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

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CONTENTS

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;

(iv) carcinogenic activity only at exposure/dose levels approaching or exceeding the maximum tolerated dose (e.g. >500 ppm inhalation or >50 mg/kgbw/d ingestion);

(v) long latency period (malignant neoplasms not occurring within the first half of the normal lifespan);

(vi) development of compound induced malignant neoplasms only after long term or life time exposure;

(vii) induction of malignant neoplasms confined to a single organ;

(viii) induction of malignant neoplasms only of a type with high and variable background incidence;

(ix) carcinogenic activity limited to one of a number of species tested;

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

Those substances classified in the DSD as Category 3 carcinogens are likely to possess some of these characteristics. Substances qualifying initially for limit C (1%) should be further considered for limits B (0.1%) or D (5.0%) on the basis of the extent to which the above criteria are satisfied.

2.4. Allocation of "*Specific Concentration Limits*"

In assessing carcinogens against the criteria in these lists, it is important that all relevant data be considered, be they human, animal or in vitro. Although the wording of the criteria has been chosen to reflect an animal data base, human information in any of the relevant areas is clearly relevant and may well be of overriding importance in determining "*specific concentration limits*". The assessment of such human data against the criteria will be a matter for expert judgment.

It is envisaged that experience in use of these principles will lead to more precise definition of the boundaries between the different *"specific concentration limits"*.

This approach to the allocation of *"specific concentration limits"* is exemplified in Table 1 in which eleven substances classified as Category 1, 2 or 3 carcinogens* by the EEC were assessed against the criteria described above.

Two of these eleven substances (aldrin and trichloroethylene) qualify for limit D on the ground of their being sufficient evidence to conclude that the mechanism of action is not relevant to man.

Of the remaining nine substances, the first five satisfy criterion (i) (genotoxic mechanism of carcinogenic action) as well as a higher proportion of the other criteria than the other four substances. It seems probable that the criteria listed are not entirely independent, in the sense that possession of a genotoxic mechanism of carcinogenic action may well increase the probability of a substance satisfying several of the other criteria. This observation, together with the implication that a carcinogen with a genotoxic mechanism of action might well not possess a threshold of activity, suggests that criterion (i) should be of prime importance in allocating *"specific concentration limits"*. It is thus proposed that these five substances should prima facie be considered for *"specific concentration limit"* B (0.1%). It is noteworthy that these five include all the DSD Category 1 and 2 carcinogens and none of those in Category 3.

In considering further which of these five should be further considered for *"specific concentration limit"* A (0.01 %), a numerical indication of

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

the strength of the carcinogenic activity becomes important. Those substances expressing activity at low dose/exposure levels are of more concern than those expressing activity only at higher levels. To assist in this process, the listed substances have been allocated to one of four categories of *"effective dose"*. The range of doses covered by these categories is described in Table 1, and the basis for categorisation is the TD_{50} as described by Gold et al. (1989). The TD_{50} is defined as the dose rate that induces tumours in half the test animals at the end of a standard lifespan in the absence of tumours in control animals. "For each species, the reported TD_{50} value is the most potent from among sites that a published author evaluated as positive". It is re-emphasised that such a TD_{50} cannot be used as a sole determinant of carcinogenic potency. Its use, however, is an aid to judgment, along with other criteria for the process of allocating *"specific concentration limits"*. Of the five substances considered above, two (bis(chloromethyl)ether and N,N'-dimethyl-nitrosamine) have a TD_{50} within dose range 1, while the other three (benzidine, vinylchloride and dimethylcarbamoylchloride) are in range 2. It is proposed that the former two substances should attract limit A (0.01%) while the other three should attract limit B (0.1%). These three are sufficiently active not to be considered for limit C (1.0%).

The remaining four chemicals (chloroform, 1,4-dioxane, methylchloride and thiourea) all satisfy the criterion for a non-genotoxic mechanism of action (i) and it is proposed that they should <u>prima facie</u> be considered for limit C (1.0%).

1,4-dioxane which satisfies very few of the criteria (ii) to (x) and has a very high effective dose (range (4)) and thiourea, which satisfies none of the criteria, should be assigned to limit D (5.0%). The remaining two chemicals (chloroform and methylchloride should retain limit C (1.0 %).

This analysis thus leads to the following groupings:

Limit A (0.01 %)	- bis(chloromethyl)ether, - N,N'-dimethylnitrosamine,
Limit B (0.1 %)	- vinylchloride, - benzidine, - dimethylcarbamoylchloride,
Limit C (1.0 %)	- chloroform, - methylchloride,
Limit D (5.0 %)	- aldrin, - trichloroethylene, - 1,4-dioxane, - thiourea.

Although of the small sample taken all Category 1 and 2 carcinogens attract limits A (0.01%) and B (0.1%) and all Category 3 carcinogens attract limits C (1.0%) and D (5.0%), this may not always be the case and Category 1 carcinogens do not necessarily attract limit A. Again, in this sample, all the carcinogens attracting limits A and B have a genotoxic mechanism of action, which is possessed by none of those attracting limits C and D. Although fair as a generalisation this may not always be the case, and it is quite possible to envisage, for example, a non-genotoxic carcinogen which expresses its activity at lower dose/exposure levels, being assigned limit B or even limit A.

3. *MUTAGENS*

A guide to the classification of mutagens has been produced by ECETOC (1987) and Arni et al. (1988). It is important that a distinction be made between the weight of evidence from mutagenicity studies which supported the conclusion that a substance was a carcinogen with a genotoxic mode of action and the scientific evidence that a substance was likely to be a

germ cell mutagen. In particular the ability to interact with and possibly cause heritable damage to germ cells is of paramount importance since "*heritable genetic damage*" is the criterion for attracting the R (Risk)46 phrase (EEC, 1979). ECETOC notes that the wording for the R46 phrase is open to more than one interpretation. Human heritable germ cell mutation transmitted from one generation to the next are by their very nature extremely difficult to detect epidemiologically and in consequence no human mutagens (EEC - Category 1) have as yet been unequivocally identified.

At present the proposed DPD states that the appropriate labelling will be required if a category 1 or 2 mutagen is present in the preparation at levels equal to or greater than 0.1%. When a category 3 mutagen is present in the preparation a concentration limit of 1 % is proposed in Annex 1 - Table 6 of the DPD (cf Appendix 2). It is accepted that they are pragmatic values covering the range of concentrations of general interest in preparations.

In this report attention has been restricted to those substances which cause heritable germ cell damage, thus reliance would primarily be placed on in vivo germ cell mutagenicity data. In the absence of such data, results of other in vivo assays may be relevant. For example, positive data from an in vivo cytogenetics assay in bone marrow together with evidence that the substance interacts with germ cell DNA could allow the conclusion that the substance should be classified as a potential germ cell mutagen.

