Committee on CARCINOGENICITY

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

COC Guidance Statement G01 – version 5.0

A Strategy for the Risk Assessment of Chemical Carcinogenicity

https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc

COC Secretariat

c/o Public Health England

Centre for Radiation, Chemical and Environmental Hazards

Chilton, Didcot, Oxfordshire OX11 0RQ

Committee on CARCINOGENICITY

COC Guidance Statement G01 v5.0

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

A Strategy for the Risk Assessment of Chemical Carcinogenicity

Introduction

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 to 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 to (by a reasonable member of the public), influence their judgement. The role of the COC is advisory and it has no regulatory status, although advice is provided to Government Departments and 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 whether and how chemicals cause cancer - the *carcinogenicity* of chemicals. This includes topics such as testing strategies, research and the risk assessment of chemical carcinogenicity. The Secretariat is provided jointly by Public Health England on behalf of the Department of Health and Social Care, and the FSA.

3. At its most fundamental level, the COC provides advice which is intended to help prevent an individual from developing cancer following exposure to chemicals in the environment.

4. Currently there are many international bodies and regulations that cover the classification and regulation of chemicals and other substances and activities for carcinogenicity, including for example, the International Agency for Research on Cancer (IARC) (IARC, 2015), the United Nations Global Harmonised Scheme (UN, 2012) and the European Union Classification, Labelling and Packaging Regulations (ECHA, 2012).

5. These approaches, which have been in place for several decades, classify chemicals based on the identification of carcinogenic harm or hazard, and do not take account of the actual likelihood of the harm or hazard being realised – the potential carcinogenic risk. As a consequence, chemicals grouped in the same

category may actually differ by up to 100 million-fold in their likelihood to cause cancer, or potency (Doe et al., 2019). These classification schemes have been underpinned by the use of the 2-year rodent bioassay (a standardised method of controlled exposure of rats or mice to a chemical in the laboratory) the results of which, in most circumstances, determines the simple classification of a chemical as a carcinogen or non-carcinogen.

6. However, over the last 20 years our ways of thinking about the aetiology of cancer has evolved to identify the mechanisms behind the onset and progression of cancer (Jacobs et al., 2016). It is now recognised that the probability of a chemical to induce cancer in humans is proportional to its carcinogenic potency, the level and duration of exposure and the degree to which it is taken up, and eliminated from, the body (Cohen et al, 2019; Doe et al, 2019; Wolf et al, 2019). The extent of co-exposure to both carcinogens and non-carcinogens is also an important consideration, as some chemicals may only show carcinogenicity when present with other triggers (including life-style factors such as obesity). New integrated approaches to assessment that are under development, such as the 'Integrated Approach to Testing and Assessment (IATA) of non-genotoxic carcinogens (NGTxC)' (Jacobs et al., 2016), would allow such interactions to be investigated. It can be seen that our understanding of carcinogenicity as a more complex, possibly dynamic process has developed to an extent where earlier approaches to the assessment of carcinogenicity no longer appear to be wholly adequate. The COC is keenly monitoring future developments in this regard.

7. Although the compatibility of the current testing and classification schemes with the new knowledge has been questioned (Boobis, 2016) any new approaches to testing and classification are still in development. For the time being this means that the current approach to the classification and associated risk assessment of the carcinogenicity of chemicals is still required. As such, the existing approach is outlined in paragraphs 11 - 51 of this document.

8. The COC recognises that the carcinogenic risk assessment approach needs to focus on human carcinogenicity and not on the identification of carcinogens *per se*. The approach needs to address issues of scale, from exposure to a substance potentially causing a person to get cancer, to considering the cellular microenvironment in which a tumour develops. Some evidence to aid this can come from well-conducted epidemiology studies, whilst other aspects will require information on mechanisms that lead to changes in the cellular microenvironment, promoting proliferation and resulting in initiation and progression of tumourigenic development.

9. Further, COC considers that the use of animal models for identifying carcinogens, which may or may not indicate carcinogenic risk in humans, should be evaluated carefully. It is also recognised that cancer occurs as a consequence of genotoxicity and/or toxicity (Doe et al, 2019), so prevention of these outcomes would also prevent cancer occurring as a result of exposure to a substance. This may

require better use of existing and shorter-term animal studies, to identify toxicity, and animal or *in vitro* studies to investigate mechanisms of action.

