

## 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. At the last meeting the committee discussed the problem of giving advice on carcinogenic risk following a single exposure to a genotoxic carcinogen and decided that the acute T<sub>25</sub> approach would not be useful in this regard.
2. Dr Carthew has indicated a number of papers which relate to the issue of the carcinogenic risk from short-term exposures. The papers are discussed below.

#### Halmes et al, 2000 (Annex 1)

3. Halmes et al (2000) state that conventional cancer risk assessments are generally predicated on the assumption that cancer risk increases as a function of the cumulative carcinogen dose. For exposure to a carcinogen at a given rate, this would mean that the excess cancer risk is a linear function of the duration of exposure. They state that this is analogous to the concept of toxicity as a linear function of concentration and time, known as Haber's Law<sup>1</sup>.
4. The authors have tested this assumption by comparing findings obtained after short-term exposures with those after lifetime exposures to the same chemicals, using the stop-exposure studies conducted by the NTP. In these studies, some animals were exposed to the test chemical for the standard 2 years, while other animals of the same strain were exposed for a more limited time, followed by an exposure-free period until sacrifice at 2 years of age. However, the shortest time to which animals were exposed in the stop-exposure studies was 13 weeks and the committee will wish to consider whether the findings are likely to apply to single exposures or even those of only a few (up to 10) days duration. Data for the 11 chemicals listed below, and in Table 1 of Annex 1, were found to be suitable for the analyses. Ten of the 11 chemicals had stop-exposure groups only in rats, and one only in mice; only data from males were used in the analysis. The NTP genetic toxicology profiles of the chemicals are given in Table 6 of Annex 1. Note that the analysis includes chemicals which are in vivo mutagens and multisite carcinogens and single-site, non-genotoxic carcinogens. The COC is only asked about the risks of single or short-term exposure to genotoxic carcinogens; the advice which would be given for the latter is that a single exposure or short-term exposure does not present any carcinogenic risk.

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<sup>1</sup> The incidence and/or severity of an adverse health effect depends on the total exposure to a potentially toxic substance. Total exposure is the exposure concentration ( $c$ ) times the duration time ( $t$ ) of exposure ie  $c \times t$  (Gaylor, 2000).

**Chemicals used in study by Halmes et al (2002)**

	<b>Route</b>	<b>Sig. endpoint (NTP)</b>
1-amino-2,4-dibromo-anthraquinone	<i>diet</i>	multiple
2,2-bis(bromomethyl)-1,3-propanediol	<i>diet</i>	multiple
1,3-butadiene	<i>inhal</i>	multiple
coumarin	<i>gavage</i>	kidney
3,4-dihydrocoumarin	<i>gavage</i>	kidney
furan	<i>gavage</i>	liver, mono cell leuk
Methyleugenol	<i>gavage</i>	multiple
<i>ortho</i> -nitroanisole	<i>diet</i>	multiple
oxazepam	<i>diet</i>	kidney (equiv)
pentachlorophenol	<i>diet</i>	nose, mesothelioma
salicylazosuphapyridine	<i>gavage</i>	bladder

5. Data from each tumour type were analysed separately. Adjusted cancer rates were fitted to a Weibull model and a likelihood ratio test was used to test whether exposure groups with stopped exposure differed markedly from the continuous-exposure groups when dose is averaged over the lifetime of the animal. The dose yielding an excess risk of 1% (ED<sub>01</sub>) was calculated, as was the averaging time that yielded perfect agreement between the observed tumour incidence in the stop-exposure study and that predicted by the model fit only to the continuous exposure data: this was called the “equivalent averaging time”.

6. In the following table, the authors summarised the results for the responses in the stop-exposure studies compared to those predicted from the chronic study. Doses for stop-exposure studies were averaged over 104 weeks for comparison with continuous groups. Tumour types are categorised based on whether the response in the stop-exposure study was significantly (p<0.01) greater than, less than, or not different from that predicted from the chronic study. A mixed response indicates that responses for some doses were greater than predicted, while those for other doses were less than predicted.

<b>Chemical</b>	<b>Significantly different<sup>a</sup></b>			
	<b>Greater</b>	<b>Less</b>	<b>Mixed</b>	<b>No difference</b>
1-amino-2,4-dibromo-anthraquinone		1		4
2,2-bis(bromomethyl)-1,3-propanediol	12			6
1,3-butadiene	5		3	5
coumarin				1
3,4-dihydrocoumarin				2
furan	1			
methyleugenol	2			5
<i>ortho</i> -nitroanisole	5	2		1
oxazepam				1
pentachlorophenol	2			
salicylazosuphapyridine				1

a. Response(s) in stop-exposure study relative to that predicted from chronic study

7. Note that it was not always possible to make a straightforward comparison between the results from the stop-exposure and long-term studies. In some cases a carcinogenic response was seen at sites in the stop-exposure group, while no tumours were found at these sites in the chronic groups; doses in the stop-exposure groups were higher than those in the continuous-exposure studies. Note also that the authors appear to have included tumour responses in the analysis which the NTP did not consider to be significant endpoints e.g. for 1,3-butadiene, NTP considered 9 tumour types to be significant (see Table 1 of Annex 1) whereas 13 tumour types were included in the analysis (see above).

8. The impact of the differences was evaluated, where possible, by comparing the ED<sub>01</sub> derived from using only the results from the chronic-exposure group(s) with that estimated by including the stop-exposure group(s). For 24 sites (6 chemicals), the ED<sub>01</sub> decreased when the stop-exposure groups were included and in 2 cases (2 chemicals) it increased (see Table 4 of Annex 1).

