CC/2016/09

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

G09 Assessing the risks of less-than-lifetime exposure to carcinogens

This paper presents a 2nd draft of the guidance statement on assessing the risks of less-than-lifetime exposure to carcinogens, which has been revised following the discussion at the last meeting. In particular the section on intermittent exposure has been added.

At the last meeting it was agreed that the original discussion paper presented in July should be available for this discussion. CC/2015/12 is attached at Annex 1.

Question for the Committee

Members are invited to comment on the structure and contents of the paper.

COC Secretariat
July 2016

Committee on CARCINOGENICITY

COC/G09 – Version 0.2

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

Assessing the Risks of Less-than-lifetime Exposure to Carcinogens

Introduction

1.   This guidance statement provides advice on the assessment of the risk of less-than-lifetime exposures 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 exposure to a carcinogen. It is sometimes necessary to provide advice following a short-term, intermediate, or intermittent exposure, or a combination thereof. All these can be considered less-than-lifetime exposures. Examples might be after a chemical accident, a food contamination incident, or exposure from soil contamination. This guideline describes methods to quantify the risk following a less-than-lifetime exposure. However, in every case when the carcinogenic risk of a less-than-lifetime exposure is assessed, it should be on a case-by-case basis, with consideration of the mode of action of the carcinogen, the length of exposure and the magnitude of the exposure. It should also be borne in mind that other, non-carcinogenic endpoints may be of significance also at the identified exposure.

Approach proposed by the Committee for genotoxic carcinogens

3.   The approach proposed is based on a publication from an ILSI/HESI[1] workshop on less-than-lifetime exposure to carcinogens held in 2009 (Felter *et al*, 2011). The approach suggested 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 requires that chemical-specific lifetime carcinogenicity data in experimental animals are available. It also makes the pragmatic assumption of a

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

linear dose-response relationship which, in reality may not be the case at the level of chemical to which humans are exposed. 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 $BMDL_{10}$[2] 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 = $\dfrac{BMDL_{10}}{\text{Daily intake of chemical}}$ x $\dfrac{\text{Days in a lifetime}}{\text{Period of short term exposure}}$

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 (assuming a lifetime of 75 years), the MOE would be:

$$\frac{2000}{5} \quad x \frac{(365 \times 75)}{7}$$

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).

5.   Consideration of the mode of action (MOA) of the carcinogen at the dose to which an individual is exposed is critical to understanding the risk. As stated in Felter et al (2011), it is likely that high-dose exposure to a genotoxic carcinogen can result in a different MOA from that expected for low-dose exposure, over a significant portion of lifetime. For example, lower-dose exposure to a genotoxic carcinogen may result in one form of adduct, but the mutagenic response may be shifted when repair processes are overwhelmed. Such an MOA will not follow a *C x T* relationship. This would be an important consideration during short-term exposures to high doses of carcinogen, such as might arise after a chemical incident. If the above methodology is not considered appropriate, advice would need to be given on a chemical- and dose-specific basis taking into account the population exposed, level and nature of exposure, and the potency of the carcinogen.

6.   Felter et al (2011) cite a number of cases where the epidemiological evidence indicates that absolute cancer risk is not proportional to *C x T*. Similarly, the assessment should take account of genetic predispositions and underlying disease states, and the toxicokinetics/toxicodynamics of the chemical concerned

Intermittent Exposures

7.   Felter et al (2011) also state that, in some instances, intermittent exposures may have different risks compared to short-term exposures. However, it is difficult to determine how Haber's Rule could be modified for intermittent exposures in the