ECETOC suggests that these absolute levels should be applied only after consideration of the factors described below and that in specific cases it may be necessary to assume a preparation to be dangerous if a germ cell mutation is present at levels less than 0.1%. As discussed for carcinogens, a wider range of limits may be appropriate and for practical purposes the following "*specific concentration limits*" are proposed:

A	0.01%
B	0.1 %
C	1.0 %

It would be anticipated that most mutagens would fall into concentration limits B or C as specified in Table VI of the DPD but that a *"specific concentration limit"* A as suggested by ECETOC may be deemed appropriate under certain circumstances.

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

As with carcinogens the presence of evidence sufficient to conclude that the means by which the response elicited is not relevant to man, can be of overriding importance in concluding that classification is not necessary. At the present time no example can be provided, so this situation remains hypothetical. If there is sufficient evidence available to conclude that the mechanism of action is not relevant to man, then exposure of the human being to the substance in question will not lead to mutation and preparations containing the substance should not require labelling as mutagenic. In practice, and given that such substances will already have been classified as mutagenic in the DSD, it is proposed that the existence of adequate evidence in this area should lead automatically to allocation of limit C (1%), without the need to consider any other criteria until such time as the DSD classification is changed.

When there is evidence for a genotoxic mode of action the ability of the mutagen to cause changes in ploidy, particularly aneuploidy should be investigated. In addition quantitative aspects of mutagenicity should be assessed by reviewing the ability to induce effects after a single exposure and/or at low dose levels. These aspects are exemplified by the following criteria which, taken together, help in defining the "potency" of a substance as a mutagen:

(i) Genetic effects

a. germ cell effects at gene and chromosome level observed in one or more than one species;

b. germ cell effects at gene or chromosome level observed in one or more than one species;

c. gene and chromosome effects in somatic cells in multiple organs and in more than one species;

d. gene or chromosome effects in somatic cells in multiple organs in a single species;

e. gene and chromosome effects in somatic cells in a single organ in more than one species;

f. gene or chromosome effects in somatic cells in a single organ in a single species.

(ii) changes in ploidy, particularly aneuploidy ;

(iii) dose related responses extending to low levels;

(iv) effects seen at doses lower than the maximum tolerated dose;

(v) effects after a single exposure.

The mutagens which have effects at the gene and at chromosome levels would prima facie apply for limit B (0.1%). Further considerations for choosing limit A (0.01%) or limit B (0.1%) should be determined by the extent to which the above criteria are satisfied. Those mutagens for which there is no unequivocal evidence for gene and chromosome damage would apply for a limit C (1%). Further considerations for choosing limit B (0.1%) or C (1.0%) should also be determined by the extent to which the above criteria are satisfied (cf Figure 2).

The above approach is exemplified in Table 2 which also includes an estimate of the lowest effective dose (LED) to cause a positive response in germ tissue in vivo. Such an approach permits the ranking with respect of their "potency" of the six existing mutagens proposed by the EEC as Category 2 or Category 3 mutagens. It is recommended that *"specific concentration limits"* be assigned as follows:

Limit A (0.01%)	- ethylene oxide (EO),
Limit B (0.1%)	- 1,2-dibromo-3-chloropropane (DBCP), - diethylsulphate (DES),
Limit C (1.0%)	- benz(a)pyrene (BaP), - hexamethyl phosphoric triamide (HMPA), - dimethylsulphate (DMS).

EO is considered to be the most potent mutagen in this series as it causes gene and chromosome effects in germ cells in more than one species and at low dose levels. Furthermore there are human data suggesting chromosomal effects following very low exposures to EO (e.g. 5 - 10 ppm, Stolley et al., 1984). Therefore, a *"specific concentration limit"* of 0.01% would be recommended for this type of mutagen if it were to be incorporated into a preparation.

DBCP and DES both cause germ cell effects but at high dose levels. Thus a *"specific concentration limit"* of 0.1% may be appropriate, although it is recognised that DBCP could attract a 0.01 % limit if it had been tested for both gene and chromosome effects. This dilemma illustrates the problem in attempting to assign a *"specific concentration limit"* to mutagens when the data base is incomplete.

The remaining three mutagens reviewed either show no unequivocal evidence of germ cell effects or do so at relatively high concentrations. Under these circumstances a *"specific concentration limit"* of 1% appears justified.

4. *TERATOGENS*

According to the DPD (EEC, 1988) those teratogens for which no specific limits appear in Annex I of the DSD should be treated generically for classification purposes, with concentration limits of 0.5 and 5% respectively for Category 1 and 2 teratogens (Annex 1 - Table 6 to the DPD; cf Appendix 2). It is accepted that they are pragmatic values covering the range of concentrations of general interest in preparations. Unlike carcinogens and mutagens ECETOC agrees that for the establishment of *"specific concentration limits"* of teratogens in preparations the two levels proposed in the DPD can be maintained i.e. 0.5 and 5%.

Teratogens are identified largely on the basis of animal experiments. Unequivocal evidence of a teratogenic action of a chemical in human beings is relatively rare, very few chemicals being classified as human teratogens compared to the large number of animal teratogens recognised.

As with carcinogens and mutagens sufficient evidence that the mechanism of action is not relevant to man will be of an overriding importance. The mechanisms of teratogenicity are still ill defined and there is a concern that one single exposure of a woman during a specific period of pregnancy may result in malformations in the offspring. As there are similarities in embryological development in all mammals, it is a reasonable assumption, in the absence of evidence to the contrary, that a substance shown to be teratogenic in an animal model possesses the potential to be a human teratogen. Hence the classification of a preparation containing a teratogen must be based on the assumption that it poses a similar hazard to women to that demonstrated in animals.

For the reasons given above it is not currently possible to propose a schematic approach to assign *"specific concentration limits"* of teratogens in preparations. When considering substances individually for the allocation of *"specific concentration limits"* a number of factors which, taken together, define the overall "potency" of a teratogen should be considered. These factors include both quantitative aspects of

demonstrated effects as well as information indicating the relevance of effects observed in animals to man.

The teratogenic "potency" of a preparation is dependent on the "potency" of the substance or substances contained therein. The criteria for determining teratogenic potency are less definitive than for most other toxic end points as mechanistic knowledge is lacking. Clearly the dose response characteristics, including the no-observed effect level, are critical to this but must have superimposed the toxic characteristics of the substance on the dam. Thus a substance which causes its effects on the foetus only at dose levels which approach those which are also maternally toxic would in general be considered less "potent" than one which causes its effects at considerably lower doses than those toxic to the dam. This must be considered in the context of potential human exposure. For example a teratogen preferentially active in the foetus but only at an exposure level which is high relative to human exposure would be of less concern than a teratogen which produces effects in animals only at levels approaching maternal toxicity but which are comparable with human exposure.

A further aspect of "teratogenic potency" is reflected by the number of species in which the substance is known to be a teratogen. Thus the more species in which a substance has a teratogenic action the higher the probability of effects in man and therefore the higher the "potency". Similarities in pharmacokinetic and metabolic action between the test species and man would also increase the level of concern. The type and frequency of malformations elicited also provides information on which "potency" can be determined. The more types of malformations or the rarer the type of effect produced, the higher is the level of concern.