10. The following COC guidance statements are available.

G01	A Strategy for the Risk Assessment of Chemical Carcinogenicity (this document)
G02	Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and Committee on Carcinogenicity
G03	Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies
G04	The use of biomarkers in carcinogenic risk assessment
G05	Defining a point of departure and potency estimates in carcinogenic dose response
G06	Cancer Risk Characterisation Methods
G07	Alternatives to the 2-year bioassay
G08	Statement on the risk assessment of the effects of combined exposure to multiple chemicals on carcinogenicity
G09	COC set of principles for consideration of risk due to less than lifetime exposure
G10	Joint statement on nanomaterial toxicology

Approach to Risk Assessment

11. Since 1982, the COC has periodically published guidelines for the evaluation of chemicals for carcinogenicity. The series of COC 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.

12. The Committee recommends a four-stage approach to the risk assessment of chemical carcinogens (Figure 1) based on the widely adopted paradigm proposed by the US National Academy of Sciences (US NAS, 1983). Further detail is provided in Figure 2.

13. Identification of a carcinogenic hazard has predominantly been based upon a review of the animal carcinogenicity data and any knowledge of effects on human

health from case reports and epidemiological studies. Other information, e.g. *in vitro* or *in silico* data, is increasingly being used to 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 mode of action (MOA) by which the substance causes cancer in humans or in experimental animals.

14. The characterisation of the hazard to humans involves determination of the dose-response relationship and can also include factors such as interspecies differences 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) as a starting point in risk assessment.

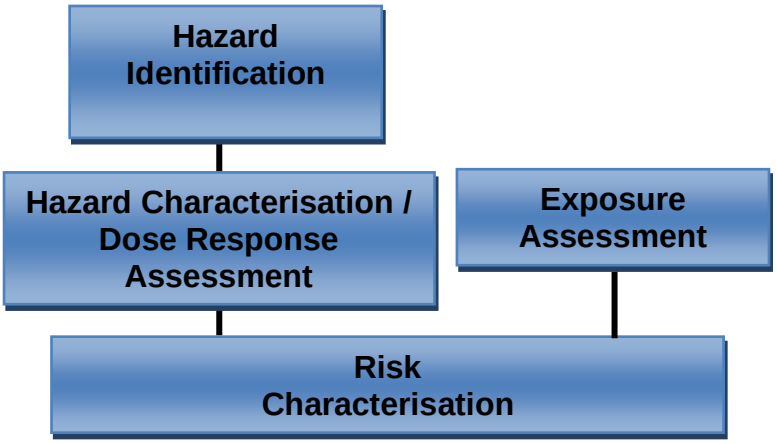

Figure 1: Four stage approach to the risk assessment, after the US National Academy of Sciences, 2005.

15. To assess the carcinogenic risk posed by a chemical, it is necessary to estimate (or model) levels of potential exposure, including, as appropriate, multiple routes of exposure (e.g. dietary, inhalational, 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).

16. Risk characterisation then draws together the evidence gathered during hazard identification and characterisation (dose response, POD etc.) and compares this to information on measured or potential levels of exposure.

17. 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) approach (see below).

