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**CC/2019/02**

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

# First draft updated Guidance Statement (G01): A Strategy for Risk Assessment of Chemical Carcinogens

## Introduction

1. The COC has periodically published guidelines for the evaluation of chemicals for carcinogenicity. The first guidance was first published in 1982 and has undergone several updates since then to reflect advances in development and validation of methods for assessing risk of chemical carcinogens.

2. A substantial revision of guidance was undertaken during the period 2010 to 2014 at which time the decision was taken to move away from periodic publication of guidance in a single document. In its place, key topics were separated into separate guidance statements, with an overarching summary statement (G01) reflecting the Committees overall strategy. This allowed for updates to be made as frequently as needed, as driven by advances in the science.

3. Since 2014, a number of the guidance statements have undergone such revisions and new guidance statements introduced. This paper (CC/2019/02) incorporates those changes into G01 to provide an draft revised overarching summary statement for discussion.

## Questions for the Committee

Members are asked to:

i. Comment on the structure and contents of the draft revised document.

ii. Consider whether the ‘Future Developments’ section is appropriate to include in the summary document and/or requires updating.

**NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat**
**March 2019**

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Committee on CARCINOGENICITY

**COC Guidance Statement G01 v5.0a**

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

# A Strategy for the Risk Assessment of Chemical Carcinogens

## Preface

1. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) is an independent advisory committee which reports to the Chief Medical Officer 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 code of practice which includes the declaration of any personal or business interests which may, or may be perceived (by a reasonable member of the public) to, influence their judgement. The role of the COC is advisory and it has no regulatory status, although advice is~~may be~~ provided to Government Departments~~departments~~ and Agencies~~agencies~~ 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 at the request of Government departments and agencies and the devolved administrations on all aspects of the carcinogenicity of chemicals. This includes topics such as testing strategies, research and the risk assessment of carcinogenic chemicals. The ~~At present, the~~ Secretariat is provided jointly by Public~~the~~ Health England~~Protection Agency~~ on behalf of the Department of Health and Social Care, and the Food Standards Agency. ~~The Health Protection Agency leads on the Secretariat.~~

~~3.~~ The COC has periodically published guidelines for the evaluation of chemicals for carcinogenicity. The first guidelines were published in 1982 and~~. These provided guidance on best practice for carcinogenicity testing, mainly in the design, conduct and interpretation of long-term animal bioassays. It was recognised that the guidelines needed to be~~ periodically reviewed and updated to reflect advances in development and validation of methods;~~, and~~ revised guidelines were published in 1991 (COC, 1991) and~~). These described the approaches that may be used in assessing potential human carcinogens for regulatory purposes. They included sections on the design and interpretation of short-term tests for carcinogenicity, long-term bioassays for carcinogenicity, and epidemiology. Overall, the 1991 guidelines presented an overview of all aspects of carcinogen identification, and some consideration of quantitative risk assessment.~~

~~4.~~3. ~~Subsequently, the COC reviewed a number of new developments including mathematical modelling, and the use of potency indices in risk assessment, setting minimal~~

~~risk levels, and a harmonised approach to evaluate the mode of action (MOA) of carcinogens. Therefore, in~~ 2004~~, it updated its guidance on the risk assessment of carcinogens~~ (COC, 2004). ~~The Committee also 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 (ICH,2012).~~

~~5.~~4. A substantial~~The most recent~~ revision of the guidance was undertaken during the period~~began in~~ 2010 to~~and is expected to be completed by~~ 2014.~~. Thereafter, individual guidance statements will be updated 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 of such a wide range of information, the decision was taken~~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 were~~will be~~ separated into distinct but interrelated guidance statements, with this overarching summary statement to draw together the Committee's recommendations and~~. The Committee intends that the guidance outlined here should~~ provide a strategy for the risk assessment of chemical carcinogens.

~~6.~~5. Since 2014, the guidance statements have undergone revision and new ones introduced. This 5th version of the overarching guidance statement incorporates those changes up to 2019.

**Introduction**

~~7.~~6. The series of guidance statements of which this is the overarching summary 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.

