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A Guide to the Classification of Preparations Containing Carcinogens, Mutagens and Teratogens

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SUMMARY AND CONCLUSIONS

The European Council Directive 88/379/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous preparations requires a manufacturer or importer to propose a classification for preparations which might be dangerous to man or the environment. In the Directive indications are given how a preparation shall be classified when it contains carcinogenic, mutagenic or teratogenic substances.

This report:

1. describes a mechanism for determining the *"specific concentration limits"* which should be applied to carcinogenic, mutagenic and teratogenic substances in determining the classification of preparations;

2. outlines indicative criteria for the choice of *"specific concentration limits"* in particular cases;

3. suggests that, in determining the classification of preparations containing carcinogenic, mutagenic and teratogenic substances, account may be taken of interactions between components and of the physical properties of the preparation to define a *"preparation specific concentration limit"* on which classification would be based;

4. recommends that toxicological test data on preparations, when available, should be allowed to contribute to carcinogenic, mutagenic and teratogenic classification of preparations.

A. INTRODUCTION

Classification and labelling of dangerous substances was first introduced with EEC Directive 67/548/EEC known as the Dangerous Substances Directive (DSD) (EEC, 1967). Since then the subject has been under almost continuous discussion and modifications have been made to the original text. The most important of these was the Sixth Amendment to this Directive of 18th September 1979 (79/831/EEC) introducing a notification procedure for new substances as well as an obligation to classify and label existing substances on the basis of available toxicological, ecotoxicological, physical and chemical data.

Detailed requirements for classification and labelling were subsequently laid down in the Guide to the Classification and Labelling of Dangerous Substances and are available as Annex VI, part IID of the DSD introduced by the Directive 83/467/EEC (EEC, 1983). This Guide describes the criteria to be used for classification of preparations and to determine Risk and Safety Phrases. Parallel to the DSD a number of specific Preparations Directives have been elaborated (e.g. on pesticides,solvents and paints etc.) (cf. Appendix 1).

With the adoption of a general Dangerous Preparations Directive (DPD) a general concept for the classification and labelling of preparations has been introduced to be implemented by June 1991.

Under the DPD the health hazards of a preparation may in general be assessed *"by one or more of the following methods: (a) by the conventional method ....using concentration limits; (b) by determining the toxicological properties of the preparation....."*. The DPD states that the latter option is not permitted when the health hazard is associated with the carcinogenic, mutagenic and teratogenic properties of substances present in the preparation.

The ultimate aim of the DPD is that all preparations should be classified on the basis of the *"specific concentration limits"* for their constituent substances which will eventually be listed in Annex 1 of the DSD to Directive 67/548/EEC (DSD). Such specific concentration limits are however not

currently available for most dangerous substances and at present it is necessary to classify most preparations using the generic concentration limits specified at point 6 of Annex 1 (Table 6) to the DPD (cf Appendix 2).

The purpose of this report is to identify and review the factors which will provide a rational basis for the allocation of such *"specific concentration limits"* and further, to review the factors relating to the substance in a particular preparation which may be taken into account before deciding on a *"preparation specific concentration limit"*.

The chemicals considered in this report are only for illustrative purposes; it is recognised that different concentration limits may be specified in various existing directives.

This report is targeted at toxicologists located within both regulatory authorities and industry who may be called upon to set such limits.

B. BACKGROUND

The EEC procedure for the classification of carcinogenic, mutagenic and teratogenic (CMT) substances is not an independent process of decision making. For its criteria the EEC lent heavily on international scientific organisations.

