

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

A Strategy for the Risk Assessment of Chemical Carcinogens – Draft 3

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 first guidelines were published 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. It was recognised that the need for guidelines needed 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 to address the difficulties that may be encountered in assessing potential human carcinogens for regulatory purposes. They 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.~~

Formatted: Committee Paragraph

Comment [F1]: Note: at the last meeting, Members asked that Annex 1 be incorporated into the text.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

4. After 1991, there were developments in mathematical modelling, and the use of potency indices in risk assessment were 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 and updated its guidance on the risk assessment of carcinogens. The Committee acknowledged the considerable developments in the harmonisation of approaches for 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).

2.5. The most recent revision of the guidance began in 2010 and is expected to be completed by 2013. Thereafter, individual guidance statements will be updated only when important new information becomes available. 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 the risk assessment of chemical carcinogens.

Introduction

3.6. 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 on human health, such as cancer. Risk is the probability that the adverse health effect will occur. 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.

4.7. 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 on 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 and 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.

Comment [F2]: Now hyperlinked to a definition in the glossary, as requested.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

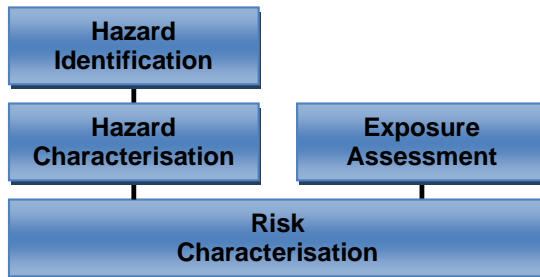


Figure 1: US National Academy of Sciences risk assessment paradigm

5-8. 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; WHO, 2009; 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 pragmatic 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.

6-9. Risk characterisation may identify the need for risk management. Within Government, risk management is the responsibility of regulators and policy makers within the Government. Risk management advice may incorporate advice from the COC on risk assessment but also needs to incorporate other factors. Therefore, the terms of reference for the COC do not include the provisioning of risk management advice, since this needs to incorporate factors other than those considered in a risk assessment. However, the COC may use methods which may assist risk managers in 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

10. Problem formulation is an essential initial step in any risk assessment. It is important to know why advice is being sought so that so that the risk assessor has a clear understanding of the policy question which the assessment will inform. This stage should define the questions to be addressed in the risk assessment, a plan of action and, if appropriate, the terms of reference.

7-11. 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

Formatted: Committee Paragraph

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

thoroughly identify the hazards posed by the substance, it is recommended that all the available human and animal carcinogenicity data are gathered and reviewed. This review should also consider available evidence of mutagenicity-genotoxicity and any other toxicity that may be relevant to understanding the mechanism or mode of action by which the substance causes cancer.

Comment [F3]: Is this the correct term?

~~8-12.~~ As ~~originally~~ stated in the 1991 ~~and 2004~~ guidelines (UK Department of Health, 1991 ~~and 2004~~), well conducted epidemiological studies ~~provide the are most valuable best source from which to 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](#)).

~~9-13.~~ 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](#)).

~~10-14.~~ 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-genotoxic mode of action is involved ~~i.e. whether mutagenicity is a key step in the carcinogenic process~~. The results from short-term mutagenicity tests will give an indication of the mutagenic hazard and, thus, the potential to cause cancer.

~~11-15.~~ Mutagenic-Genotoxic potential should be assessed according to the [guidance](#) issued by the COC's sister committee, the Committee on Mutagenicity [of Chemicals in Food, Consumer Products and the Environment](#) (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-genotoxic hazard.

Comment [F4]: ?

~~12-16.~~ 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-genotoxic mode of action. A substance should be considered to be a mutagenic-genotoxic carcinogen only when there is evidence that it causes cancer as a result of its mutagenic activity; substances should be regarded as being mutagenic-genotoxic and carcinogenic where there is adequate evidence of mutagenic-genotoxic and carcinogenic activity but insufficient evidence that the mutagenic-genotoxic activity is responsible for the observed carcinogenicity; and substances for which there is only evidence of mutagenicitygenotoxicity, but no evidence of human or animal carcinogenicity, should be regarded as mutagenic-genotoxic and potentially carcinogenic.

Comment [O5]: ?

~~13-17.~~ In the absence of information to the contrary, it is prudent to assume that chemicals which are genotoxicmutagenic and carcinogenic have the potential to mutate DNA at any level of exposure and that such damage could lead to tumour

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

development. Therefore, any level of exposure is considered to carry some degree of carcinogenic risk.

14-18. Non-**genotoxicmutagenic** carcinogens are those chemicals for which there is sufficient evidence of carcinogenicity from epidemiological or animal studies, and no evidence of **genotoxicmutagenic** activity (on the basis of the [COM Guidance](#) on the assessment of **genotoxicmutagenic** 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).

15-19. These frameworks are of value in assessing carcinogenic risk. The HRF provides a systematic approach ~~for the~~ [evaluation of](#) 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 α 2 μ -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

16-20. Hazard ~~C~~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 carcinogenic response occurs as the result of **genotoxicmutagenic** activity (discussed ~~later below under~~ [Risk Characterisation](#)).

17-21. Epidemiological studies provide the most appropriate data source for the quantitation of dose-response in the hazard characterisation process, although exposure estimation in [these](#) 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

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

uncertainties introduced when extrapolating between species. A further uncertainty is the extrapolation of results seen at the high doses used in animal studies to produce an estimate of risk at levels of human exposure. In general, dose-response analyses from animal studies are of most value in ranking potency within chemical groups, such as structurally related groups of ~~genotoxic~~~~mutagenic~~ carcinogens.

