

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

### COC Guidance Statements

#### Introduction

1. At the last meeting, Members discussed paper [CC/2010/01](#) which set out a proposal for revision of the way in which the COC guidance on the risk assessment of carcinogens is presented, which paralleled similar changes to the COM guidance. In essence, the proposal was that specific elements of the COC guidance should be drawn out into detailed guidance statements, with a single overarching summary guidance statement to draw together the detailed advice. This will make the COC guidance clearer by making good use of the internet features (such as hyperlinks), and make it easier to draft and update the guidance, one topic at a time.
2. The Secretariat has begun to edit the [2004 COC guidance](#) booklet to fit with the new style of presentation, drawing out sections of text which would better sit in specific detailed guidance statements. An initial draft of the overarching guidance statement is presented in Annex A. This is very much a work in progress and only limited updating has been made to the 2004 text (a tracked changes version can be e-mailed to Members if they wish to see the edits which have been made).
3. The intention is to draft and publish the over-arching statement (G1), then to work through each of the individual underpinning statements (Annex B contains a list of possible guidance statements), before returning to re-evaluate the overarching statement and consider whether any changes are needed in light of detailed discussion of the underpinning guidance statements.
4. At the last meeting, the Secretariat identified a number of specific COC statements that contain guidance on generic aspects of carcinogen risk assessment. Members have provided helpful comments on these, which have been drawn together in Annex B. The majority of statements were considered to remain relevant, albeit with minor updates.
5. The Secretariat proposes that the information contained within the existing statements should be summarised, updated and included in a proposed new specific guidance statement on “Assessment and Interpretation of Animal Carcinogenicity Studies (G3)”.
6. Based on Members’ comments, the statement on the ILSI/HESI alternative cancer models would seem to be in need of updating. Perhaps

this could take the form of an additional guidance statement on “Alternative Assays to the 2-Year Bioassay (G4)”.

7. The Committee is asked to discuss the proposed approach to presenting the COC Guidance, and the content and layout of the draft over-arching statement. At present it would be helpful if Members could identify areas of the text that require substantial revision, or where Committee opinion differs from that which is presented in the text.

8. Whilst preparing this draft, the Secretariat has identified a number of issues that may have developed or altered since 2004. Whilst reviewing the draft guidance statement in Annex A, the following questions may help stimulate discussion:

- Q1) Previously the COC guidance recommended a four stage approach (Hazard Identification, Hazard Characterisation, Exposure Assessment, Risk Characterisation). Whilst this paradigm is well established, it does not fit well with the new divisions in the guidance statement. Reference to the paradigm has been retained as a framework in the in the revised over-arching statement, but the guidance stipulate a rigid four stage approach. **Are Members content with this change?**
- Q2) When giving an overview of the risk assessment process, the previous guidelines refer to several references: Australian Department of Health and Ageing and Environmental Health (enHealth) Council, 2002; The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 1996; and the previous COC guidelines, 1991). **Does the Committee consider that this list of references needs to be updated? If so, which of the recent evaluations would be worthy of reference?**
- Q3) Paragraphs 9 and 10 of Annex A mention epidemiological and animal carcinogenicity data. These paragraphs now refer to new specific guidance statements which should cover these two areas (to be drafted in due course). **Does this proposal seem sensible?**
- Q4) At the time of writing, final edits are being made to the consultation draft of the COM guidance. The consultation draft will be forwarded to COC Members as soon as it is available. Since this has a direct impact upon COC guidance, it is important that COC Members are aware of and content with the approach to assessing mutagenic activity proposed by COM. **COC Members may wish to provide feedback to COM, either collectively or individually.**
- a. The text relating to mutagenicity testing (paragraphs 12 – 15) has been edited to relate to the new COM guidance. **Are Members content with the revised reference to mutagenicity testing and the COM guidance?**

- b. The draft COM Guidance makes clear the difference between genotoxicity and mutagenicity. Mutagenicity (which results from certain types of genotoxicity) may be a key event in carcinogenicity; however, genotoxicity does not necessarily result in mutation. **Therefore, should COC guidance refer to 'genotoxic carcinogens' or 'mutagenic carcinogens'?**
  - c. COM Guidance now does not specifically require *in vivo* tests. The text in paragraphs 13 and 14 of Annex A requires a chemical to have been identified as an *in vivo* mammalian mutagen in order to be considered to be a potential genotoxic carcinogen. **Should this be revised to allow suitable *in vitro* mammalian cell testing to be sufficient to indicate a potential mutagenic mode of action?**
  - d. Paragraph 13 of Annex A has been added to explain the difference between mutagenic carcinogens, substances that are mutagenic and carcinogenic, and substances that are mutagenic and possibly carcinogenic. **Does the Committee agree with this distinction?**
- Q5) Paragraphs 15 and 16 discuss non- mutagenic (or genotoxic) mechanisms and the human relevance framework. **Does this section need to be updated?**
- Q6) In the previous guidance, the hazard characterisation section is divided into two parts: potency estimates (T25 and TD<sub>50</sub>), and 1:100,000 risk estimate extrapolations from mathematical models. Things have moved on somewhat in this area. It is proposed that this be taken as separate topics in two guidance statements: The first (G5) would cover methods for deriving a point of departure, i.e. the T25 and TD<sub>50</sub> approaches, alongside NOAEL and BMDL<sub>10</sub>; the second (G6) would cover low-dose extrapolation. Since the Committee does not favour low dose extrapolation, a further statement (G8) could discuss the scientific basis of risk characterisation / risk management methods, such as the margin of exposure, minimal risk levels, and the Threshold of Toxicological Concern (TTC) approach.
- a. **Does separating this aspect of the guidance into three separate statements seem sensible?**
  - b. **Does the COC wish to recommend a default method for defining a point of departure?**
- Q7) In the 2004 guidance, the Committee considered that "*In general, dose-response analyses from animal studies are of most value in ranking potency within chemical groups, such as structurally related groups of putative mutagenic carcinogens.*" This has been retained in paragraph 18 of Annex A. **Does the Committee still hold this view?**

