CC/2018/02

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

Development of a framework (algorithm) for consideration of risk due to less than lifetime exposure

Introduction

1. The COC has previously considered the issue of less than lifetime (LTL) exposure to genotoxic and non-genotoxic carcinogens. LTL 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. Chronic health-based guidance values (HBGVs) such as the acceptable daily intake (ADI) and tolerable daily intake (TDI) are based on standard animal toxicity studies with daily dosing regimens. The question that arises is how representative these are for human LTL exposure scenarios which may be 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 (Gerats 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. Managing advice during and after an incident;

   b. Setting guidelines to protect health as a result of a specific exposure scenario.

4. Examples of LTL exposures that have been considered in the past by Government departments/agencies will be provided during the meeting.

5. An update on approaches utilised by various authoritative bodies (with a focus on margin of exposure (MOE) approaches) was given to the COC in November 2017 (paper CC/2017/19) to enable discussions as to how best to provide guidance in this area. Members agreed that a general set of principles (or risk framework or algorithm) that could be considered when assessing LTL exposures, would form a key part of such guidance.

6. Since the discussion in November 2017, the Joint FAO/WHO Joint Expert Committee for Food Additives (JECFA) has published some recent considerations

with respect to LTL exposures (JECFA, 2018). These are given in full in Annex 1 and summarised below.

7. There does not appear to be one general approach that is applicable to all possible LTL exposures for adults and children. This paper therefore presents a number of important areas of relevance (the set of principles) that should be considered in assessing risk from LTL exposures, on a case-by-case basis, to ensure that estimations of risk are both protective of health and not overly conservative. It is anticipated that this set of principles could form the guidance from the COC. As required these principles could be formulated into specific frameworks by individual Government departments and agencies.

Recent JECFA work

8. JECFA (2018) highlight specific populations/endpoints that should be treated with concern when addressing LTL exposures through the oral route (Annex 2). Although these do not appear to address carcinogens specifically, coupled with mode of action (MOA) considerations they may provide helpful insight as to the significance of MOE calculations (Step 3A).

Proposal for a COC set of principles

9. 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.

10. 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.

Step 1 - Framing the question: what is the specific LTL scenario being assessed for risk?

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

- **Define the exposed population(s)** – consideration of: life-stage (to encompass infant, toddler, child, adult, as defined on a scenario specific basis); body weights; for inhalation exposure levels of physical activity (low, medium, high); numbers of individuals exposed. *Note: if exposure of specific target groups can be ruled out, then they do not need to be included in the risk assessment.*

- **Define the exposure scenario** – consideration of: is this a planned future exposure or an exposure that has already happened and is either ongoing or

stopped; routes of exposure; are there multiple routes of exposure; whether exposure(s) is continuous or fluctuating or intermittent, or a peak above ongoing background exposure; duration(s); average and peak levels of exposure(s) (including consideration of how exposure(s) has been determined); whether environmental degradation of the parent chemical occurs and if exposure(s) to these products is possible / has been determined; simultaneous exposure(s) from 'background' sources to parent and degradation product(s) if appropriate; whether calculation of body burden is appropriate (linked to accumulative properties of the particular chemical(s) and duration of exposure(s)).

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

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

- **Consideration of the MOA of the carcinogen(s) of interest** – is there a biologically relevant and understood MOA by which the chemical (and degradation product if appropriate) causes neoplasia; where possible, genotoxic potential should be evaluated to establish if DNA reactivity is a key step in the MOA, i.e. whether the chemical is a genotoxic or non-genotoxic carcinogen (*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*); does the MOA suggest dose-rate-dependency, impairment of repair mechanisms or targeting of particular life stages that may impact on LTL exposure assessments.

- **Characterisation of chemical(s) of concern** – for non-genotoxic carcinogens: have dose-response relationships been defined for cancer and other toxicological end-points; is cancer the most applicable endpoint for short-duration LTL exposures; is the dose route, duration and intermittency used to generate hazard data relevant to the LTL scenario being considered; has a dose-response relationship been defined for neoplastic outcomes on which a health-based-guidance value might be based. Genotoxic carcinogens are assumed to have no threshold level of effect.