Substances attracting a limit of 0.5% would be expected to fulfil at least some of the following effects:

(i) insufficient evidence (e.g. metabolic or pharmacokinetic data) to conclude that the mechanism of action is not relevant to man;

(ii) minor foetal abnormalities in significant excess in relation to the historical control data in more than one species;

(iii) major foetal abnormalities in significant excess in relation to the historical control data in a single species;

(iv) unusual and rare foetal abnormalities;

(v) foetotoxicity (including teratogenicity) in the absence of maternal toxicity;

(vi) foetal abnormalities associated with a steep dose response relationship;

(vii) foetal abnormalities at low exposure levels;

(viii) foetal abnormalities following a single exposure;

(ix) insufficient evidence that the substance has a relatively low bioavailability by the relevant exposure route in human beings.

Criteria for the allocation of a 5% concentration limit are:

(i) sufficient evidence (e.g. appropriate metabolic or pharmacokinetic data) to conclude that the mechanism of action is not relevant to man;

(ii) minor foetal abnormalities in significant excess in relation to the historical control data in only one species;

(iii) only one type of minor foetal abnormality is observed;

(iv) a common type of foetal abnormality is observed;

(v) foetal abnormalities are only evident at maternally toxic doses;

(vi) foetal abnormalities observed associated with a shallow dose response relationship;

(vii) foetal abnormalities are observed only at high exposure levels;

(viii) foetal abnormalities are observed only after multiple exposures;

(ix) sufficient evidence that the substance has a relatively low bioavailability by the relevant exposure route in human beings.

In Table 3 five chemicals proposed as Category 2 teratogens by the EEC have been assessed against these criteria which, taken together, define the "potency" of a teratogen. In addition an estimate of the quantitative aspects of the dose leading to effects is obtained by using the lowest observed effect level and no-effect level from those studies that did provide such information.

This analysis leads to the following groupings:

Limit A (0.5%)	- arsenic and compounds, - lead acetate, - Warfarin,
Limit B (5%)	- benz(a)pyrene, - ethylene thiourea.

From this tabulation, arsenic, lead acetate and Warfarin clearly qualify for the 0.5% category as most of the criteria are met and the lowest effect levels are also relatively low. Benz(a)pyrene clearly qualifies for the 5% category as the data largely do not fit the criteria and the lowest effect level is relatively high. Nevertheless, as a no-effect level has not been clearly established in the published literature some uncertainty must attach to this classification. The data on ethylene thiourea does not fit some of the criteria but the lowest effect and no-effect levels are relatively high (cf Table 3) and thus fits it the 5% category.

D. DETERMINATION OF PREPARATION SPECIFIC CONCENTRATION LIMITS

The DPD currently does not allow for modification of concentration limits listed in Annex 1 to the DSD but does envisage the possibility of the manufacturer of the preparation taking into account interactions between components and the physical properties of a preparation. ECETOC recommends that this option be considered in appropriate circumstances. The allocation of a *"preparation specific concentration limit"* for a CMT substance in a particular preparation should only be made after full consideration of the physical and chemical characteristics of the preparation in which the CMT substance is present.

Tables 4, 5 and 6 represent schematically the procedures to be used for the establishment of *"specific and preparation specific concentration limits"*. This chapter only outlines the basic principles of establishing *"preparation specific concentration limits"* and no attempt has been made to represent real situations in existing preparations.

ECETOC, **however, recommends that for some preparations the possibility of proposing *"preparation specific concentration limits"* for components should be considered.**

1. THE EXTENT TO WHICH THE PROPERTIES OF THE SUBSTANCE ARE MODIFIED BY THOSE OF THE PREPARATION

This broad area may be divided as follows.

1.1 Interactions between the CMT Substance and Other Components may occur as a Result of Physical, Chemical or Biological Factors

Physical interaction may, for example, reduce the volatility and therefore exposure to a specific CMT component of the preparation. An example of physical interaction might be a polymer containing residual monomer (e.g. vinylchloride monomer in polyvinylchloride; dyestuffs

embedded in polymers) but where the normally volatile monomer is tightly bound to the polymer particles, thus significantly reducing the exposure potential.

Chemical interaction may destroy a substance or produce a new one. If this occurs within a preparation, then clearly the nature and composition of that preparation will change and it will need classification according to its new composition. Chemical interaction is exemplified by the possible formation of a highly "potent" carcinogen such as bis(chloromethyl)ether in a preparation containing hydrochloric acid and hexamethylenetetramine. Another example is the possible formation of nitrosamines if a preparation contained nitrite and a secondary or tertiary amine.

Biological interaction can take place in a number of ways, resulting in reduced or enhanced activity. Such interactions are considered to be rare in practical exposure experience but have been demonstrated experimentally and should therefore not be neglected.

The bioavailability of the components of the preparation may be altered by any of the above factors and a judgement made as to whether this alteration is sufficient to have a significant impact on the concentration limit of the CMT component of the preparation.

1.2. <u>The Physical Properties of the CMT Substance in Relation to those of the Preparation, in so far as these determine Exposure Potential</u>

Volatility is of particular relevance and a volatile substance in a preparation of relatively low volatility may indicate the need for stricter classification (and vice versa).

An academic example illustrating the principle of varying bioavailability is the observation that benz(a)pyrene in mineral oil and acetone formulations produce different skin tumour response (Doek and Hunt, 1977).

Liquids incorporated into essentially solid formulations (e.g. plasticisers) may have a significant reduced potential for dermal absorption. Also the presence of a substance in true solution as opposed to in suspension can influence absorption.

Exposure to powders may also be significantly decreased when they are presented in a granular product formulation.

These considerations may indicate a higher or a lower concentration limit than that indicated by the *"specific concentration limit"* specified in Annex 1 of the DSD.

2. *ESTABLISHMENT OF THE HEALTH HAZARD OF A PREPARATION BY DIRECT DETERMINATION OF THE TOXICOLOGICAL PROPERTIES OF THE PREPARATION*

The most scientific basis from which to determine whether a preparation poses a health hazard is to assess the toxicological properties *"by means of the methods specified in point B of Annex 5 to the DSD* (EEC, 1967)". Where a toxicological property has been established the present DPD (EEC, 1988) precludes the use of this information *"for classifying the preparation ... in the case of carcinogenic, mutagenic and teratogenic effects."* Where experimental data on the preparation itself are available they should not be ignored and, therefore, form part of the overall assessment and, if appropriate, determine the classification.

ECETOC recommends that these particular aspects of the Directive should be reconsidered as so called single technical substances may also contain impurities, so making a clear distinction between substance and preparation potentially difficult.

