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Appendix B to CC/2011/02

Committee on
CARCINOGENICITY

COC/G 1 – Version 4 draft 2 (2011)

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

A Strategy for the Risk Assessment of Chemical Carcinogens – Draft 2

Preface

1. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) is an independent committee of experts 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](#) which includes 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 which may be used as the basis for regulatory decisions or policies.
2. As set out in its [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 (which leads), 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 document. Instead, the key topics that underpin the guidance on the risk assessment of carcinogens will be separated into distinct 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 gives the Committee's views on the general principles and emerging scientific discoveries relevant to 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

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of that adverse health effect occurring. When a carcinogenic hazard is identified, the level of risk will depend on circumstances such as the nature and degree of exposure to the chemical in question.

5. The recommended approach is based on the risk assessment paradigm proposed by the National Academy of Sciences (Figure 1, adapted from US National Academy of Sciences, 1983). Initial identification of a carcinogenic hazard is based upon a review of the animal carcinogenicity data, and any knowledge of effects on human health from case reports and epidemiological studies. These data should be assessed together 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 factors such as interspecies 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.

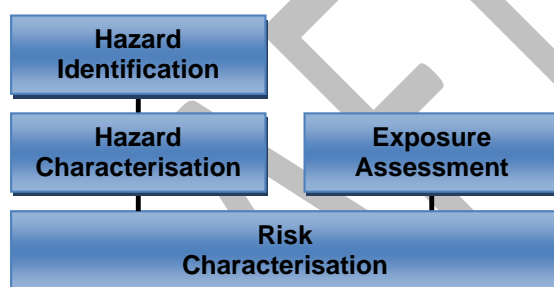


Figure 1: US National Academy of Sciences risk assessment paradigm

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 (US EPA, 2005; IARC, 2010; McGregor *et al*, 2010). 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. Risk management is the responsibility of regulators and policy makers within the Government. The terms of reference for the COC do not include providing risk management advice, since this needs to incorporate factors other than those

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considered in a risk assessment. Methods have been proposed that can be used to 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 because there is 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 is 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, the validity of design and the interpretation of the data need to be considered carefully. 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 proposes a strategy for evaluating the available data on the mutagenicity and genotoxicity of a substance, and recommends 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, DNA adducts, mutational spectra and other biomarkers (Guidance Statement G7 ([link](#))), to help to assess whether a carcinogen has a mutagenic mode of action. A substance should be considered to be a mutagenic carcinogen only when there is evidence that it causes cancer as a 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

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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 mutagenic and potentially carcinogenic.

14. In the absence of information to the contrary, it is prudent to assume that chemicals which are mutagenic and carcinogenic have the potential to mutate DNA at any level of exposure and that such damage could lead to tumour development. Therefore, any level of exposure is considered to carry some degree of carcinogenic risk.

15. Non-mutagenic carcinogens are those chemicals for which there is sufficient evidence of carcinogenicity from epidemiological or animal studies, and no evidence of mutagenic activity (on the basis of the [COM Guidance](#) on the assessment of mutagenic hazard). Some information about mode of action is necessary for an adequate consideration of such carcinogens. In 2001, the IPCS (International Programme on Chemical Safety) proposed a structured approach for the assessment of the overall weight of evidence for a postulated mode of action (Sonich-Mullin *et al.* 2001,) and, subsequently, the Risk Sciences Institute of the International Life Sciences Institute (ILSI/RSI) 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). Recently, IPCS has developed a HRF based on the IPCS mode of action framework and the ILSI/RSI HRF (Boobis AR *et al* 2006).

16. These frameworks are of value in assessing carcinogenic risk. The HRF provide 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 rat mammary tumours caused by a surge of luteinising hormone (Cohen SM *et al* 2003).

Hazard Characterisation

17. Hazard Characterisation involves a qualitative description of the nature of the hazard and a quantitative description of the dose-response relationship. The purpose of dose-response analysis is to investigate the magnitude of response (in terms of severity or incidence) within the dose range used in either an animal or human study. This assists in the estimation of response and, ultimately, risk from exposure to the concentrations of the chemical in the environment, food etc, which are usually 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: the absorption, distribution, metabolism and excretion (ADME) of the chemical; its mode of action; and the variability in susceptibility between species and within humans. In particular, use of the dose-response relationship in the final assessment of risk will depend on whether or not the

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carcinogenic response occurs as the result of mutagenic activity (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, because of the 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 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 from a study, such as the dose level associated with a tumour incidence which is 10% above the incidence in the control group. Various methods for deriving a point of departure are discussed in Guidance Statement G5 (link). [“Points of departure and defining levels of (no) effect”]

Comment [F1]: Members: is this what you wanted the title of Statement G5 changed to?