Defining a Point of Departure in a Carcinogen Dose-Response

~~18-22.~~ 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"]

Formatted: Highlight

Formatted: Highlight

Potency estimates

~~19-23.~~ There are a number of methods for the characterisation of hazard due to ~~genotoxic~~~~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.

~~20-24.~~ Points of departure such as [T25](#), [TD₅₀](#) and [BMD_{L10}](#) have been used to estimate the relative potency of ~~genotoxic~~~~mutagenic~~ carcinogens; ~~currently, with~~ 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~~ ~~genotoxic~~ mode of action and there are no confounding toxicokinetic characteristics. To date, there has been relatively little use of PEFs for carcinogenicity although a number of PEF schemes have been proposed for the risk assessment of mixtures of polycyclic aromatic hydrocarbons (PAHs) in environmental media (Expert Panel on Air Quality Standards, 1999; Dutch National Institute of Public Health and the Environment, 2001).

Formatted: Font: 12 pt

~~21-25.~~ Relative potency estimates could have some pragmatic use in carcinogenic risk assessment as an aid ~~in the~~ ~~to~~ prioritising [of](#) 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~~ ~~is not necessary~~ to rank the carcinogenic potency of non-~~genotoxic~~~~mutagenic~~ carcinogens, for which tolerable exposure levels can be derived using an approach based on knowledge of mode of action, identification of no

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

adverse effect level, and 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

22-26. Curves may be fitted to dose-response data from animal studies for either ~~genotoxic~~mutagenic or non-~~genotoxic~~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](#)).

23-27. 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.

24-28. 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

25-29. 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 Concern² (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~~estimated from dietary surveys, food diaries, questionnaires, and the analysis of foods for the chemical of concern

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

(IPCS, 2000; Food Standards Agency, 2011). To assess the intake of chemicals from soil, 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.

~~26-30.~~ Measurements of exposure may be subject to error. A major potential source is the assumption which is made about samples below the limit of detection e.g. that these could be assumed to be present at the LOD, or to be zero, or to be some level inbetween. This can have a profound effect on the estimates of exposure. Other sources of 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

~~27-31.~~ Biomarkers of exposure can give an indication of the level of ~~an individual's~~ exposure of an individual 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).

~~28-32.~~ 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, ~~therefore,~~ as a marker of exposure in epidemiological studies. Biomarkers are discussed further in Guidance Statement G7 ([link](#)). It is essential that a biomarker is appropriately characterised and validated before any conclusions are drawn from its use. ~~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

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

~~29-33.~~ 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 ~~genotoxic/mutagenic~~ activity, or whether there is a lack of relevant ~~genotoxic/mutagenic~~ activity along with a plausible alternative mode of action.

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

~~30-34.~~ The risk assessment of chemical carcinogens is dependant on the mechanisms of carcinogenicity and the relationship between dose and tumour response. For most non-~~genotoxic/mutagenic~~ carcinogens, it is accepted that there is a threshold dose, below which no effect is observed. Many non-~~genotoxic/mutagenic~~ carcinogens induce tumours as a secondary effect arising from an initial toxic effect, for which a 'threshold' dose may be identified (Ashby *et al.*, 1996). It follows that these substances are unlikely to pose a carcinogenic risk at dose levels at and below the given threshold that does not produce the primary toxic effect (Williams, 2001). Human relevance frameworks^{HRF} (see paragraph 196) may enhance the clarity and transparency of the risk assessment.

~~31-35.~~ A health based intake value can be derived where there is adequate evidence to support a threshold for carcinogenicity, an exposure level/dose can be derived at or below which there is estimated to be no risk of carcinogenicity for humans. This evidence should demonstrate that the compound and metabolites do not have ~~genotoxic/mutagenic~~ activity and provide evidence of a plausible non-~~genotoxic/mutagenic~~ mode of action for the observed carcinogenicity. The health based guidance value/derived exposure level 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 healthtake account of potential interspecies and intraspecies differences in susceptibility. Examples of ~~s~~ include the (ADI), used for food additives or pesticide residues in food; the (TDI), used by many agencies for environmental contaminants; and the (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.

~~32-36.~~ 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 possible 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 when extrapolating data from toxicity studies.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

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 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](#)).

~~33-37.~~ This approach may be used for non-genotoxic carcinogens provided that the underlying mode of action is adequately understood. Carcinogenicity should then be considered as part of an assessment of the overall toxicological profile for a compound. The lowest exposure level derived for any toxicological endpoint considered to be relevant to humans could then be used as a health based guidance value for that compound. 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. The health based guidance value represents a single estimate of an ~~dose (or exposure level)~~ 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, ~~if based on carcinogenicity,~~ the nature and dose-response relationship for carcinogenicity of the substance in question.

34. 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.

Formatted: No bullets or numbering

Non-threshold Carcinogenicity [mutagenic carcinogens; stochastic carcinogens]

~~35-38.~~ From what is known about the mechanism of action of ~~genotoxic~~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 ~~these~~ carcinogens. Estimation of risk at environmental levels of exposure ~~would~~ generally ~~relies on~~ ~~inquire 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 ~~genotoxic~~mutagenic carcinogens.

Comment [F6]: ?

