This is a background paper for discussion.
It does not reflect the view of the Committee and must not be quoted, cited or reproduced

CC/2020/07

Committee on CARCINOGENICITY

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

Guidance Statement (G06) Cancer Risk Characterisation Methods – update 1.1

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

2. These updates included the separation of the overall guidance into individual documents during 2012 – 2014 to allow faster revisions to be made in the case of rapidly developing areas. This included a separate document addressing Cancer Risk Characterisation Methods (G06).

3. Guidance document G06 was last updated in 2018. The paper presented here proposes some additional amendments to the document for members to consider.

Questions for the Committee

4. Members are asked to:

   i. Comment on the suggested amendments in the draft updated document.

   ii. Highlight any new areas that are not currently included.

NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat
July 2020

This is a background paper for discussion.
It does not reflect the view of the Committee and must not be quoted, cited or reproduced

Committee on CARCINOGENICITY

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

COC Guidance Statement G06 –version 1.1 draft v 0.b

Cancer Risk Characterisation Methods

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

COC Secretariat
c/o Public Health England
Centre for Radiation, Chemical and Environmental Hazards
Chilton, Didcot, Oxfordshire OX11 0RQ

© Crown copyright 2018

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit OGL or email psi@nationalarchives.gsi.gov.uk. Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned. Any enquiries regarding this publication should be sent to COC@phe.gov.uk.

Introduction....4
Risk Characterisation approaches endorsed by the Committee....5
Estimation of cancer risk by extrapolation from human studies....5
Compounds with no identifiable threshold of effect (Non-threshold 5
carcinogenicity)....5
As Low As Reasonably Practicable 5
Margin of Exposure approach....6
Minimal Risk Levels....7
Compounds with a threshold of effect (Threshold carcinogenicity) 8
Uncertainty Factor Approach 8
Other approaches....10
Estimation of cancer risk by low dose extrapolation of animal data....10
Linear extrapolation to identify a Derived Minimal Effect Level (DMEL) 10
T25 Approach....10
Summary....12
References....14

Introduction

1. This guidance statement provides an overview of the approaches to characterising the risks associated with exposures to chemical carcinogens. It is part of a series of guidance statements by the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment and should be read in conjunction with these, and in particular ~~G01, G02 (not yet published),~~G01 (A strategy for the risk assessment of chemical carcinogens), G02 (Synthesising Epidemiology Evidence Subgroup (SEES) Report), ~~G03 and G05.~~G03 (Hazard identification and characterisation: conduct and interpretation of carcinogenicity studies) and G05 (Points of departure and potency estimates).

2. Risk characterisation is the fourth stage of the risk assessment paradigm and brings together the hazard identification and characterisation stages and the exposure assessment process. For carcinogenic effects, the risk characterisation approach used depends on the mechanisms of carcinogenicity and the relationship between dose and carcinogenic response. For most non-genotoxic carcinogens, it is accepted that there is a threshold dose, below which no effect is observed. In contrast, for compounds which are genotoxic and carcinogenic and for which there are no mechanistic data to suggest a threshold for genotoxicity, or for substances where no mode of action or threshold for effect has been identified, it is currently considered prudent to assume that no threshold for carcinogenicity exists. The processes of hazard identification and hazard characterisation (G03) are therefore key to determining the approach to be taken in risk characterisation.

Risk Characterisation approaches endorsed by the Committee

Estimation of cancer risk by extrapolation from human studies

3. The use of epidemiological studies for identification of carcinogenic hazard is valuable and it is important that data from human studies are used where feasible~~.~~ (G02). Well designed and appropriately powered human studies with quantitative exposure data are particularly helpful in providing a basis for estimating risk in the general population, and *where possible should be the starting point for risk characterisation.* If not available, animal data can be used though ~~these~~this must be interpreted with caution.

4. All the available human data should be reviewed and consideration given to how the studies can be used to estimate the risks in the exposure scenario under investigation (in the COC's case often in food, water or from the environment).

