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

Guideline Statement G09: Assessing the risks of acute or short-term exposure to carcinogens. Amended draft.

This Guidance Statement was circulated for the November meeting but was not discussed, due to lack of time. Please find attached a slightly amended version, following comments received before and after the November meeting. The statement is based on paper CC/2015/12, which was discussed at the July meeting, and the Committee's comments and views on the approach described in that paper. Members are asked for comments on the draft Guidance Statement.

Secretariat
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Committee on CARCINOGENICITY

COC/G09 – Version 0.1 (amended)

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

Assessing the Risks of ~~Acute or Short-Term~~Less-than-lifetime Exposure to Carcinogens

Introduction

1. This guidance statement provides advice on the assessment of the risk of ~~acute and short-term~~less-than-lifetime exposure 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. It should be read in conjunction with the other guidance statements, in particular, G01 on the overall strategy of risk assessment of chemical carcinogenicity, G05 on defining a point of departure and potency estimates in carcinogenic dose response, and G06 on risk characterisation methods.

2. The risk characterisation methods described in G06 assess the carcinogenic risk of a chemical following a lifetime~~, or long-term,~~ exposure to a carcinogen. It is sometimes necessary to provide advice following a ~~single exposure or exposure over a few days or weeks~~shorter period of exposure, for example, after a chemical accident~~, or~~ a food contamination incident, or from soil contamination. This guideline describes a method to quantify the risk following a less-than-lifetime exposure to a carcinogen.

Approach proposed by the Committee for genotoxic carcinogens

3. The approach proposed is based on a publication from an ILSI/HESI[a] workshop on less-than-lifetime exposure to carcinogens held in 2009 (Felter *et al*, 2011). The approach is based on the concept of Haber's Law, which holds that toxicity (*k*) is related to the concentration of the toxic chemical (*C*) and the time of exposure (*T*) i.e.

$$C \times T = k.$$

The approach ~~also~~ requires that chemical-specific lifetime carcinogenicity data in experimental animals are available. It also makes the pragmatic assumption of a linear dose-response relationship which, in reality, may not be the case at the level of chemical to which humans are exposed~~, and that the data support a linear dose-~~

[a] International Life Sciences Institute/Health and Environmental Sciences Institute

~~response relationship~~. In the framework, Haber's Rule is defined as uniformly distributing the acceptable cumulative lifetime dose over the total number of exposure days during less-than-lifetime exposure, thereby allowing for a higher daily intake than would be the case for lifetime exposure.

4. This approach should be combined with the Margin of Exposure (MOE) approach, which is described in Guidance Statement G06. A lower 95% confidence limit of the benchmark dose for a 10% response ($BMDL_{10}$) is calculated using data from an animal lifetime exposure study on the chemical in question. The principles in Felter et al (2011) are then applied to assess the MOE for short-term exposure for a defined period i.e.

$$MOE = \frac{BMDL_{10}}{\text{Daily intake of chemical}} \times \frac{\text{Days in a lifetime}}{\text{Period of short term exposure}}$$

For example, if the $BMDL_{10}$ was 2000 mg/kg/day, for an intake of 5 mg/kg bw/day over a period of 7 days, the MOE would be:

$$\frac{2000}{5} \times \frac{(365 \times 75)}{7}^{b}$$

Thus, whereas the MOE for lifetime exposure would be only 400, for the short term exposure it would be in excess of 1,000,000 or 'highly unlikely to be a concern'. Examples of the use of this approach can be found in Van den Berg *et al* (2014) and Reeuwijk *et al* (2014).

Non-genotoxic carcinogens

5. For most non-genotoxic carcinogens, a sustained dose and duration of exposure is required for a carcinogenic response. If exposure duration does not allow for this sustained effect, then it is unlikely for a human cancer risk to exist. Some examples provided by Felter *et al* (2011) are:

- Activation of nuclear receptors such as constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor alpha (PPAR-α), and the aryl hydrocarbon receptor (Ah).
- The role of sustained toxicity as a requisite factor in the induction of nasal tumours in rats exposed to high doses of various chemicals, or in the rodent forestomach with chemicals given by intragastric installation.
- Endocrine tumours, where sustained trophic drive is necessary, e.g. TSH-dependent thyroid tumours.

Therefore, for a non-persistent chemical acting by these mechanisms, the risk from short-term exposure could be considered negligible. However, any assessment must be taken on a case-by-case basis, with consideration of the mode of action. Chemicals acting by other mechanisms may produce a carcinogenic response after

[b] Based on an estimated life expectancy of 75 years.

a relatively short exposure (~~*ref protein kinase inhibitor*~~). Also, if exposure is substantial and elimination of the compound is slow (e.g. polychorinated dibenzo-p-dioxins, asbestos), an acute or short-term exposure could still lead to a carcinogenic risk, as the internal exposure will be prolonged. Felter et al (2011) cite a number of cases where the epidemiological evidence indicates that cancer risk is not proportional to (*C x T*), for example, smoking, where the data indicate that the risk may be more heavily influenced by duration. Similarly, the assessment should take account of the lifestage during exposure, genetic predispositions and underlying disease states, and the toxicokinetics/toxicodynamics of the chemical concerned.

Comment [FP1]: Can members suggest a non pharmaceutical chemical which causes cancer following a relatively short exposure?

Comment [FP2]: Committee: Do you want to include this? The susceptibility of children to carcinogens is a subject which was raised under the 2015 horizon scanning exercise.

Summary

6. When assessing the risk of acute or short-term exposure to carcinogens, every chemical must be considered on a case-by-case basis. For most genotoxic carcinogens, a~~n~~ method based on the concept of Haber's Law, used together with the Margin of Exposure approach, can be used. For non-genotoxic chemicals, there should be careful consideration of the mode of action and of whether a less-than-lifetime exposure would be likely to have the same carcinogenic effect as lifetime exposure.

COC

Date

References

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