenic and carcinogenic activity of areca nut extracts and derived compounds in experimental systems. In particular, the potent carcinogenic activity of the areca-derived nitrosamine, MNPN had been confirmed, and methyl and cyanoethyl adducts had been detected in the DNA of the target tissues in which the tumours developed. There was evidence that endogenous nitrosation of areca nut alkaloids can occur in animals and humans; and areca nut derived nitrosoamines, including MNPN, have been detected in the saliva of betel quid chewers.

   - There were very limited data from epidemiological studies on the effect of betel or areca nut products without tobacco, which did not allow any conclusion to be drawn. There was, however, sufficient epidemiological evidence of a link between the chewing of betel quid containing tobacco and cancer in humans.

   - The Committee concluded that the use of these products without tobacco was possibly carcinogenic in humans.

Considerations by other expert bodies

10. The International Agency for Research on Cancer (IARC) assessed the use of betel quid in 2003 and concluded that both chewing of betel quid and areca nut should be categorised as Group 1 (known) human carcinogens. In its conclusions it stated that there is sufficient evidence in humans to conclude

[10] The conclusions can be found in the 1994 report of the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (HMSO, 1994).

that betel quid chewed without tobacco causes oral cancer. IARC also concluded that there was sufficient evidence in animals to confirm the carcinogenicity of betel quid and areca nut without tobacco (IARC, 2003). The 2003 report followed up a previous review from 1985 in which it was concluded that there was inadequate evidence for the carcinogenicity of betel quid chewed without tobacco.

Studies published since 1993

11. Most of the epidemiological data available concerns the use of areca nut in betel quid or pan masala and the link with oral cancers and pre-cancerous lesions. The epidemiological studies are summarised in Table 1.

12. Other epidemiological data have linked the use of areca nut with other cancers such as liver cancers. There are also some limited animal studies and *in vitro* studies. The studies linking betel quid use with liver cancer have been summarised in Table 2.

Discussion

13. The Committee considered the data that had been published since its previous discussion and agreed with the recent IARC conclusions, as given above. The Committee considered that most of the evidence suggested that areca nut is a site of contact carcinogen acting by a genotoxic mechanism, and noted that there was some evidence that a non-genotoxic mechanism could also be involved. It seems likely that the carcinogenic mechanism involved nitrosation of the alkaloids present in the areca nut, which form N-nitroso products that can be detected in saliva. The Committee noted that these have been demonstrated to have mutagenic activity *in vitro*. Most of the available data indicates that areca nut and betel quid cause cancer of the oral cavity where the quid can be held for significant amounts of time.

14. The Committee concluded that, although there was insufficient evidence to definitively link the use of areca nut as a food ingredient with an increased incidence of cancer, this use should be regarded as potentially carcinogenic. The studies reviewed did not appear to show variations in cancer incidence in populations using differently prepared areca nut products; this and the possible genotoxic mode of activity led the Committee to conclude that areca nut may be carcinogenic in all forms.

Summary

15. The Committee was satisfied that there was sufficient epidemiological evidence to conclude that areca nut, when used in the form of betel quid or pan masala, is carcinogenic to humans. This relates primarily to an increased risk of oral cancers from the keeping the areca nut or betel quid in the mouth for a significant length of time. Members also considered that the use of areca nut as a food ingredient may also result in an increased risk of cancer.

COC/08/S2
July 2008

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Table 1: Human epidemiological studies on areca nut and betel quid usage and the link to oral cancers.

Study	Cases (No.)	Controls (No.)	Cancer types	Published results
Sankaranarayanan *et al* (1989)	228	456 (age and sex matched)	Carcinoma: Tongue (188) Buccal floor (40)	Regular use of betel quid with tobacco was associated with an increase in the incidence of the two types of cancer studied.
Ko *et al* (1995)	107 (m=104, f=3)	194 (age and sex matched)	Oral carcinoma	Compared with abstainers, betel quid chewers had an OR of 8.5, CI of 4.4-16.2 of developing oral cancer.
Warnakulasuriya *et al* (1999)	7521 (m=5072, f=2449)	-	Lip, mouth, pharynx, nasal cavity, larynx, bronchus	Age of onset was significantly lower in Chinese and Asian populations than in other groups
Merchant *et al* (2000)	79	149 (age, sex, hospital and time of attendance matched)	Oral squamous cell carcinoma, OSF1	After adjustment individuals with OSF were 19.1 times more likely to develop oral cancer than those without and individuals using betel quid without tobacco were 9.9 times more likely to develop oral cancer than non-users. Risk of oral cancer increased with higher intakes of betel quid with and without tobacco.
Hasibe *et al* (2000)	100	47773	Erythroplakia	Current chewing habits were 74.5% and 83.7% amongst male and female cases respectively. The adjusted odds ratio for regular chewers was 19.8 (95% confidence interval 9.8-40) after adjustment.
Znaor *et al* (2003)	1563 oral, 636 pharyngeal 566 oesophageal. All male.	1711 male patients with non-tobacco related cancers and 1927 healthy male hospital visitors.	Oral (lip, tongue mouth), pharyngeal (oropharynx, hypopharynx and pharynx), oesophageal	An increased risk for oral cancers of over 2 fold and a 60% increased risk for oesophageal cancers were observed among chewers without tobacco. Among chewers with tobacco, the increase in risk was 5-fold.for oral cancers and 2-fold for pharyngeal and oesophageal cancers.