- Q8) The hazard characterisation section (paragraphs 20 to 22, and later in paragraph 44 of the overall summary) talks about relative potency estimates (T25 and TD<sub>50</sub>). The review of these approaches in the 2004 guidance explains that potency estimates should not be used for quantifying risks, although they can be used to rank chemicals within a particular group (such as structurally related groups of putative genotoxic chemicals). In paragraph 16 of the April 2009 COC minutes, Members explained that that, unlike Dioxins, Potency Equivalence Factors are an oversimplification of interactions in PAH mixture. **Are there circumstances where points of departure can be used as potency estimates or to derive Potency Equivalence Factors for mutagenic carcinogens?**
- Q9) The discussion of mathematical models (paragraphs 23 to 25) focuses on extrapolation to 1:100,000 cancer risk. Modelling of the dose-response is becoming increasingly useful in determining points of departure, such as the BMDL<sub>10</sub> that are usually interpolated within the range of observed response. The 2004 guidance is critical of mathematical modelling with extrapolation to low doses, **should this be revised to focus criticism on extrapolation?**
- Q10) Exposure assessment (paragraphs 26 to 29) is presented, in the 2004 guidance, as being part of the risk assessment paradigm. However, the discussion mainly relates to biomarkers (which are not necessarily the main method of evaluating exposure in a risk assessment). Detailed discussion of biomarkers would seem more appropriate in a separate guidance statement (and/or in the epidemiology guidance statement). **Aside from the use of biomarkers, should this section mention generic approaches to assessing exposure in a risk assessment (food intakes databases, environmental monitoring, etc.)?**
- Q11) Paragraphs 37 to 38 mention minimal risk level, TTC and T25 potency estimates. As suggested in Q4)c, the discussion of these has been moved to a separate guidance statement (G8). **Do Members consider the conclusions about these methods should be retained pending review of Guidance Statement 8 which covers these topics?**
- a. The 2004 guidance suggests that use of minimal risk levels (dividing the point of departure by a set 'margin of exposure') *"would apply solely to contaminants for which exposure was unavoidable and to impurities in materials, products and formulations which are subject to regulatory assessment schemes."* **Does the Committee still consider these restrictions on the use of this approach to be appropriate?**
  - b. Previously only the T25 approach was referred to in relation to potency ranking. **Should this be restricted specifically to the T25 point of departure or is the use of other well derived**

**points of departure, such as the TD<sub>50</sub> and BMDL<sub>10</sub> also equally valid?**

- Q12) A number of data gaps and research needs were identified (Paragraph 41). **To what extent have these been filled/advanced, and are there any additional points to add?**
- Q13) An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity has been drawn up based on the diagram in the previous guidance. This is further explained in paragraph 42. **Are Members content with the process outlined in this framework?**
- Q14) In the previous guidance it was considered appropriate that exposure to mutagenic carcinogens should be ALARP. The margin of exposure may help characterise the risk and inform risk management / communication. However, it is conceivable that a mutagenic carcinogen may be of relatively low carcinogenic potency, yet have high toxicity (added to the end of paragraph 43). **Do the Committee wish to recommend that the lowest relevant non-cancer health based guidance value should also be considered alongside the MoE?**

**Secretariat  
November 2010**



CC/2010/08 – Annex A

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

**COC Guidance Statements**

**Initial draft of the Overarching Guidance Statement (COC/G 01)**



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

**A Strategy for the Risk Assessment of Chemical Carcinogens – Draft 1**

**Preface**

1. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) is an expert advisory committee which reports to the Department of Health and the Chair of the Foods Standards Agency (FSA). The Committee comprises independent experts and lay members, who serve in their own capacity and observe a published [code of practice](#) including principles relating to the declaration of possible conflicting interests. The role of the COC is advisory and it has no regulatory status, although advice may be provided to Government agencies and departments may be used as the basis for regulatory decisions or policies.
2. As set out in the [Terms of Reference](#), the remit of the Committee is to advise on all aspects of the carcinogenicity of chemicals, such as testing strategies, research and the risk assessment of carcinogenic chemicals, at the request of Government departments and agencies. At present, the Secretariat is provided jointly by the Health Protection Agency (on behalf of the Department of Health (who lead), and the Food Standards Agency.
3. The COC has periodically published guidelines for the evaluation of chemicals for carcinogenicity (Annex 1 outlines the history of COC guidance development). The most recent revision of guidance began in 2010. Due to the breadth of the subject, and in order to make best use of the flexibility of the internet as a medium for publication, it has been decided to move away from periodic publication of guidance in a single guidance document. Instead, the key topics that underpin the guidance on carcinogen risk assessment will be separated into separate but interrelated guidance statements, with this overarching summary statement to draw together the Committee's recommendations. The Committee intends that the guidance outlined here should provide Government departments and regulatory agencies with a strategy for risk assessment of chemical carcinogens.

**Introduction**

4. This series of guidance statements presents the Committee's views on the general principles and emerging scientific discoveries in connection with carcinogenic hazard and risk assessment. The term hazard describes the intrinsic capacity of a chemical to cause an adverse effect, such as cancer, on human health. Risk is the probability of that adverse health effect occurring. When a carcinogenic

hazard is identified, the level of risk will depend on particular circumstances, such as the nature and degree of exposure to the chemical in question.