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

~~36-39.~~ The most precautionary approach to reducing the risk from such chemicals would be to prevent exposure completely. However, in many cases e.g. environmental contaminants, this is not practical. Therefore, the widely accepted approach is to adopt measures to ensure that levels are controlled so that exposure is as low as reasonably practicable (ALARP) which, in some cases, might mean preventing exposure. However, under specific circumstances, e.g. very low exposures to genotoxic contaminants or impurities, a pragmatic in some cases minimal risk level may be identified for these compounds to aid risk management decisions. The derivation of a minimal risk level for a genotoxic carcinogen involves assessment of all available dose-response data for carcinogenicity to identify an appropriate point of departure, and the use of expert judgement to derive an appropriate uncertainty factor to apply to it. 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, for any genotoxic carcinogen, there may be a carcinogenic risk at any exposure, although this may be very small. Therefore, ideally, the principle of ALARP should apply, whether or not a minimal risk level for a genotoxic carcinogenic contaminant or impurity can be estimated. 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.

~~37-40.~~ 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~~2010). 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 margins between this value and estimates of exposure to the chemical are then calculated. A judgement can be made on the basis of the size magnitude of these MOE.

~~38-41.~~ The use of potency estimates has a role in the prioritisation of chemicals considered to be mutagenic-genotoxic carcinogens but they are not considered adequate for quantifying cancer 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

~~39-42.~~ Humans are exposed to a variety of mixtures, of chemicals both either by simultaneously or and sequentially exposure to chemicals. GenotoxicMutagenic 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.

~~40-43.~~ 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

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

assessing the carcinogenic risk posed by a mixture of substances, which are discussed further in [Guidance Statement G9](#).

Future Developments

41-44. 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 [high content techniques, such as genomics](#) and [proteomics techniques](#), particularly the development of [genomic/proteomic appropriate](#) databases, methods of bioinformatic and statistical analysis of data and pattern recognition, and information on the normal range of [gene expression variation](#).
- The development of toxicological methods to refine extrapolation between animals and humans.

Overall Summary

42-45. Figure 2 sets out an overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

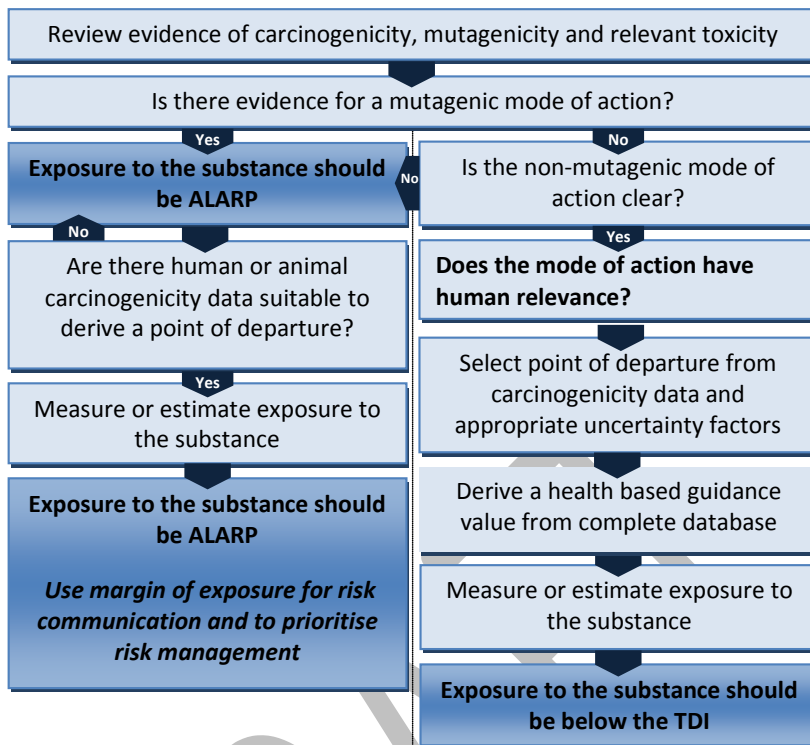


Figure 2: An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity.

Comment [F7]: Revised Figure 2 to be tabled at meeting

46. Carcinogenicity data on chemicals should be evaluated on a case-by-case basis, taking into account the weight of all available evidence. It is not possible to provide a universally applicable list of data that will be needed for an assessment of carcinogenicity because the range of data will differ with circumstances. However, the guidance outlined here is intended to provide a strategy that could be adopted for the risk assessment of chemical carcinogens.

Formatted

47. The COC recommends a four-stage evaluation for the risk assessment of carcinogens procedure. Initial identification of a carcinogenic hazard at stage 1 should be based upon a review of the toxicity data and of any knowledge of effects on human health. It is essential to determine whether carcinogens act via a genotoxic or non-genotoxic mechanism. A chemical can be tested for genotoxicity using the strategy recommended by the COM (link). Hazard characterisation (stage 2) should provide a qualitative description of the nature of the hazard and determine the dose-response relationship from animal and/or human studies. During this stage it is important that factors such as interspecies variation in susceptibility and ~~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 are considered is critical.~~ Exposure assessment (stage 3) should estimate probable human exposure. The final stage (risk characterisation)

Formatted: Highlight

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

draws together evidence of the hazard and dose-response, and places it in the context of the measured or estimated level of human exposure.