The classification of human carcinogens and mutagens of the International Agency for Research on Cancer (IARC) was an important model for classification methods (Supplement 7 and Preamble of the IARC Monographs). This process assesses the weight of evidence for human and animal carcinogenicity and genotoxicity and does not normally consider mechanistic or pharmacokinetic information, which may be of importance in determining the relevance of experimental data to man. In a previous report general guidance was given for the classification of new and existing carcinogenic, mutagenic and teratogenic substances (ECETOC, 1986). In general, classification schemes are limited to available information concerning a carcinogenic, mutagenic or teratogenic hazard identification*. The EEC classification is the criterion for attracting specific R(Risk) phrases*. None of these schemes take into account other factors critical to risk assessment e.g. exposure or mechanistic considerations.

The DPD adds a new dimension to the classification process namely an attempt to determine the level at which the CMT substance presents an unacceptable risk to the potentially exposed population. This being the case the opportunity presents itself to introduce those factors normally considered during risk assessment. These include, for example exposure potential, mechanism of action, potency, metabolism and pharmacokinetics. Thus a toxicity classification whilst still relevant, ceases to be the only factor in our analysis. These aspects will be elaborated in the following chapters as

*Appendix 3 contains the working definitions of the terms used in this report and the significance of the R (Risk) phrases (EEC, 1979).

appropriate.

For the purpose of this report ECETOC defines two types of concentration limits: *"specific concentration limits"* and *"preparation specific concentration limits"*.

"*Specific Concentration Limits*"

The exercise of defining these limits for individual substances in preparations contains some elements of risk assessment. For a given substance, it is necessary to define a concentration level above which preparations containing that substance would be regarded as "dangerous", thus attracting appropriate classification and labelling. Conversely, preparations containing less than the defined concentration level of that substance should be regarded as not "dangerous" on account of the properties of that substance.

The classification of substances as carcinogens, mutagens and teratogens for the purpose of the DSD is an exercise in the assessment of intrinsic toxicity. Thus Category 1 carcinogens, for example, are so classified because there is an accepted causal relationship between exposure and effect in man, although no differentiation is made between the substances with respect to potency. With Category 2 carcinogens there is good evidence that the substance causes cancer in animals, although again potency is not taken into account, nor is an assessment made of the relevance of such data in predicting hazard to the human being, although it is normally assumed that Category 2 carcinogens would be carcinogenic for man. Thus it does not follow that a Category 1 carcinogen is necessarily more dangerous for man than a Category 2 carcinogen, but rather that circumstances have arisen in the past in which its toxic effect in the human being has become evident.

The process to be described for allocating *"specific concentration limits"* under the DPD applies equally to all substances classified under the DSD as carcinogenic, mutagenic or teratogenic. This process enables a *"specific concentration limit"* for an individual substance for a given property to be determined independently from the determination of the original CMT

classification within the DSD. This procedure should be performed by the EEC expert committee who assigns these limits for inclusion in Annex 1 of the DSD.

The elements of the risk assessment process inherent in the definition of *"specific concentration limits"* require a review of factors relevant to the risk presented by the substance in question in preparations, and the exercise is thus not limited solely to a consideration of the DSD classification category assigned to the substance.

"Preparation Specific Concentration Limits"

An assessment along the above lines would satisfy the requirements of the present Dangerous Preparations Directive (DPD) for determining a concentration limit for inclusion in Annex 1 of the DSD. Each CMT substance, however, could be further considered in the context of a particular preparation in question before a *"preparation specific concentration limit"* is determined. Factors relating to physical properties and the potential for interaction would be relevant and may be used to determine the level at which that particular preparation attracts *the original classification symbol and risk phrase* attached to the substance under the DSD.

C. DETERMINATION OF SPECIFIC CONCENTRATION LIMITS

1. *INTRODUCTION*

Definition of *"specific concentration limits"* for individual substances must of necessity (cf. Chapter B) involve elements of risk assessment. This should include a review of the quality and quantity of data relating to the biological property in question. In the case of all three effects (CMT), the potency of the substance is a crucial factor which must be assessed and taken into account. Other factors will depend on the effect under consideration and are considered in detail in subsequent sections.