5. The recommended approach is based on the National Academy of Sciences risk assessment paradigm (Figure 1, adapted from US National Academy of Sciences, 1983). Initial identification of a carcinogenic hazard is based upon a review of the carcinogenicity and mutagenicity data, the results of toxicity testing, and any knowledge of effects on human health from epidemiological studies. This should be assessed along with data on mutagenicity and any other toxicity that may be relevant to understanding the mode of action by which the substance causes cancer. The characterisation of the hazard to humans involves determination of the dose response relationship, which can also include such factors as inter-species variation in susceptibility, mechanism of action and mode of carcinogenesis. Having understood the dose response it may be possible to define a level of effect (such as 10% tumour incidence) to use as a point of departure in risk assessment.

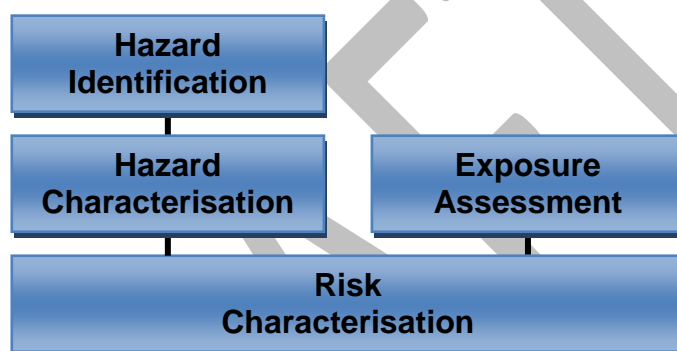


Figure 1: US National Academy of Sciences risk assessment paradigm

6. In order to assess the risks posed by a chemical carcinogen, it is necessary to estimate (or model) levels of potential exposure; if necessary, considering multiple routes of exposure (dietary, inhalational, drinking water, dust ingestion, dermal absorption, etc.). Issues and concerns relating to hazard identification, hazard characterisation and exposure evaluation have been extensively reviewed elsewhere (Australian Department of Health and Ageing and Environmental Health (enHealth) Council, 2002; The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 1996; and UK Department of Health, 1991). Risk characterisation draws together the evidence gathered during hazard assessment (dose response, point of departure, etc.) and compares this to information on measured or potential levels of exposure. It may be possible to define levels of tolerable exposure for substances that do not cause cancer as a result of mutagenic activity, or minimal risk levels for substances that are both mutagenic and carcinogenic; thus it is important to consider the mechanism by which the chemical causes cancer, or at least to establish the carcinogenic mode of action.

7. Risk characterisation may identify the need for risk management. The terms of reference for the COC does not include providing risk management advice, since this needs to incorporate many other factors; thus, risk management is the responsibility of regulators and policy makers within the Government. Methods

have been proposed that provide a systematic approach to making risk management decisions, such as the Margin of Exposure (MoE), the derivation of minimal risk levels and the Threshold of Toxicological Concern (TTC).

### **Hazard Identification**

8. Typically, a substance is referred to the COC due to there being some evidence of carcinogenicity in its toxicological profile; therefore, there are likely to be epidemiological or animal studies showing evidence of carcinogenicity. In order to thoroughly identify the hazards posed by the substance, it is recommended that all the available human and animal carcinogenicity data be gathered and reviewed. This review should also consider available evidence of mutagenicity and any other toxicity that may be relevant to understanding the mechanism or mode of action by which the substance causes cancer.

9. As originally stated in the 1991 guidelines (UK Department of Health, 1991), well conducted epidemiological studies provide the best means of identifying human carcinogenic hazard. Detailed guidance on the interpretation of human epidemiological studies and case reports is provided in Guidance Statement G2 ([link](#)).

10. For some substances, there may be no human data, or epidemiological studies may be of inadequate design or have insufficient power to adequately assess carcinogenic hazard. Where appropriate epidemiological data are lacking, as is often the case, potential human carcinogens may be identified in animal studies. As with epidemiology studies, careful consideration is needed with respect to uncertainties within animal studies, such as the validity of design and the interpretation of the data. Guidance Statement G3 discusses the conduct and interpretation of animal carcinogenicity studies ([link](#)).

11. When assessing the risks arising from a chemical carcinogen it is important to consider the mechanism(s) by which the chemical causes cancer; in particular, whether a mutagenic mode of action is involved. The results from short-term mutagenicity tests will give an indication of the mutagenic hazard and, thus, the potential to cause cancer.

12. Mutagenic potential should be assessed according to the [guidance](#) issued by the COC's sister committee, the Committee on Mutagenicity (COM). In its guidance, the COM propose a strategy for evaluating the available data on the mutagenicity and genotoxicity of a substance, and recommend appropriate tests to conduct in the absence of sufficient data, as well as suitable *in vitro* and *in vivo* follow-up tests where it is necessary to further characterise the mutagenic hazard.

13. In some instances, it may be possible to use target organ mutagenicity data (Guidance Statement G2 [link](#)), DNA adducts, mutational spectra and other biomarkers (Guidance Statement G7 ([link](#))), to add to the weight of evidence linking a carcinogen to a mutagenic mode of action. Substances should be considered to be mutagenic carcinogens only when there is evidence that cancer is caused as the result of its mutagenic activity; substances should be regarded as being mutagenic and carcinogenic where there is adequate evidence of mutagenic and carcinogenic

activity but insufficient evidence that the mutagenic activity is responsible for the observed carcinogenicity; and substances for which there is only evidence of mutagenicity, but no evidence of human or animal carcinogenicity, should be regarded as being mutagenic and possibly carcinogenic.