~~8.~~7. The Committee recommends a four-stage approach to the risk assessment of chemical carcinogens (Figure 1)~~ which is~~ based on the widely adopted paradigm proposed by the US National Academy of Sciences (US NAS, 1983). Identification of a carcinogenic hazard has predominantly been~~is~~ based upon a review of the animal carcinogenicity data and any knowledge of effects on human health from case reports and epidemiological studies. Other~~, although other~~ information, e.g. *in vitro*~~ (*in vitro*~~ or *in silico*~~*in silico*~~ data, is increasingly being used to~~) may~~ give an indication of carcinogenic potential. These data should be assessed together with data on

genotoxicity and any other toxicity that may be relevant to understanding the MOA by which the substance causes cancer. ~~The characterisation of the hazard to humans involves determination of the dose-response relationship, and can also include factors such as interspecies variation in susceptibility, MOA and mechanism of action. Having understood the dose response, it may be possible to define a level of effect to use as a point of departure in risk assessment.~~

~~9.~~8. The characterisation of the hazard to humans involves determination of the dose-response relationship and can also include factors such as interspecies variation in susceptibility, MOA and mechanism of action. Having understood the dose response, it may be possible to define a level of effect to use as a point of departure (POD) in risk assessment.

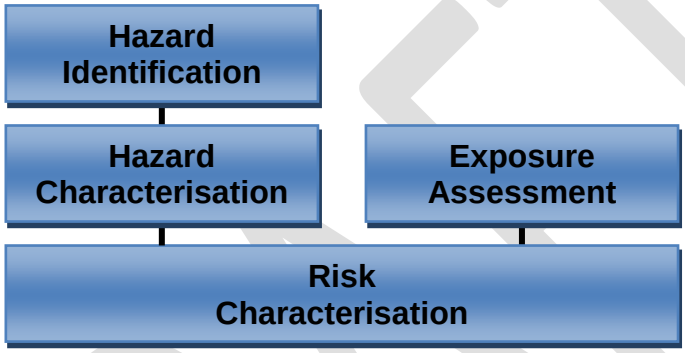


*Figure 1: Four stage approach to the risk assessment of chemical carcinogens, after the US National Academy of Sciences, 1983.*

~~10.~~9. To~~In order to~~ assess the risk posed by a chemical carcinogen, it is necessary to estimate (or model) levels of potential exposure, including as appropriate via~~. If necessary,~~ multiple routes of exposure ~~should be considered~~ (e.g. dietary, inhalational, drinking water, dust ingestion, dermal absorption). Issues and concerns relating to hazard identification, hazard characterisation and exposure evaluation have been reviewed extensively elsewhere (US EPA, 2005; IPCS, 2009; IARC, 2010; McGregor *et al*, 2010). Risk characterisation draws together the evidence gathered during hazard identification and characterisation (dose response, POD~~point of departure~~ etc.) and compares this to information on measured or potential levels of exposure.

~~11.~~10. Risk characterisation may identify the need for risk management. Within Government, risk management is the responsibility of regulators and policy makers. 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 provision of risk management advice. However, the COC may use methods which may assist risk managers in making decisions, such as the Margin of Exposure (MOE)~~(MoE)~~ approach ~~and the derivation of minimal risk levels~~ (see below).

**Risk assessment**

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Problem formulation

~~12.~~11. Problem formulation is an essential initial step in any risk assessment. It is important to know why advice is being sought 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.

Hazard identification

~~13.~~12. Typically, a substance is referred to the COC because there is some evidence of carcinogenicity in its toxicological profile. To ~~In order to~~ identify thoroughly the hazards posed by the substance, it is recommended that all the available human and animal carcinogenicity data are gathered and reviewed, ideally following established guidelines for systematic review and reporting (Moher D *et al.*, 2009). This review should also consider available evidence of genotoxicity and any other toxicity that may be relevant to understanding the mechanism or MOA by which the substance may cause cancer.

~~14.~~13. Well~~As stated in the 1991 and 2004 guidelines, well~~ conducted epidemiological studies are the most valuable source from which to identify human carcinogenic hazard. Detailed guidance on synthesising~~the interpretation of human~~ epidemiological evidence ~~studies and case reports~~ is provided in Guidance Statement G02 (Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and Committee on Carcinogenicity).~~G2 ["Interpretation of evidence of carcinogenicity in humans: epidemiology and case reports"].~~

~~15.~~14. 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 may be~~are~~ lacking, and potential human carcinogens may be identified from animal studies. ~~As with epidemiology studies, the validity of design and the interpretation of the data need to be considered carefully.~~ Guidance Statement G03 (Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies)~~G3~~ discusses the conduct and interpretation of animal carcinogenicity studies.

15. Guidance Statement G07 (Alternatives to the 2-year bioassay) provides an overview of approaches that have been proposed as alternatives to the 2-year bioassay and should be considered in conjunction with G03. It is written in four parts, covering: *in vivo* assays; cell transformation assays; developing methodologies and strategies; and alternative testing paradigms.