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[2] $BMDL_{10}$: lower 95% confidence limit of the benchmark dose for a 10% response

absence of toxicology data that are representative of the exposure scenario. They propose that a practical default approach would be to consider the total number of days' exposure. Using this approach when no appropriate intermittent toxicology data are available, an exposure expected to occur about once every 10 days would be treated in the same manner as a daily exposure for 10% of a lifetime. This is a pragmatic approach that is expected to be conservative due to reasons such as: with an intermittent exposure, either the pharmacokinetics (i.e. not reaching or maintaining steady state) or MOA (i.e. recovery time) would allow for higher acceptable levels (Felter et al, 2011). It is noted that TK/TD data, toxicity studies with intermittent dosing, or, in rare cases, human data that more directly apply to the specific exposure scenario may allow for better risk estimates for intermittent exposures. Specifically, it can be argued that for the same daily exposure at the same dose rate (e.g. 5 mg/kg/day continuous daily exposure for 10% of a lifetime vs. 5 mg/kg/day intermittent exposure once every 10 days for a lifetime), it is more likely that the intermittent exposure will be associated with a lower risk. This is because it is more likely that the continuous exposure would saturate DNA repair capacity or other physiological processes, whereas the intermittent exposure would allow time for DNA repair and other adaptive or inducible physiological processes. Thus, this is a pragmatic approach that is expected to be conservative for the reasons stated above. If chemical-specific data are available, these can be considered to allow deviation from Haber's Rule in individual cases.

Low level background exposures

8.   In some cases, a less-than-lifetime, raised exposure may occur to a genotoxic chemical to which there is a background low level daily exposure. In this case, it would be important to add the low level exposure to the short-term, increased exposure when calculating the MOE of the less-than-lifetime exposure. The MOE for both the low lifetime exposure and the higher level, shorter-term exposures should be calculated and advice given accordingly.

Non-genotoxic carcinogens

9.   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. 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.

Summary

10.   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 and in most exposure situations, an 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. In all cases, assessments should be carried out on a case-by-case basis, with consideration of the mode of action of the carcinogen, the length of exposure and the magnitude of the exposure.

COC
Date (to be added when draft statement is finalised)

CC/2016/09 Annex 1

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

G09 Assessing the risks of less-than-lifetime exposure to carcinogens

This annex contains discussion paper CC/2015/12.

COC Secretariat
July 2016

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

Assessing the Risks of Acute and Short-term Exposure to Carcinogens

Introduction

1.   The COC has yet to write Guideline Statement G9 on 'Assessing the risk of acute and short-term exposure to carcinogens'. The Committee considered this topic in 2007 and 2011 and the conclusions of these discussions are given below to stimulate discussion of a way forward before drafting the statement.

Background

2.   Public Health England and other government departments and agencies sometimes have to provide advice on the carcinogenic risk following a single exposure to a genotoxic carcinogen, for example, following a chemical accident. There is evidence from animal studies that a single exposure to potent genotoxic carcinogens may be associated with higher cancer risk during later life stages. In 2006, the Committee concluded that the acute T25 approach would not be useful for the potency ranking of single exposure genotoxic carcinogens.

3.   Members stated that clarification was needed on whether the concern was about the consequences of single exposures or of short-term exposures. If the latter, it might be more useful to compare short-term with long-term exposures, rather than using single dose studies. However, such data were rarely published and some of the available data had been used in the above exercise. One member pointed out that there were some papers in the literature which might indicate a way forward. These were considered in early 2007 (CC/2007/1). Members considered that the approach to assessing the risk of short-term exposure in a paper by Halmes et al (2000) on the NTP stop-exposure studies and 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) or $C \times T = k$, was not useful. Members commented that it was unlikely that the data from stop-exposure studies of at least 13 weeks duration could be extrapolated to the exposure durations of concern (<10 days). Members also noted that there were some problems with the analysis conducted by Halmes et al, such as the use of tumour responses from some stop exposure studies that were not considered significant in the long-term NTP studies. Members were unhappy with the concept that there was a simple linear relationship between duration of exposure and cancer risk from genotoxic carcinogens for the following reasons: DNA repair processes could be significant at low doses, a

non-linear response could occur due to the complexity of the carcinogenic process, and genotoxic carcinogens may have different effects e.g. at high doses some genotoxic carcinogens could also promote cancer via a cytotoxic mechanism. The relationship could also be affected by latency.

