COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Statement on COT principles for assessing risks from less than lifetime exposure or variable exposure over a lifetime

Introduction

1. The Committee on Carcinogenicity (COC) published principles for consideration of risk from carcinogens due to less than lifetime exposure in 2019 (COC, 2019). The COT considered the applicability of these principles to other toxicological endpoints considered by the COT using cases from the COT's past work. The principles set out here are based on the COC principles with some modification to reflect the endpoints considered by the COT.

2. In comparison to the COC principles, the title has been expanded to reflect that, in most cases, the COT is not considering exposure that is shorter than a lifetime and then ceases, but rather exposure that is over a lifetime but varies over that lifetime, being substantially higher for a certain portion of that lifetime. For example, this may be due to exposure being higher in a particular life-stage or due to a short-lived contamination incident.

3. Chronic health-based guidance values (HBGVs) such as the acceptable daily intake (ADI), tolerable daily intake (TDI) or tolerable weekly intake (TWI) are estimates of the amount of a chemical, expressed on a body weight basis, that may be ingested regularly (e.g. daily, weekly) over a lifetime without appreciable risk. They are often based on chronic toxicity studies, but in some cases may be based on shorter term data such as reproductive toxicity or developmental toxicity studies where endpoints from these studies occur at lower dose levels. One question that arises is how relevant these chronic HBGVs are for exposure that is shorter term, for example due to an incident such as an accidental release. Another question that arises is how to assess risks if the exposure is within the HBGV when averaged over a lifetime or a period of time relevant to the basis upon which the HBGV was established, but exceeds it for a shorter period of that lifetime such as in childhood or

due to short-term increased contamination. Infants and children may require particular consideration as they are potentially sensitive subgroups.

4. Such less than lifetime exposures, or exposures that are higher on a less than lifetime basis, may initially be compared to the HBGV established to be protective of lifetime exposure. However, in the case that a refinement to the risk assessment is required, the following steps are intended as a set of principles to guide the risk assessment process for a specific less than lifetime or variable exposure scenario. Acute (one-off) exposure is not considered here, as acute reference doses (ARfDs) are established where required. The steps are also illustrated in Figure 1.

Step 1 – What is the scenario being assessed for risk?

Step 1A – Define the exposed population(s)

5. The aim of this step is to define the population or population subgroup of interest. The particular life stages of exposed individuals (or those with the higher exposure) should be considered. Some age groups or life stages may have greater susceptibility, which may also need to be taken into account in the assessment of risk (e.g. infants, children, unborn infants, pregnant women, the elderly), if this has not been adequately addressed in establishing the HBGV.

Step 1B – Define the exposure scenario

6. The aim of this step is to characterise the less than lifetime or variable exposure scenario that is being considered. Consideration should be given to:

- Whether the exposure is/was short term or is ongoing
- Is the total 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 to the chemical from the same or other sources?
- Is the substance under consideration produced endogenously and, if so, how do endogenous levels compare with the exposure level?
- Whether exposure is continuous, fluctuating, or intermittent, peaks above background exposure, or is life-long but variable.
- Duration of exposure, or duration of raised exposure
- Average and peak levels of exposure(s) (including consideration of how exposure(s) has/have been measured or estimated)
- 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 bioaccumulative properties of the particular chemical(s) and duration of exposure(s).

Step 2 – What are the hazards being assessed?

7. Human and animal toxicological data and evaluations relating to the chemical of interest should be collated to assist with the hazard identification process. If the chemical is genotoxic and carcinogenic and if no threshold can be assumed then the COC principles on less than lifetime exposure should be followed, following the steps for a genotoxic carcinogen. Otherwise, consideration should be given to the following:

- The toxicokinetic properties, including the potential for rapid metabolism or accumulation to occur
- Dose-response relationships for all endpoints
- Potency, particularly when the time to the adverse effect occurring is known to be rapid
- Whether there is evidence for reversibility of changes following cessation of exposure
- Whether the endpoint used as the basis for the chronic HBGV is the most applicable endpoint for the less than lifetime or variable (LTLV) exposure(s) being assessed, and if so, whether the point of departure for this endpoint is similar or higher in a shorter-term study than that used as the basis of the chronic HBGV
- How the points of departure relevant to different life stages compare to the point of departure used as the basis for the chronic HBGV
- Are the dose route, duration and intermittency of the studies used to generate hazard data relevant to the LTLV scenario being considered?