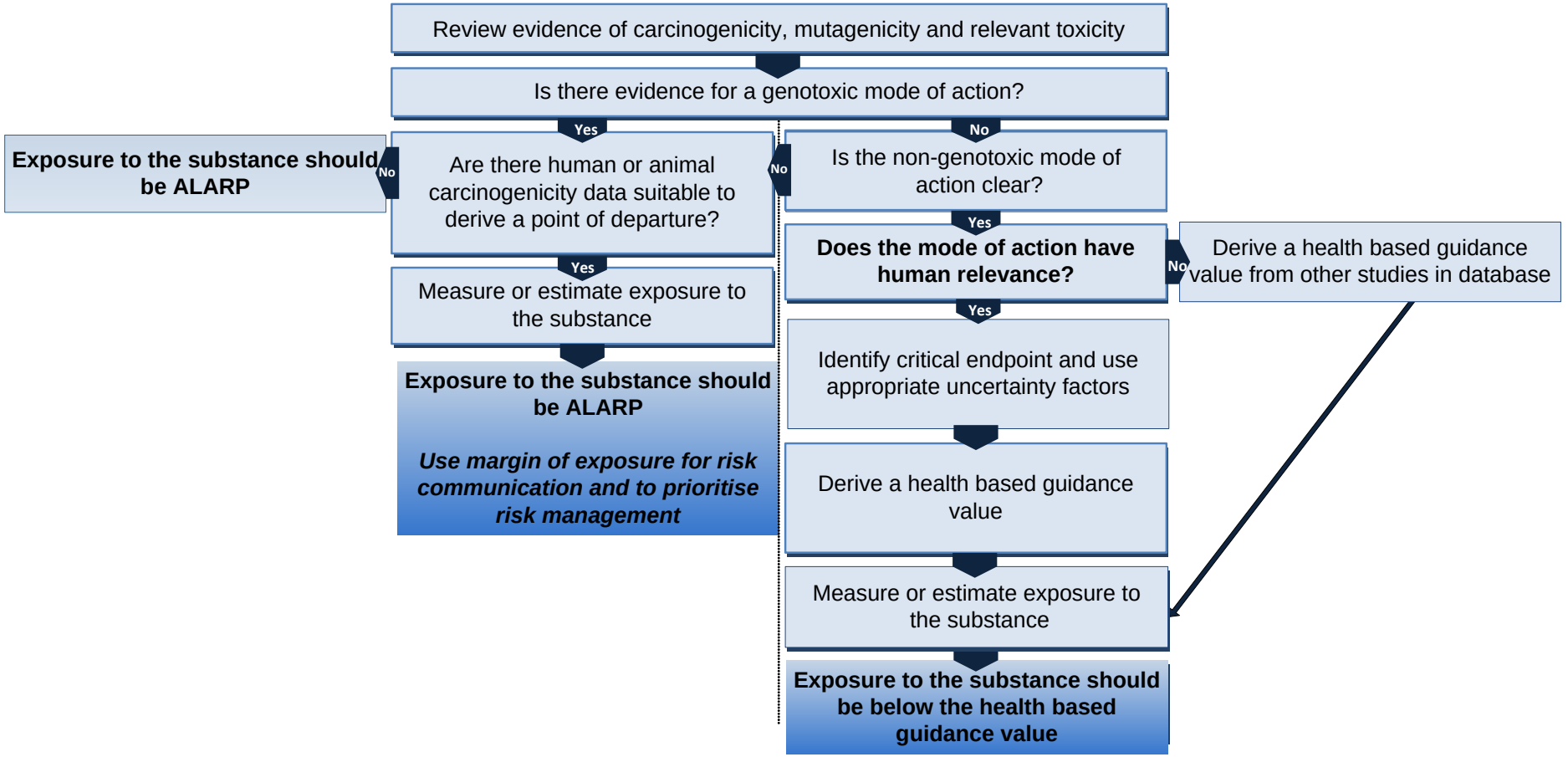

Figure 2: An overview framework for risk assessment of substances possessing evidence of carcinogenic or mutagenic activity

Problem formulation

18. 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

19. Typically, a substance is referred to the COC because there is some evidence of carcinogenicity in its toxicological profile. 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 (G02 (Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and Committee on Carcinogenicity); G03 (Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies). 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.

20. Well conducted epidemiological studies are the most valuable source of data from which to identify human carcinogenic hazard. Detailed guidance on synthesising epidemiological evidence is provided in Guidance Statement G02.

21. For some substances, appropriate epidemiological data may be lacking, and potential human carcinogens may be identified from animal studies. Guidance Statement G03 (discusses the conduct and interpretation of animal carcinogenicity studies.

22. 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.

23. 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 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) to help assess whether a carcinogen has a genotoxic MOA.

24. 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.

25. For carcinogens with genotoxic activity, in the absence of mechanistic data to suggest a threshold for genotoxicity, or for carcinogens where no MoA, or threshold for effect has been or can be identified, it is prudent to assume that no threshold for carcinogenicity exists (G06 – Cancer Risk Characterisation Methods).

Hazard Characterisation / Dose Response Assessment

26. 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 duration i.e. the dose-response relationship. Important factors that can affect this relationship are: the absorption, distribution, metabolism and excretion (ADME) of the chemical, its MOA, and the variability in susceptibility between species and among humans. How the dose-response relationship is used in the final assessment of risk will depend on whether the carcinogenic response occurs as the result of genotoxic activity (discussed below under Risk Characterisation).