14. It is prudent to assume that, in the absence of information to the contrary, substances that are mutagenic and carcinogenic have the potential to mutate DNA at any level of exposure and that such damage could lead to tumour development. Thus, a compound identified as an **in vivo mammalian** mutagen should be regarded as being a potential mutagenic carcinogen for which it is assumed that there is no discernible threshold and any level of exposure carries some degree of carcinogenic risk.

15. Non-mutagenic carcinogens are those substances where there is sufficient evidence of carcinogenicity from epidemiological or animal studies, in the absence of mutagenic activity (having followed the [COM Guidance](#) on the assessment of mutagenic hazard). Some information on their mode of action is necessary for an adequate consideration of such carcinogens. The IPCS (International Programme on Chemical Safety) has proposed a structured approach for the assessment of the overall weight of evidence for a postulated mode of action (Sonich-Mullin *et al.* 2001). More recently the Risk Sciences Institute of the International Life Sciences Institute has proposed a human relevance framework (HRF) which extends the IPCS mode of action approach by incorporating a systematic evaluation and comparison of animal and relevant human data. (Cohen SM *et al* 2003; 2004; Meek *et al* 2003)

16. The IPCS and ILSI frameworks are of value in assessing carcinogenic risk. The human relevance framework (HRF) proposal developed by the Risk Sciences Institute of the International Life Sciences Institute provides a systematic approach to evaluating whether the key events in the mode of action of carcinogenic responses in experimental animals would be plausible in humans. The published report from the ILSI working group cites a number of tumourigenic responses in experimental animals that are generally regarded as irrelevant for humans such as  $\alpha$ 2 $\mu$ -globulin-associated male rat kidney tumours and inhibition of leutenising hormone surge-related rat mammary tumours (Cohen SM *et al* 2003).

### **Hazard Characterisation**

17. Hazard Characterisation involves a qualitative description of the nature of hazard together with a quantitative description of the dose-response relationship. The purpose of dose-response analysis is to investigate the magnitude of response (severity or incidence) within a dose range in animal bioassays or human epidemiology studies in order to assist in the estimation of response (and ultimately risk) due to environmental levels of exposure, which are often much lower. The relationship between dose and response may be used to aid hazard characterisation by allowing a comparison of carcinogenic potency. However, other important factors that can affect this relationship and should be further considered are: absorption, distribution, metabolism and excretion (ADME); mode of action; and variability in susceptibility between species and within humans. In particular, use of the dose-response relationship in the final assessment of risk will vary depending on

whether or not a carcinogenic response occurs as the result of the mutagenic activity of the substance (discussed later in Risk Characterisation).

18. Epidemiological studies provide the most appropriate data source for the quantitation of dose-response in the hazard characterisation process, although exposure estimation in the studies is often limited. Although dose-response relationships may be evident in animal studies, the relevance and applicability to the human dose-response should be assessed on a case-by-case basis, due to uncertainties introduced when extrapolating between species. In general, dose-response analyses from animal studies are of most value in ranking potency within chemical groups, such as structurally related groups of putative mutagenic carcinogens.

#### *Defining a Point of Departure in a Carcinogen Dose-Response*

19. A point of departure is a defined level of effect that can be determined from dose-response data generated from human or animal study data; such as the dose level associated with a 10% tumour incidence above control levels. Various methods for deriving a point of departure are discussed further in Guidance Statement G5 ([link](#)). [Summary of COC advice on deriving Points of departure... does the Committee wish to recommend a default method of deriving a point of departure?]

#### *Potency estimates*

20. There are a number of methods for the characterisation of hazard due to mutagenic carcinogens. These follow a ranking approach whereby chemical substances are classified with regard to tumourigenicity on the basis of potency. In this context, potency is ideally represented by the position and shape of the dose-effect or dose-response curve, but the value of a particular point on the curve (point of departure) is often used as a surrogate. The Committee recognises that where comparative data on tumourigenicity are lacking, it may be possible to use a surrogate measure of potency, such as specific DNA damage observed in target organs.

21. Points of departure such as T25, TD<sub>50</sub> and BMDL<sub>10</sub>, have been used to estimate relative carcinogenic potency for chemicals that are members of a particular class of mutagenic carcinogens; these methods are discussed further in Guidance Statement G5 ([link](#)). Potency Equivalence Factors (PEFs) have been suggested in circumstances where there is a good surrogate compound for comparison, e.g. PAH's (Collins, 1998). To date, there has been relatively little use of PEFs for carcinogenicity.

22. Relative potency estimates could have some pragmatic use in carcinogenic risk assessment as an aid to prioritising carcinogenic substances (e.g. for risk re-evaluation), are not adequate for quantifying cancer risks. The uncertainties inherent in potency ranking mean that relative potencies should not be over interpreted. For example, it is unclear whether the relative ranking identified in the observed dose range would be maintained at low doses, and whether the relative potency in animal studies would be applicable to humans. In addition, it would be inappropriate to rank the carcinogenic potency of non-mutagenic carcinogens, for

which tolerable exposure levels can be derived using an approach based on knowledge of mode of action, identification of no adverse effect level, and use of uncertainty factors. For such substances, consideration should also be given as to whether the assessment of precursor effects, identified as being part of the carcinogenic mechanism, may provide a better way of identifying and representing the carcinogenic potency of the substance (Williams, 2001).

