Committee on CARCINOGENICITY

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

COC Guidance Statement G09 – version v1.0

COC set of principles for consideration of risk due to less than lifetime exposure

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

COC set of principles for consideration of risk due to less than lifetime exposure

1. Less than lifetime (LTL) exposure is broadly defined as 'any exposure that is not continuous daily exposure, for example, short-term, intermediate or intermittent, or a combination of these' (Felter et al., 2011).

2. Health-based guidance values (HBGVs) such as the acceptable daily intake (ADI) and tolerable daily intake (TDI) (an estimate of the amount of a chemical, expressed on a bodyweight basis, that people can be exposed to daily over a lifetime without appreciable risk to health), are usually based on standard animal toxicity studies with daily dosing regimens, often of chronic duration. The question that arises is how representative these are for human LTL exposure scenarios that may be short-term, intermittent or fluctuating in nature. Potentially sensitive sub-groups, including infants and children, have been highlighted as requiring particular consideration in terms of LTL exposures, due to their life-stage (Geraets et al., 2016), although data to allow comparison with adults for most effects are limited.

3. For UK Government departments and agencies, the need for guidance on LTL exposure falls into two broadly defined areas:

   a. Setting guidelines to protect health as a result of a specific exposure scenario (i.e. prospective risk assessment).

   b. Managing advice during and after an incident (i.e. retrospective risk assessment);

4. Chemical exposures that are shorter than a lifetime may result from planned activities or may be unplanned, such as in an incident scenario. Activities may be occupational or consumer related and may include environmental exposures via air, food, soil and water.

5. The following steps are designed as a set of principles to guide the risk assessment process for a specific LTL scenario, and assumes some level of expertise of the assessor. This document is not intended as guidance in the formal sense as users are encouraged to adapt the principles as needed in response to the available data and other case by case considerations. The steps are illustrated in Figure 1.