48. Where there is clear evidence that the carcinogenic activity of a chemical is mediated exclusively by a non-genotoxic mode of action that is relevant to human health, the Committee recommends the adoption of a threshold approach to risk characterisation. Thus a method based on the identification of a suitable point of departure for carcinogenicity or for a precursor event linked to tumour induction, and the use of uncertainty factors is appropriate, as is used in other areas of chemical risk assessment.

~~43-49. If a putative carcinogen is found to be potentially genotoxic, the Committee recommends a non-threshold approach to risk assessment. The assumption of no threshold, together with the practical difficulties of using low doses of human relevance in animal carcinogenicity studies, has led to the development of mathematical models that attempt to provide a "best estimate" of the likely extrapolation of the dose-response curve below the lowest experimental data points. These models may give an impression of precision which cannot be justified from the approximations and assumptions upon which they are based. Therefore, it is recommended that the most precautionary approach to reduce the risk from mutagenic substances would be the widely accepted approach of ALARP (as low as reasonably practicable) should ideally be adopted by risk managers. 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; In addition, the margin of exposure approach may can 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. e. 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 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). However, ideally, exposure to non-threshold carcinogens should be ALARP.~~

~~44. 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.~~

~~45-50. The Committee emphasises the importance of further research in order to refine the process of risk assessment. This includes:~~

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

- 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 [high content techniques, such as genomics](#) and [proteomics techniques](#).
- The development of toxicological methods to refine extrapolation between animals and humans.

COC

[Month Year]

References

- Albertini RJ, Anderson D, Douglas GR, Hagmar L, Hemminki K, Merlo F, Natarajan AT, Norppa H, Shuker DE, Tice R, Waters MD,
- Aitio A. (2000) IPCS guidelines for the monitoring of genotoxic effects of carcinogens in humans. International Programme on Chemical Safety. *Mutation Research*, 463 (2),11-72.
- Albertini R, Clewell H, Himmelstein MW, Morinello E, Olin S, Preston J, Scarano L, Smith MT, Swenberg J, Tice R & Travis C. (2003) The use of non-tumor data in cancer risk assessment: reflections on butadiene, vinyl chloride, and benzene. *Regulatory Toxicology Pharmacology*, 37:105-32
- Alexander J, Reistad R, Hegstad S, Frandsen H, Ingebrigtsen K, Paulsen JE & Becher G. (2002) Biomarkers of exposure to heterocyclic amines: approaches to improve the exposure assessment *Food Chemical Toxicology*, 40:1131-7
- Arif JM & Gupta RC (1997) Detection of DNA-reactive metabolites in serum and their tissue distribution in mice exposed to multiple doses of carcinogen mixtures: role in human biomonitoring. *Carcinogenesis*, 17, 2213-2219
- Ashby J & Tennant RW. (1994) Prediction of rodent carcinogenicity for 44 chemicals: results. *Mutagenesis*, 9:7-15
- Ashby J, Kier L, Wilson AG, Green T, Lefevre PA, Tinwell H, Willis GA, Heydens WF & Clapp MJ (1996) Evaluation of the potential carcinogenicity and genetic toxicity to humans of the herbicide acetochlor. *Human and Experimental Toxicology*, 15:702-35
- Aston JP, Ball RL, Pople JE, Jones K & Cocker J. (2002) Development and validation of a competitive immunoassay for urinary S-phenylmercapturic acid and its application in benzene biological monitoring. *Biomarkers*, 7(2): 103-12
- Bailer, A.J. & Portier, C.J. (1993) An index of tumorigenic potency. *Biometrics*, 49: 357-365
- Barlow SM, Kozianowski G, Wurtzen G, Schlatter J. (2001) "Threshold of toxicological concern for chemical substances present in the diet. Report of a workshop, 5-6 October 1999, Paris, France. *Food Chemical Toxicology*, 39:893-905
- Beach AC, Gupta RC(1992). Human biomonitoring and the 32P-postlabeling assay. *Carcinogenesis*, 13, 1053-1074.
- Bechtold WE & Henderson RF (1993) Biomarkers of human exposure to benzene. *Journal of Toxicology and Environmental Health*, 40:377-86
- Benford D, Bolder PM, Carthew P, Coulet M, DiNovi M, Leblanc J-C, Renwick AG, Selzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T (2010). Application of the eMargin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. *Food Chem Toxicol* 48, S2-S24.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

- Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D Farland W (2006). IPCS Framework for analysing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology* 36(10), 781-792
- Boogaard PJ & van Sittert NJ (1995) Biological monitoring of exposure to benzene: a comparison between S-phenylmercapturic acid, trans, trans-muconic acid, and phenol. *Occupational and Environmental Medicine*, 52, 611-620
- Borgert CJ, Price B, Wells CS et al (2001) Evaluating chemical interaction studies for mixture risk assessment. *Human Ecol Risk Assessment* 7 259-306
- Cheeseman MA, Machuga EJ, Bailey AB. (1999) A tiered approach to threshold of regulation. *Food Chemical Toxicology*, 37:387-412
- Clewell H.J., Gentry P.R., Gearhart J.M., Allen B.C. & Anderson M.E. (2001) Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. *Science of the Total Environment*, 274(1-3), 37-66
- Coggon d, Rose R, Barker DJP. *Epidemiology for the Uninitiated*. 4th Edition, 1997. BMJ Publishing Group.
- Cohen SM, Meek ME, Klaunig JE, Patton DE, Fenner-Crisp PA (2003). The human relevance of information on carcinogenic modes of action: overview. *Critical Reviews in Toxicology*, 33 (6): 581-9.
- Cohen SM, Klaunig J, Meek E, Hill RN, Pastoor T, Lehman-McKeeman L, Bucher J, Longfellow DG, Seed J, Dellarco V, Fenner-Crisp P and Patton D. (2004). Evaluating the human relevance of chemically induced animal tumours. *Toxicological Sciences*, 78, 181-186.
- Collins JF, Brown JP, Alexeeff GV & Salmon AG. (1998) Potency equivalency factors for some polycyclic aromatic hydrocarbons and polycyclic aromatic hydrocarbon derivatives. *Regulatory Toxicology Pharmacology*, 28:45-5
- Counts JL & Goodman JI (1995) Principles Underlying Dose Selection for, and Extrapolation from, the Carcinogen Bioassay: Dose Influences Mechanism. *Regulatory Toxicology and Pharmacology*, 21:418-421
- Crump KS (1994) Use of mechanistic models to estimate low-dose cancer risks. *Risk Analysis*, 14, 1033-1038
- Crump KS (1996) The linearized multistage model and the future of quantitative risk assessment. *Human & Experimental Toxicology*, 15, 787-798.
- DEFRA and Environment Agency (2002) Contaminants in Soils: Collation of Toxicological Data and Intake Values for Humans. Consolidated Main Report, CLR Report No 9. Available from the R&D Dissemination Centre, WRC plc, Swindon.
- Doerge DR, Young JF, McDaniel LP, Twaddle NC, Churchwell MI (2005). Toxicokinetics of acrylamide and glycidamide in B6C3F1 mice. *Tox Appl Pharmacol* 202(3), 258-267.
- Duggan MJ & Lambert BE (1998) Standards for Environmental, Non-threshold, Carcinogens: A Comparison of the approaches used for radiation and chemicals. *Annals of Occupational Hygiene*, 42:315-323
- Dybing E, Sanner T, Roelfzema H, Kroese D & Tennant RW (1997) T25: a simplified carcinogenic potency index: description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity. *Pharmacological Toxicology*, 80, 272-279
- Dybing E (2002). Development and implementation of the IPCS conceptual framework for evaluating mode of action of chemical carcinogens. *Toxicology*, 181-182, 121-5
- Eastin, WC (1998) The National Toxicology Program Evaluation of Transgenic Mice as Predictive Models for Identifying Carcinogens. *Environmental Health Perspectives*, 106, 81-84
- ECETOC Technical Report No. 83 (2002) the use of T25 estimates and alternative methods in the regulatory risk assessment of non-threshold carcinogens in the European Union.
- Edler L & Kopp-Schneider A (1998) Statistical models for low dose extrapolation. *Mutation Research*, 405, 227-236
- Edler L, Poirier K, Dourson M, Kleiner J, Mileson B, Nordmann H, Renwick A, Slob W, Walton K & Wurtzen G (2002) Mathematical modelling and quantitative methods. *Food and Chemical Toxicology*, 40,283-326
- Environment Agency (2009). Updated technical background to the CLEA model. Science Report SC050021/SR3. Environment Agency, Bristol. Environmental Health Criteria No 155 (1993) : Biomarkers and Risk Assessment: Concepts and Principles. International Programme on Chemical Safety, World Health Organisation, Geneva.
- Environmental Health Criteria, No. 202 (1998) Selected Non-heterocyclic Polycyclic Aromatic Hydrocarbons. International Programme on Chemical Safety, World Health Organisation, Geneva.
- Environmental Health Criteria, No. 210 (1999) Principles for the assessment of risks to human health from exposure to chemicals. International Programme on Chemical Safety, World Health Organisation, Geneva.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