#### *Low Dose Extrapolation of Dose-Response Models*

23. Dose-response data from animal studies for either mutagenic or non-mutagenic carcinogens may be fitted using mathematical equations, as an attempt to extrapolate numerical estimates of risk from human exposure. Many mathematical models have been developed for use in assessing carcinogenic risk (Edler *et al.*, 2002; Edler & Kopp-Schneider, 1998) but most are only loosely compatible with current understanding of mechanisms of chemical carcinogenesis and they have not been comprehensively validated. These models and low dose extrapolation are discussed further in guidance statement Guidance Statement G5 (link). Quantitative risk assessment often requires extrapolation of mathematical models of cancer risk, over many orders of magnitude, from the tumour incidence data within the observed range of standard carcinogenicity bioassays, to a dose that is predicted to produce tumour incidence levels of the order of 1:100,000.

24. Mathematical modelling beyond the observed range of the dose response curve does not take into consideration the complexity of events that occur between exposure to a chemical carcinogen and the induction of a neoplasm. In addition, many of the models make a number of assumptions that may be incorrect for the particular carcinogenic chemicals or responses. These mathematical models rarely take human variability into account and, although species differences can be taken into account by correcting the dose in animal studies to a human equivalent dose by inter-species scaling/toxicokinetic modelling; other species differences, such as in the target organ or tissue concentration-response, present additional uncertainties.

25. In conclusion, these mathematical models of dose response do not simulate the carcinogenic processes adequately, which means that the accuracy at extrapolated low doses is uncertain. Therefore the Committee does not recommend their use for routine risk assessment.

#### **Exposure Assessment**

26. The objective of exposure assessment is to estimate probable human exposure by determining source, magnitude and duration of exposure to the substance, as well as the routes by which it may enter the body. Although exposure assessment in humans is a crucial stage in the assessment of risk, it is frequently identified as the main area of uncertainty in the overall risk assessment process.

27. [Exposure measures? Food diaries, Intakes database?, environmental monitoring etc.]

### *Biomarkers of exposure*

28. Biomarkers of exposure can give an indication of the level of an individual's exposure to a carcinogenic substance. This may be achieved by assaying levels of the chemical, a metabolite or a reaction product in blood, urine, saliva, cerebrospinal fluid, and other biological samples. For example, benzene may be directly measured in blood, (Weisel et al 1996) or as its S-phenylmercapturic acid metabolite in urine (Weisel et al 1996, Boogaard and Van Sittert, 1995). Alternatively, specific reaction products with macromolecules, such as DNA or protein adducts (Schut & Shiverick 1992, Farmer 1999, Farmer 2003), can provide evidence of exposure, uptake and distribution of the carcinogenic substance. For example, haemoglobin adducts have been used as a biomarker of exposure to 1,3 butadiene (Osterman-Golkar et al. 1996) and both haemoglobin and DNA adducts have been used to assess exposure to glycidamide, an active metabolite of acrylamide (ref).

29. Biomarkers can provide valuable information for use in the risk assessment process, not only for exposure assessment of the general population, but also to aid the interpretation of epidemiological studies. Biomarkers are discussed further in Guidance Statement G7 (link). It is important that a biomarker is well validated. Validation should include: adequate evidence to support the relationship between exposure, the biomarker and the end-point of interest (i.e. cancer); an evaluation of the sensitivity and specificity of the biomarker (limit of detection, precision and accuracy); investigation of intra- and inter-individual variation in a non-exposed population; a clear relationship between dose and biomarker level; and understanding of sample stability post-collection. It is essential that a biomarker is appropriately characterised and validated before any conclusions are drawn from its use.

### **Risk Characterisation**

30. Risk Characterisation draws together evidence of the hazard and dose-response, and places it in the context of the measured or estimated level of human exposure. The mode of action is the key factor in the characterisation of risk posed by a potential carcinogen. The way in which carcinogenic risk is characterised is dependent upon whether there is evidence of mutagenic activity, or whether there is a lack of relevant mutagenic activity along with a plausible alternative mode of action.

### *Threshold Carcinogenicity [Non-mutagenic carcinogens; non-stochastic / deterministic carcinogens]*

31. Risk assessment of chemical carcinogens is dependant on the mechanisms of carcinogenicity and the relationship between dose and tumour response. For most non-mutagenic carcinogens, it is accepted that there is a threshold dose, below which no effect is observed. Many non-mutagenic carcinogens induce tumours as a secondary effect arising from an initial toxic effect, for which a 'threshold' may be identified (Ashby *et al.*, 1996). It follows that these substances are unlikely to pose a carcinogenic risk at dose levels below a given threshold that does not produce the

primary toxic effect (Williams, 2001). Human relevance frameworks (see paragraph 16) may enhance the clarity and transparency of the risk assessment.

32. A health based guidance value can be derived where there is adequate evidence to support a threshold for carcinogenicity. This evidence should demonstrate that the compound and metabolites do not have mutagenic activity and provide evidence of a plausible non-mutagenic mode of action for the observed carcinogenicity. The health based guidance value should be based on a point of departure for carcinogenicity or on a precursor event linked to tumour induction (see Guidance Statement G5, [link](#)). The robustness of this evaluation is dependent on the quality of the animal bioassays and dose setting procedure and on the available information to support the mode of action. The point of departure is divided by an appropriate uncertainty factor to give a health based guidance value, which is the amount of a chemical to which an individual can be exposed, daily, over their lifetime, without appreciable risk to their health. Examples of health based guidance values include the Acceptable Daily Intake (ADI), used for food additives or pesticide residues in food; the Tolerable Daily Intake (TDI), used by many agencies for environmental contaminants; and the Reference Dose (RfD) used by US agencies. Clearly, when setting the health based guidance value for such a compound consideration has to be given to the overall toxicological profile, as it is possible that a lower point of departure could be identified for another non-cancer adverse effect.

