

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

T25: Recent Developments, and ECETOC Workshop on proposed uses in chemical carcinogen regulation

Introduction

1. The COC has recently been considering approaches to ranking the potency of carcinogens. At the last meeting, the committee saw a paper from the DH Toxicology Unit which ranked a sample of air pollutants using a number of different potency indices, including the T25 (CC/01/17). Members had previously agreed that it would be valuable to update the COC view of the T25 but agreed to wait for publication of the report of an ECETOC workshop on the T25. A prepublication summary report of this workshop is now available. This paper discusses recent proposals for the use of the T25 in classification and labelling of carcinogens, and in human cancer risk assessment, and the report of the ECETOC workshop.

Previous COC advice

2. The COC considered the use of the T25 to estimate carcinogenic potency in 1995 and reached the following conclusions:

- The Committee reviewed the recent proposal to use the T25 to estimate the carcinogenic potency of chemicals. The T25 can be defined as the daily dose (expressed as mg/kg bw/day) resulting in a tumour incidence of 25% at a specific tissue, after correction for spontaneous incidence, within the standard study period for that species. It is simple to calculate the T25 from carcinogenicity bioassay data and there is no need to undertake an analysis of the dose-response curve; but no allowance is made for the effect of intercurrent mortality during its calculation. Hence the T25 is a relatively crude estimate of potency.
- The Committee agreed that, at present, there was little information to ascertain the value of using the T25 to assess carcinogenic potency, particularly with respect to whether it is possible to identify different levels of carcinogenic potency using the T25. There was no information on the concordance between T25 and TD50 rankings. It was agreed that the T25 should be used with caution in the ranking of chemical carcinogens.
- The Committee endorsed its previous view that potency indices can be used as part of the information required to rank genotoxic chemical carcinogens, but are not appropriate to the ranking of non-genotoxic carcinogens. The Committee concluded that the TD50 was still the most practical quantitative estimate of carcinogenic potency available for the ranking of genotoxic carcinogens.

Correlation of T25 with TD50

3. In a 1997 paper, Dybing et al studied the correlation between the T25 and TD50 for a number of chemicals. (This paper was circulated at the June COC meeting as an appendix to CC/01/17, but is attached here as Annex 1 for ease of reference). The authors calculated the T25 for 113 chemicals tested and classified as carcinogens in the US National Cancer Institute/National Toxicology Programme (NCI/NTP). The method by which the T25 is calculated is described in the paper and in CC/01/17 (Annex 1, paragraph 15). The T25 values for 110 of these chemicals were compared with TD50 values for the same tumour sites as published in the Carcinogenic Potency Database (CPDB) of Gold et al. (1984, 1986, 1987, 1990, 1993 and 1995), also identified in US NCI/NTP studies. A log-log plot of T25 versus TD50 values for these 110 chemicals had a slope of 1.05 (linear slope 1.72), a correlation coefficient of 0.96 and a p value of <0.0001. The authors conclude from this that the use of the T25 index is an acceptable parameter describing carcinogenic potency.

4. Dybing et al also undertook an analysis of the correlation between carcinogenic potency and site and species specificity using two sets of NCI/NTP carcinogens. These carcinogens were identified by Tennant (1993) as either TC carcinogens (T=transpecies, C=common multiple site; n=51) or SS carcinogens (showing a highly restricted pattern of tumour induction in a specific site in a single sex of a single species; n=62). The median and mean T25 values were calculated for each group of carcinogens and are given below:

	T25(mg/kg bw/day)	
	Median	Mean
TC carcinogens	16	59
SS carcinogens	178	583

There was an order of magnitude difference between the T25 for the TC carcinogens as a group and the SS carcinogens. However, the authors note that there is a considerable overlap in potency between individual TC and SS carcinogens.

5. The authors also evaluated the relationship between carcinogenic potency and mutagenicity as assessed in the Ames test. Of the 50 TC carcinogens tested for mutagenicity, 82% were positive, compared with 40% of the 62 SS carcinogens. The median and mean T25 values for the group of Ames positive carcinogens was then compared with those of the Ames negative carcinogens. The Ames positive carcinogens were, as a group, approximately 3 times as potent as the Ames negative group.