Step 3 – Assessment of risk

8. The COT considers that the risk assessment of chemicals other than those which are genotoxic and carcinogenic should be carried out through establishment of an HBGV where feasible, by application of uncertainty factors to a point of departure. Alternatively, where the data are not sufficient to establish an HBGV, a margin of exposure (MOE) to a point of departure may be calculated.

9. The chronic HBGV (e.g. ADI, TDI or TWI) reflects a level of intake that people may be exposed to over a lifetime without appreciable risk. It should be noted that the use of an HBGV or MOE based on long term toxicity studies may be considered precautionary when applied to short duration LTLV scenarios.

10. Where the LTL scenario being assessed indicates exposure higher than the chronic HBGV, or a chronic HBGV is exceeded only on an LTLV basis and exposure averaged over lifetime is within the chronic HBGV, qualitative estimations of risk need to be made using evidence from the collated exposure (Step 1) and hazard (Step 2) data. Uncertainties that are inherent in the estimate of risk should be clearly defined and the impact on the overall estimate understood.

11. If the MOE approach is utilised a judgement will be required 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.

12. 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 establish a short term HBGV may be considered appropriate. Alternatively, application of a Haber's rule[1]-based approach may be considered, especially if exposure needs to be prolonged for adverse effects to occur, for example for chemicals which bioaccumulate. The toxicokinetics of the substance should be considered and judgements on the appropriate approach made on a case-by-case basis.

13. Following these steps, the conclusion may be drawn that the LTLV exposure is of no concern and communicated to risk managers. Otherwise, if further refinement of the assessment is not feasible or uncertainty in the assessment cannot be reduced, the assessment of risk should be communicated to risk managers.

Notes on refining the risk assessment

14. As described above, where LTLV exceedance is seen of a chronic HBGV, refinement of the assessment should be considered through consideration of:

- Whether a refined exposure assessment can be conducted

- The contribution of the LTLV exposure to chronic background exposure (e.g. in terms of body burden)

- Whether the result of a shorter term study is a more appropriate basis for risk assessment of the LTLV scenario being considered – providing that exposure over a time frame relevant to the basis of the chronic HBGV is also less than the chronic HBGV.

15. The toxicokinetics of the substance should be carefully considered. For bioaccumulative chemicals, a steady state would be reached at some point, at which no further accumulation would occur. The use of a Haber's rule-based approach may be appropriate where the less-than-lifetime period of raised exposure is less than the half-life of elimination, but not where it is greater. Judgements on the appropriate approach should be made on a case-by-case basis. If the data are available, the assessment should be based on internal exposure rather than external (e.g. dietary).

16. Where possible, toxicokinetic or toxicodynamic modelling would be helpful in assessing risks from LTLV exposures. Information on mode of action would also be useful.

17. Use of the Risk21 matrix[2] may support refinement of the risk assessment by enabling visualisation of the uncertainty in the exposure and toxicity data.

---

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

[2] The Risk21 matrix provides a visual comparison of exposure and toxicity information. Users input exposure and toxicity data for a chemical and the Risk21 matrix webtool plots the intersection area and overlays a risk matrix represented as a heat map. It is available at https://risk21.org/.

18. In some cases, even after application of the suggested refinements, the LTLV exposure may still be of concern. In such cases, there is no established guidance on assessing the risk and these need to be treated on a case-by-case basis. Care needs to be taken when communicating the potential risk, which will also differ on a case-by-case basis.

Summary

19. Where exposures are short-term or vary over a lifetime, the COT recommends that the exposures in the window of raised exposure are initially compared to an HBGV that has been established to be protective for long term exposure. However, in cases where exposure averaged over a time frame relevant to the basis upon which the HBGV is established is less than the HBGV but shorter term exposure exceeds it, this Statement recommends approaches that may be taken to refine the risk assessment, if required. These include the use of a short-term HBGV, provided that long term exposure is less than the chronic HBGV, or the use of a Haber's-rule based approach. However, the toxicokinetics of the substance should be considered carefully and judgement on the appropriate approach made on a case-by-case basis. A Haber's rule based approach may be appropriate in some cases for chemicals which bioaccumulate but not in others. For example, it may be appropriate where the less-than-lifetime period of raised exposure is less than the half-life of elimination, but not where it is greater.