16. When assessing the risks from a chemical carcinogen, it is important to consider the mechanism(s) by which the chemical causes neoplasia; in particular, whether a genotoxic MOA is involved i.e. whether DNA-reactivity is a key step in the

carcinogenic process. ~~The results from short-term tests for genotoxicity will give an indication of the mutagenic hazard and, thus, the potential to cause cancer.~~

~~17.~~ 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, 2011). ~~In its guidance, the COM proposes a strategy for evaluating the available data on the 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 genotoxic hazard.~~

17. In some instances, it may be possible to use target organ mutagenicity data, DNA adducts, mutational spectra and other biomarkers (Guidance Statement G04 The use of biomarkers in carcinogenic risk assessment)~~G4)~~ to help ~~to~~ assess whether a carcinogen has a genotoxic MOA.

18. A substance should be considered to be:

- a *genotoxic carcinogen* only when there is evidence that it causes cancer as a result of its mutagenic activity;
- *genotoxic and carcinogenic* where there is adequate evidence of genotoxic and carcinogenic activity but insufficient evidence that the genotoxic activity is responsible for the observed carcinogenicity;
- *genotoxic and potentially carcinogenic* when there is only evidence of genotoxicity, but no evidence of human or animal carcinogenicity.

19. In the absence of information to the contrary, it is prudent to assume that chemicals which are genotoxic and carcinogenic have the potential to alter DNA at any level of exposure which~~and that such change~~ could lead to tumour development. All levels ~~Therefore, any level~~ of exposure are therefore~~is~~ considered to carry some degree of carcinogenic risk.

20. Non-genotoxic carcinogens are those chemicals for which there is sufficient evidence of carcinogenicity from epidemiological or animal studies, and good evidence of an absence of genotoxic activity (on the basis of the COM Guidance 2011).~~on the assessment of genotoxic hazard).~~ Some information about MOA is necessary for an adequate consideration of such carcinogens.

~~20.~~21. In 2001, the International Programme on Chemical Safety (IPCS) proposed a structured approach for the assessment of the overall weight of evidence for a postulated MOA (Sonich-Mullin *et al.*, 2001). This was~~) and,~~ subsequently extended by~~,~~ the Risk Sciences Institute of the International Life Sciences Institute (ILSI/RSI) to produce~~proposed~~ a human relevance framework (HRF) ~~which extends the IPCS MOA approach by incorporating a systematic evaluation and comparison of animal and relevant human data~~ (Cohen *et al.,* 2003, 2004; Meek *et al.,* 2003). In 2006~~Recently~~, IPCS ~~has~~

developed a HRF based on the IPCS MOA framework and the ILSI/RSI HRF (Boobis *et al.*, 2006) which ~~2006). The utility of this framework was demonstrated when it~~ was consolidated and updated~~used to show that there is clear evidence of a MOA involving cytotoxicity and cell proliferation for formaldehyde-induced nasal tumours~~ in 2013~~rats and mice and that this MOA is considered relevant~~ to reflect acquired experience~~humans, despite limitations~~ in its use and incorporate emerging areas in toxicity testing and non-testing methods (Meek et al., 2013~~the human data (McGregor *et al.*, 2006~~).

~~21.~~22. ~~These frameworks are of value in assessing carcinogenic risk.~~ The HRF provides a systematic approach to evaluate~~for the evaluation of~~ whether the key events in the MOA of carcinogenic responses in experimental animals would be plausible in humans. It highlights~~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, e.g.~~such as~~ α2u-globulin-associated male rat kidney tumours~~, and mammary gland tumours caused by inhibition of the luteinising hormone surge in Sprague-Dawley rats~~ (Cohen *et al.*, 2004).

Hazard Characterisation

~~22.~~23. Hazard characterisation involves a qualitative description of the nature of the hazard and a quantitative description of the change in effect caused by differing doses of a chemical substance after a certain exposure time i.e. the dose-response relationship. Important factors that can affect this relationship~~chemical substance after a certain exposure time i.e. the dose-response relationship. The purpose of analysing the dose-response relationship is to investigate the magnitude of response (in terms of severity or incidence) within the dose range used in an animal study or within the range of exposures experienced in a human study. This helps to estimate the response and, ultimately, the risk from exposure to the concentrations of the chemical in the environment, food etc. These are usually much lower than those used in animal studies and often than those to which individuals have been exposed in human studies. 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 considered further~~ are: the absorption, distribution, metabolism and excretion (ADME) of the chemical, its MOA, and the variability in susceptibility between species and among humans. How~~In particular, how~~ the dose-response relationship is used in the final assessment of risk will depend on whether~~or not~~ the carcinogenic response occurs as the result of genotoxic activity (discussed below under Risk Characterisation).