4.   A second paper by Murdoch et al (1992) was not considered helpful either. A third paper by Bos et al (2004) proposed a pragmatic approach to assessing the carcinogenic risk following short-term exposure to genotoxic carcinogens, using the premise that tumour incidence is linearly related to the cumulative dose of a chemical. Members had a number of criticisms of the proposed approach but suggested that it may be possible to adapt the method by using the MOE approach and that this might provide a pragmatic approach to the risk assessment of short-term exposures to genotoxic carcinogens, although there would be some associated degree of uncertainty.

5.   In 2011, the Committee reviewed a publication by Felter *et al* (2011) ([Annex 1](#)) from an ILSI/HESI workshop on less-than-lifetime exposure to carcinogens held in late 2009 (CC/2011/16). The approach suggested relies heavily on Haber's rule (see paragraph 3) provided that chemical-specific carcinogenicity data 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. At the workshop, similar concerns had been expressed about drawing conclusions from the NTP stop exposure studies as those previously expressed by the COC. Overall, the COC considered that, as general guidance, the ILSI/HESI framework was informative but there was concern that the underlying approach was directed towards the US approach to cancer risk assessment which is based on quantitative risk assessment of animal data. It was considered reasonable to use this as one of the references in compiling the Guidance Statement G9 but the Committee did not consider that it should be integrated into UK risk assessment.

6.   However, the Felter *et al* (2011) paper makes some useful points as regards non-genotoxic carcinogens. For these, 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 are provided:
- 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, if exposure is substantial and elimination of the compound is slow (e.g. PCDDs, asbestos), a short-term or acute exposure could still lead to a carcinogenic risk, as the internal exposure will be prolonged.

7.   The paper also discusses a list of considerations to be made when assessing the risk of an acute or short-term exposure to a chemical: such as human specific factors (such as life-stage) and chemical-specific factors (such as mode of action) (Annex 1 pp 516-517). These indicate that any assessment of the risk of acute or short-term exposure to a chemical should be made on a case-by-case basis.

Examples where ILSI/HESI approach has been used

8.   Van den Berg *et al* (2014) calculated the safety of estragole from both long term and short-term (1-2 weeks) exposure to fennel teas using the Margin of Exposure (MOE) approach. Fennel-based teas are traditionally used in many parts of Europe for the symptomatic treatment of digestive disorders and the relief of symptoms during inflammation of mucous membranes of the upper respiratory tract. However, fennel may contain active ingredients of concern such as estragole, which has been shown to be genotoxic and carcinogenic. A number of authors have calculated the MOE for estragole from daily consumption of fennel teas. In all cases, the MOEs have been below 10,000[1], indicating that there may be a concern and a priority for risk management.

9.   Van den Berg *et al* (2014) measured the amount of estragole in 34 samples of fennel teas from various countries. They calculated MOEs by comparing the previously calculated $BMDL_{10}$ values of 3.3-6.5 mg/kg bw/day for the induction of hepatocellular carcinomas in female mice with the estimated daily intakes of estragole resulting from the consumption of 1-3 cups of fennel tea. MOEs obtained for adults were generally $\geq$ 10,000, especially when one cup of fennel tea is used daily during a lifetime (75 years). MOEs for use of fennel tea by children were generally <10,000, indicating a priority for risk management. However, van den Berg *et al* (2000) reasoned that home-made fennel based teas are generally only used during periods of gastrointestinal complaints. The European Medicines Agency had previously indicated that fennel based teas should not be used for more than 2 weeks by adults and less than one week by children under the age of 12. They applied the principles in Felter et al (2011) to assess the potential risk for short-term estragole exposure during a period of one week (children) and two weeks (adults), presumably:

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[1] See Annex 2 for COC's advice on MOEs and likelihood of concern.

$$\text{MOE} = \frac{\text{BMDL}_{10}}{\text{Daily intake of chemical}} \quad x \quad \frac{(365 \times 75)^a}{(7 \text{ or } 14)^b}$$

[a]: Days in a lifetime
[b]: Days in one or two weeks

This resulted in MOE values which were 3 orders of magnitude higher than those obtained when assuming lifetime daily use of fennel based tea, giving no reason for risk management actions.