27. When assessing the carcinogenic risks from a chemical, 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.

28. Genotoxic carcinogens are chemicals for which there is sufficient evidence of carcinogenicity from epidemiological or animal studies, and good evidence of genotoxic activity. Conversely, non-genotoxic carcinogens are those for which there is good evidence of an absence of genotoxic activity but sufficient evidence of carcinogenicity (on the basis of the COM Guidance 2011). Some information about MOA is necessary for an adequate consideration.

29. 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).

30. Epidemiological studies in general might provide the most appropriate data source for the quantitation of the relationship between exposure to a chemical and its effect in humans. However, the estimation of exposure in epidemiological studies may be too limited for this. The relevance and applicability of dose-response relationships derived in animal studies to humans 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.

31. The human relevance of the identified effects can be assessed based on the MOA and human relevance framework (HRF) which may enhance the clarity and transparency of the risk assessment. (Cohen *et al.,* 2003, 2004; Meek *et al.,* 2003; Boobis *et al.,* 2006; Meek et al., 2014).

Defining a Point of Departure in a Carcinogenic Dose-Response

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

Points of departure

33. POD such as the no observed adverse effect level (NOAEL), and the lower 95% confidence limit of the benchmark dose (BMD and BMDL) for a predefined response over control levels have been used for risk assessment purposes for both genotoxic and non-genotoxic carcinogens. Where suitable data are available, the BMD methodology is recommended by the COC to inform a risk assessment; where BMD cannot be used, the NOAEL approach is advised.

Potency ranking

34. The Threshold of Toxicological Concern (TTC) approach can help to identify the likely level of concern associated with exposure to a chemical with known structure and with unknown toxicity. Certain chemical classes and those subject to regulatory approvals requiring toxicity data are excluded from the TTC approach. The methodology aids the prioritisation of chemicals for carcinogenicity evaluation. These methods are discussed further in Guidance Statement G05.

35. Relative potency estimates could have some pragmatic use 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 overinterpreted.

Exposure Assessment

36. The objective of exposure assessment is to estimate probable human exposure by determining source, magnitude, frequency and duration of exposure to

the carcinogenic substance, as well as the routes by which it may enter the body. Exposure assessment is an increasingly important aspect of carcinogenic risk assessment, given the increasing use of approaches such as the TTC (see above) and the MOE (see below).

37. A number of methods are used to estimate human exposure to a chemical from food or the environment, dictated to a certain extent by the question which the assessment will inform (see paragraph 18). 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). 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 & Defra, 2014). For chemicals in water, the intake is estimated based on the concentration of the chemical in water and default assumptions of ingestion volumes and body weights (WHO, 2017).

38. Consideration of the pattern of likely exposure is important. Often exposures are intermittent or occur for a specified period of time, while 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.

39. Although exposure assessment in humans is crucial to the assessment of risk, it is frequently identified as an area of uncertainty in the overall risk assessment process, as it is often ranked and not quantitative. Where measurements are available, a major source of uncertainty can be introduced through the assumption that is made about exposure to 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. 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, which introduces inaccuracy into the exposure data. Therefore, when conducting assessments, it is important to assess the quality of the measurements and to use statistical techniques data that take account of possible measurement errors when analysing the data (Coggon *et al.*, 1997; IPCS, 2000).

40. Errors in exposure estimates may also be introduced through the method used to collect data. If surveys are used, error can occur due to inaccurate responses to questions or the inaccurate recording of an accurate response. Occupational records/histories are also frequently used to estimate exposures but again can be subject to error as actual levels are not being measured. These errors may be either differential (i.e. related to disease status), which can introduce bias into the results, in either direction. When errors are not differential (i.e. not related to disease status) any resulting bias has a tendency towards the null value, thus producing an underestimation of the true effect.

Biomarkers of exposure

41. Biomarkers of exposure 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. 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.

Risk Characterisation

42. Risk characterisation draws together evidence of the hazard identification and characterisation, 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 and depends on whether the substance 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.

43. 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, with linear extrapolation to environmentally relevant levels; environmental epidemiology studies can also be used if available. Confounding may be a concern for both types of study.

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

44. From what is known about the MOA of genotoxic carcinogens, in the absence of mechanistic data to suggest a threshold for carcinogenicity, it is currently assumed that there is no threshold. In reality, there are many endogenous DNA repair mechanisms and it may be possible for a low level of pro-mutagenic 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.

45. 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.

46. 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 usually the $BMDL_{10}$ is generated by modelling the dose-response data from an animal carcinogenicity study. 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.

