

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

COC Guidance Statements Series

Introduction

1. The Committee's Terms of Reference¹ stipulate that its remit is to provide advice on the carcinogenic risk of substances to man and advise on important general principles or new scientific discoveries in connection with carcinogenic risks. Since its formation, the COC has provided both chemical specific advice and guidance on the generation and interpretation of carcinogenicity data. The latter guidance appears within Committee statements, minutes and in the COC guidance on a strategy for the risk assessment of chemical carcinogens (last revised in 2004).
2. There are several drawbacks to this approach:
 - Valuable advice can be difficult to access when hidden within statements and minutes.
 - It may not be apparent when previous guidance has been revised in a subsequent statement or Committee minutes.
 - Comprehensive guidance booklets are difficult to draft with Committee consensus; and elements of the guidance may soon become out of date, meaning the whole document would require review.
3. The COM is currently considering a proposal to change the way Committee guidance is presented. It is proposed that guidance is issued as a series of guidance statements. These would be in addition to the existing statement series, which would then be reserved for chemical specific statements. Each guidance statement would be assigned a number (G1, G2, etc.), which it would retain through subsequent versions, so that revisions would be easily identifiable. Annex A of this paper shows a mock up of how this might appear on the COC website, and Annex B contains a suggested list of the existing COC guidance (extracted largely from COC guidance, statements and minutes).
4. Guidance statements would generally be concise and cover a specific topic, such as potency estimates or the use of biomarkers. This would facilitate the initial drafting of the statement and any subsequent revisions,

¹ See the COC website: <http://www.iacoc.org.uk/termsref/%20index.htm>

should this become necessary. It would also be possible to include overarching guidance statements on risk assessment, which would draw together and summarise concepts, referring (and hyper-linking) to the relevant guidance statements containing more detailed discussion of the topic.

5. Consultation or collaboration with other advisory committees, such as the Committee on Toxicity (COT) and Committee on Mutagenicity (COM) may be necessary on overlapping topics; as has already occurred for guidance on toxicogenomics and use of target organ mutagenicity data. This could result in the publication of joint guidance statements.

6. It may be appropriate to seek comments on draft guidance statements from the wider scientific community, as was done for the 2004 version of the guidance booklet. This could be achieved by posting final draft guidance statements on the Committee's website, inviting comments which would be considered at the next meeting. If any additional drafting is considered necessary by the Committee, the final text could then be agreed by Chairman's action, or at a subsequent meeting, as appropriate.

7. It is suggested that, during the annual horizon scanning exercise, the Committee could examine the list of guidance statements and identify those subjects which Members consider are due for review.

8. Summary of the benefits of the guidance statements approach:

- Ease of drafting
- Ease of review
- Clarity of publication
- Continuity of referencing
- Inclusion of hyperlinks (within and outside the COC guidance)
- Allow out of date advice to be removed or replaced.

Questions for the Committee

9. Members are asked to discuss the proposed approach.

- a) Do Members have any comments, concerns or suggestions on how the approach may be improved?
- b) Is the Committee content for the approach to be implemented?

**Secretariat
June 2010**

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COC Guidance Statements Series

Mock-up of a COC Guidance Statements webpage

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

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Guidance Statements

The COC terms of reference include generic advice to Government Departments and Regulatory Agencies on the risk assessment of carcinogens and associated topics. These guidance documents present its advice on risk assessment, and experimental methods and analysis. These are considered accurate at time of publication. As the science which underpins each of these guidance documents advances, the Committee may consider it necessary to review the topic and re-issue a revised version.

Carcinogen Risk Assessment

| | | | |
|--|-------|-----|-----|
| A Strategy for the Risk Assessment of Chemical Carcinogens | 2004 | G01 | v 3 |
| An overarching statement which presents the Committee's recommended general approach to assessing the carcinogenicity of a chemical. | | | |
| Carcinogenic Potency Assessment | | G02 | |
| Committee opinions on the assessment of carcinogenic potency, derivation of minimal risk levels, an low dose extrapolation | | | |
| The use of Biomarkers in Carcinogenic Risk Assessment | | G03 | |
| Committee conclusions on the use of biomarkers of exposure and biomarkers of effect in carcinogen risk assessment | | | |
| Risk Assessment of Mixtures of Chemical Carcinogens | 2010? | G04 | v 1 |
| A statement on the dissection of chemical mixtures for testing and suggested potential targets for interaction regarding mutagenic activity. | | | |
| COC statement on the investigation of interaction between genotype and chemicals in the environment on the induction of cancer | 2002 | G05 | v 1 |
| The Committee concluded that so far there was no consistent or strong interaction between the genotype of an individual and chemical induced cancer. However the Committee could not discount the possibility that important interactions would not be discovered in the future. | | | |

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

COC Guidance Statements Series

List of the existing COC guidance extracted from the current guidance booklet, existing statements and minutes

The proposal made to COM was that the guidance statements could be split into strategic and methodological guidance. It would seem appropriate to make a similar distinction for COC.

The first strategic statement (G01: A Strategy for the Risk Assessment of Chemical Carcinogens) would be developed from the existing guidance booklet. It would act as an overarching statement which presents the Committee's recommended general approach to assessing the carcinogenicity of a chemical. The revised document would cover the general principles of elements of carcinogen risk assessment, with much of the detail in the present guidance booklet moved to detailed daughter statements (such as, mode of action, G02; modelling carcinogenic potency, G03; and biomarkers ,G04).