9. Calculation of the equivalent averaging times for tumours/sites, where possible, indicated that most averaging times were less than the full 2 years, suggesting that short-term exposures (i.e. 13–66 weeks) were generally more effective in producing tumours than continuous exposure studies would predict.

#### Bos et al, 2004 (Annex 2)

10. Bos et al (2004) address the problem on which the COC is being asked for advice: whether short-term exposure (1-10 days) to a carcinogenic substance may contribute to tumour development and, if so, whether this contribution to the cancer risk can be quantified. They summarise the views of other bodies which have considered this problem. The Health Council of the Netherlands defined a dose-rate correction factor (DRCF) as the factor by which the tumour incidence caused by a specific dose of a chemical carcinogen at long-term, low dose rates is to be multiplied to derive the tumour incidence at short-term, high-dose rates (Verhagen et al, 1994). A number of authors have attempted to estimate the magnitude of the DRCF, either by reviewing available data on animals or humans exposed short-term or acutely, or by using mathematical modelling. The resulting figures range from 0 (the risk of a young child acutely exposed to a late-stage carcinogen developing a tumour at 70 years of age) to 8.3 (derived from animal studies on methyl nitrosourea).

11. The authors also address the topic of subpopulations at extra risk from short-term exposure and comment that it is reasonable to assume that humans will be more susceptible at specific life stages and much less at others. They make the general point that which populations will be at extra risk of an acute exposure depends, among other factors, on the mechanism of action of the carcinogen, the target tissue, and the stage of carcinogenesis affected.

12. The authors conclude by proposing 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. The approach begins by defining “acute exposure” as  $\leq 10$  days and this

is further subdivided into a single-day exposure or 2-10 days. The acceptable risk is based on the “standard” Virtually Safe Dose (VSD) used in the Netherlands which is the dose which, after lifetime exposure, would give a 1 in  $10^6$  additional risk of cancer. Setting a human lifetime at 25,000 days (c.70 years) and making a linear extrapolation of the VSD to a one or 2-10 day exposure, the authors propose an “acceptable” daily dose of (25,000 x VSD) or (2,500 x VSD), respectively.

13. The approach also considers the VSD for a particular sensitive subpopulation. The authors recognise that the available data do not provide a sound basis for setting a DRCF but propose a pragmatic figure of 10. This is applied to the sensitive subpopulations resulting in “negligible” risks of (2,500 x VSD) for a single-day exposure and (250 x VSD) for a 2-10 day exposure.

14. The decision tree associated with this approach is given in Figure 1 of Annex 2.

#### Murdoch et al, 1992 (Annex 3)

15. According to Murdoch et al (1992), with intermittent or time-dependent exposures, lifetime risk is often approximated on the basis of a Lifetime Average Daily Dose (LADD), which is derived by averaging the cumulative dose into equal daily doses over a lifetime. They derive a lifetime equivalent constant dose (LECD), using the concept of relative effectiveness of dosing at different points in time, which gives the same lifetime risk as the actual time-dependent exposure pattern. The ratio  $C = \text{LECD}/\text{LADD}$  then provides a measure of accuracy of risk estimates based on the LADD, as well as a basis for correcting such estimates. Theoretical results based on the Armitage-Doll Multistage Model and the Moolgavkar-Venzon-Knudson two-stage birth-death-mutation (BDM) model, suggest that the maximum value of C, which represents the factor by which the LADD may lead to underestimates of risk, will often lie in the range 2 to 5-fold.

16. The authors illustrate the practical application of these results to two examples in which exposure patterns vary over time. The first example, which is the most relevant, deals with establishing exposure guidelines for carcinogenic volatile organics present in the atmosphere of astronauts working in a closed space station for limited periods. The correction factor C at age  $y = 70$  years was calculated for the multistage model under assumptions about the age at start of exposure, the duration of exposure, the number of stages in the model (1-6) and which of the stages is the dose-dependent stage. There were two main findings. Firstly, there was almost no difference in the values of C for the different durations of exposure, when other assumptions were held constant ie the model predicts that the risk is very nearly proportional to the length of exposure period within the range tested. Secondly, the largest value of C was 2.06, with the smallest as low as 0.03, indicating that the LADD is unlikely to substantially underestimate, but may substantially overestimate, the actual risk corresponding to the LECD. Similar results were reached with the BDM model.

17. The authors conclude that accurate estimates of carcinogenic risk require detailed information on the temporal patterns of exposure and knowledge of mechanism. However, they comment that it is possible to place plausible upper

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bounds on the error in estimates of risk based on the lifetime average daily dose. This paper is quoted in the EPA Guidelines for Carcinogen Risk assessment (see Annex 4) which conclude that, for each dose-response assessment, it is important to critically evaluate all information pertaining to less-than-lifetime exposure (EPA, 2005).

### Questions

18.1 Presumably the committee would agree that, for exposure to a carcinogen at a given rate, excess cancer risk is a linear function of the duration of exposure. However, does the committee agree that excess cancer risk is a linear function of concentration and time? Is it not possible that high exposures for several weeks may result in a different cancer risk than the same total dose administered over a lifetime, for example, because of more sustained cell proliferation at higher doses.

18.2 Can any conclusions be drawn from the paper by Halmes et al (2000) which would assist in the risk assessment of single or short-term (up to 10 days) exposure to genotoxic carcinogens?

18.3 What are Members' views on the paper by Bos et al (2004) and on their proposal for a pragmatic approach to assessing the carcinogenic risk following short-term exposure to genotoxic carcinogens?

18.4 Do Members have any comments on the paper by Murdoch et al (1992)?

16.5 Do Members consider that these papers indicate a way forward on providing advice on the risks of acute or short-term exposure to genotoxic carcinogens?

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## References

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