- Environmental Health Criteria No 222 (2001) Biomarkers in Risk Assessment: Validity and Validation. International Programme on Chemical Safety, World Health Organisation, Geneva.
- [Expert Panel on Air Quality Standards \(1999\) Polyaromatic Hydrocarbons.](http://web.archive.nationalarchives.gov.uk/20060715141954/http://www.defra.gov.uk/environment/airquality/aqs/poly/6.htm)
<http://web.archive.nationalarchives.gov.uk/20060715141954/http://www.defra.gov.uk/environment/airquality/aqs/poly/6.htm> Accessed 5 July 2011.
- Fang JL, Vaca CE, Valsta LM & Mutanen M. (1996) Determination of DNA adducts of malonaldehyde in humans: effects of dietary fatty acid composition. *Carcinogenesis*, 17, 1035-40
- Farmer PB & Sweetman GMA (1995) Mass spectrometric detection of carcinogenic adducts. *J. Mass Spectrometry*, 30, 1369-1379
- Farmer PB. (1999) Studies using specific biomarkers for human exposure assessment to exogenous and endogenous chemical agents. *Mutation Research*, 428:69-81
- Farmer PB (2004). Exposure biomarkers for the study of toxicological impact on carcinogenic processes. International Agency for Research on Cancer. Scientific Publications, 157, 71-90
- Food Standards Agency. Dietary surveys. <http://www.food.gov.uk/science/dietarysurveys/> Accessed 15 March 2011.
- Ferrier H, Nieuwenhuijsen M, Boobis A and Elliott P (2002). Current knowledge and recent developments in consumer exposure assessment of pesticides: A UK perspective. *Food Additives and Contaminants*, 19, 837-852.
- Friesen MD, Kaderlik K, Lin D, Garren L, Bartsch H, Lang NP, Kadlubar FF. (1994) Analysis of DNA adducts of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in rat and human tissues by alkaline hydrolysis and gas chromatography/electron capture mass spectrometry: validation by comparison with ³²P-postlabeling. *Chemical Research in Toxicology*, 7, 733-9
- Gaylor DW, Kodell RL, Chen JJ, Springer JA, Lorentzen RJ & Scheuplein RJ (1994) Point estimates of cancer risk at low doses. *Risk Analysis*, 14, 843-849
- Gold LS, Sawyer CB, Magaw R, Backman GM, de Veciana M, Levinson R, Hooper NK, Havender WR, Bernstein L, et al. (1984) A Carcinogenic Potency Database of the standardized results of animal bioassays. *Environmental Health Perspectives*, 58, 9-319
- Gold LS, Slone TH, & Bernstein, L. (1989) Summary of carcinogenic potency (TD50) and positivity for 492 rodent carcinogens in the Carcinogenic Potency Database. *Environmental Health Perspectives*, 79, 259-272
- Gold LS, Manley NS, Slone TH & Rohrbach L (1999). Supplement to the Carcinogenic Potency Database (CPDB): Results of Animal Bioassays Published in the General Literature in 1993 to 1994 and by the National Toxicology Program in 1995 to 1996. *Environmental Health Perspectives*, 107, 527-600
- Gold LS, Gaylor DW, Slone TH. (2003) Comparison of cancer risk estimates based on a variety of risk assessment methodologies. *Regulatory Toxicology Pharmacology*, 37, 45-53.
- Groopman JD, Wild CP, Hasler J, Junshi C, Wogan GN, Kensler TW (1993) Molecular epidemiology of aflatoxin exposures: validation of aflatoxin-N7-guanine levels in urine as a biomarker in experimental rat models and humans. *Environmental Health Perspectives*, 99, 107-113
- Groopman JD, Wild CP, Hasler J, Junshi C, Wogan GN, Kensler TW. Molecular epidemiology of aflatoxin exposures: validation of aflatoxin-N7-guanine levels in urine as a biomarker in experimental rat models and humans. *Environ Health Perspect.* 1993; 99:107-113
- Groopman JD, Kensler TW (1999) The light at the end of the tunnel for chemical-specific biomarker: daylight or headlight? *Carcinogenesis*, 20: 1-11
- Hanes B & Wedel T (1985) A selected review of risk models: one hit, multi hit, multi-stage, probit, Weibull and pharmacokinetic. *Journal of the American College of Toxicology*, 4, 271-278
- Harley HO & Sielken RL (1977) Estimation of safe doses in carcinogenic experiments. *Biometrics*, 33, 1-30
- Hecht SS (2002) Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. *Carcinogenesis*, 23, 907-22
- IARC – International Agency for Research on Cancer (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 99 (2010) Some Aromatic Amines, Organic Dyes, and Related Exposures, Preamble.* IARC, Lyons
- IGHRC – The Interdepartmental Group on Health Risk from Chemicals (2002) Assessment of chemical carcinogens: Background to general principles of a weight of evidence approach. MRC Institute for Environment and Health, Leicester

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

- IGHRC – The Interdepartmental Group on Health Risk from Chemicals (2003) Uncertainty factors: Their use in human health risk assessment by UK Government. MRC Institute for Environment and Health, Leicester
- International Expert Panel on Carcinogen Risk Assessment (1996) The use of mechanistic data in the risk assessment of ten chemicals: an introduction to the chemical-specific reviews. *Pharmacology and Therapeutics*, 71:1-5 (Special Issue)
- International Programme on Chemical Safety – IPCS (2000). Monograph no. 214: Human exposure assessment. WHO, Geneva.
- Kensler TW, Qian GS, Chen JG & Groopman JD (2003) Translational strategies for cancer prevention in liver. *Nature Reviews Cancer*, 3, 321-329
- Krewski D, Cardis E, Zeise L & Feron VJ (1999) Empirical approaches to risk estimation and prediction. In Moolgavkar S, Krewski D, Zeise L, Cardis E, & Moller H (Eds) *Quantitative Estimation and Prediction of Human Cancer Risks*. IARC Scientific Publications No. 131. International Agency for Research on Cancer, Lyon. 131-178
- Krewski D, Gaylor D & Szyzkowicz M. (1991) A model-free approach to low-dose extrapolation. *Environmental Health Perspectives* 90:279-285
- Kroes R, Galli C, Munro I, Schilter B, Tran L, Walker R, Wurtzen G. (2000) Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. *Food Chemical Toxicology*, 38, 255-312
- Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F Vos JG and Wurtzen G (2004). Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chemical Toxicology*, 42, 65-83.
- Lovell DP & Thomas G (1996) Quantitative risk assessment and the limitations of the linearised multistage model. *Human & Experimental Toxicology*, 15, 87-104
- Mantel N & Bryan WR (1961) Safety testing of carcinogenic agents. *J National Cancer Institute*, 27, 455-470
- Marczynski B, Rozynek P, Elliehausen HJ, Korn M, Baur X. (1997) Detection of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, in white blood cells of workers occupationally exposed to styrene. *Archives of Toxicology*, 71, 496-500
- Douglas McGregor, Alan Boobis, Marco Binaglia, Phil Botham, Laurence Hoffstadt, Sue Hubbard, Thomas Petry, Anthony Riley, Dirk Schwartz, and Christa Hennes (2010). Guidance for the classification of carcinogens under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). *Critical Reviews in Toxicology* 40(3), 245-285.
- Meek ME, Renwick A, Ohanian E, Dourson M, Lake B, Naumann BD & Vu V (2002) Guidelines for application of chemical-specific adjustment factors in dose/concentration-response assessment. *Toxicology*, 181-182: 115-120
- Meek ME, Butcher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Critical Reviews in Toxicology*, 33 (6): 591-653.
- Mitchelmore CL & Chipman JK (1998) DNA strand breakage in aquatic organisms and the potential value of the comet assay in environmental monitoring *Mutation Research*, 399(2):135-47
- Moolgavkar S, Krewski D, Schwarz M. (1999) Mechanisms of carcinogenesis and biologically based models for estimation and prediction of risk. *IARC Scientific Publications*, 131,179-237
- Munro IC, Kennepohl E & Kroes R (1999) A procedure for the safety evaluation of flavouring substances. *Food Chemical Toxicology*, 37, 207-232
- Mure K, Hayatsu H, Takeuchi T, Takeshita T & Morimoto K. (1997) Heavy cigarette smokers show higher mutagenicity in urine. *Mutation Research*, 373, 107-11
- Nakijima M, Takeuchi T, Takeshita T & Morimoto K (1996) 8-Hydroxydeoxyguanine in human leukocyte DNA and daily health practice factors: Effects of individual alcohol sensitivity. *Environmental Health Perspectives*, 104, 1336-1338
- Nielsen F, Mikkelsen BB, Nielsen JB, Andersen HR, Grandjean P. (1997) Plasma malondialdehyde as biomarker for oxidative stress: reference interval and effects of life-style factors. *Clinical Chemistry*, 43, 1209-14
- Nordic Council of Ministers. Potency Ranking of Carcinogenic Substances. Report from a Nordic Working Party. Miljørapport 1985:4E. The State Pollution Control Authority, Oslo, 1986.
- OECD (1998) OECD principles on good laboratory practice (as revised in 1997). Paris, Organisation for Economic Co-operation and Development, Environmental Directorate, Chemicals Group and Management Committee