33. The uncertainty factor reflects the uncertainties involved in extrapolating findings in animals to humans (inter-species differences) as well as taking into account that there may be differences in sensitivity to the adverse effect among the human population (inter-individual variation). A default uncertainty factor of 100 (based on a factor of 10 for inter-species variation and a factor of 10 for inter-individual variation) is often used. Other factors may also be included, on a case-by-case basis, to account for the quality of the toxicity/carcinogenicity data (such as the use of short duration studies or of a Low Observed Adverse Effect Level, LOAEL, rather than a No Observed Adverse Effect Level, NOAEL), as well as the nature or severity of the toxic effect. The Committee on Toxicity (COT) Working Group on Variability and Uncertainty in Toxicology report provides a review of uncertainty factors in greater detail ([COT, 2007](#)).

34. The health based guidance value represents a single estimate of a dose (or exposure) for a human that is considered to be without appreciable risk, the so-called deterministic or non-stochastic approach. Normally, no numerical estimate is provided of the confidence limits for this value. Any exposure below the derived health based guidance value is unlikely to be associated with an appreciable risk to health. Qualitative estimations of risk above this level should be considered on a case-by-case basis, taking into account the frequency, duration and extent by which it is exceeded, and the nature and dose-response relationship for carcinogenicity of the substance in question.

35. This approach may be used for non-mutagenic carcinogens provided that the underlying mode of action is adequately understood. A health based guidance value derived for carcinogenicity can then form part of a general assessment of the toxicity of the substance; where the adverse effect yielding the lowest health based guidance value would ultimately be used for risk assessment.

*Non-threshold Carcinogenicity [mutagenic carcinogens; stochastic carcinogens]*

36. From what is known about the mechanism of action of mutagenic carcinogens, it is currently assumed that, in the absence of mechanistic data to suggest a threshold for mutagenicity, it is not possible to identify a threshold for carcinogenicity. Estimation of risk at environmental levels of exposure generally relies on the extrapolation of the dose response obtained from epidemiology or experimental animal studies. However, the COC considers that it is not valid to extrapolate carcinogenic risk from high levels of exposure, to give an acceptable estimate of risk at environmental levels of exposure. Guidance Statement G8 ([link](#)) presents a range of alternative approaches considered by the Committee for characterising risk of mutagenic carcinogens.

37. The most precautionary approach to reducing the risk from such chemicals would be to adopt measures such that levels should be controlled so that exposure is as low as reasonably practicable (ALARP). In some cases such as contaminants or impurities, the ALARP approach may be supplemented by deriving a minimal risk level, i.e. a dose considered to represent a negligible or tolerable carcinogenic risk, in order to aid in risk management decisions. In such circumstances, it should still be recognised that, where practicable, efforts to reduce exposure should be made, even when levels are below the minimal risk level, so as to be in keeping with the ALARP principle.

38. The COC considers that the margin of exposure, where an appropriate point of departure from cancer study data is divided by the level of exposure, can be a useful tool for risk communication and risk management prioritisation. The use of potency estimates, such as the T25 approach, has a role in the prioritisation of chemicals considered to be mutagenic carcinogens but not in the risk assessment process. The Threshold of Regulation / Threshold of Toxicological Concern (TTC) approach can help to identify priorities for carcinogenicity evaluation particularly for chemicals not subject to regulatory approval schemes.

**Assessment of Mixtures**

39. Humans are exposed to a variety of mixtures of chemicals. Mutagenic carcinogens may occur in the same mixture as substances capable of promoting the growth of mutant cells. Cancer is a multi stage process and carcinogens can act, and interact, at many points within the process.

40. The Committee considers that it is not possible for the risk assessment process to account for the combined action of every possible mixture of carcinogens at all possible levels of exposures over all possible time frames. Nevertheless, Members have identified some general principles which may be considered when assessing the carcinogenic risk posed by a mixture of substances, which are discussed further in [Guidance Statement G9](#).

## Gaps and Research Needs

41. The Committee considers the following to be key areas for research
- Clarification of the shape of the dose-response curve at very low doses and low estimated risks. Further development of PBTK/TD modelling for use in conjunction with chronic carcinogenicity studies to inform on risk assessment at low doses.
  - Identification and significance for risk assessment of proposed biological markers of tumour precursors and related processes (e.g. pre-neoplastic foci, biomarkers, DNA adducts and repair). Further investigation of biological responses at environmentally relevant doses.
  - Further development and validation of genetically modified animal models including studies to define changes to dose-response due to genetic modification, as well as to investigate their biological basis.