References

COC (2019). COC set of principles for consideration of risk due to less than lifetime exposure. Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC). COC Guidance Statement G09 v1.0, September 2019

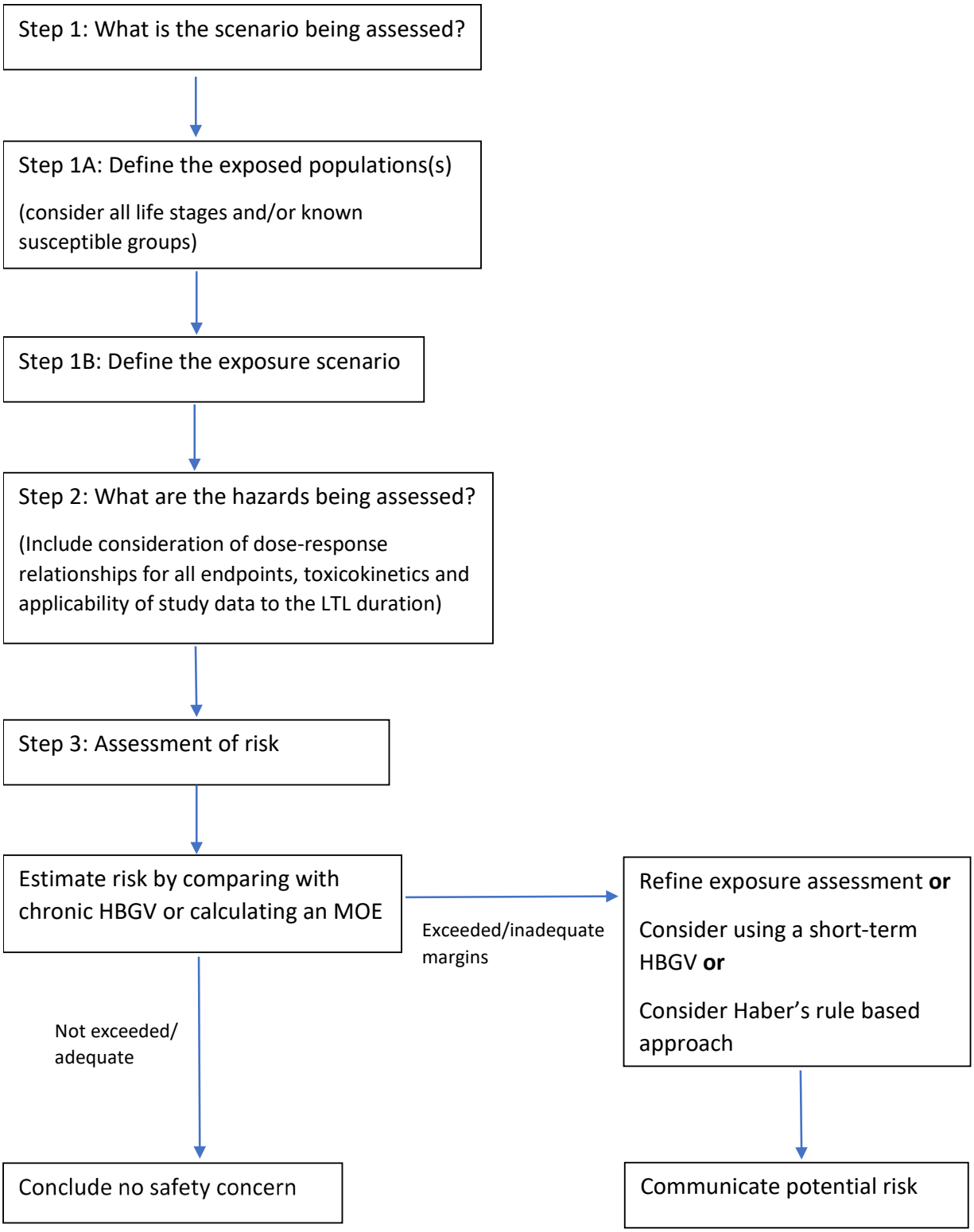

Figure 1: Flowchart to illustrate the process of assessing risks from less than lifetime or variable (LTLV) exposures. Where appropriate, toxicokinetic or toxicodynamic modelling could be applied to refine any of the steps.