Table 1: Human epidemiological studies on areca nut and betel quid usage and the link to oral cancers. *continued*

Study	Cases (No.)	Controls (No.)	Cancer types	Published results
Lee *et al* (2003)	219	876 (age and sex matched)	OL[2] (125 patients) and OSF1 (94 patients)	The risk of developing the two preneoplastic lesions studied was 22.3-40.7 fold higher in regular chewers of betel quid than in those who had never chewed. Ex-chewers were 7.1-12.1 times more likely to develop these lesions than non-chewers. Of the factors investigated, betel quid was found to be the strongest risk factor for OSF and OL.
Ranganathan *et al* (2004)	185	185 (age and sex matched)	OSF[1]	All OSF patients in this study had a history of chewing betel quid. Only low levels of areca nut use (in all forms) was seen in the control group, but higher use of alcohol and tobacco smoking was observed.
Chitra *et al* (2004)	90	90 (age and sex matched)	Squamous cell carcinoma of the oesophagus	Odds ratio between cases and controls for areca nut usage was 2.8 with a CI of 1.3-5.9.

1 Oral sub-mucous fibrosis – a pre-cancerous condition shown to precede oral cancer and manifests itself through discolouration of the oral mucosa and decreased flexibility of the cheeks.

2 Oral leukoplakia – A pre-cancerous lesion

Table 2: Human epidemiological studies on areca nut and betel quid usage and the link to other cancers.

Study	Cases (No.)	Controls (No.) (if applicable)	Cancer types	Published results
Srivatanakul *et al* (1991)	65 (47 M & 18 F)	65 (age and sex matched)	HCC[a]	The study suggests that regular use of betel quid conferred a higher risk of HCC although this was not statistically significant.
Tsai *et al* (2001)	263	263 (age and sex matched)	HCC[a]	The authors concluded that there was an association between regular betel quid use and HCC after controlling for confounding factors such as cirrhosis. A weak synergistic relationship was proposed between betel quid use and hepatitis B and C virus and the development of HCC.
Tsai *et al* (2004)	210	420 (210 patients with cirrhosis and 210 healthy controls) (age and sex matched)	HCC[a] complicating cirrhosis	Betel quid chewing was found to be an independent risk factor for HCC in patients with chronic viral infections. Evidence of a link in otherwise healthy patients was very weak and the authors concluded that betel quid was not a risk factor for HCC complicating cirrhosis in subjects without chronic viral hepatitis.

[a] Hepatocellular Carcinoma

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Declaration of COC members' interests during the period of this report

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	INTEREST	COMPANY	INTEREST
Professor D H Phillips (Chair)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Servier Buller Jeffries (Solicitors)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Honorarium Honorarium	NONE	NONE
Dr C Allen	NONE	NONE	NONE	NONE
Professor A Boobis OBE	Banco Santander Barclays Bank BG Group BT Group Centrica Halifax National Grid Transco Scottish Power Astellas Pharma Sumitomo Chemical (UK) PLC Howrey LLP	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy	GlaxoSmithKline FSA Department of Health ILSI HESI Elsevier JMPR JECFA (vet drugs) EFSA PPR	Support by Industry Research Contract Unpaid member of Board of Trustees Editor-in-Chief Food & Chemical Toxicology Member
Dr P Carthew	Unilever	Salary	NONE	NONE
Professor P B Farmer	Banco Santander Bradford & Bingley Foreign & Colonial Friends Provident Health Effects Institute Torotrak ILSI HESI	Shareholder Shareholder Shareholder Shareholder Research Committee Member Shareholder Committee Member	American Chemistry Council CEFIC	Research support and Conference attendance expenses. Research Support

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	INTEREST	COMPANY	INTEREST
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Professor D Harrison	The Forensic Institute University of Edinburgh Lothian NHS Response Genetics (University consultancy no fee payable.) University of Florida (University consultancy) University of Canberra (University consultancy)	Shareholder	PI Medical Research (Scotland) Chair EMMS Nazareth Member Scientific Advisory Committee, Yorkshire Cancer Research	Non specific research funding from Cancer Research UK. Breakthrough, CSO & other grant agencies. Trusteee Trustee (Healthcare Charity) Trustee
Ms D Howel	NONE	NONE	NONE	NONE
Dr B G Miller	Scottish Power	Shareholder	NONE	NONE
Professor R A Roberts	AstraZeneca HBOS P & O	Salary Shareholder Shareholder	NONE	NONE
Professor D E G Shuker	NONE	NONE	NONE	NONE
Dr P Vineis	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer	Salary Shareholder	NONE	NONE