~~23.~~24. In theory, epidemiological studies might provide the most appropriate data source for the quantitation of the relationship between exposure to a chemical and its effect. However, the estimation of exposure in epidemiological studies is usually too limited for this. The relevance and applicability of~~Although~~ dose-response relationship derived~~relationships may be evident~~ in animal studies~~, the relevance and applicability~~ to humans~~the human dose-response~~ should be assessed on a case-by-

case basis, because of the 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 the, usually lower, levels of human exposure.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 carcinogens.

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

25. Various methods for deriving a POD*point of departure* are discussed in Guidance Statement G05 (Defining a point of departure and potency estimates in carcinogenic dose response).

*G5 ["Points of departure and potency estimates"].*

*Potency estimates*

24.26. 23. There are a number of methods for the characterisation of hazard from genotoxic carcinogens. These rank chemicals 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 (PODpoint 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.

27. PODs24. Points of departure such as the no observed adverse effect level (NOAEL), the dose resulting in 25% tumour response (T25), the dose resulting in 50% tumour response ($TD_{50}$)T25, $TD_{50}$ and the lower 95% confidence limit of the BMD for a 10% response over control levels (BMDL) have been used to estimate the relative potency of genotoxic carcinogens with the benchmark dose (BMD) methodology recommended by the COC. Some of these PODs can also be used as a basis for deriving a health-based guidance value (HBGV) for non-genotoxic carcinogens.

*Potency ranking*

25.28. widely favoured. The Threshold of Toxicological Concern (TTC) approach can also help to identify priorities for carcinogenicity evaluation, particularly for chemicals not subject to regulatory approval schemes. These methods are discussed further in Guidance Statement G05.Guidance Statement G5.

26.29. Relative potency estimates could have some pragmatic use in carcinogenic risk assessment as an aid in prioritising genotoxic carcinogenic substances, 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.~~

Exposure Assessment

30. The objective of exposure assessment is to estimate probable human exposure by determining source, magnitude, frequency 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 TTC (see above)~~Threshold of Toxicological Concern~~ and the MOE~~Margin of Exposure~~ (see below). A number of methods are used to estimate human exposure to a chemical from food or the environment,~~. To some extent, the appropriate method and model to use will be~~ dictated to a certain extent by the policy question, which the assessment will inform (see paragraph 11). For example, the intake of chemicals from food can be estimated from dietary surveys, food diaries, questionnaires, and the analysis of foods for the chemical of concern (IPCS, 2000; Food Standards Agency, 2019).~~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).

31. Consideration of the pattern of likely exposure is important. Often exposures are intermittent or occur for a specified period of time. In contrast, animal toxicity studies are often conducted with continuous daily dosing. The COC guidance on less than lifetime (LTL) exposure, Guidance Statement G09 (COC set of principles for consideration of risk due to less than lifetime exposure) provides a set of principles to guide assessing such instances.

~~27.~~ 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.

~~28.~~32. ~~Measurements of exposure may be subject to error.~~ A major source of error is the assumption that is made about levels below the limit of detection (LOD). A chemical substance could be assumed to be present at the LOD, or at zero, or at some value in between.~~inbetween.~~ This can have a profound effect on the estimates of exposure. Other sources of error may be an inaccurate measurement of the level of the chemical~~ due to instrument error~~ or, in surveys, an inaccurate response to a question or the inaccurate recording of an accurate response. These errors may be either systematic, which will introduce bias into the results, or random. Measurement errors introduce inaccuracy into the exposure data and, therefore, when conducting assessments, it is important to assess the quality of the measurements and to use statistical techniques in the analysis of the data that take account of possible measurement errors (Coggon *et al.*, 1997; IPCS, 2000).

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*Biomarkers of exposure*

~~29.~~ Biomarkers of exposure can give an indication of whether exposure has occurred and, in some cases, the level of 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, and other biological samples. Alternatively, specific reaction products with macromolecules, such as DNA or protein adducts (Schut & Shiverick, 1992; Farmer, 1999; Farmer, 2004), 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).~~

~~30.~~ Biomarkers can provide valuable information for use in the risk assessment process when appropriately characterised and validated. 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 G04.~~G4. It is essential that a biomarker is appropriately characterised and validated before any conclusions are drawn from its use. This should include:~~

- ~~adequate evidence to support the relationship with exposure,~~
- ~~an evaluation of the sensitivity and specificity[1] of the biomarker (limit of detection, precision and accuracy),~~
- ~~ascertaining the half-life of the biomarker,~~
- ~~investigation of intra- and inter-individual variation in a non-exposed population,~~
- ~~assessment of the effect of confounding exposures,~~
- ~~a clear relationship between dose and biomarker level,~~

~~31.~~33. ~~understanding of sample stability post-collection.~~

Risk Characterisation

34. 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 MOA 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 a carcinogen has an identifiable threshold of effect or not. In most instances, genotoxic and carcinogenic substances are considered as not having a threshold of effect, while non-genotoxic substances often have an identifiable threshold, however this is not always the case as outlined in G06 (Risk Characterisation Methods).