Potency estimates

20. There are a number of methods for the characterisation of hazard due to mutagenic carcinogens. These follow a ranking approach whereby chemicals 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, TD₅₀ and BMDL₁₀ have been used to estimate the relative potency of mutagenic carcinogens; currently, the BMD methodology is widely favoured. 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, there is evidence that the chemicals all act by the same mutagenic mode of action and there are no confounding toxicokinetic characteristics. 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), but are not considered 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. Also, 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

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use of uncertainty factors. For such substances, the risk assessor should also consider 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 Data

23. Curves may be fitted to dose-response data from animal studies for either mutagenic or non-mutagenic carcinogens 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. At present, there are no accepted biologically informative models. The models and low dose extrapolation are discussed further in Guidance Statement G5 ([link](#)).

24. Low-dose extrapolation 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. This is termed 'quantitative risk assessment'. 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 do not fully account for human variability and, although some species differences can be taken into account by correcting the dose in animal studies to a human equivalent dose by interspecies 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. Exposure assessment is an increasingly important aspect of carcinogen risk assessment, given the increasing use of approaches such as the Margin of Exposure and the Threshold of Toxicological Concern' (see below). A number of methods are used to estimate human exposure to a chemical from food or the environment. For example, the intake of chemicals from food can be measured by dietary surveys, food diaries, questionnaires, and the analysis of foods for the chemical of concern (IPCS, 2000; Food Standards Agency, 2011). To assess the intake of chemicals from soil,

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modelling of likely exposure patterns may be used together with chemical analysis of the soil (Environment Agency, 2009). Although exposure assessment in humans is crucial to the assessment of risk, it is frequently identified as the main area of uncertainty in the overall risk assessment process.

27. Measurements of exposure may be subject to error, which may be an inaccurate measurement of the level of the chemical due to instrument error or, in surveys, this could be an inaccurate response to a question or the inaccurate recording of an accurate response. These errors may be either systematic, which will produce bias into the results, or random. Measurement errors introduce inaccuracy into the exposure data and, therefore, in conducting assessments, it is important to assess the quality of the measurements and to use statistical techniques in the analysis of the data which take account of possible measurement errors (Coggon *et al*, 1997; IPCS, 2000).

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. 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 (Doerge *et al*, 2005, Vesper *et al* 2010).

29. Biomarkers can provide valuable information for use in the risk assessment process. However, in human chemical-induced carcinogenicity, there is usually a long latency period between exposure to the carcinogen and the clinical onset of cancer. Biomarkers can be of limited use as a measure of historical exposure and thus as a marker of exposure in 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 with exposure; 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

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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 intake 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, it is important to consider the overall toxicological profile has to be considered, 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 (interspecies differences) as well as taking into account that there may be differences in sensitivity to the adverse effect among the human population (interindividual variation). A default uncertainty factor of 100 (based on a factor of 10 for interspecies variation and a factor of 10 for interindividual 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. For some chemicals, there may be information about the comparative toxicokinetic or toxicodynamic differences between humans and animals which enables chemical-specific adjustment factors to be used in place

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of the default factors. 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, in the absence of mechanistic data to suggest a threshold for mutagenicity, it is currently assumed that 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 the high levels of exposure used in animal carcinogenicity studies, 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 the risk of mutagenic carcinogens.

37. The most precautionary approach to reducing the risk from such chemicals would be to adopt measures that ensure that levels are controlled so that exposure is as low as reasonably practicable (ALARP). In some cases a minimal risk level may need to be derived, 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 should be made to reduce exposure, 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 (MOE) approach can be a useful tool for risk communication and risk management prioritisation (Benford D *et al*, 2009). In this approach, a point of departure is generated by modelling the dose-response data from an animal carcinogenicity study. The point of departure used is usually the lower 95% confidence value of the benchmark dose for a 10% response over control levels (BMDL₁₀). The margin between this value and estimates

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of exposure to the chemical are then calculated. A judgement can be made on the basis of the size of these MOE.