47. 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 for these compounds to aid risk management decisions.

48. 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, the principle of keeping exposures ALARP applies, regardless of the level of concern indicated by the MOE or minimal risk level.

Compounds with a threshold of effect (Threshold Carcinogenicity)

49. For most non-genotoxic carcinogens, it is accepted that there is a threshold dose, below which no effect occurs. Where there is adequate evidence for a plausible MOA, which supports a threshold for carcinogenicity, an estimated exposure level can be derived at or below which there is no appreciable risk of carcinogenicity in humans. The derived exposure level should be based on a POD for carcinogenicity or, more likely, on a precursor event linked to tumour induction (see Guidance Statement G05). 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.

50. 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 an estimated dose in humans without appreciable risk over a lifetime. 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 (see G06).

51. As discussed in paragraph 44, 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 this approach of using uncertainty factors to derive a HBGV would be appropriate.

Assessment of combined exposures

52. Humans are exposed to a variety of chemicals, both simultaneously (e.g. in a single product, or at a total exposure at a point in time) and over time, which may affect tumour formation. Cancer is a multi-stage process and carcinogens can act, and interact, at many points within the process.

53. Some general principles which may be considered when assessing the carcinogenic risk posed by a combined exposure to substances, are discussed further in Guidance Statement G08 (Statement on the risk assessment of the effects of combined exposure to multiple chemicals on carcinogenicity).

Assessment of Nanomaterials

54. 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 statement 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

55. 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 carcinogenicity.

56. The COC recommends a four-stage evaluation procedure, outlined in Figures 1 and 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. 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 draws together evidence of the hazard and dose-response, and places it in the context of the measured or estimated level of human exposure.

57. 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 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.

58. If a putative carcinogen is found to be potentially genotoxic, the Committee recommends a non-threshold approach to risk assessment. It is recommended that ALARP should always be considered by risk managers. In addition, the MOE approach can be used to aid risk communication and prioritise risk management when there are adequate carcinogenicity and exposure data.

59. The Committee is keeping a watching brief on ongoing developments in knowledge of the carcinogenic process and appropriate strategies to assess chemicals for potential carcinogenicity.

Future Developments

60. The Committee believes the following to be key areas to aid future developments in risk assessment for carcinogenicity and would welcome developments to strengthen these:

- Clarification of the shape of the dose-response curve at very low doses and low estimated risks e.g. by assessing the minimum dose 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 and models for the assessment of carcinogenicity which incorporate the principles of the replacement, refinement and reduction of animals in research (the 3Rs). A greater use of *in silico* tools and incorporation of human cell lines to *in vitro* assays could provide valuable information before any appropriate *in vivo* testing is carried out.

- 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.
- Improved methodology for accurate exposure assessment, including development and validation of biomarkers of exposure and effect.
- Improved assessment of the potential effects of co-exposures and less-than-lifetime exposures on cancer development.
- Development of longitudinal studies to provide a resource for future research on the risk assessment of carcinogenicity.

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.

Boobis AR, Cohen SM, Dellarco VL, Doe JE, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC et al. (2016). Classification schemes for carcinogenicity based on hazard - identification have become outmoded and serve neither science nor society. Regulatory Toxicology and Pharmacology, 82: 158-166.

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.

Cohen SM, Boobis AR, Dellarco VL, Doe JE, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC (2019) Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regulatory Toxicology and Pharmacology 103, 100-105.

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. Accessed 15th February 2019.

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.

Defra (2014). SP1010 – Development of category 4 screening levels for assessment of land affected by contamination. http://randd.defra.gov.uk/Default.aspx?Module=More&Location=None&ProjectID=18341 Accessed 15th February 2019.

Doe JE, Boobis AR, Dellarco V, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC (2019) Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. Regulatory Toxicology and Pharmacology 103, 124-129.

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.

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.

Jacobs M, Colacci A, Louekari K, et al. (2016). International regulatory needs development of an IATA for non-genotoxic carcinogenic chemical substances. ALTEX, 33(4).

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.

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.

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. Accessed 15th February 2019.

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.

WHO (2017). Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=9A5A4FCD277C924C685CE36BAD8E4331?sequence=1 Accessed 15th February 2019.

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

Wolf DC, Cohen SM, Boobis AR, Dellarco VL, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Doe JE (2019) Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. Regulatory Toxicology and Pharmacology 103, 86-92.