~~[1] Note that the terms 'sensitivity' and 'specificity' have different meanings here than they do in the context of mutagenicity testing.~~

~~32.~~35. Dose-response data from human studies can be extrapolated to estimate the exposure associated with a low excess lifetime cancer risk. Occupational epidemiology studies are most commonly used, and extrapolation is frequently linear.~~ Conventionally, non-threshold carcinogenicity is often referred to as genotoxic carcinogenicity and threshold carcinogenicity as non-genotoxic carcinogenicity.~~

*Compounds with no identifiable threshold of effect (Non-threshold Carcinogenicity)*

~~33.~~36. The risk assessment of chemical carcinogens is dependent on the mechanism of carcinogenicity and the relationship between dose and tumour response. From what is known about the MOA~~mechanism of action~~ of genotoxic carcinogens, in the absence of mechanistic data to suggest a threshold for carcinogenicity, it is currently assumed that there is none. In reality, there are many endogenous DNA repair mechanisms and it may be possible for a low level of promutagenic DNA damage to be tolerated and repaired. Therefore, if there is good reason to consider that a threshold MOA is appropriate, in principle it may be possible to identify a threshold. However, the unambiguous experimental demonstration of a biologically meaningful threshold for mutagenicity requires extensive dose-response and MOA data and so, in most cases, the assumption of no threshold is used in the risk assessment of a genotoxic carcinogen. The topic of thresholds for *in vivo* mutagens is discussed further in COM Guidance Statement G05~~G5~~.

~~32. Estimation of risk from a genotoxic carcinogen at environmental levels of exposure would generally require extrapolation of the dose response obtained from epidemiology or experimental animal studies. However, the COC considers that it is not valid to extrapolate from the observed dose range in animal carcinogenicity studies through many orders of magnitude to give an estimate of excess lifetime risk at environmental levels of exposure, e.g. 1 case of cancer in a population of 1 million (1 in $10^6$), because of the uncertainties involved. This methodology generates a false sense of precision which cannot be justified.~~

~~33. Dose-response data from human studies can also be extrapolated to estimate the exposure associated with a low excess lifetime cancer risk. Occupational epidemiology studies are most commonly used and extrapolation is frequently linear, although specific models have been derived when there is evidence of deviation from linearity in the dose-response relationship. Estimation of risk from human studies requires extrapolation through a much lower range of exposures than if animal studies are used but there are still uncertainties with this approach. Guidance Statement G6 [“Risk characterisation methods”] discusses this further and presents a range of alternative approaches considered by the Committee for characterising the risk of genotoxic carcinogens.~~

37. The most precautionary approach to reduce the risk from such chemicals would be to prevent exposure completely. However, in many cases e.g. for environmental contaminants, this is not possible. Therefore, the widely accepted risk management approach is to ensure that levels are controlled so that exposure is as low as reasonably practicable (ALARP) which, in some cases, might mean preventing exposure.

38. The COC considers that the MOE approach can be a useful tool for risk communication and risk management prioritisation (Benford *et al*, 2010). In this approach, a POD is generated by modelling the dose-response data from an animal carcinogenicity study. The POD used is usually the $BMDL_{10}$. 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 magnitude of these MOEs.

~~34.~~39. However, under specific circumstances, e.g. very low exposures to genotoxic contaminants or impurities, a pragmatic approach is encouraged by identifying the minimal risk level~~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 POD~~point of departure~~, and the use of expert judgement to derive an appropriate uncertainty factor to apply to it. 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 applies, regardless of the level of concern indicated by the MOE~~should apply, whether~~ or ~~not a~~ minimal risk level. ~~is identified for a genotoxic carcinogenic contaminant or impurity.~~

~~35. The COC considers that the Margin of Exposure (MOE) approach can be a useful tool for risk communication and risk management prioritisation (Benford *et al*, 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 limit of the BMD for a 10% response over control levels ($BMDL_{10}$). 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 magnitude of these MOE.~~

*Compounds with a threshold of effect (Threshold Carcinogenicity~~carcinogenicity~~)*

~~36.~~40. ~~The risk assessment of chemical carcinogens is dependent on the mechanisms of carcinogenicity and the relationship between dose and tumour response.~~ For most non-genotoxic carcinogens, it is accepted that there is a threshold dose, below which no effect occurs. Many non-genotoxic 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). HRFs ~~Human relevance frameworks~~ (see paragraph 21) may enhance the clarity and transparency of the risk assessment.

