

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

### Review of a publication from an ILSI/HESI workshop on less-than-lifetime exposure to carcinogens

#### Introduction

1. During the Horizon scanning exercise at the COC meeting in November 2009, attention was brought to the fact that ILSI/HESI workshop was to be held on less-than-lifetime (LTL) exposure to carcinogens and, in November 2010, that a manuscript had been submitted for publication following this workshop. Members were keen to be informed of the outcome of these discussions and any frameworks and processes which emerged from this.

2. The paper is Appended ('A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens' - Felter et al 2011 Crit. Rev. Tox. **41(6)** 507-544).

The paper is briefly reviewed here and Members are invited to discuss the framework that has been proposed.

3. The COC discussed the risk assessment of acute or short-term exposure to carcinogens in 2006 and 2007. It concluded that the acute T25 approach would not be useful for the potency ranking of single exposure genotoxic carcinogens (CC/06/19 and CC/MIN/2006/3). It also considered 3 papers on the issue of acute or short-term exposure (CC/07/1 and CC/MIN/07/1). These included the paper by Hames et al (2000) on the NTP stop-exposure studies and the paper by Bos et al (2004) discussed in appendices E and G of the attached paper, respectively. Members were unhappy with the concept presented 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 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. Members noted that it might be possible to adapt the method proposed in the paper by Bos et al (2004) by using the MOE approach to provide a pragmatic approach to the risk assessment of short-term exposures to genotoxic carcinogens, but that there would be some associated degree of uncertainty. No further progress has been made with this.

Paper by Felter et al (2011)

4. The paper states that the ILSI/HESI workshop arose following a HESI MISTEC multisector meeting in December 2009, from which the present impetus for estimating potential human cancer risk from LTL exposures arose. Participants of the workshop reviewed relevant literature beforehand and the workshop comprised mainly of small break-out groups. The principle of less-than-lifetime is used broadly to mean any exposure which is not continuous, daily exposure including short-term and intermittent exposures. The paper includes many appendices which are excellent up-to-date summaries of a number of associated topics (see below). The paper and the appendices provide an overview of the workshop, the history and describe a proposed framework for assessing risk from LTL exposures to carcinogens

5. The current risk assessment paradigms described are principally those developed by the US Environment Protection Agency (EPA) although the JECFA and EFSA margin of exposure (MOE) and ALARA approaches are also discussed. Furthermore, it is noteworthy that the majority of the participants of the workshop are US based, although there are a number of Europeans who contributed to the manuscript compilation, including members of the COC and COM and a representative from the Dutch National Institute for Public Health and Environment [RIVM].

6. The concept originally introduced as Haber's rule in the 1920s in the context of acute inhalation toxicity (i.e. concentration /dose [c] x time of exposure [t] = toxic effect [k]) to describe the relationship between concentration of the toxic chemical, the time of exposure and the toxic effect is considered to remain applicable. From this, the US EPA specified a default assumption that the lifetime cumulative dose (LCD) is the appropriate dose-metric for cancer risk assessment. In turn, when assessing LTL exposure duration, it is assumed that a high dose over a shorter time period is equivalent to a low dose over a lifetime exposures period ( $k = C_1 \times T_1 = C_2 \times T_2$ ). However it is discussed that more intense, less frequent exposure may produce dose-rate effects and a dose rate correction factor (DRCF) needs to be introduced to correct for these variables.

7. Some possible scenarios which may benefit from guidance on short or intermittent exposures are listed (e.g – contaminant in a pesticide applied to a crop during a single growing season, accidental release of chemicals): It is stated that consideration should be given to defining various exposure durations in humans so that a practical approach to risk assessment methodology is offered. It is important that life stage exposure factors (e.g. early vs later life), physicochemical properties and toxicokinetics are taken into account.

8. The proposed framework (Figure 3 of the paper) consists of a number of sequential questions laid out as a decision tree – these are discussed in length in the paper:

Q1: Are there sufficient chemical-specific and/or (Q)SAR data from which to estimate human excess cancer risk assuming daily lifetime exposure?

Q2: Is there sufficient evidence for a nonlinear dose-response for the cancer endpoint?

Q3: Is the combination of low exposure/dose and limited time for the exposure scenario in question such that, given all the available data, a negligible cancer risk is expected?

Q4: Is Haber's rule (CxT) an appropriate way to estimate the cancer risk or acceptable exposure with adjustments if necessary?

The scope of the work did not include the development of case studies illustrating how the decision tree could work and the development of a suite of case studies was recommended. Guidance on application of the DRCF would also be useful.

9. The following Appendices are also presented:

A: Cancer Biology – outlining the basic science of cancer development in man

B: Cancer risk assessment – history and further developments

Introduces international approaches, JECFA, IPCS and the principle of ALARA. Also an introduction to the JECFA and EFSA MOE approach (BMDL), EPA (US) and Health Canada Cancer Potency Database (CPDB TD 50)

C: Other methods for estimating cancer risk when chemical specific data are limited.

Short term *in vitro* mutagenicity assays

Correlation between MTD and carcinogenic potency

QSAR and *in silico* approaches

TTC

D: Haber's rule (background and reference to the application in cancer risk assessment)

E: Data to consider in developing methods for assessing less than lifetime cancer risk.

- Stop-exposure studies of carcinogens carried out by the NTP
- Studies using equal daily doses
- Studies using unequal daily doses
- Examination of total dose and time exposure using diethylnitrosamine (studies by Druckery et al 1963, 1967)
- Summary of less than lifetime animal exposure studies
- Single dose exposure to carcinogens
- Further evaluation of single dose carcinogen database
- Case studies comparing single and continuous exposures to carcinogens
- Summary of single-dose exposure to carcinogens
- Neonatal mouse studies

F: Statistical models: dose rate correction factors

G: Publications addressing less than lifetime exposure and possible ways to assess

- Bos et al 2004 Acute exposure to genotoxic carcinogens

- Pharmaceuticals (FDA,EMA) – staged TTC approaches for genotoxic contaminants in drugs

H: Exposures during life stages with potentially increased susceptibility.

#### Questions for the Committee

- What are Members' views of the paper and the appendices in general?
- Do Members agree that the approach outlined in Figure 3 is an appropriate, pragmatic way of assessing risk from LTL exposures to carcinogens? Alternatively, would Members support the use of this framework for chemicals for which there are sufficient chemical-specific data from which to estimate human excess cancer risk following daily lifetime exposure?
- Should these frameworks be integrated into UK risk assessment approaches?
- Do Members think that the COC has reviewed sufficient information to produce the Guidance Series statement G09 (Assessing risks of acute or short-term exposure to carcinogens) or should we await the publication of case-studies using this framework?

Secretariat/HPA Toxicology Unit  
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