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

(OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring No. 1 –ENV/MC/CHEM (98)17)

Osterman-Golkar S, Peltonen K, Anttinen-Klemetti T, Landin HH, Zorcec V, Sorsa M. (1996) Haemoglobin adducts as biomarkers of occupational exposure to 1,3-butadiene. *Mutagenesis*, 11, 145-9

Paulsson B, Granath F, Grawé J, Ehrenberg L, Törnqvist M (2001) The multiplicative model for cancer risk assessment: applicability to acrylamide. *Carcinogenesis*, 22, 817-819

Peto R, Pike MC, Bernstein L, Gold LS & Ames BN (1984) The TD50: a proposed general convention for the numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. *Environmental Health Perspectives*, 58, 1-8

Phillips DH. (1997) Detection of DNA modifications by the 32P-postlabelling assay. *Mutation Research*, 378, 1-12

Portier CJ, Hedges JC & Hoel DG (1984) Age-specific models and tumour onset for historical control animals in the National Toxicology Programs carcinogenicity experiments. *Cancer Research*, 46,4372-4378

Repace JL, Jinot J, Bayard S, Emmons K & Hammond SK. (1998) Air nicotine and saliva cotinine as indicators of workplace passive smoking exposure and risk. *Risk Analysis*, 18, 71-83

Richard AM (1998) Structure-based methods for predicting mutagenicity and carcinogenicity: are we there yet? *Mutation Research*, 400, 493-507

[Dutch National Institute of Public Health and the Environment \(2001\), Re-evaluation of human-toxicological maximum permissible risks levels RIVM report 711701 025.](#)

Formatted: Font: Calibri, 9 pt

Formatted: Font: Calibri, 9 pt

Formatted: Font: Calibri, 9 pt

Formatted: Font: Calibri, 9 pt

Schut HAJ & Shiverick KT (1992) DNA adducts in humans as dosimeters if exposure to environmental, occupational or dietary genotoxins. *FASEB Journal*, 6, 2942-2951

Schoket B, Phillips DH, Poitier MC, Vincze I (1993). DNA adducts in peripheral blood lymphocytes from aluminium plant production workers determined by 32P-postlabelling and enzyme linked immunosorbent assay. *Environmental Health Perspectives*, 99, 307-309.

Shuker DE & Farmer PB (1992) Relevance of urinary DNA adducts as markers of carcinogen exposure. *Chemical Research in Toxicology*, 5, 450-60

Shuker DE, Prevost V, Friesen MD, Bartsch H. (1993) Noninvasive methods for measuring DNA alkylation in experimental animals and humans. *Environmental Health Perspectives*, 101 Supplement 3, 151-3

Shuker DE (1999) DNA adducts in mammalian cells as indicators of exposure to carcinogens IARC Scientific Publications 1999; 146, 287-308.

Shuker D (2002) The enemy at the gates? DNA adducts as biomarkers of exposure to exogenous and endogenous genotoxic agents. *Toxicology Letters*, 134, 51-56.

Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice JM & Younes M (2001) IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regulatory Toxicology Pharmacology*, 34, 146-52

UK Department of Health (2000) Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment: Guidance on a strategy for testing of chemicals for mutagenicity. (<http://www.doh.gov.uk/com/comivm.htm>)

US EPA Guidelines for carcinogen risk assessment. EPA/630/P-03/001F. http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF

US FDA (1995) Food additives: Threshold of regulation for substances used in food-contact articles (final rule). *Federal Register* 60(136), 36582-36596

US NAS (National Academy of Science) (1983) National Research Council, Committee on the Institutional Means for Assessment of Risks to Public Health: Risk assessment in the Federal Government: Managing the process. Washington, DC, National Academy Press, pp1-50

Van den Berg M, Birnbaum L, Bosveld A, Brunström B, Cook P, Feeley M, Giesy J, Hanberg A, Hasegawa R, Kennedy S, Kubiak T, Larsen J, van Leeuwen F, Liem A, Nolt C, Peterson R, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Wærn F & Zacharewski T (1998) Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife. *Environmental Health Perspectives*, 106, 12, 775-792.

Van den Brandt P., Voorrips L., Hertz-Picciotto I., Boeing H., Speijers G., Guittard C., Kleiner J., Knowles M., Wolk A. & Goldbohm A. (2002) The contribution of epidemiology. *Food and Chemical Toxicology*, 40:387-424

Verna L, Whysner J & Williams GM (1996) 2-Acetylaminofluorene mechanistic data and risk assessment: DNA reactivity, enhanced cell proliferation and tumour initiation. *Pharmacology and Therapeutics*, 71:83-105.

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

Vesper HW, Caudill SP, Osterloh JD, Mayets T, Scott D, Meyers GL (2010). Exposure of the US population to acrylamine in the National Health and Nutrition Examination Survey 2003-4. *Environ Health Perspect* 118(2), 278-283.

Weibull (1951) Statistical distribution function of wide applicability. *J Applied Mechanisms*,18, 293-302

Weisel C, Yu R, Roy A and Georgopoulos P. (1996). Biomarkers of environmental benzene exposure. *Environmental Health Perspectives*, 104, 1141-1146.

WHO (1991) World Health Organisation. Evaluation of certain food additives and contaminants. Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 806. WHO, Geneva

[WHO \(2009\) International Programme on Chemical Safety. Environmental Health Criteria Monograph 240. Principles and methods for the risk assessment of chemicals in food. WHO, Geneva](#)

Whysner J, Clifford-Conaway C, Verna L & Williams GM (1996) Vinyl Chloride mechanistic data and risk assessment: DNA reactivity and cross-species quantitative risk extrapolation. *Pharmacology and Therapeutics*, 71:7-28

Williams GM (2001) Mechanism of chemical carcinogenesis and application to human cancer risk assessment. *Toxicology*, 166:3-10

Williams GM, Iatropoulos MJ & Weisburger JH (1996) Chemical carcinogenic mechanisms of action: implications for testing methodology. *Experimental and Toxicological Pathology*, 48, 101-111

Wu Y, Chen J, Ohshima H, Pignatelli B, Boreham J, Li J, Campbell TC, Peto R & Bartsch H (1993) Geographical association between urinary excretion of N-nitroso compounds and oesophageal cancer mortality in China. *International Journal of Cancer*, 54:713-719

Yeowell-O'Connell K, Jin Z & Rappaport SM (1996) Determination of albumin and hemoglobin adducts in workers exposed to styrene and styrene oxide. *Cancer Epidemiology Biomarkers Prevention*, 5 (3),205-15.

Zeise L, Cardis E, Hemminki K & Schwarz M (1999) Quantitative Estimation and Prediction of Cancer Risk: Review of Existing Activities. In Moolgavkar S, Krewski D, Zeise L, Cardis E, & Möller H (Eds) *Quantitative Estimation and Prediction of Human Cancer Risks*. IARC Scientific Publications No. 131. International Agency for Research on Cancer, Lyon. 11-59

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

Glossary

Acceptable daily intake: estimate of the amount of a substance in food or drink, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Formatted: Font: Bold

Benchmark dose (BMD): a point of departure (qv) in a carcinogenicity bioassay at which there is a specified increase in cancer incidence above the level in the control group.

Formatted: Font: Bold

BMD₁₀: lower 95% confidence limit of the benchmark dose for a 10% response.

Formatted: Subscript

Mechanism of action: an understanding of the molecular basis for an effect and its detailed description, so causation can be established in molecular terms.

Formatted: Font: Calibri, 12 pt

Formatted: Font: Calibri, 12 pt

Formatted: Font: 12 pt, Bold

Minimal risk level: defined in this document as an estimate of daily human exposure to a chemical, identified by expert judgement, that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime).

Formatted: Font: 12 pt

Formatted: Font: Bold

Formatted: Font: 12 pt

Mode of action: a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. It describes key cytological and biochemical events, i.e. those that are both measurable and necessary to the observed carcinogenicity, in a logical framework. It contrasts with mechanism of action (qv).

Formatted: Font: Bold

Formatted: Font: 12 pt

Reference dose: an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Formatted: Font: 12 pt

Formatted: Font: Bold

Formatted: Font: 12 pt

T25: the dose eliciting a 25% increase in the incidence of a specific tumour above the background level.

Formatted: Font: Bold

TD₅₀: the daily dose required to halve the probability of remaining without tumours at the end of a standard life span.

Formatted: Font: Bold

Formatted: Font: Bold, Subscript

Tolerable daily intake: estimate of the amount of a contaminant, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk

Formatted: Font: Bold

Health based guidance value: an estimate of the amount of a chemical to which a person can be exposed in a specified period of time (e.g. daily) over a lifetime without appreciable risk to health.

Formatted: Font: Bold

Formatted: Font: 12 pt

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

This is a draft statement for discussion. It should not be quoted, cited or reproduced.

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 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).