~~37.~~41. Where there is adequate evidence for a plausible~~, non-genotoxic~~ MOA, which supports a threshold for carcinogenicity, an exposure level can be derived at or below which there is estimated to be no risk of carcinogenicity in humans. ~~Where the carcinogenicity data are obtained from animal studies, the MOA should be relevant to humans.~~ The derived exposure level should be based on a POD~~point of departure~~ for

carcinogenicity or, more likely, on a precursor event linked to tumour induction (see Guidance Statement G05).~~Guidance Statement G5).~~ 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 MOA. ~~The point of departure is divided by an appropriate uncertainty factor to take account of potential interspecies and intraspecies (interindividual) differences in susceptibility.~~

~~38.~~42. PODs are divided by an appropriate uncertainty factor to derive a HBGV. Examples of health-based guidance values include the Acceptable Daily Intake (ADI), used for food additives or pesticide residues in food, and the Tolerable Daily Intake (TDI), used by many agencies for environmental contaminants. The HBGV represents a single estimate of an exposure level for a human that is considered to be without appreciable risk. The uncertainty factor reflects the uncertainties involved in extrapolating findings in animals to humans (interspecies differences) and 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 in experimental animals. Other factors may also be included, on a case-by-case basis. The Committee on Toxicity (COT) Report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment provides a review of uncertainty factors in greater detail (COT, 2007). ~~COT, 2007).~~

~~39. The above approach may be used for non-genotoxic carcinogens provided that the underlying MOA is adequately understood. Carcinogenicity should then be considered as part of an assessment of the overall toxicological profile for a compound when deriving a health based guidance value. 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 exposure level for a human that is considered to be without appreciable risk, the so-called deterministic or non-stochastic approach. 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.~~

~~40.~~43. As discussed in paragraph 36, it may be possible to identify a threshold for a genotoxic carcinogen if there is good reason to consider that a threshold MOA is appropriate. In such a case, in principle, it would be possible to use an appropriate PoD~~the No Observed Adverse Effect Level (NOAEL)~~ for the genotoxic effect in the risk characterisation of the chemical.

**Assessment of Mixtures**

~~41.~~44. Humans are exposed to a variety of mixtures, either by simultaneous or sequential exposure to chemicals. Multiple genotoxic 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.

~~42.~~45. 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 G08 (Statement on the risk assessment of the effects of combined exposures to chemical carcinogens).~~Guidance Statement G8.~~

**Assessment of Nanomaterials**

46. Nanomaterials are increasingly present in the environment to which humans are exposed and are defined as having at least one dimension with a size of less than 100 nm. These materials may require a different risk assessment strategy and an initial joint statemen to advise on this from the three Committees, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the COC has been prepared (see G10: Joint statement on nanomaterial toxicology).

**Overall Summary**

~~43.~~47. 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 data will differ with circumstance. However, the guidance outlined here is intended to provide a strategy that could be adopted for the risk assessment of chemical carcinogens.

~~44.~~48. The COC recommends a four-stage evaluation procedure, outlined in Figure 1, with further detail provided in Figure 2. Initial identification of a carcinogenic hazard should be based on 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. Hazard characterisation 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 the mechanism (or at least mode) of action that gives rise to the observed carcinogenicity are considered. Exposure assessment should estimate probable human exposure. The final Risk Characterisation stage ~~(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.

49. Where there is clear evidence that the carcinogenic activity of a chemical is mediated exclusively by a non-genotoxic MOA 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 POD~~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.

~~45.~~50. If a putative carcinogen is found to be potentially genotoxic, the Committee recommends a non-threshold approach to risk assessment. It is recommended that the widely accepted approach of ALARP ~~(as low as reasonably practicable)~~ should always be considered~~adopted~~ by risk managers, where possible, for exposure recommendations. In addition, the MOE~~margin of exposure~~ approach 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, i.e. low exposures to contaminants or impurities, by the setting of a minimal risk level based on expert judgement of available data.~~

**Future Developments**

~~46.~~51. 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 alternative methods for identification of carcinogens which incorporate the principles of the replacement, refinement and reduction of animals in research (the 3Rs).
- Further research into validation and standardisation of high content techniques, such as genomics and proteomics, particularly the development of appropriate databases, methods of bioinformatic and statistical analysis of data and pattern recognition, and information on the normal range of variation.
- The development of toxicological methods to refine extrapolation between animals and humans, such as PBPK modelling.
- The contribution of epigenetic effects to the development of human cancer.