5. It is important to note that there is uncertainty in using human data, often due to poor exposure assessments and the need to adjust data for relevant confounders. However, using such data avoids the additional uncertainty associated with extrapolation from animals to humans. While animal studies have the advantage of defined exposure levels and a controlled study population, they are generally conducted using substantially higher levels of exposure than humans would encounter, and there are additional uncertainties associated with species extrapolation.

Estimation of cancer risk by extrapolation from animal studies

6. Risk characterisation of potential carcinogens is commonly based on animal studies especially a two-year bioassay in rodents. The use of these bioassays has been questioned (for example: Wolf et al., 2019; Doe et al., 2019; Cohen et al., 2019) in terms of their relevance to humans and from an ethical perspective. Therefore, it appears likely that these long-term studies may not be undertaken as frequently in the future and alternative strategies for the assessment of potential carcinogens are being developed (G07).

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

~~6.~~7. For carcinogens with genotoxic activity, in the absence of mechanistic data to suggest a threshold for genotoxicity, or carcinogens where no threshold for effect has been or can be identified, it is prudent to assume that no threshold for carcinogenicity exists.

As Low As Reasonably Practicable

8. For such carcinogens, the Committee recommends that risk managers adopt measures to ensure that levels are controlled so that exposure is as low as

reasonably practicable (the ALARP approach). However, in some cases to aid in risk management decisions, the ALARP approach may be supplemented by providing information on the margin of exposure (MOE) between a point of departure (POD~~)~~; see G05) and likely human exposure. Alternatively, for contaminants or impurities, a pragmatic minimal risk level may be derived which is a dose representing a negligible carcinogenic risk.

~~7.~~9. It is important to note that ALARP remains the overriding principle even when the MOE or minimal risk level suggests there is unlikely to be a concern for human health.

Margin of Exposure approach

10. This approach is a way of prioritising and assisting with the communication of the risks associated with unavoidable exposure to genotoxic chemical carcinogens. It has been developed and used by the European Food Safety Agency (EFSA), the World Health ~~Organisation~~Organization (WHO) and the International Life Sciences Institute (ILSI), amongst others (EFSA, 2005; JECFA 2005; O'Brien *et al.,* 2006; reviewed by Benford, 2016). It is also seeing increasing use for chemicals where no threshold can be identified, including carcinogens, e.g. arsenic, but also where other health effects are observed, as in the case of e.g. lead.

11. The MOE is the numerical value obtained by dividing a POD on the dose response curve by estimated human exposure to the chemical. The preferred POD is generally accepted to be the lower 95% confidence limit of the benchmark dose (BMDL)1, although others have been suggested (Barlow *et al.*, 2006). The COC considers the BMDL to be preferable to the T25 as a POD where the T25 is the dose eliciting a 25% increase in the incidence of a specific tumour above the background level2. This is because the BMDL takes into account uncertainty regarding the shape of the dose-response relationship, within the observed dose range of carcinogenicity studies.

12. Some analyses of data have been carried out to determine the appropriate benchmark response (BMR) to use as a basis for a MOE approach. It was found that, in most cases when using animal data, the data from which the BMDL is derived are such that using a response of less than 10% would make the resulting BMDL more uncertain and similarly affect the resultant MOE (Benford *et al.* 2010).

~~8.~~13. The Committee considers that, although ALARP should always apply for compounds with no identifiable threshold of effect, the MOE is a useful means by which to prioritise and communicate the risks from exposure to genotoxic carcinogens.

[1] Further details of the BMDL and its derivation can be found in the COC Guidance Statement G05: Points of Departure and Potency Estimates

[2] Further details of the T25 and its derivation can be found in the COC Guidance Statement G05: Points of Departure and Potency Estimates

~~9.~~14. The Committee has proposed the system in Table 1 for banding MOE values, when based on the lower 95% confidence limit of the benchmark dose ($BMDL_{10}$) from an animal study. This expands proposals for the interpretation of the magnitude of the MOE that were made by JECFA and EFSA, where there was a consensus that a MOE greater than 10,000 indicated low concern. It is hoped that the banding system might improve the communication of advice on genotoxic carcinogens to wider audiences.