Before a preparation can be correctly classified a thorough knowledge of the substances involved and the chemical classes to which they belong is necessary. A comprehensive literature search is thus an essential starting point and the data should be critically reviewed, considering the adequacy of the protocol for the chemical under test and whether it meets currently acceptable guidelines.

Consideration of a substance which possesses more than one characteristic toxic property may indicate the need for more than one *"specific concentration limit"* for that substance. The classification of preparations containing such a substance should take separate account of each of these limits.

It is essential that assignment of the *"specific concentration limits"* be conducted on a case by case basis.

2. *CARCINOGENS*

At present it is proposed under the DPD that carcinogens for which *"specific concentration limits"* do not appear in Annex 1 of the DSD should be treated generically for classification purposes in preparations, with

concentration limits of 0.1 % applying to Category 1 and 2 carcinogens and 1.0 % to Category 3 carcinogens.

As discussed above the DSD classification into Categories 1,2 and 3 is not in itself a sufficient basis for allocating a *"specific concentration limit"*, and these substances should be considered individually. It is likely to be necessary to use a wider range of limits, since some carcinogens may be of concern at levels below 0.1 % while others will be of little concern at 1 % or greater.

The concentration limits of 0.1 and 1.0% derive from Annex 1 - Table 6 of the DPD (cf Appendix 2). It is accepted that they are pragmatic values more or less central in the range of concentrations of interest for carcinogens in preparations. While it is anticipated that most carcinogens would attract one or other of these limits on individual consideration, it is proposed that for practical purposes the following concentration limits should be adopted:

A	0.01 %
B	0.1 %
C	1.0 %
D	5 %

As with limits B and C, there is no specific scientific justification for limits A and D, but it is assumed that these limits span essentially the full range of concentrations over which carcinogens in preparations are likely to be of concern.

In order to assign a *"specific concentration limit"*, the "potency" of the substance as a carcinogen in man is the factor which requires detailed consideration. In this report the term "potency" is defined as the magnitude with respect to dose, of the activity (carcinogenic, mutagenic or teratogenic) of a substance in the species under consideration. This

definition requires amplification and the subject is discussed in ECETOC (1982), to which the reader is referred. The approach adopted in this report (ECETOC, 1982) is to express "potency" in terms of the presence or absence of a number of factors (expressed below) which, taken together, cover dose, intensity and incidence and relate specifically to the species of concern (i.e. man).

The relevance to man of the mechanism of carcinogenic action in animals (if known) can be of overriding importance. In the absence of sufficient scientific evidence to demonstrate the lack of relevance to man, it must be assumed that effects shown in animals may also occur in man.

In the case of carcinogens the expression of both dose and intensity (or incidence) is so complex as to preclude the calculation of a simple overall mathematical index of potency such as the TD_{50} approach described by Gold et al. (1989), although this latter concept can be of value in particular circumstances (see below).

2.1. Procedure

The schematic approach to the allocation of *"specific concentration limits"* for substances classified as Category 1, 2 or 3 carcinogens by the EEC is exemplified in Figure 1.

If there is sufficient evidence available to conclude that the mechanism of action is not relevant to man, then exposure of human beings to the substance in question will not lead to cancer and preparations containing the substance should not require labelling as carcinogenic. In practice, and given that such substances will already have been classified as carcinogenic in the DSD, it is proposed that the existence of adequate evidence in this area should lead automatically to allocation of limit D (5%), without the need to consider any other criteria until such time as the DSD classification is changed.

When the mechanism of action is relevant to man, a second step is the assessment of the evidence for a genotoxic mode of action. According to

current thinking, evidence for a genotoxic mechanism suggests that a threshold for carcinogenic activity is difficult to justify. In the absence of a clearly defined threshold caution should be exercised and a genotoxic mechanism of carcinogenic action is therefore pivotal in the initial choice of *"specific concentration limits"*. Those carcinogens for which there is evidence for a genotoxic mechanism would in general qualify for limit B (0.1%); those with a non-genotoxic mechanism would in general qualify for a limit C (1%).