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- Improved methodology for accurate exposure assessment, including development and validation of biomarkers of exposure.
- Development of longitudinal studies to provide a resource for future research on carcinogen risk assessment.

**COC Guidance Statement G01 v5.0a - DRAFT**
**Month Year TBC**

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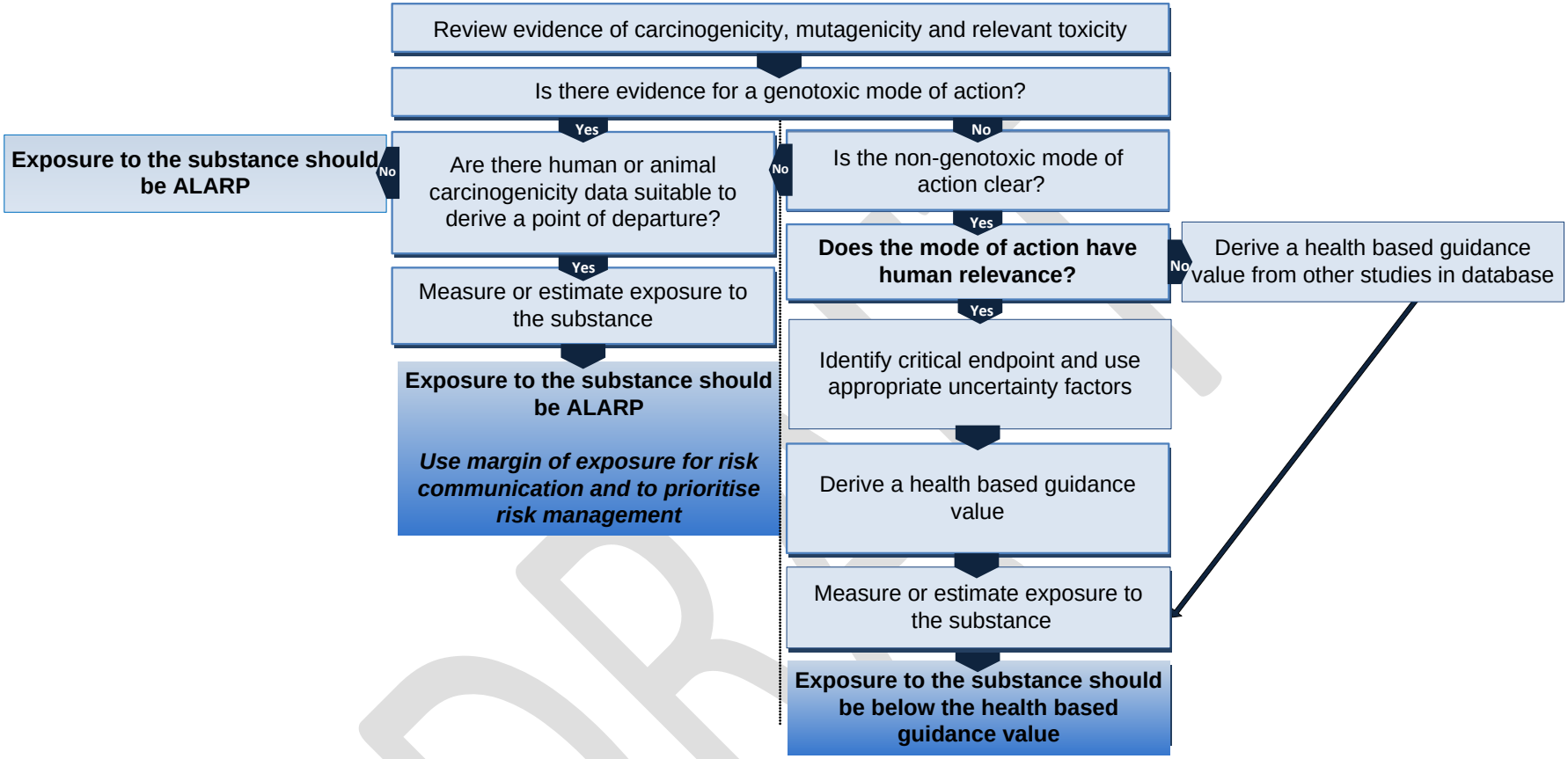


**Figure 2: An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity**

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## References

Ashby J, Kier L, Wilson AG, Green T, Lefevre PA, Tinwell H, Willis GA, Heydens WF and Clapp MJ (1996). Evaluation of the potential carcinogenicity and genetic toxicity to humans of the herbicide acetochlor. Human and Experimental Toxicology, 15:702-35.

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 and Wildemann T (2010). Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food Chem Toxicol, 48: S2-S24.