~~10.~~15. When other PODs are used, for example if based on human data, the MOE should be considered on a case-by-case basis.

Table 1: Banding of MOE values based on a ~~$BMDL_{10}$~~$BMDL_{10}$ from an animal study to aid risk communication

Margin of Exposure	Interpretation
<10,000	May be a concern
10,000-1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be a concern

Minimal Risk Levels

16. Under certain specific circumstances, for example very low exposures to genotoxic and carcinogenic contaminants or impurities, a pragmatic minimal risk level for these compounds may be identified. This minimal risk level3 would be 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).

17. The minimal risk level does not negate the need, where practicable, for efforts to reduce exposure, even when levels are below the minimal risk level. This is because for any genotoxic and carcinogenic chemical, there is still a carcinogenic risk (although this may be very small) at any exposure level, and thus the policy adopted by risk managers of controlling levels to ALARP should always apply. Indeed, this advice applies whether or not a minimal risk level for a genotoxic and carcinogenic contaminant or impurity can be estimated or achieved.

~~11.~~18. The derivation of a minimal risk level for a genotoxic and carcinogenic contaminant or impurity involves assessment of all available dose-response data for carcinogenicity to determine an appropriate POD and use of expert judgement to identify a suitable margin between this POD and a level of exposure which would result in a minimal risk. One proposal is that a suitable margin might be 10,000

[3] It should be noted that the minimal risk levels described here differ to those used by the US Agency for Toxic Substances and Disease Registry.

(Gaylor, 1994; Gold *et al*, 2003), which parallels the MOE approach, where an MOE of 10,000 is considered to be unlikely to be of concern when based on a $BMDL_{10}$ from an animal study. For a genotoxic and carcinogenic contaminant or impurity, a comparison of the minimal risk level with estimated exposure can be informative to risk managers.

~~12.~~19. The Committee considers that this approach should apply solely to contaminants for which exposure was unavoidable and to impurities in materials, products and formulations which are subject to regulatory assessment schemes.

Compounds with a threshold of effect (Threshold carcinogenicity)

Uncertainty Factor Approach

20. Many non-genotoxic carcinogens induce tumours as a secondary adverse effect arising from an initial toxicological effect, which has a threshold (Ashby *et al.* 1996). It follows that, for these substances, there is no carcinogenic risk at dose levels that do not produce the primary toxicological event, i.e. at doses below the threshold (Williams, 2001). Therefore, where there is adequate evidence to support a threshold for carcinogenicity (i.e. the compound and metabolites are not DNA reactive and there is an adequate evaluation of the mode of action (MOA) for tumours observed in animal studies), the Committee considers that an approach based on the use of uncertainty factors should be adopted.

~~13.~~21. The risk characterisation of non-genotoxic carcinogens can also be improved by adopting proposals such as those published by the IPCS on mode of action in animals and the ILSI human relevance framework. These approaches can serve to enhance the clarity and transparency of the risk characterisation process (Sonich-Mullin *et al.* 2001; Cohen *et al.,* 2003; Cohen *et al.*, 2004; Meek *et al.*, 2003; Boobis *et al.*, 2006; Meek et al., 2014). The OECD has developed guidance on adverse outcome pathways (AOPs), which share many characteristics of and build on the concepts of the MOA framework and these areas ~~have been~~ considered by the COC (see CC/2016/08).

22. The risk characterisation for non-genotoxic carcinogens should ideally be based on a BMDL for carcinogenicity or, more often, for a precursor event linked to tumour induction, though ~~often~~ a No or Low Observed Adverse Effect Level (NOAEL~~) is~~ or LOAEL) can be used. The robustness of this evaluation is dependent on the quality of the animal bioassays, or human studies if relevant and available, on the dose setting procedure and on the available information to support the MOA. Where the carcinogenicity data are obtained from animal studies, the MOA should be relevant to humans. The BMDL is divided by an appropriate uncertainty factor to give a health-based guidance value (HBGV) i.e. an estimated dose in humans without appreciable risk over a lifetime. Examples of such ~~health-based guidance values~~HBGVs are an Acceptable Daily Intake (ADI), which is used for food additives or pesticide residues in food, or a Tolerable Daily Intake (TDI), such as is used for environmental contaminants. However, in the risk characterisation of a non-genotoxic carcinogen, it is important to consider all relevant toxicological endpoints

caused by the chemical and the uncertainty factor which should be applied, before deciding on the appropriate ~~health-based guidance value.~~ HBGV.