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TABLE 1

CARCINOGENS - ASSESSMENT AGAINST POTENCY CRITERIA

Chemical	EEC cat.	Mechanism relevant to humans	(i) Genotoxic mechanism	(ii) Increase in neo-plasms	(iii) Number of neoplasms per tissue	(iv) Exposure level	effective dose (2)	(v) Latency period	(vi) Number of doses	(vii) Variety of organs	(viii) Nature of neoplasms	(ix) Induction in different species	(x) Bioavai-lability
Benzidine	1	/	/	/	/	/	2	U	/	*	*	*	/
Bis(chloromethyl)ether	1	/	/	/	/	/	1	U	U	*	*	*	/
Vinylchloride	1	/	/	/	/	/	2	/	/	/	/	/	/
Dimethylcarbamoylchloride	2	/	/	*	/	/	2	U	/	/	*	U	/
N,N'-dimethylnitrosamine	2	/	/	/	/	/	1	/	/	/	/	/	/
Aldrin	3	*	*	*	*	/	1	*	*	*	*	*	/
Chloroform	3	/	*	/	/	/	3	*	*	/	*	/	/
1,4-dioxane	3	/	*	/	U	*	4	*	*	*	*	*	/
Methylchloride	3	/	*	/	U	*	U	*	*	*	*	/	/
Thiourea	3	/	*	*	*	*	3	U	*	*	*	*	/
Trichloroethylene	3	*	*(1)	/	*	/	4	/	*	/	*	/	/

Symbols: / = data fit criteria * = data do not fit criteria U = unknown

Notes: (1) In general non-mutagenic in vivo, although isolated reports have suggested marginal genotoxic effects

(2) Effective dose : 1. - TD50 < 1 mg/kgbw/d cf p. 14

2. - 1 < TD50 < 10 mg/kgbw/d

3. - 10 < TD50 < 100 mg/kgbw/d

4. - TD50 > 100 mg/kgbw/d

The data used in compiling the above table was obtained from published information (e.g. IARC-Monographs).

TABLE 2

MUTAGENS - ASSESSMENT AGAINST POTENCY CRITERIA

Chemical	EEC cat. (x)	Mechanism relevant to humans	i) Genetic effects in vivo							ii)	iii)	iv)	v)	Lowest effective dose in germ cells
			Germ cells				Somatic cells							
			Gene and Chrom.	More than 1 species	Gene or chrom.	More than 1 species	Gene or chrom.	In multiple organs	More than 1 species	Changes in ploidy	Low level dose-related response	Effects at high dose-levels only	Effects after single exposure	
Benzo(a)pyrene	2	/	*	*	Chrom.	*	/	/	/	/	/	*	/	500 mg/kgbw
1,2-Dibromo-3-Chloroprane	2	/	U	U	Chrom.	*	/	/	/	U	/	*	/	10-100 ppm
Diethyl Sulphate	2	/	U	U	Chrom.	*	/	*	*	/	*	/	/	150 mg/kgbw
Ethylene Oxide	2	/	/	/	both	/	/	/	/	U	/	*	/	10 ppm
Hexamethylphosphoric Triamide	2	U	*	*	*	*	/	*	*	U	/	*	*	U
Dimethylsulphate	3	U	*	*	*	*	/	*	*	/	*	/	*	U

Symbols: / = Data fit criteria * = data do not fit criteria U = unknown (x) = not yet published in Off. J.

Note: The data used in compiling the above table was obtained from published information (e.g. IARC-Monographs).

TABLE 3

TERATOGENS - ASSESSMENT AGAINST POTENCY CRITERIA

Chemical	EEC cat. (x)	i) Mechanism relevant to humans	ii) Minor abnormalities in more than 1 species	iii) Major abnormalities in 1 species	iv) Rare effects	v) Foeto-toxicity without maternal toxicity	vi) Dose response	vii) Effects at low level	viii) Effects after one exposure observed	ix) Bioavailability	Lowest effect level mg/kgbw/d	No observed effect level mg/kgbw/d
Arsenic and compounds	2	U	/	/	/	/	U	*	/	U	0,5 rat	U
Lead Acetate	2	U	/	/	/	/	U	/	/	U	3 monkey	U
Warfarin Phosphate or Coumafen	2	U	/	/	/	/	U	/	/	U	U	U
Benzo(a)pyrene	2	U	*	/	*	*	*	*	*	U	80 rat	U
Ethylene Thiourea	2	U	/	/	/	/	*	*	/	U	10 rat	5 rat

Symbols: / = data fit criteria * = data do not fit criteria U = unknown (x) = not yet published in Off. J.

Note: The data used in compiling the above table was obtained from published information (e.g. IARC-Monographs).

FIGURE 1

GENERALISED SCHEME FOR ASSESSING IMPACT OF BIOLOGICAL PROPERTIES OF A SUBSTANCE ON ALLOCATION OF SPECIFIC CONCENTRATION LIMITS (CARCINOGENICITY)