Use of potency considerations in classification and labelling of dangerous substances

6. EU Directive 67/548/EEC deals with the classification, packaging and labelling of dangerous substances. There are 15 classes of “danger”, such as “explosive”, “very toxic”, “carcinogenic” or “dangerous to the environment”. Annex 1 to EU Directive 67/548/EEC contains a list of some 5000 “existing” and “new” dangerous substances for which classification and labelling have been agreed at Community level according to the degree of hazard. Recommendations on the classification and labelling of “existing” substances are made by Commission Working Groups including the CMR Working Group which harmonises the classification and labelling of carcinogenic, mutagenic and reprotoxic substances. An important element of classification and labelling are the specific concentration limits specified for a range of substances in Annex 1 to Directive 67/548/EEC. These apply to dangerous preparations, which are mixtures of substances of which one is a specified dangerous substance. If a preparation contains a dangerous substance at a concentration which exceeds the specific limit in this annex, the preparation is classified as dangerous. The CMR Working Group has recently recommended that, for carcinogens, the establishment of these specific concentration limits should take into account the potency of a carcinogen and that the T25 should be used as the measure of potency (EC, 1999; Sanner et al, 1997). The Working Group’s guidance as to how potency considerations may be included in the setting of specific concentration limits for carcinogens is attached at Annex 2 and outlined below.

7. In the EU system, substances are classified as carcinogens in one of three categories:

Category 1: Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2: Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of

- appropriate long-term animal studies,
- other relevant information.

Category 3: Substances which cause concern for man owing to possible carcinogenic effects

but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

Concentration limits are specified above which a substance or a preparation has to be classified as a carcinogen. This can be a specific concentration limit, as given in Annex 1 to 67/548/EEC, or a general limit described in a later directive (88/379/EEC). The general limits are 0.1% for Category 1 and 2 carcinogens, and 1% for Category 3 carcinogens.

8. The Working Group has proposed incorporating a consideration of carcinogenic potency in this classification scheme, where sufficient information is available to do this. The preferred measure of potency is the T25, which the group chose largely because it is relatively easy to calculate. The T25 value would be used to place a chemical classified as carcinogenic into one of three arbitrarily selected potency ranges, as follows:

Carcinogens of high potency: T25 value less than ≤ 1 mg/kg bw/day

Carcinogens of medium potency: 1 mg/kg bw/day < T25 value ≤ 100 mg/kg bw/day

Carcinogens of low potency: T25 value > 100 mg/kg bw/day.

The guidance states that the rationale for deriving the 1 and 100 mg/kg bw/day levels was that the majority of carcinogens are expected to fall into the medium potency range.

9. The guidance discusses a number of elements which might modify the preliminary potency evaluation. These include: knowledge of the dose-response relationship, the site/species/strain and gender specificity and toxicokinetics. Knowledge of the mechanism and the relevance of the mechanism to humans can also be used to modify the potency evaluation. In the case of non-genotoxic carcinogens, the guidance states that if a NOAEL is identified from the experimental data and the underlying mechanism(s) support a threshold, reference to the NOAEL may be used for setting a specific concentration limit for the carcinogen.

10. The Working Group proposes the following concentration limits according to the categorisation and final potency classification of a carcinogen:

EU Carcinogen Category	1	2	3
Potency Group			
Carcinogens of high potency	0.01%*	0.01%*	0.1%
Carcinogens of medium potency	0.1%	0.1%	1.0%
Carcinogens of low potency	- **	1.0%	1-5%***

* highly potent Category 1 or 2 carcinogens can be assigned a specific concentration limit lower than 0.01% on a case-by-case basis following in depth consideration of all the available data.

** classified human carcinogens will generally be of high or medium potency in order to be recognised as such.

This review was prepared as a draft discussion document for the Committee. It does not represent the final views of the committee.

*** on a case-by-case basis.

Proposal for use of T25 in human cancer risk assessment

11. Some EU Competent Authorities, through an EU Commission Working Group (on the Technical Meetings for Risk Assessment for Existing Substances), have proposed the use of the T25 in the context of ongoing EU work on “existing” substances (ie industrial chemicals which have not previously undergone a formal EU assessment of health or environmental safety) under the Existing Substances Regulation (EC, 2000). A copy of the guidelines drawn up by the Working Group is attached at Annex 3.

