**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:

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

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

[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**
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## 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 |