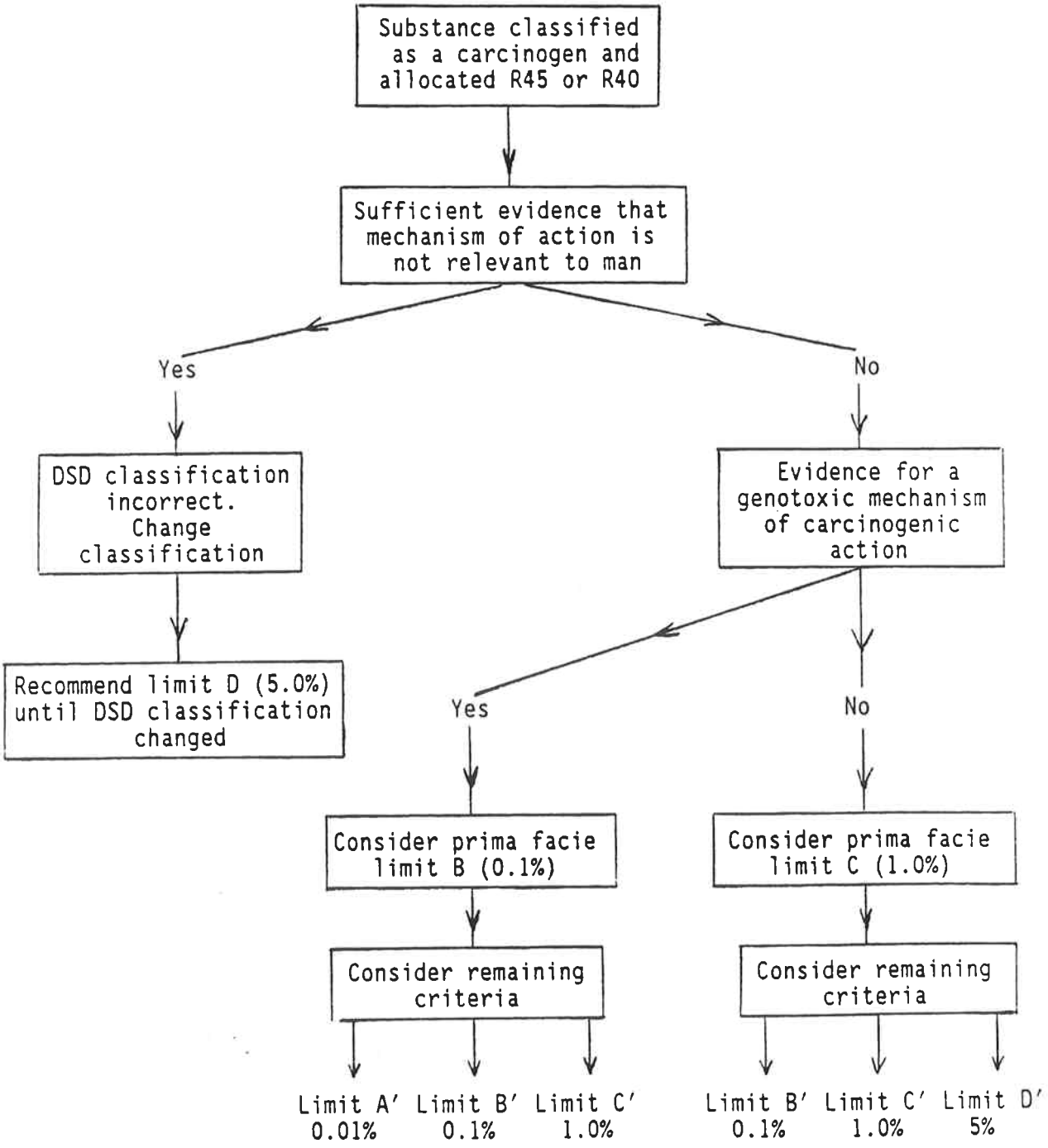


FIGURE 2

GENERALISED SCHEME FOR ASSESSING IMPACT OF BIOLOGICAL PROPERTIES OF A SUBSTANCE ON ALLOCATION OF SPECIFIC CONCENTRATION LIMITS (MUTAGENICITY)