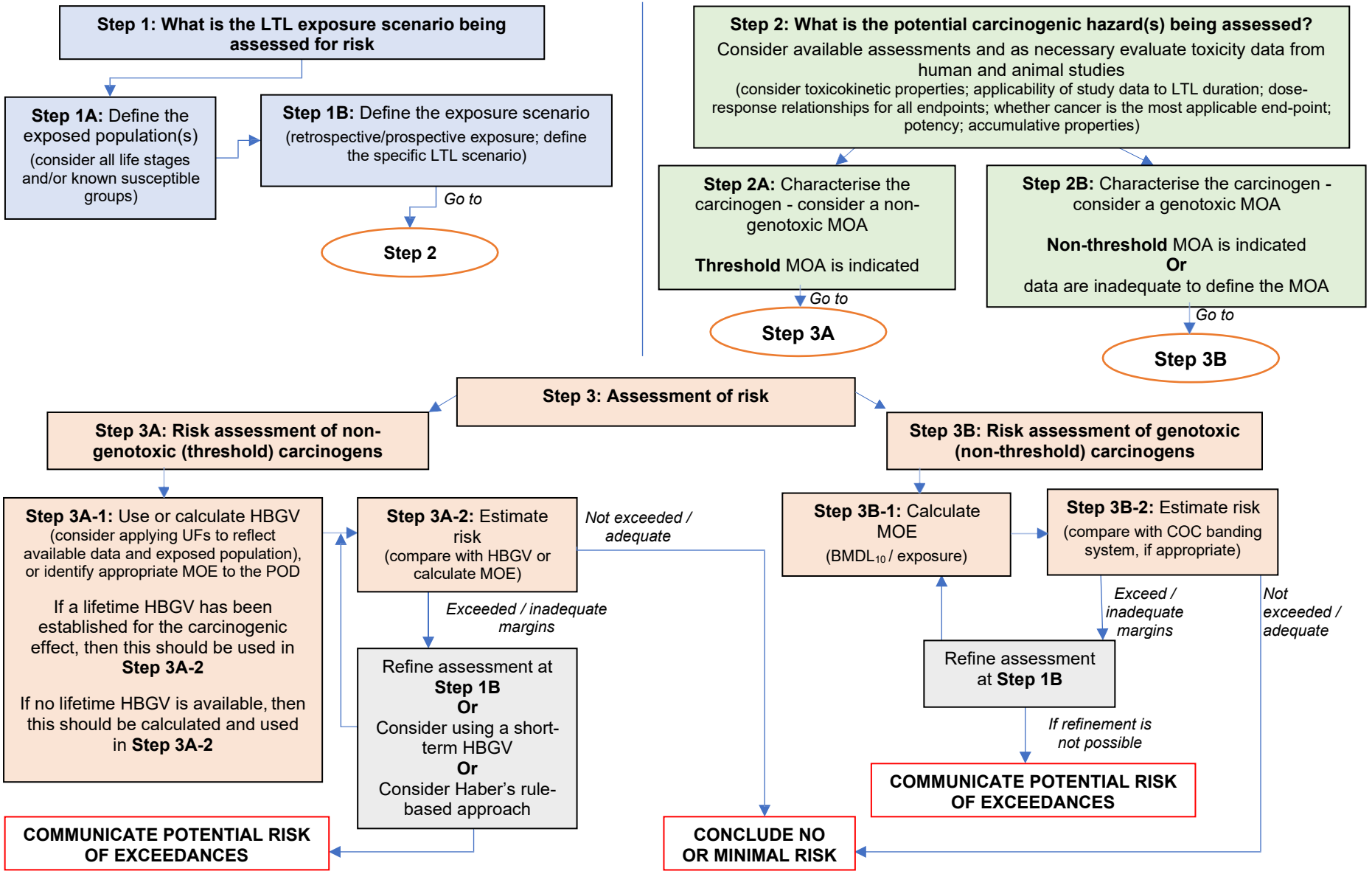

FIGURE 1: Flow chart to illustrate application of a set of principles for consideration of risk due to less than lifetime exposure

Step 1 - What is the LTL scenario being assessed for risk?

Note: Current COC guidance to assist with the assessment of exposure to carcinogens (G01 and G04) is available.

Step 1A - Define the exposed population(s)

6. The aim of this step for retrospective risk assessments is to define who has been exposed to the carcinogen(s) of interest, and for prospective risk assessments, the population that is likely to be exposed. Consideration should be given to:

- the numbers of individuals exposed;
- particular life stages of exposed individuals (to encompass infant, toddler, child, adult). Some age groups may have greater susceptibility following exposure (e.g. the unborn infant, pregnant women and the elderly) which may need to be taken into account during the assessment of risk in Step 3. *Note: if exposure of specific target groups can be ruled out, then they do not need to be included in the assessment*.

Step 1B - Define the exposure scenario

7. The aim of this step is to define the characteristics of the specific LTL exposure to a carcinogen that has or is likely to occur. Consideration should be given to:

- whether the exposure is ongoing or has ceased (retrospective only);
- is the cumulative exposure measured (i.e. the total amount of exposure over the defined period)?
- whether there is a single or multiple route(s) of exposure;
- is there normally a background level of exposure from the source(s) being considered?
- are other background sources present (from water, food, air, consumer products etc.);
- is the substance under consideration produced endogenously and if so, how do endogenous levels compare with the exposure level?
- whether exposure(s) is/was continuous, fluctuating or intermittent, or peaks above ongoing background exposure;
- duration(s) of exposure(s);
- average and peak levels of exposure(s) (including consideration of how exposure(s) has been measured or estimated as an indication of accuracy);
- if environmental and/or physiological degradation of the parent chemical occurs, whether the degradation products are also carcinogenic and co-exposure(s) with the parent is possible / has been determined;
- whether, for inhalation exposure, levels of physical activity (low, medium, high) during the exposure period are known;

- whether calculation of body burden is possible and/or appropriate (linked to accumulative properties of the particular chemical(s) and duration of exposure(s)).

Step 2 - What is the potential carcinogenic hazard(s) being assessed?

Note: Current COC guidance to assist with the hazard identification and characterisation of carcinogens (G01 and G03) is available.

8. Human and animal toxicological data and evaluations relating to the carcinogen(s) of interest should be collated to assist with the hazard identification process; this should include consideration of non-carcinogenic endpoints, as carcinogenesis may not be the most sensitive endpoint for to the scenario being considered. The aim of this step is to determine how the carcinogen of interest should be evaluated in Step 3 (Assessment of Risk).