23. The uncertainty factor allows for the uncertainties involved in extrapolating findings in animals to humans (interspecies variation) and in the differences in sensitivity to the adverse effect among the human population (inter-individual variation). Other factors may also be used, on a case-by-case basis, to take into account the quality of the toxicity data and the nature of the toxic effect. The uncertainty factor used is in essence an MOE which results in there being no concern for human health.

24. The numerical value of the uncertainty factor needs to be considered on a case-by-case basis, but as a general default a value of 100 (based on a factor of 10 for interspecies variation and a factor of 10 for inter-individual variation) is frequently used when based on adequate animal data. Higher uncertainty factors might be used for non-genotoxic carcinogenicity depending on the quality of the animal data and uncertainties in evaluation of the toxicological data. If available data provide adequate information on inter-species or human variability, the default values may be replaced in part or entirely by chemical-specific adjustment factors (CSAF) (Meek *et al.* 2002). WHO/IPCS published guidance on CSAF in 2005 (WHO, 2005) and a WHO/IPCS Chemical Risk Assessment Network working group reviewed the experience gained since publication of this guidance. A summary of their findings relating to CSAF development and guidance was published by Bhat et al. (2017).

25. The approaches to deriving uncertainty factors have been reviewed in detail by the Interdepartmental Group on Health Risks of Chemicals document (IGHRC, 2003) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 2007). EFSA has also discussed uncertainty factors and when they should be used or considered (EFSA, 2012).

~~14.~~26. The application of uncertainty factors generates a single estimate of a dose (or exposure) for a human that is considered to be without appreciable risk over a lifetime, the so-called deterministic approach. Normally, no numerical estimate is provided of the confidence limits for this value. Any exposure below the derived ADI or TDI is considered to produce no appreciable risk. Qualitative estimations of risk above this level need to be considered on a case-by-case basis, taking into account the frequency, duration and extent by which it is exceeded, and the nature and dose-response relationship for carcinogenicity, or other relevant form of toxicity of the substance in question. The Committee considers that this approach may be used for non-genotoxic carcinogens provided that the underlying mode of action is adequately understood.

~~15.~~27. In the absence of an ADI or TDI, the margin between the estimated exposure and the BMDL for carcinogenicity, precursor event or other sensitive endpoint derived from long-term bioassays (i.e. the MOE), can be informative to risk managers in deriving risk management policies.

Other approaches

Estimation of cancer risk by low dose extrapolation of animal data

28. In the US EPA Guidelines for Carcinogen Risk Assessment (2005), linear extrapolation from a POD on the dose response curve in animals to the origin, adjusting for background, is advised under specific circumstances. One circumstance is when there are data to suggest a linear response below the POD. This could be for substances which are DNA reactive and have mutagenic activity. Alternatively, it could be in situations where human exposure or body burden (the total amount of a chemical present in the body at a given time) is close to doses associated with precursor events in the carcinogenic process and extrapolation would be in the approximately linear part of the dose-response curve. Linear extrapolation is also advised for use when the data are insufficient to establish a mode of action for a tumour site and where a linear component below the POD is scientifically plausible (US EPA, 2005).

~~16.~~29. The Committee does not recommend the use of this approach because the resultant cancer risk estimate has a degree of precision which does not reflect the uncertainties about the shape of the dose response curve orders of magnitude below the doses administered in animal studies. Instead, the Committee recommends using the MOE approach to characterise the risk of such compounds.