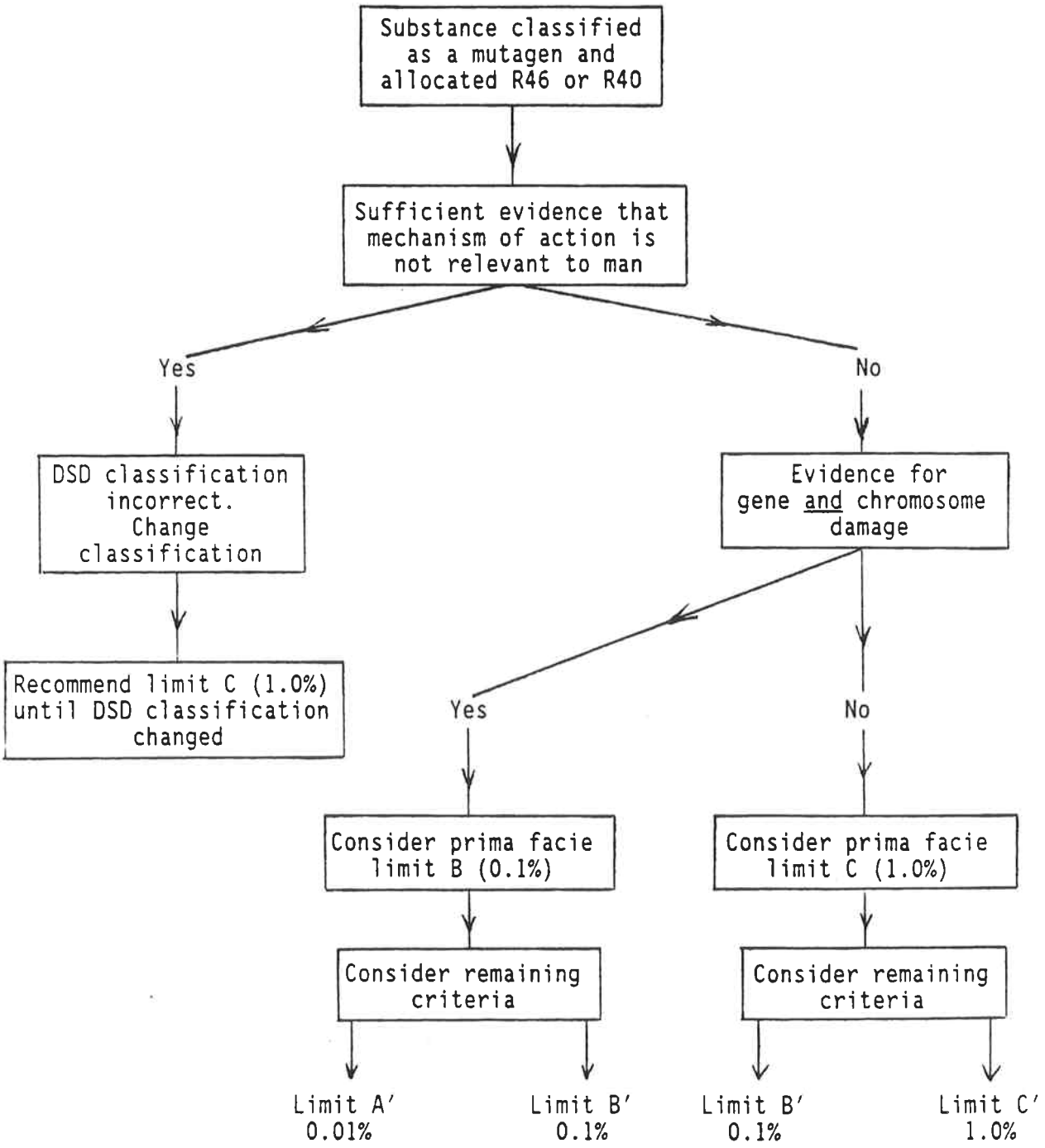


Figure 3

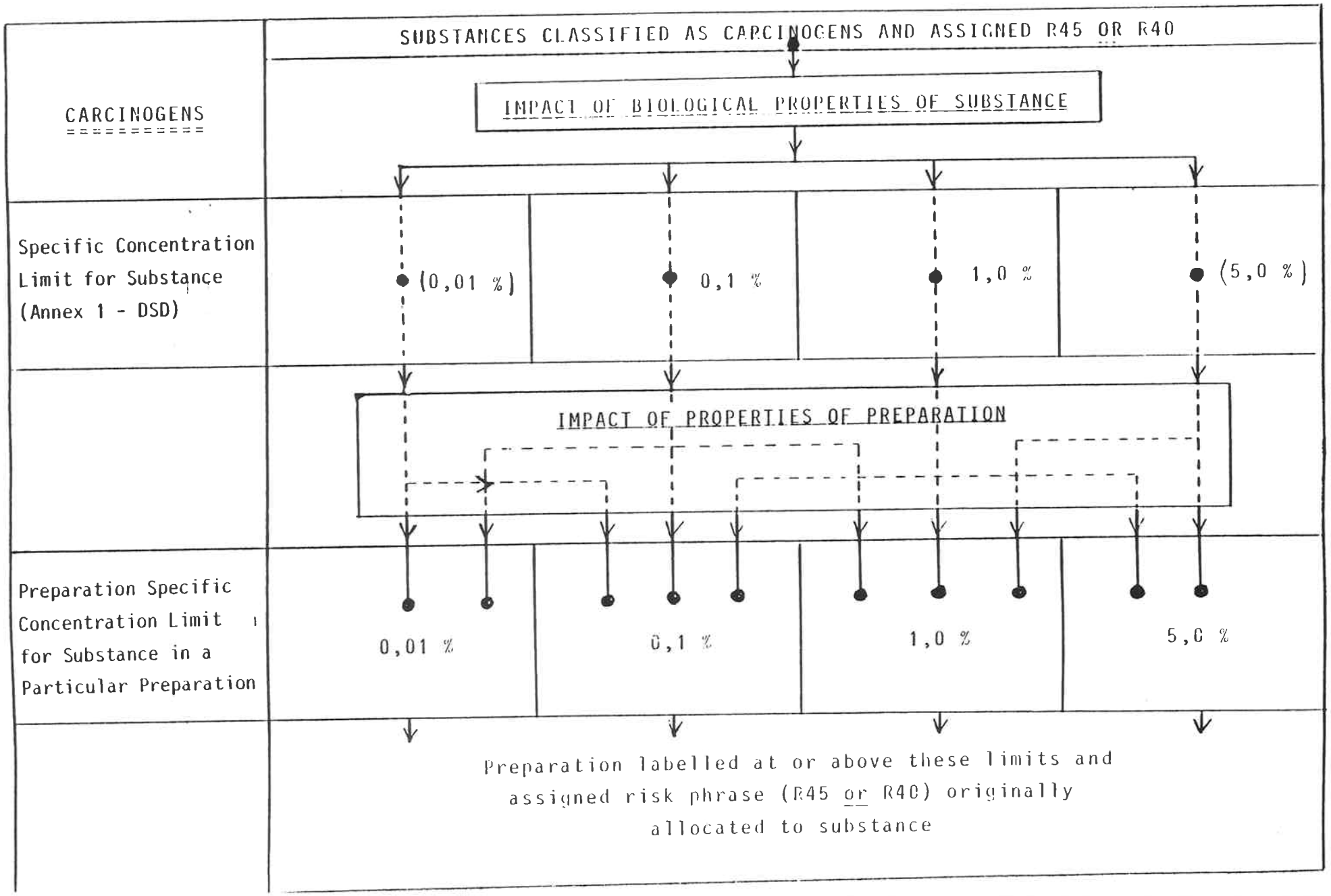

CARCINOGENS
SUBSTANCES CLASSIFIED AS CARCINOGENS AND ASSIGNED R45 OR R40
IMPACT OF BIOLOGICAL PROPERTIES OF SUBSTANCE
Specific Concentration Limit for Substance (Annex 1 - DSD)
(0,01 %)
0,1 %
1,0 %
(5,0 %)
IMPACT OF PROPERTIES OF PREPARATION
Preparation Specific Concentration Limit for Substance in a Particular Preparation
0,01 %
0,1 %
1,0 %
5,0 %
Preparation labelled at or above these limits and assigned risk phrase (R45 or R40) originally allocated to substance