10.   Reeuwijk *et al* (2014) analysed 50 herbal food supplements claiming to reduce weight for active pharmacological ingredients (APIs) that can be used for the treatment of overweight and obesity. A number of APIs were identified, including the laxative phenolphthalein, a suspected carcinogen. Risk assessment of phenolphthalein, using a BMDL$_{10}$ value of 85 mg/kg bw/day for the induction of hystiocytic sarcomas in B6C3F$_1$ male mice (NTP, 1996) and the estimated daily intakes of phenolphthalein from the herbal supplements taken over a lifetime, resulted in MOE values of 96-30,000. [The NTP genotoxicity data on phenolphthalein are equivocal – negative in the Ames test with and without S9 but positive in the *in vivo* mouse peripheral blood micronucleus test for both male and female mice].

11.   Reeuwijk *et al* (2014) reasoned that herbal food supplements may only be used for relatively short periods of several weeks or months. Applying the principle in Felter *et al* (2011) to assess the potential risk of short-term exposure during a period of several weeks or months on an estimated life expectancy of 75 years resulted in MOE values which may be 2 or 3 orders of magnitude higher than those obtained when assuming life-term (75 years) daily use of the supplements and, therefore, of lower concern.

12.   Galloway *et al* (2013) state that the default Threshold of Toxicological Concern (TTC) for genotoxic carcinogens of 0.15 µg/day gives an estimated risk of 1 in 10^6 excess cancer cases in humans over a lifetime. This has been calculated to be equivalent to a total dose of 3.83 mg over a lifetime of 70 years. Using the ILSI/HESI approach, the daily dose for 6 months to give the same risk is 3.83/182 days or 21.1 µg/day.

Considerations for Guideline Statement G9

13.   Would the Committee wish to define 'acute' and 'short-term' in the guideline statement. For example, the Felter *et al* (2011) paper defined acute as $\leq$ 14 days and short-term as $\geq$14 days to 1 year. However, acute exposure could be defined as $\leq$ 1 day and short-term as 2 days to 6 months.

14.   It is suggested that the guidance recommends that every request for advice on the carcinogenic risk of an acute or short-term exposure should be taken on a

case-by-case basis, with consideration of the mode of action of the carcinogen and the life-stage of the person exposed.

15.   For genotoxic carcinogens, provided that chemical-specific carcinogenicity data are available from which a $BMDL_{10}$ can be calculated, Haber's Rule can be used combined with the MOE approach, as illustrated in van den Berg *et al* (2014) and Reeuwijk *et al* (2014) above, to give an estimate of the likelihood of concern from short-term exposure. Although we cannot be sure that the dose-response relationship is linear, it is a plausible worst-case assumption.

16.   For non-genotoxic carcinogens, if a sustained dose and duration of exposure is required for a carcinogenic response, and the compound is eliminated quickly, the risk from a short-term exposure could be considered negligible. However, if the compound is persistent, this may not be the case. Would it be possible to quantify this risk if there was quantitative data from lifetime exposure?

17.   In all cases, various factors will have to be borne in mind, if the data are available, such as the life stage during exposure, genetic predispositions and underlying disease states, toxicokinetics/toxicodynamics. Are there any other factors to be considered?

COC Secretariat
June 2015

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Assessing the Risks of Acute and Short-term Exposure to Carcinogens

Felter SP et al (2011). A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Critical Reviews in Toxicology 41(6): 507-544.

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

Assessing the Risks of Acute and Short-term Exposure to Carcinogens

Margins of Exposure

The COC discussed the Margin of Exposure (MOE) concept in 2006-7 as a tool to aid risk management and decided on the following interpretations of the size of the MOE:

MOE band	Interpretation
<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