9. Following evaluation of the available data, and confirmation that carcinogenesis is the most relevant endpoint for risk assessment, consideration should be given as to whether there is a biologically relevant mode of action (MOA) by which the chemical (and degradation product if appropriate) causes neoplasia. Of particular importance is whether the MOA exhibits a threshold and, in the evaluation of the genotoxic potential whether DNA reactivity is a key step in the MOA, i.e. whether the chemical is a genotoxic or non-genotoxic carcinogen.

Step 2A - Characterisation of the carcinogen(s) of concern - consideration of a non-genotoxic MOA.

10. Where the available data indicates that the carcinogen acts via a non-genotoxic MOA, consideration should be given to:

- have toxicokinetic properties been defined, including the potential for rapid metabolism or accumulation to occur;
- are dose-response relationships available for cancer and other toxicological end-points;
- whether cancer is the most applicable endpoint for the short-duration LTL exposure(s) being assessed (for example, would exposure levels that are protective of an endpoint early in the adverse outcome pathway such as irritation also protect against a later carcinogenic endpoint OR are there other adverse effects unrelated to carcinogenicity that should be protected for on a shorter-term basis);
- are the dose route, duration and intermittency of the studies used to generate hazard data, relevant to the LTL scenario being considered;
- the availability of suitable human data from occupational or epidemiology studies which can be used to derive a HBGV;

- has a dose-response relationship (in humans or animals) been defined for neoplastic outcomes on which a HBGV might be based;
- have cumulative exposure effects been assessed either in human or animal studies;
- potency of the carcinogen, particularly where tumour development (latency period) is known to be rapid;
- whether there is evidence for reversibility of pre-carcinogenic and carcinogenic changes following cessation of exposure.

11. Where the available data suggests a genotoxic MOA, the considerations outlined in Step 2B should be followed.

Step 2B - Characterisation of the carcinogen(s) of concern - consideration of a genotoxic MOA

12. Genotoxic carcinogens are assumed to have no threshold of effect. *NOTE: if there is no evidence relating to the MOA for a given carcinogen then it is assumed to have a non-threshold MOA - as per COC G01 and G03.*

13. Other important considerations that may have a particular impact on LTL exposures that should be taken into account during the assessment of risk in Step 3 include whether the MOA suggests:

- dose-rate-dependency;
- impairment of repair mechanisms; and
- targeting of particular life stages.

14. Considerations listed under Step 2A may also apply to genotoxic carcinogens if an endpoint other than carcinogenesis is identified as the predominant risk for the LTL scenario.

Step 3 - Assessment of risk

15. Combining findings from the exposure and hazard assessments needs to be carried out on a case-by-case basis and COC guidelines of risk characterisation methods (G06) are available. Other tools that may also support the risk assessment include the RISK21 software (Embry et al., 2014) and the threshold of toxicological concern (TTC) (EFSA, 2019). Separate guidance is available for the risk assessment of a mixture containing chemical carcinogens[1].

[1] Statement on the risk assessment of the effects of combined exposures to chemical carcinogens. Available at: https://www.gov.uk/government/publications/risk-assessment-of-mixtures-of-chemicalhttps://www.gov.uk/government/publications/risk-assessment-of-mixtures-of-chemical-carcinogenscarcinogens.

Step 3A - Risk assessment of non-genotoxic (threshold) carcinogens

16. COC guidance recommends that the risk assessment of non-genotoxic carcinogens be carried out through derivation of a HBGV where feasible, by application of appropriate uncertainty factors (UFs) to a point of departure (POD). The HBGV (e.g. ADI or TDI) reflects the dose that one can be exposed to, **over a lifetime**, without appreciable risk to health. However, certain criteria need to be met:

- there is adequate evidence to support a threshold for carcinogenicity in that the compound and/or its metabolites are not DNA reactive; and
- there is adequate evaluation of the MOA for the tumours observed in animal studies and its applicability to humans.

Step 3A-1 - Use or Calculate a HBGV

17. Ideally HBGVs developed in the UK, especially if available for the source of exposure under consideration, should be used as the starting point for the assessment. Otherwise if available, HBGVs developed by other agencies, national authorities from other countries or by international institutions should be considered, taking into account the applicability to the scenario, and the relevance of the UFs applied to the risk assessment.