Step 3 - Assessment of risk

Linking of 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. Separate guidelines are applicable 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-chemical-carcinogens.

Step 3A - Genotoxic carcinogens

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

- **Calculation of MOE** – this is derived by dividing a point of departure (POD) (see COC guidance on points of departure and potency estimates, G05) on the dose response curve by the estimated human exposure to the chemical. The use of Haber's rule to calculate an effect level is not considered appropriate by the COC due to its approach of assumed simple linearity.

- **Estimating Risk** – 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:

  <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

  Although these bandings are for lifetime exposure (i.e. worst case) they may be helpful indicators of 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).

  If other PODs are used (e.g. no observed adverse effect level, NOAEL), 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) recommendations, Annex 2).

Step 3B - Non-genotoxic carcinogens

COC guidance recommends that the risk assessment of non-genotoxic carcinogens be carried out through derivation of a health-based guidance value (HBGV), by application of appropriate uncertainty factors (UFs) to a POD. The HBGV (e.g. ADI, TDI) reflects the dose that one can be exposed to, over a lifetime, without adverse effects occurring. 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 that there is adequate evaluation of the MOA for the tumours observed in animal studies and its applicability to humans*. Where data are not sufficient to establish a HBGV, an MOE approach can also be utilised based on the most appropriate POD.

- **Use or Calculation of health-based guidance value** – the preferred POD for derivation of a HBGV is the BMDL, however this may not be available, and NOAELs can be used. Appropriate UFs should be chosen to reflect differences in toxicokinetics and toxicodynamics between animals and humans and between humans – default UFs may be applied by individual departments and agencies. Where no HBGV is available, an MOE approach may have been utilised by others and could be investigated.

- **Estimation of risk** – 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). If the MOE approach has been 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.

Step 3C: Risk assessment for susceptible adults, children and infants

- Is there a known increased vulnerability (suspected or proved) of any specific sub-group of the exposed individuals to the chemical(s) of concern? If yes, then 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. *Note: in all age groups, the use of additional UFs should be explained in the risk assessment.*

Questions for the Committee

11. Members are asked to consider this paper and in particular:

    i. Does the ‘set of principles’ outlined above cover the considerations to be made in the assessment of LTL exposures?

    ii. Are there any other aspects that need to be included?

    iii. Can the ‘set of principles’ form the COC guidance on less-than-lifetime exposure?

NCET at WRc/IEH-C under contract supporting the PHE COC Secretariat
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Abbreviations/Glossary

ADI: Acceptable daily intake

ALARP: As low as reasonably practicable

BMDL: Bench mark dose lower bound

HBGV: Health-based guidance value

JECFA: Joint FAO/WHO Joint Expert Committee for Food Additives

LTL: Less than lifetime exposure

MOA: Mode of action

MOE: Margin of exposure

NOAEL: No observed adverse effect level

POD: Point of departure

T_{25}: The dose likely to produce cancer in 25% of the population studied

TDI: Tolerable daily intake

UF: Uncertainty factor

References

Felter, S.P., Conolly, R.B., Bercu, J.P. et al. (2011) A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Critical Reviews in Toxicology. 41, 507–544.

Geraets, L., Nijkamp, M., Ter Burg, W. (2016) Critical elements for human health risk assessment of less than lifetime exposures. Regulatory Toxicology and Pharmacology. 81, 362 – 371.

JECFA (2018) Evaluation of certain veterinary drug residues in food: eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series; no 1008.

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DEVELOPMENT OF A FRAMEWORK (ALGORITHM) FOR CONSIDERATION OF RISK DUE TO LESS THAN LIFETIME EXPOSURE

Evaluation of certain veterinary drug residues in food: eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives

Pages 4-9 of WHO technical report series; no. 1008. Available from: http://www.who.int/foodsafety/publications/jecfa-reports/en/

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Secretariat
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