Linear extrapolation to identify a Derived Minimal Effect Level (DMEL)

30. Within the technical guidance for the risk assessment of substances under the European REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation, two approaches are proposed for dealing with "non-threshold" genotoxic carcinogens. One is based on linear extrapolation from animal bioassay data to a low level of risk and the other is based on application of a large ‘assessment factor’ to a suitable reference point on the dose-response for carcinogenicity. The recommended assessment factor for use with a $BMDL_{10}$ as a POD is 10,000. The latter approach was included because not all risk assessment bodies in the EU approve the use of the linear extrapolation approach (ECHA, 2012).

~~17.~~31. For the reasons described in paragraph ~~28~~30, the Committee would not recommend using the linear extrapolation approach suggested by ECHA to derive a DMEL. The recommended ‘assessment factor’ used in the second approach parallels the lowest MOE value at which exposure is unlikely to be of concern. The Committee highlights that the ALARP principle should also apply.

T25 Approach

32. The T25 (see Guidance Statement ~~G05: Points of Departure and Potency Estimates)~~G05) has also been proposed as a basis for calculating risk from human exposure to carcinogens (Dybing *et al*. 1997). The appropriate animal T25 is selected and converted to an equivalent Human T25 (HT25) by the use of scaling factors for interspecies differences, based on difference in metabolic rate. The

human health risk is then estimated by linear extrapolation to human exposure levels. The European Chemicals Agency (ECHA) has continued to use this methodology when the dose response data from old two-year studies have been poor (e.g. ECHA, 2017).

~~18.~~33. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) has evaluated the use of T25 estimates for regulatory risk assessment of non-threshold carcinogens (ECETOC, 2002). It identified limitations in the methodology and concluded that the data and approach advocated were not sufficient to support quantitative risk assessment. The COC concurs with this view.

Summary

~~19.~~34. For carcinogens which do not show a threshold for effect, exposure should be as low as reasonably practicable (ALARP). In addition, the Committee recommends that the Margin of Exposure approach be adopted as a tool to indicate the level of concern in situations where exposure if unavoidable. When it is necessary to set a standard or guideline value for a genotoxic contaminant, identification of a Minimal Risk Level may be appropriate. For risk assessment of chemicals where a threshold has been established, the Committee advocates the use of the uncertainty factor approach.

COC Guidance Statement G06 ~~v1.~~update 1.1
~~September 2018~~

This is a background paper for discussion.
It does not reflect the view of the Committee and must not be quoted, cited or reproduced

References

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

Barlow S, Renwick AG, Kleiner J, Bridges JW, Busk L, Dybing E, Edler L, Eisenbrand G, Fink-Gremmels J, Knaap A, Kroes R, Liem D, Müller DJG, Page S, Rolland V, Schlatter J, Tritscher A, Tueting W & Würtzen G (2006) Risk assessment of substances that are both genotoxic and carcinogenic Report of an International Conference organized by EFSA and WHO with support of ILSI Europe. Food and Chemical Toxicology, 44, 1636-1650.

Benford, D (2016). The use of dose-response data in a margin of exposure approach to carcinogenic risk assessment for genotoxic chemicals in food. Mutagenesis, 31, 329-331.

Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T (2010). Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food and Chemical Toxicology, 48 Suppl 1, S2-24.

Bhat VS, Meek MEB, Valcke M, English C, Boobis A & Brown R (2017). Evolution of chemical-specific adjustment factors (CSAF) based on recent international ~~experience; increasing utility and facilitating regulatory acceptance. Crit Rev Toxicol, 47, 729-749~~
experience; increasing utility and facilitating regulatory acceptance. Crit Rev Toxicol, 47, 729-749

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D, Farland W (2006) IPCS framework for analyzing the relevance of a cancer mode of action for humans. Critical Reviews in Toxicology, 36, 781-92.