12. In summary, the guidelines propose the following steps for deriving an estimated human lifetime cancer risk level for a carcinogen.

12.1 The T25 for a chemical is calculated from the available carcinogenicity data, as described in Dybing et al, 1997. The method therefore implicitly uses linear high-to-low dose extrapolation for non-threshold carcinogens.

12.2 A scaling factor is applied to the T25 to take account of basic metabolic differences between humans and the test species used in the carcinogenicity study from which the T25 has been calculated. For oral and dermal doses, the scaling factor proposed is the proportion of body weights raised to the 0.75 power ie [weight of human/weight of test species]^{0.75}. This is proposed to take account of differences in caloric demands. Examples of dosage scaling factors, based on default weights, are given in Table 2 of Annex 3. Dividing the T25 by the scaling factor gives the human T25 (HT25).

12.3 No additional uncertainty factor is considered necessary to account for possible interspecies differences, because the study with the most sensitive species/site is used as starting point and because of the conservative character of the linear extrapolation used. However, good data on differences in toxicokinetics and/or toxicodynamics could be incorporated into the risk assessment and the HT25 adjusted if necessary. No additional safety factor is proposed for intraspecies differences. The reasons cited are the conservative linear model and that the available data at this point do not suggest humans to be more sensitive than the most sensitive species.

12.4 The lifetime cancer risk at a given exposure is calculated by dividing the estimated exposure by (HT25 x 4) where (HT25 x 4) denotes the tumourigenic dose in humans corresponding to linear extrapolation to 100% incidence,

eg	HT25	= 343 ug/kg bw/day,
	Exposure level	= 0.01 ng/kg bw/day
	Lifetime cancer risk level	= (0.00001/[343 x 4]) = 7.3x10⁻⁹

The lifetime cancer risk can be qualified if information is available which indicates that the actual human lifetime cancer risk may be higher or lower than that calculated on the basis of the animal data eg from epidemiological studies, dose-response relationships, site/species/gender activity, mechanistic relevance to humans, toxicokinetics or structure-activity relationships.

ECETOC Workshop

13. In November 2000, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) held a workshop to promote discussion of the scientific issues underlying methods for the risk assessment of chemical carcinogens, in response to the proposals outlined above advocating use of the T25 in the classification and risk assessment of carcinogens. An overview of the workshop is attached at Annex 4 (Roberts et al, in press). The overview notes that there seemed to be general agreement that there was sufficient basis for using the T25 dose as an index of carcinogenic potency and therefore as part of the hazard assessment process. However, its use in risk assessment was regarded as more controversial. Some

participants expressed reservations about the current “two-tier” approach for risk assessment of carcinogens depending on whether a chemical is considered to be genotoxic or non-genotoxic. An alternative approach was proposed using the T25 for all carcinogens (whether genotoxic or not). However, others considered that the derivation of a single figure for human cancer risk based on the T25 implied a spurious accuracy and the assumption of a linear dose-response relationship in every case was not justified. Moreover, there seemed to be no way to validate this approach.

Discussion

14. The T25 has been developed as a measure of carcinogenic potency which is simple to calculate. Members are asked to consider the further information provided above on the use of the T25 in hazard assessment, in particular, as proposed for use in classification and labelling of preparations containing carcinogens. Members are also invited to comment on the proposals for the use of the T25 in human cancer risk assessment, although the topic of quantitative risk assessment for carcinogens will be discussed in more detail at a future meeting and there will be a further opportunity for discussion of these proposals at that time.

15. The committee is asked, in particular, to address the following questions:

- does the information on the correlation between the TD50 and the T25 indicate that the T25 is an acceptable alternative to the TD50 as a measure of the potency of genotoxic carcinogens?
- can the T25 be applied to both genotoxic and non-genotoxic carcinogens or does the committee still consider that it is inappropriate to use it to rank non-genotoxic carcinogens?
- is it reasonable to use the T25 as a measure of potency to refine the classification and labelling of preparations containing carcinogens, as proposed by the CMR Working Group?

Secretariat
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