18. The preferred POD (see COC guidance on points of departure and potency estimates, G05) for derivation of a HBGV is the benchmark dose ($BMDL_{10}$), however this may not be available, and a no observed adverse effect level (NOAEL) can be used. Appropriate UFs (see 'Note on dealing with uncertainty' below) should be chosen to reflect differences in toxicokinetics and toxicodynamics between animals and humans and between humans, and default UFs applied may vary by individual Government departments and agencies. It may be appropriate, if the data allow, to define a Chemical Specific Adjustment Factor (CSAF) which takes into account species differences or human variability in either toxicokinetics or toxicodynamics, allowing modification of the relevant 10-fold uncertainty factor (COT, 2007).

19. Where data are not sufficient to establish a HBGV, a margin of exposure (MOE) approach can also be utilised based on the most appropriate POD and taking account of uncertainty as outlined below. In addition, where an MOE approach has been utilised by others, this should be considered for use.

20. It should be noted that use of an HGBV or MOE based on long-term toxicity studies may be considered precautionary when applied to short duration LTL scenarios.

Step 3A-2 - Estimate risk

21. Where the LTL exposure scenario being assessed indicates exposure to levels higher than the HBGV, qualitative estimations of risk need to be made using

evidence from the collated exposure data (Step 1) and hazard data (Step 2). Uncertainties that are inherent in the estimate of risk should be clearly defined and the impact on the overall estimate understood (i.e. whether inclusion of uncertain data leads to an under or overestimate of risk; see 'Note on dealing with uncertainty' below).

22. If the MOE approach is utilised, a value judgement will be needed as to whether the magnitude of the MOE allows for sufficient uncertainty with respect to the available toxicological database, and any differences between animals and humans. Judgement is therefore needed on a case-by-case basis.

23. Refinements to the risk assessment may be judged applicable where data allow (see 'Note on refining the risk assessment' below). In addition, the use of a shorter-term study to define a short-term HBGV may be appropriate where carcinogenic or precursor effects are concentration dependent. Alternatively, application of a Haber's rule[2]-based approach may be considered for non-genotoxic carcinogens, especially if effects need to be prolonged for carcinogenicity to occur or bioaccumulation is evident.

Step 3B - Risk assessment of genotoxic carcinogens

24. All exposures to genotoxic carcinogens should be managed according to the 'as low as reasonably practicable' (ALARP) principle. The MOE, described below, may assist with the evaluation of risks concerning *unavoidable* exposure to genotoxic chemical carcinogens.

Step 3B-1 - Calculate the MOE

25. The MOE is derived by dividing a POD (see COC guidance on points of departure and potency estimates, G05), preferably the $BMDL_{10}$, on the dose response curve by the estimated human exposure to the chemical. It should be noted that other levels of the BMD can be used (e.g. $BMDL_{05}$) which will be dependent on the best fit of the curve to the available data.

26. The use of Haber's rule to calculate an effect level is **not considered** appropriate for genotoxic carcinogens, especially potent genotoxins, by the COC, due to its approach of assumed simple linearity.

Step 3B-2 - Estimate Risk

27. COC have proposed a banding system for MOE values *for neoplastic effects when calculated with $BMDL_{10}$ from a chronic animal study using tumour incidence as the effect of concern.* These are:

[2] Haber's rule states that the incidence and/or severity of a toxic effect depends on the total exposure, i.e. exposure concentration (c) rate times the duration time (t) of exposure ($c \times t$).

<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

28. Although these bandings are for lifetime exposure (i.e. worst case) they may be helpful indicators when considering individual LTL scenarios of shorter durations. Where MOEs are lower than the indicative bands, qualitative estimations of risk need to be made on a case-by-case basis, taking into account collated evidence from exposure (Step 1) and hazard data (Step 2). It is essential that inherent uncertainties in the estimate of risk are clearly defined and the impact on the overall estimate understood (i.e. whether inclusion of uncertain data leads to an under or overestimate of risk: see 'Note on dealing with uncertainty' below).