39. The use of potency estimates has a role in the prioritisation of chemicals considered to be mutagenic carcinogens but not in the risk assessment process. The Threshold of Toxicological Concern (TTC) approach (also known as Threshold of Regulation) can help to identify priorities for carcinogenicity evaluation particularly for chemicals not subject to regulatory approval schemes.

Assessment of Mixtures

40. Humans are exposed to a variety of mixtures of chemicals both simultaneously and sequentially. 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.

41. 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](#).

Future Developments

42. 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 e.g. by assessing the minimum effect needed to trigger a downstream effect when studying mechanism of action.
- 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 transgenic animal models including studies to define changes to dose-response due to genetic modification, as well as to investigate their biological basis.
- Further research into validation and standardisation of genomic and proteomic techniques, particularly the development of genomic/proteomic databases, methods of bioinformatic and statistical analysis of data and pattern recognition, and information on the normal range of gene expression.
- The development of toxicological methods to refine extrapolation between animals and humans.

Overall Summary

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

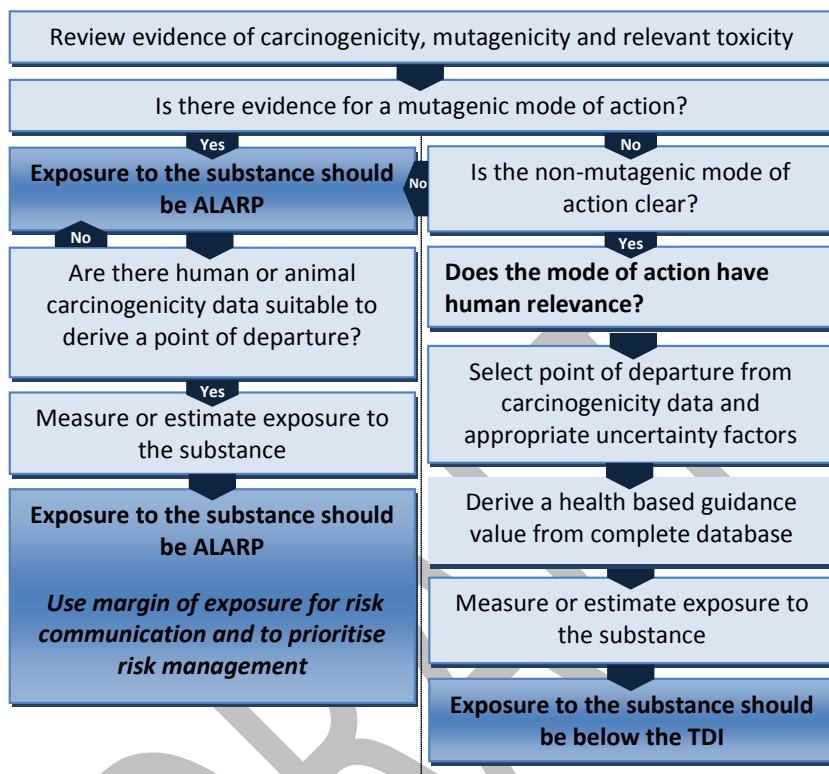


Figure 2: An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity.

44. 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 for which the database is not adequate 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; the margin of exposure approach may be used to aid risk communication and prioritise risk management when there are adequate carcinogenicity and exposure data. This could 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. Potency estimates can be used to rank

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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 to keep any exposure to mutagenic carcinogens as low as reasonably practicable (ALARP).

Comment [DM2]: Does the Committee still accept this? Should reference to PAHs be removed? If it is kept, should this refer to Points of Departure, rather than potency estimates?

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:

- Clarification of the shape of the dose-response curve at very low doses and low estimated risks.
- Identification of biological markers of tumour precursors and related processes and clarification of their significance for risk assessment.
- Further investigation of biological responses at environmentally relevant doses.
- Further development and validation of transgenic animal models.
- Further research into, validation and standardisation of genomic and proteomic techniques.
- The development of toxicological methods to refine extrapolation between animals and humans.

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

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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 had been suggested. 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 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).

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