2.2. Genotoxic Carcinogens

For the genotoxic carcinogens also other criteria should be considered. On the basis of these general principles, substances attracting limit B (0,1%) would be expected to show at least some of the following characteristics (on the basis of human or animal data) thus demonstrating a relatively high "potency" when considered from the point of view of effects in man:

(i) evidence for a genotoxic (as opposed to a non-genotoxic) mechanism of carcinogenic action, usually but not necessarily on the basis of positive responses in in vivo and in vitro mutagenicity studies;

(ii) a large increase in the incidence of malignant neoplasms (at least a fourfold increase over the background incidence in that strain of animal);

(iii) multiple (2 or more) malignant neoplasms in affected tissues, (assessed per tissue per animal);

(iv) carcinogenic activity at exposure/dose levels low relative to the maximum tolerated dose (e.g. <500 ppm inhalation or <50 mg/kgbw/d ingestion);

(v) short latency period (malignant neoplasms occurring within the first half of the normal lifespan);

(vi) development of compound induced malignant neoplasms after a single or very few exposures/doses;

(vii) induction of malignant neoplasms in a variety of organs (2 or more);

(viii) induction of malignant neoplasms of a rare pathological type in organs with a low natural incidence of neoplasia;

(ix) induction of malignant neoplasms in a number of species;

(x) insufficient evidence that the substance has a relatively low bioavailability by the relevant exposure route in man.

The factors contained in the above list are based on those defined in ECETOC (1982) as those likely to lead experts to judge that a substance has a high carcinogenic potency. Substances described in the DSD as Category 1 or 2 carcinogens will have shown some of these characteristics.

High cancer incidence at low exposure levels (ii), (iii), (iv) is self explanatory as an indication of potency, but the dose/response characteristics should be assessed in the context of both toxicity and potential for human exposure. High incidence of cancer only at near-lethal exposure levels is of reduced relevance, and results obtained by routes of exposure or at exposure levels which do not reflect potential human exposure should be appropriately qualified. A short latency period (v) and induction of tumours after a single or very few exposures (vi) are factors also associated with high potency (e.g. nitrosamines, Bartsch and Montesano, 1984; 1,6 dinitropyrene, Ohgaki et al., 1984). Neoplasms in multiple target organs (vii) and in more than one species (ix) may reflect high potency suggesting that the substance may well be active in other, untested species such as human beings. Induction of malignant neoplasms in organs with a low natural incidence of neoplasia (viii) is another factor which increases concern. For example the induction of angiosarcoma of the liver (a very rare tumour)

by vinyl chloride in rats, mice and man leads to more concern than do mouse hepatocellular carcinomas induced by a variety of chemicals such as dieldrin and trichloroethylene (the mouse has a very high spontaneous liver tumour incidence) (Grasso and Hardy, 1975).

Finally evidence relating to bioavailability (x) should be considered; extent of absorption may vary considerably from one species to another and some carcinogens may be activated (or inactivated) by enzymatic, chemical or microbial activity in the gut of one species but not of another, e.g. azo dyes (Watabe et al., 1980; Milman and Peterson, 1984).

Carcinogens with a genotoxic mode of action which generally attract concentration limit B (0.1%) should be further considered for concentration limits A (0.01%) and C (1.0%) on the basis of the extent to which the above criteria are satisfied.

2.3. Non - Genotoxic Carcinogens

In contrast to the above, carcinogens initially attracting limit C (1.0%) would be expected to show at least some of the following characteristics, when considered from the point of view of effects in man:

(i) evidence for a non-genotoxic (as opposed to a genotoxic) mechanism of carcinogenic action usually on the basis of negative *in vivo* and *in vitro* studies;

(ii) a small increase in the incidence of malignant neoplasms (less than a fourfold increase over the background incidence in that strain of animal);

(iii) a small number (less than 2) of malignant neoplasms per individual tissue per animal;