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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

Attached is the first draft of this Guideline Statement. It is based on paper CC/2015/12, which was discussed at the last meeting, and the Committee's comments and views on the approach described in that paper. Members are asked for comments on the draft Guideline Statement.

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

Assessing the Risks of Acute or Short-Term Exposure to Carcinogens

Introduction

1. This guidance statement provides advice on the assessment of the risk of acute and short-term 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 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, for example, after a chemical accident or a food contamination incident. This guideline describes a method to quantify the risk following a less-than-lifetime exposure to a carcinogen.

Approach proposed by the Committee

3. The approach proposed is based on a publication from an ILSI/HESI¹ 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 and that the data support a linear dose-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.

¹ International Life Sciences Institute/Health and Environmental Sciences Institute

This is a draft statement for discussion. It does not necessarily represent the views of the Committee.

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 (BMDL₁₀) is calculated using data from a 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.

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

For example, if the BMDL₁₀ was 2000 mg/kg/day, for an intake of 5 mg/kg bw/day over a period of 7 days, the MOE would be:

$$\frac{2000}{5} \times \frac{(365 \times 75)^2}{7}$$

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 a relatively short exposure (*ref protein kinase inhibitor*). Also, if exposure is substantial and elimination of the compound is slow (e.g. polychlorinated 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

Comment [FP1]: At the last COC meeting, Chris Powell mentioned a very potent protein kinase inhibitor.

² Based on an estimated life expectancy of 75 years.

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cases where the epidemiological evidence indicates that cancer risk is not proportional to $(C \times T)$, 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 [FP2]: Committee: Do you want to include this? The Committee has previously decided that there is no need to make an adjustment for exposures to carcinogens during early childhood.

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 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

DRAFT