Figure 4

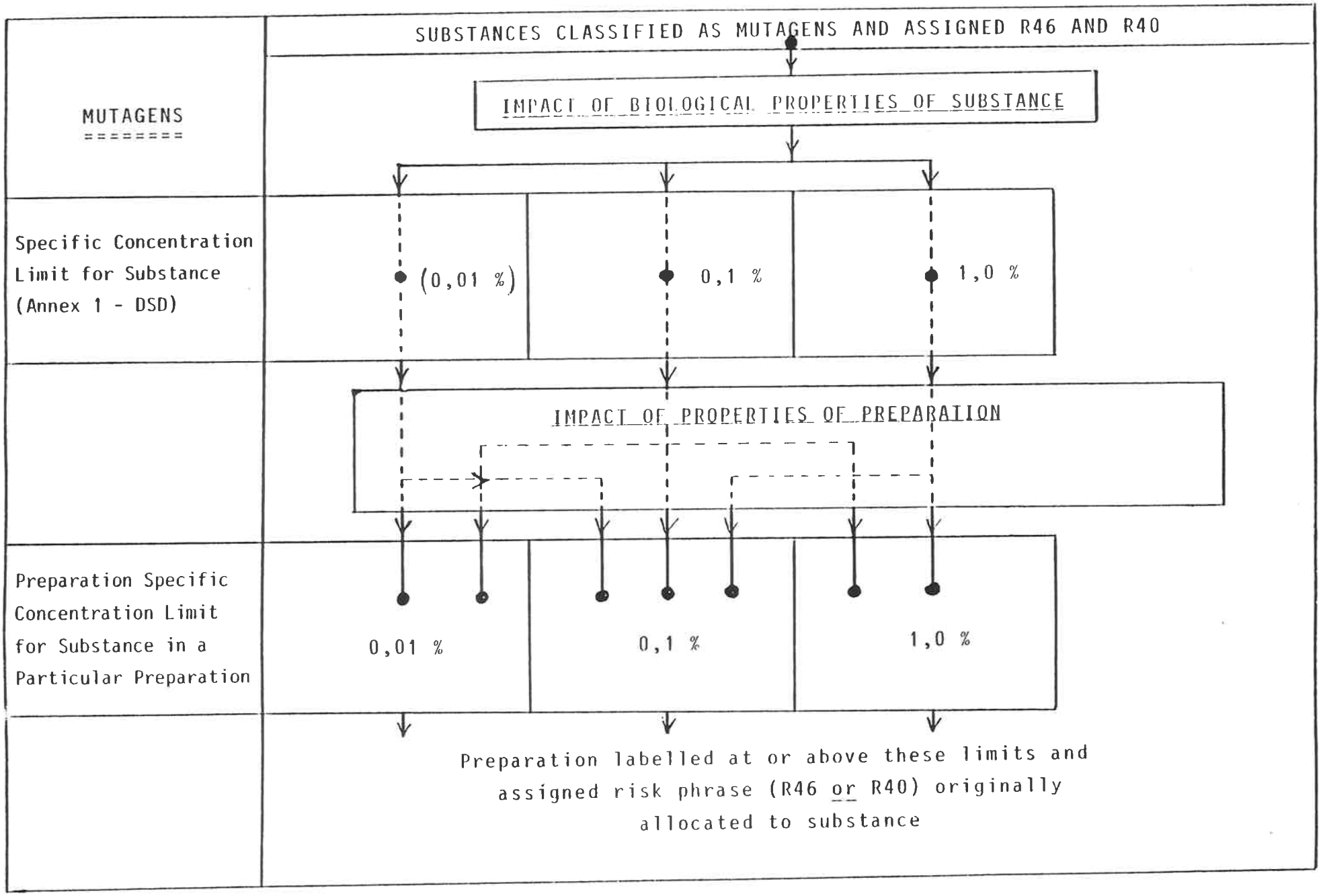
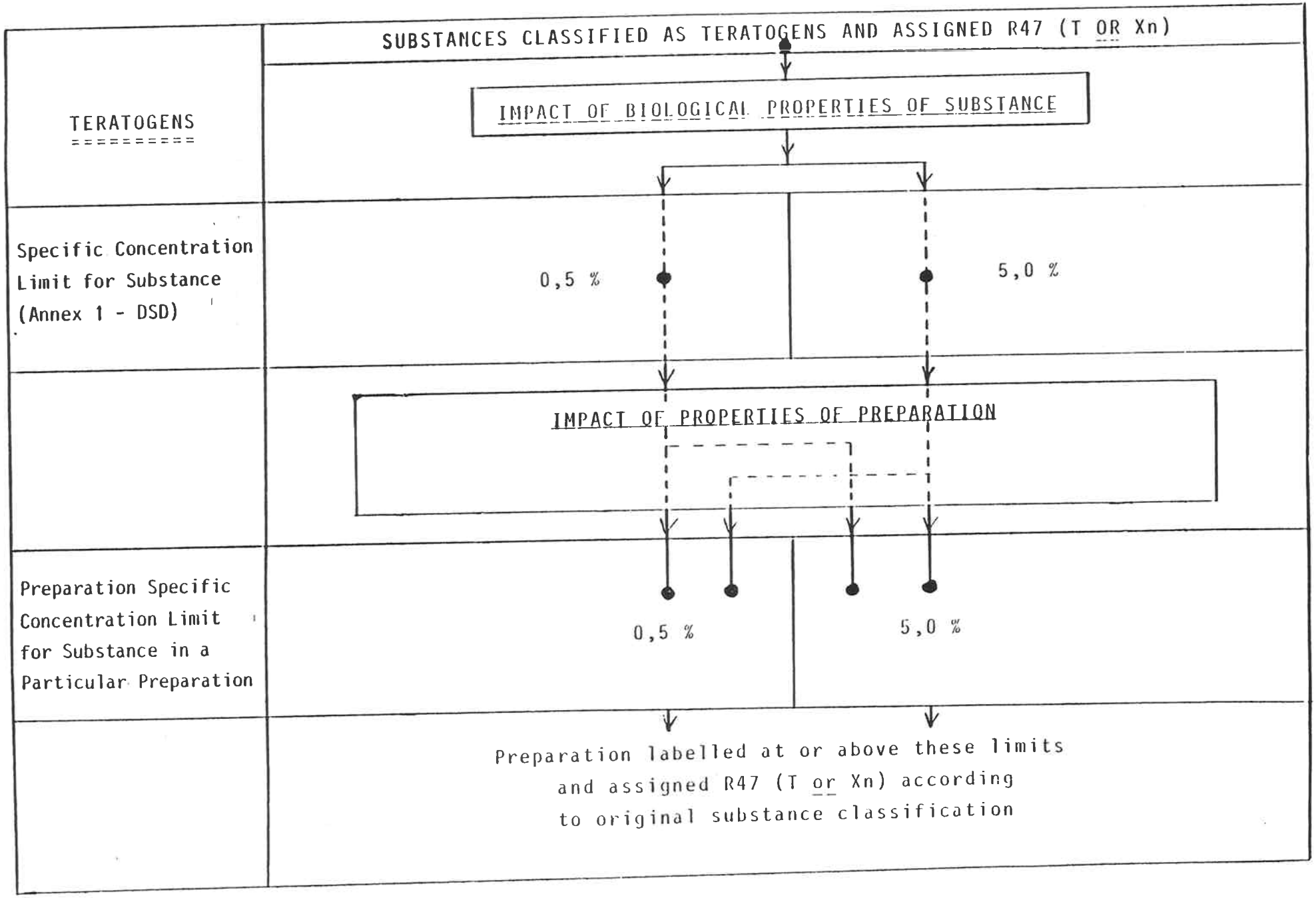

MUTAGENS
SUBSTANCES CLASSIFIED AS MUTAGENS AND ASSIGNED R46 AND R40
IMPACT OF BIOLOGICAL PROPERTIES OF SUBSTANCE
Specific Concentration Limit for Substance (Annex 1 - DSD)
(0,01 %)
0,1 %
1,0 %
IMPACT OF PROPERTIES OF PREPARATION
Preparation Specific Concentration Limit for Substance in a Particular Preparation
0,01 %
0,1 %
1,0 %
Preparation labelled at or above these limits and assigned risk phrase (R46 or R40) originally allocated to substance

Figure 5


TERATOGENS
SUBSTANCES CLASSIFIED AS TERATOGENS AND ASSIGNED R47 (T OR Xn)
IMPACT OF BIOLOGICAL PROPERTIES OF SUBSTANCE
Specific Concentration Limit for Substance (Annex 1 - DSD)
0,5 %
5,0 %
IMPACT OF PROPERTIES OF PREPARATION
Preparation Specific Concentration Limit for Substance in a Particular Preparation
0,5 %
5,0 %
Preparation labelled at or above these limits and assigned R47 (T or Xn) according to original substance classification

APPENDICES

APPENDIX 1

MAIN EXISTING EEC DIRECTIVES ON DANGEROUS SUBSTANCES AND PREPARATIONS

DANGEROUS SUBSTANCES DIRECTIVE (DSD)

- Council Directive 67/548/EEC of 27 June 1967 on the approximation of the laws of the Member States relating to the classification, packaging and labelling of dangerous substances.

  This directive has been amended and adapted several times and continues to be amended and adapted.

  It includes a number of annexes, out of which are of special relevance to this document:

  Annex I: it lists dangerous substances with their name(s), symbol(s), R and S phrases. It will be updated to indicate concentration limits corresponding to each identified category of danger.

  Annex V: it details the test methods applicable to the determination of the physical chemical, toxicological and ecotoxicological properties of substances and preparations.

  Annex VI: it details the criteria of classification and labelling of dangerous substances and preparations (in particular, the part II (D) of this Annex entitled Guide to the classification and labelling of dangerous substances and preparations).

PREPARATION DIRECTIVES

- Council Directive 78/631/EEC of 26 June 1978 on the approximation of the Laws of the Member States relating to the classification, packaging and labelling of dangerous preparations (pesticides).

- Council Directives 73/173/EEC of 4 June 1973 on solvents and 77/728/EEC of 7 November 1977 on paints, etc..., cease to apply upon entry into force of Directive 88/379/EEC on dangerous preparations.

- DANGEROUS PREPARATIONS DIRECTIVE (DPD): Council Directive 88/379/EEC of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations adapted by the Commission Directive 89/178/EEC of 22 February 1989.

  This directive introduces the concept of concentration limits which is the object of this document in the case of CMT substances (cf. Appendix 2).