29. If other PODs are used (e.g. NOAEL; BMDL other than for a 10% response), or sources of data (e.g. human studies), the proposed bands are not applicable and expert judgement is required to consider the level of concern indicated by the MOE on a case-by-case basis (see for example, JECFA (2018)).

Conclusion of Step 3

30. Following Steps 3A-2 or Step 3B-2, a conclusion can either be drawn that the less-than-lifetime exposure is of no risk (thresholded mechanism) or minimal risk (non-thresholded mechanism), and this assessment fed back to risk managers.

31. Otherwise, if further refinement of the assessment is not feasible or the uncertainty in the assessment cannot be reduced (see below), the assessment of risk should be communicated and discussed with risk managers.

Note on dealing with uncertainty

- Uncertainty is an inherent part of all steps within a risk assessment and, to aid transparency, should be identified, assessed, documented, and communicated.

- UF is a generic term used in the UK (also called assessment factor, safety factor and variability factor by other organisations) for the numerical factor applied to PODs from toxicity data to account for uncertainty in extrapolating animal data to derive HBGVs in humans.

- UFs are also used where there is evidence that humans or a human subpopulation have a greater (or lesser) sensitivity than the subjects of the critical study (animal or human) being used to derive a HBGV. If there is a known increased vulnerability (suspected or proven) of any specific sub-group of the exposed individuals to the chemical(s) of concern, then the application of additional UFs should be considered in the risk assessment process. If vulnerability is unknown, for susceptible populations a higher risk should be assumed and additional UFs employed.

- Approaches to the use of UFs and consideration of dealing with uncertainty within risk assessments is considered in the COC guidelines of risk characterisation methods (G06) and COT Working Group on Variability and Uncertainty in Toxicology (COT, 2007).

- Guidelines for performing an uncertainty analysis (qualitative or quantitative) are available from several organisations including: EFSA (2018); ECHA (2012); and WHO/IPCS, (2008).

Note on refining the risk assessment

32. The use of default UFs that are generic and not chemical- or species-specific may result in HBGVs that are overly cautious, leading to an overestimate of potential risk. For non-genotoxic carcinogens, where an exceedance of the HBGV is seen, refinement of the assessment should be undertaken through consideration of:

- Whether a refined exposure assessment can be carried out (e.g. using non-standard assumptions of intakes);

- The contribution of the LTL exposure to chronic background exposure (e.g. in terms of body burden or cumulative exposure);

- Whether the results from a shorter-term study is a more appropriate basis for risk assessment of the scenario being considered.

33. Use of the Risk21 software may support refinement of the risk assessment by enabling visualisation of the uncertainty in the exposure and toxicity data.

34. In some circumstances, it should be recognised that even following application of the suggested refinements listed in paragraphs 32 and 33, the LTL exposure may still exceed the HBGV. In such cases, there is currently no established guidance on assessing the risk and these need to be treated on a case by case basis. Expert judgement will need to be applied by the risk assessor to consider potential mode of action. For example, a short duration LTL exposure to a genotoxic carcinogen may present a greater risk than a longer LTL exposure to a non-genotoxin that acts via a thresholded inflammatory process. Care needs to be taken when communicating the potential risk of exceedances, which will also differ on a case by case basis.

35. It is hoped that new ways of assessing carcinogenicity that are currently under development will enable the principles listed here to evolve into more robust guidance on LTL exposures in the near future.

Summary

36. Where exposures occur that are short-term, intermittent or fluctuating, the COC recommends an appropriate risk assessment be undertaken. This document

provides a set of principles against which such an assessment can take place, utilising the available evidence. For carcinogens that do not show a threshold for effect, the ALARP principles apply, but a refined risk assessment based on an MOE approach can be undertaken. Where a threshold of effect for a chemical has been identified, the basis of any less-than-lifetime exposure assessment can be established HBGVs.

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September 2019

Abbreviations

ADI	Acceptable daily intake
ALARP	As low as reasonably practicable
BMDL	Bench mark dose lower bound
CSAF	Chemical specific adjustment factor
HBGV	Health-based guidance value
LTL	Less than lifetime exposure
MOA	Mode of action
MOE	Margin of exposure
NOAEL	No observed adverse effect level
POD	Point of departure
TDI	Tolerable daily intake
TTC	Threshold of toxicological concern
UF	Uncertainty factor

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