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D and Farland W (2006). IPCS Framework for analysing the relevance of a cancer MOA for humans. Critical Reviews in Toxicology, 36(10): 781-792.

COC - Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (1991). Guidelines for the evaluation of chemicals for carcinogenicity. Report on Health and Social Subjects no. 42. Department of Health, London.

COC - Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (2004). Guidance on a strategy for the risk assessment of chemical carcinogens. Department of Health, London, UK.

Coggon D, Rose R and Barker DJP. Epidemiology for the Uninitiated. 4th Edition, 1997. BMJ Publishing Group.

Cohen SM, Meek ME, Klaunig JE, Patton DE and 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.

COM – Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (2011). A strategy for testing of chemicals for genotoxicity. https://www.gov.uk/government/publications/a-strategy-for-testing-of-chemicals-for-genotoxicity. ~~http://iacom.org.uk/guidstate/index.htm.~~ Accessed 15th February 2019~~6 August 2012~~.

COT - Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (2007). Variability and uncertainty in toxicology of chemicals in food, consumer products and the environment. Food Standards Agency, London, UK. https://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut. Accessed 15th February 2019.

Doerge DR, Young JF, McDaniel LP, Twaddle NC and Churchwell MI (2005). Toxicokinetics of acrylamine and glycidamide in B6C3F1 mice. Tox Appl Pharmacol, 202(3): 258-267.

This is a preliminary paper for discussion. It does not represent the views of the Committee and must not be quoted, cited or reproduced.

Environment Agency (2009). Updated technical background to the CLEA model. Science Report SC050021/SR3. Environment Agency, Bristol.

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. IARC, Lyon, France.

Food Standards Agency. National diet and nutrition survey. https://www.gov.uk/government/collections/national-diet-and-nutrition-survey. Accessed 15th February 2019.

IARC – International Agency for Research on Cancer (2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 99: Some Aromatic Amines, Organic Dyes, and Related Exposures, Preamble. IARC, Lyons, France.

ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Safety Guidelines. http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html. Accessed 15 February 2019~~6 August 2012~~.

IPCS - International Programme on Chemical Safety (2000). Human exposure assessment. Environmental Health Criteria Monograph no. 214: WHO, Geneva.McGregor D, Bolt H, Cogliano V and Richter-Reichhelm H-B (2006). Formaldehyde and glutaraldehyde and nasal cytotoxicity: Case study within the context of the 2006 IPCS human framework for the analysis of a cancer. Critical Reviews in Toxicology, 36(10): 821-835.

McGregor D, Boobis A, Binaglia M, Botham P, Hoffstadt L, Hubbard S, Petry T, Riley A, Schwartz D and Hennes C (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, Butcher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J and Patton DE (2003). A framework for human relevance analysis of information on carcinogenic modes of action. Critical Reviews in Toxicology, 33 (6): 591-653.

Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. (2014), New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J. Appl. Toxicol., 34: 1-18.

Moher D, Liberati A, Tetzlaff J and Altman DG (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097vv

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This is a preliminary paper for discussion. It does not represent the views of the Committee and must not be quoted, cited or reproduced.

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

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

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 and Younes M (2001). IPCS conceptual framework for evaluating a MOA for chemical carcinogenesis. Regulatory Toxicology Pharmacology, 34: 146-52.

US EPA - Environmental Protection Agency. Guidelines for carcinogen risk assessment (2005). EPA/630/P-03/001F. US EPA, Washington DC. https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment. ~~http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF.~~ Accessed 15th February 2019~~6 August 2012~~.

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

Vesper HW, Caudill SP, Osterloh JD, Mayets T, Scott D and 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.

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

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## 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.

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

**BMDL**: the lower 95% confidence limit of the benchmark dose.

**$BMD_{10}$**: lower 95% confidence limit of the benchmark dose for a 10% response.

**Dose-response relationship:** the change in effect caused by differing doses of a chemical after a certain exposure time.

**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.

***In silico***: a term used to describe a computerised analysis of the structure of a chemical to assess its carcinogenic potential

***In vitro***: a term used to describe effects in biological material outside the living animal.

***In vivo***: a term used to describe effects in living animals (literally "in life").

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

**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).

**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).

**Neoplasia**: the abnormal proliferation of benign or malignant cells.

**No Observed Adverse Effect Level (NOAEL):** The highest administered dose at which no adverse effect has been observed.

**Point of departure:** 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.

**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.

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

**$TD_{50}$**: the daily dose required to halve the probability of remaining without tumours at the end of a standard life span.

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~~**Threshold of Toxicological Concern (TTC)**: a concept that refers to the establishment of a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to human health.~~

~~**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~~

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