## Overall Summary

42. Figure 2 sets out an overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity.

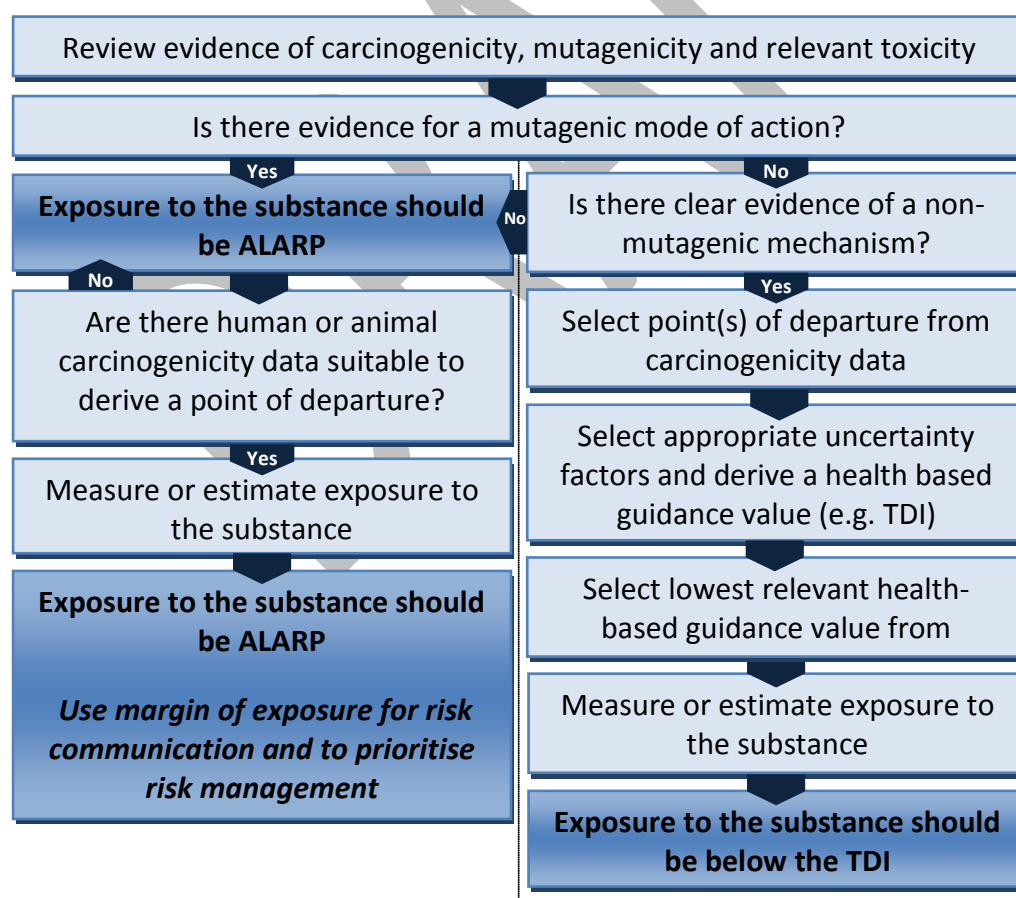


Figure 2: An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity.

43. When assessing the risk posed by a substance with demonstrable carcinogenic activity, understanding the mechanism (or at least mode of action) that gives rise to the observed carcinogenicity is critical. The most precautionary approach to reduce the risk from mutagenic substances would be to reduce or limit exposure to a level that is as low as reasonably practicable (ALARP). This is because it is not generally possible to identify a level of exposure that is without risk of gene mutation, and hence cancer, as discussed in paragraph 14. Exposure to carcinogenic substances with an inadequate database to demonstrate a lack of mutagenic activity should also be ALARP. Although it is not possible to define a level of exposure that is without risk; where there are adequate carcinogenicity and exposure data, the margin of exposure approach may be used to aid risk communication and prioritise risk management. It is conceivable that a mutagenic carcinogen may be of relatively low carcinogenic potency, yet have high toxicity; thus, health based guidance values derived for non-cancer toxicological endpoints should also be considered during risk characterisation.

44. This can be supplemented in specific situations e.g. low exposures to contaminants or impurities by the setting of a minimal risk level for contaminants and impurities that are mutagenic and carcinogenic, based on expert judgement of available data. The use of potency estimates can be used to rank priorities for mutagenic carcinogens within a particular class of compounds (e.g. polycyclic aromatic hydrocarbons which are also mutagenic and carcinogenic). The Committee considers it important keep any exposure to mutagenic carcinogens as low as reasonably practicable (ALARP).

45. Where there is clear evidence that the carcinogenic activity is mediated exclusively by a non-mutagenic mode of action that is relevant to human health, a threshold based approach is recommended. Thus, the lowest relevant and suitably derived point of departure should be selected and appropriate uncertainty factors should be applied in order to derive a health based guidance value. This value should then be fed into the overall toxicological risk assessment and lowest relevant health based guidance value should be selected from the overall evaluation of toxic and carcinogenic effects.

46. The Committee emphasises the importance of further research in order to refine the process of risk assessment. This includes the development of toxicological methods to refine extrapolation between animals and humans. In addition, biomarkers of effect need to be further investigated to aid in the extrapolation of low doses and exposure. Continued research on carcinogenic mechanisms with the ultimate aim of developing appropriate models for low dose extrapolation is also required.

**COC**  
**[Month Year]**

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## **Annex 1**

The COC first published guidelines for the evaluation of chemicals for carcinogenicity in 1982. These dealt in the main with the design, conduct and interpretation of long-term animal bioassays and provided guidance to the relevant government departments and agencies on best practice for testing at that time. The need for guidelines to be periodically updated, to reflect advances in development and validation of methods, was recognised and revised guidelines were published in 1991, which addressed the evaluation of chemicals as potential carcinogens. The emphasis of the 1991 guidelines was directed at difficulties that may be encountered in assessing potential human carcinogens for regulatory purposes it included sections concerning the design and interpretation of short-term tests for carcinogenicity and long-term bioassays for carcinogenicity, as well as epidemiology.

Overall, the 1991 guidelines presented an overview of all aspects of carcinogen identification, including some consideration of quantitative risk assessment.

Since 1991, there were developments in mathematical modelling, and the use of potency indices in risk assessment has been suggested. In addition, proposals had been presented for setting minimal risk levels, as well as a harmonised approach for evaluating the mode of action of carcinogens. Therefore, in 2004 the COC reviewed these areas and with the intention of updating their guidance on the risk assessment of carcinogens. The Committee acknowledged the considerable developments in the harmonisation of approaches to the assessment of carcinogens in the area of human medicines. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published guidelines for the harmonisation of carcinogenicity testing requirements for human medicines ([www.ifpma.org/ich1.html](http://www.ifpma.org/ich1.html)).