Cohen SM, Meek ME, Klaunig JE, Patton DE, Fenner-Crisp PA (2003). The human relevance of information on carcinogenic modes of action: overview. Critical Reviews in Toxicology, 33, 581-9

Cohen SM, Klaunig J, Meek E, Hill RN, Pastoor T, Lehman-McKeeman L, Bucher J, Longfellow DG, Seed J, Dellarco V, Fener-Crisp P and Patton D. (2004). Evaluating the human relevance of chemically induced animal tumours. Toxicological Sciences, 78, 181-186

Cohen, S.M., Boobis, A.R., Dellarco, V.L., Doe, J.E., Fenner-Crisp, P.A., Moretti, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., and Wolf, D.C. (2019) Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regul. Toxicol. Pharmacol. 103, 100-105

COT (2007) Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment. Available from ~~http://cot.food.gov.uk~~http://cot.food.gov.uk

Doe, J.E., Boobis. A.R., Dellarco, V., Fenner-Crisp, P.A., Moretti, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G. and Wolf D.C. (2019) Chemical carcinogenicity revisited 2: Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. Regul. Toxicol. Pharmacol., 103, 124-129

Dybing E, Sanner T, Roelfzema H, Kroese D & Tennant RW (1997) T25: a simplified carcinogenic potency index: description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity. Pharmacology and Toxicology, 80, 272-279

ECETOC (2002) The use of T25 estimates and alternative methods in the regulatory risk assessment of non-threshold carcinogens in the European Union. Technical Report No. 83

ECHA (2012) Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1.

ECHA (2017) Opinion on 4,4'-methylene-bis-[2-chloroaniline] (MOCA). Committee for Risk Assessment (RAC).

EFSA (2005) Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. doi:10.2903/j.efsa.2005.282

EFSA (2012) Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal,10 (3), 2579.

Gaylor DW, Kodell RL, Chen JJ, Springer JA, Lorentzen RJ & Scheuplein RJ (1994). Point estimates of cancer risk at low doses. Risk Analysis,14, 843-850

Gold LS, Gaylor DW, Slone TH (2003) Comparison of cancer risk estimates based on a variety of risk assessment methodologies. Regulatory Toxicology Pharmacology, 37, 45-53

Hodgson JT & Darnton A (2000) The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Annals of Occupational Hygiene, 44, ~~565-601.~~565601.

IGHRC – The Interdepartmental Group on Health Risk from Chemicals (2003) Uncertainty factors: Their use in human health risk assessment by UK Government. MRC Institute for Environment and Health, Leicester

JECFA (2005) Evaluation of certain food contaminants (Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 930.

Meek ME, Boobis, A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J & Vickers C (2014). New developments in the evoluation and application of the WHO/IPCS framework on mode of action/species concordance analysis. J Appl Toxicol, 34, ~~1-18.~~118.

Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD, Longfellow DG, Pastoor T, Seed J, Patton DE (2003). A framework for human relevance analysis of information on carcinogenic modes of action. Critical Reviews in Toxicology, 33, 591-653

Meek ME, Renwick A, Ohanian E, Dourson M, Lake B, Naumann BD & Vu V (2002) Guidelines for application of chemical-specific adjustment factors in dose/concentration-response assessment. Toxicology, 181-182, 115-120

O'Brien J, Renwick AG, Constable A, Dybing E, Müller DJ, Schlatter J, Slob W, Tueting W, van Benthem J, Williams GM & Wolfreys A (2006) Approaches to the risk assessment of genotoxic carcinogen in food: A critical appraisal. Food and Chemical Toxicology, 44, 1613-1635.

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

US EPA (2005) Guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-03/001F, 2005

WHO/IPCS (World Health Organization/International Programme on Chemical Safety) (2005). Chemical-Specific Adjustment Factors (CSAF) for interspecies differences and human variability: guidance document for the use of data in dose/concentration-response assessment. (IPCS harmonization project document no. 2). WHO/IPCS/01.4, 1-96. Geneva, Switzerland. Available from: ~~http://www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf~~www.inchem.org/documents/harmproj/harmproj/harmproj2.pdf

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

Wolf, D.C., Cohen, S.M., Boobis, A.R., Dellarco, V.L., Fenner-Crisp, P.A., Moretti, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G. and Doe, J.E. (2019) Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based oncontemporary knowledge. Regul. Toxicol. Pharmacol., 103, 86-92