The statement on mixtures of carcinogens, currently being revised, would also sit amongst this suite of papers (G05); as would the statement on gene-environment interactions (G06) which the Committee recently agreed was due for review. Similarly, the joint COM/COC statement on target organ mutagenicity data could also be included here (G07).

Other topics could form new guidance statements where conclusions have, thus far, only been reported in the minutes (such as the margin of exposure and threshold of toxicological concern (TTC) concepts, G07, and short term exposure to carcinogens, G08).

Methodological guidance papers (G10 to G16) have been taken directly from existing COC statements and, if Members chose to adopt this method, it would be prudent to review these statements to ensure they are still relevant and up-to-date.

For ease of reference, guidance statements would contain web 'hyperlinks' to other COC guidance documents. Similarly, specific terms could be linked to an appropriate definition within a glossary (perhaps taken initially from the Annual Report). It may also be possible to provide a curated set of links to relevant guidance from other organisations, with a brief statement of why the Committee considers it worthy of note.

Guidance Statements

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Carcinogen Risk Assessment

[A Strategy for the Risk Assessment of Chemical Carcinogens](#) 2004 G01 v 3

An overarching statement which presents the Committee's recommended general approach to assessing the carcinogenicity of a chemical.

[Carcinogenic Hazard Assessment: Consideration of Genotoxicity and Mode of Action](#) G02

COC endorsement of the principles laid down in the Committee on Mutagenicity Guidance, and recommendations for the evaluation of the weight of evidence for a carcinogenic mode of action

[Carcinogenic Hazard Characterisation: Potency Estimates, Dose-Response Modelling and Minimal Risk Levels](#) G03

Committee opinions on the assessment of carcinogenic potency, derivation of minimal risk levels, an low dose extrapolation

[The use of Biomarkers in Carcinogenic Risk Assessment](#) G04

Committee conclusions on the use of biomarkers of exposure and biomarkers of effect in carcinogen risk assessment

[Risk Assessment of Mixtures of Chemical Carcinogens](#) draft G05

A statement on the dissection of chemical mixtures for testing and suggested potential targets for interaction regarding mutagenic activity.

[COC statement on the investigation of interaction between genotype and chemicals in the](#) 2002 G06 v 1

[environment on the induction of cancer](#)

The Committee concluded that so far there was no consistent or strong interaction between the genotype of an individual and chemical induced cancer. However the Committee could not discount the possibility that important interactions would not be discovered in the future.

[The use of Target organ mutagenicity data in carcinogenicity risk assessment](#)

2005 G07 v 1

A joint COM and COC statement concluded that *in vivo* carcinogen target organ mutagenicity and genotoxicity studies can provide valuable information on the mode-of action of carcinogenic responses seen in rodents. Such studies can provide supporting information for use by regulatory authorities in carcinogen risk assessment on a case-by-case basis.

[Carcinogen Risk Management tools](#)

G08

[New statement from minutes] A discussion of the scientific basis for risk management tools, such as the Margin of Exposure (MOE) and Threshold of Toxicological Concern (TTC)

[Assessing the Risks of Acute or Short-Term Exposure to Carcinogens](#)

2007 G09

New statement from minutes

Experimental methods and analysis

These Statements are not intended as new or alternative guidelines on the conduct of genotoxicity studies. They are intended to provide recommendations on the interpretation of test results. Statements may also offer comments on new and emerging tests.

[Accelerator mass spectrometry - an aid to carcinogen risk assessment](#)

2000 G10 v 1

The COC noted that AMS is an expensive, but highly sensitive and reproducible technique. However, the biological significance of the very low levels of binding that may be observed is difficult to assess.

[Neonatal rodent bioassay](#)

1998 G11 v 1

Members were consulted on ICH proposals for a neonatal rodent bioassay. Overall, the Committee concluded that there was no current evidence to support the use of the neonatal mouse or rat bioassays as apart of the regulatory testing strategy for human medicines.

[Longevity in carcinogenicity studies in rats](#)

2000 G12 v 1

On the basis of a database of animal survival in chronic carcinogenicity studies, the COC concluded that unacceptable survival at termination (<50%) in carcinogenicity tests is predominantly confined to Charles-River Sprague-Dawley rats. Survival in long-term carcinogenicity bioassays should be compliant with current UK and EC guidelines. Dietary restriction in carcinogenicity studies should be applied with caution.

[Minimum duration of carcinogenicity studies in rats](#) 2002 G13 v 1

The COC concluded that there was insufficient evidence to recommend a change to the international guidelines for the conduct of long term carcinogenicity bioassays, that for a negative result to be acceptable in a rat carcinogenicity bioassay, survival should be at least 50% in all groups at 24 months.

[The use of toxicogenomics in toxicology](#) 2004 G14 v 2

A joint COT, COC and COM statement. Toxicogenomics may assist in the interpretation of data (particularly on mode of action) on a case-by-case basis but cannot be used routinely to screen for hazards.

[Nanomaterial Toxicology](#) 2005 G15 v 1

A position statement from COT, COC and COM with a suggested initial strategy for toxicology testing of nanomaterials.

[ILSI/HESI research programme on alternative cancer models](#) 2002 G16 v 1

The COC concluded that none of the models used in the programme were suitable as a replacement for the mouse carcinogenicity bioassay. Models included transgenic assays and neonatal mouse assays

Glossary of Terms

[Glossary of terms](#)

Links to Other Guidance

[Link](#)

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