DRAFT



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

### COC Guidance Statements

#### Revised List of Potential New Guidance Statements

		Year	Version
G 01	<b>A Strategy for the Risk Assessment of Chemical Carcinogens</b>  An overarching statement which presents the Committee's recommended general approach to assessing the carcinogenicity of a chemical.	2011	4
G 02	<b>Interpretation of Evidence of Carcinogenicity in Humans: Epidemiology and Case Reports</b>  Advice on how epidemiological studies and case reports can be used to inform carcinogen risk assessment		1
G 03	<b>Hazard identification and characterisation: Assessment and Interpretation of Animal Carcinogenicity Studies</b>  [summary text]		1
G 04	<b>Alternatives to the 2-Year Bioassay</b>  [summary text]		1
G 05	<b>Defining a Point of Departure in a Carcinogen Dose-Response.</b>  A discussion of various points of departure, including: NOAEL, T25, TD <sub>50</sub> and BMDL <sub>10</sub>		1

G 06	<a href="#">Low Dose Extrapolation of Cancer Risk</a> [summary text]		1
G 07	<a href="#">The use of Biomarkers in Carcinogenic Risk Assessment</a> [summary text]		1
G 08	<a href="#">Risk Characterisation Methods</a> Committee opinions on the derivation of minimal risk levels, the margin of exposure, threshold of toxicological concern		1
G 09	<a href="#">Risk Assessment of Mixtures of Chemical Carcinogens</a> A statement on the dissection of chemical mixtures for testing and suggested potential targets for interaction regarding mutagenic activity.	2010	1
G 10	<a href="#">Assessing the Risks of Acute or Short-Term Exposure to Carcinogens</a> [summary text]		1
G 11	<a href="#">Nanomaterial Toxicology</a> A position statement from COT, COC and COM with a suggested initial strategy for toxicology testing of nanomaterials.	2005	1

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

### COC Guidance Statements

#### Members' Comments on Existing Guidance Statements

2005: [The use of Target organ mutagenicity data in carcinogenicity risk assessment](#)

A statement on the definitions of threshold mutagens, possible modes of threshold activity, and experimental approaches to the determination of thresholds.

- A large part of the statement on the use of target organ mutagenicity data in carcinogen risk assessment is a report on the presentations and discussions at a joint COC/COM meeting on this topic. It is therefore not easy to consider an update of this, in view of it being a factual record of an event. The use of suitable assays for studying target organ mutagenicity, such as the use of transgenic animals, the Comet assay and DNA binding studies has increased over the 5 years since the production of the statement, and a completely revised version could be produced listing some of the applications of these techniques for target organ studies. Although this would certainly be of interest, my personal view is that this topic could be kept on the pending list and reconsidered in a few years when a little more data is available.
- The conclusions that such studies can provide supporting information for use by regulatory authorities in carcinogen risk assessment on a case-by-case basis seems excellent to me.

2000: [Accelerator mass spectrometry - an aid to carcinogen risk assessment](#)

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.

- The accelerator mass spectrometry statement is good and the conclusions are still up to date. There have been several applications of the technique since 2000 (e.g. acrylamide, aflatoxin B1, ethylene oxide, tamoxifen, PhIP, alkylanilines, ochratoxin, nicotine,

nitrobenzene, methyl tert-butyl ether, 8-oxodG). Many of these were used for interesting MOA studies (e.g. distinguishing between mechanisms, low level dose-response relationships). An update of this statement may be appropriate at this time, and relatively straightforward to do.

1998: [Neonatal rodent bioassay](#)

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.

- There may be room for a minor update as there is some limited evidence that adds further weight to our stated concerns that the model only picks up genotoxic carcinogens and only weak ones amongst those
- The bottom line here still seems valid.

2000: [Longevity in carcinogenicity studies in rats](#)

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.

- This seems to be still accurate and valid with respect to long term conventional assays, particularly as noted in the statement that 'survival in long-term carcinogenicity bioassays should be compliant with current UK and EC guidelines for the acceptability of a negative result from such studies'.

2002: [Minimum duration of carcinogenicity studies in rats](#)

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.

- Although there has been further comment on the issue of both survival and dietary restriction in the 10 years intervening since the last statement, the overall conclusions remain in keeping with the new OECD guidelines of 2009 and the draft guidance nearing completion. Hence it may be worthwhile updating to show our opinion in relation to

the current guidance something which may not represent too much work.

- This seems to be still accurate as far as 2 year bioassays are concerned. However, there has been much recent discussion about shorter studies being acceptable – even from FDA (Jacobson-Kram, 2010; Cohen 2010). This probably worthy of an additional review and comment.

Jacobson-Kram, D. Cancer risk assessment approaches at the FDA/CDER: Is the era of the 2-year bioassay drawing to a close? *Toxicologic Pathology* 38, 169-170 (2010).

Cohen, S.M. An enhanced 13-week bioassay: An alternative to the 2-year bioassay to screen for human carcinogenesis. *Experimental and Toxicologic Pathology* 62, 497-502 (2010).

2002: [ILSI/HESI research programme on alternative cancer models](#)

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

- A lot of water has passed over the bridge since this statement was made and it is now acceptable to use these short term studies in transgenic mice as alternatives to the 2 year mouse assay. Although I don't think they are as widely used as proponents suggest, they are being certainly being used by industry (Storer et al., 2010). The current situation probably merits further review.

Storer, R.D., Sistare, F.D., Reddy, M.V. & DeGeorge, J.J. An industry perspective on the utility of short-term carcinogenicity testing in transgenic mice in pharmaceutical development. *Toxicologic Pathology* 38, 51-61 (2010).