APPENDIX 2

SELECTION OF THE MOST RELEVANT SECTIONS OF COUNCIL DIRECTIVE

of 7 June 1988

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations

(88/379/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100A thereof,

Having regard to the proposal from the Commission (1),

In cooperation with the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas it is important to adopt measures with the aim of progressively establishing the internal market over a period expiring on 31 December 1992; whereas the internal market shall comprise an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

Whereas rules on dangerous substances have already been laid down in Council Directive 67/548/EEC of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (4), as last amended by Directive 79/831/EEC (5);

Whereas rules on certain dangerous preparations having very specific uses have already been laid down:

— in Council Directive 73/173/EEC of 4 June 1973 on the approximation of Member States' laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous preparations (solvents) (6), as last amended by Directive 80/781/EEC (7),

— in Council Directive 77/728/EEC of 7 November 1977 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of paints, varnishes, printing inks, adhesives and similar products (8), as last amended by Directive 83/265/EEC (9),

Whereas, despite the abovementioned Community provisions, the rules, if any, applying to certain dangerous preparations in the Member States exhibit considerable differences as regards classification according to the degree of risk; whereas these differences constitute a not insignificant barrier to trade and directly affect the establishment and functioning of the common market;

Whereas it is therefore necessary to remove this barrier by approximating the relevant legislation existing in the Member States and incorporating in it the *'acquis communautaires'*;

Whereas this Directive must, at the same time, ensure protection for the general public and, in particular, of persons who come into contact with dangerous preparations in the course of their work or in the pursuit of a hobby, of consumers, especially children and the visually handicapped, and also for the environment;

Whereas provisions on the classification, packaging and labelling of the preparations must be laid down at Community level; whereas the provisions concerning the information appearing on the label, the dimensions of the label and the assignment of the various danger symbols, standard phrases concerning risks and safety advice have also to be brought into line with Directive 67/548/EEC;

Whereas some preparations, although they contain constituents which are dangerous to health, are not necessarily dangerous in the form in which they are placed on the market; whereas there are exceptions, however, and whereas the latter must be the subject of special labelling, as appropriate, in accordance with the provisions of Directive 67/548/EEC as amended by Directive 79/831/EEC, or of Annex II to this Directive;

Whereas the assessment of the health hazards of a preparation may, under Article 3, be carried out by a calculation method, by determining the toxicological properties according to well-defined test methods or by a combination of the two; whereas Directive 86/609/EEC stipulates in Article 7 (2) that an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the

(1) OJ No C 317, 10. 12. 1986, p. 10 and OJ No C 353, 30. 12. 1987, p. 1.
(2) OJ No C 318, 30. 11. 1987, p. 73 and Decision of 13 April 1988 (not yet published in the Official Journal).
(3) OJ No C 189, 28. 7. 1986, p. 1.
(4) OJ No 196, 16. 8. 1967, p. 1.
(5) OJ No L 259, 15. 10. 1979, p. 10.
(6) OJ No L 189, 11. 7. 1973, p. 7.
(7) OJ No L 229, 30. 8. 1980, p. 57.
(8) OJ No L 303, 28. 11. 1977, p. 23.
(9) OJ No L 147, 6. 6. 1983, p. 11.
(10) OJ No L 358, 18. 12. 1986, p. 1.

use of an animal, is reasonably and practically available; whereas this Directive makes use of the results of assessments of toxicological properties only when these are already known and entails no obligation to conduct further experiments on animals;

Whereas the label constitutes a basic tool for users of the preparations by giving them the initial essential concise information; whereas it nevertheless needs to be supplemented by a two-fold system of more detailed information, one intended for professional users, and the second for the bodies appointed by the Member States and whose responsibility it is to give information reserved solely for medical purposes, both curative and preventive;

Whereas dangerous preparations may, although conforming to the provisions of this Directive, nevertheless constitute a danger to health or the environment; whereas it is therefore advisable to provide a procedure to reduce this danger;

Whereas the Commission will, on the basis of information to be supplied by the Member States be obliged to submit a report, within two years of application of this Directive, concerning any inadequacies or loopholes, as compared with the present Directive, in Council Directive 78/631/EEC of 26 June 1978 on the approximation of the laws of the Member States relating to the classification, packaging and labelling of dangerous preparations (pesticides) (1), as last amended by Directive 84/291/EEC (2); whereas on the basis of this report, the Commission will, if appropriate, submit the necessary proposals,

HAS ADOPTED THIS DIRECTIVE:

Article 1

1. The purpose of this Directive is to approximate the laws, regulations and administrative provisions of the Member States on the:

— classification,

— packaging, and

— labelling

of preparations dangerous to man and the environment when they are placed on the market in the Member States.

2. This Directive shall apply to preparations which are placed on the market in the Member States and which:

— contain at least one substance classified as dangerous, within the meaning of Article 2, and

— are regarded as dangerous within the meaning of Article 3.

This Directive shall also apply to the preparations listed in Annex II.

3. This Directive shall not apply to:

(a) medicinal or veterinary products as defined by Directive 65/65/EEC (3), as last amended by Directive 87/21/EEC (4);

(b) cosmetic products as defined by Directive 76/768/EEC (5), as last amended by Directive 86/199/EEC (6);

(c) mixtures of substances which, in the form of waste, are covered by Directive 75/442/EEC (7) and Directive 78/319/EEC (8), as last amended by the Act of Accession of Spain and Portugal;

(d) pesticides covered by Directive 78/631/EEC, as last amended by Directive 83/291/EEC;

(e) munitions and explosives placed on the market with a view to obtaining a practical effect by explosion or a pyrotechnic effect.

In addition, this Directive shall not apply to:

(f) foodstuffs in a finished stage intended for the final consumer;

(g) animal feedingstuffs in a finished stage intended for the final consumer;

(h) the carriage of dangerous substances by rail, road, inland waterway, sea or air;

(i) preparations in transit which are under customs supervision provided they do not undergo any treatment or processing.

Article 2

The definitions appearing in Article 2 of Directive 67/548/EEC, with the exception of the definition in paragraph 1 (d) thereof, shall apply to this Directive.

Article 3

1. The general principles of the classification and labelling of preparations shall be applied according to the criteria in Annex VI to Directive 67/548/EEC, save where the alternative criteria referred to below are applied.

2. The requisite physico-chemical properties for the classification of preparations shall be determined by the methods specified in Annex V (A) to Directive 67/548/EEC.

(1) OJ No L 206, 29. 7. 1978, p. 13.
(2) OJ No L 144, 30. 5. 1984, p. 1.
(3) OJ No 22, 9. 2. 1965, p. 369/65.
(4) OJ No L 15, 17. 1. 1987, p. 36.
(5) OJ No L 262, 27. 9. 1976, p. 169.
(6) OJ No L 149, 3. 6. 1986, p. 38.
(7) OJ No L 194, 25. 7. 1975, p. 39.
(8) OJ No L 84, 31. 3. 1978, p. 43.

(j) Preparations shall be regarded as:

carcinogenic and assigned at least the symbol and indication of danger 'toxic', if they contain a substance producing such effects, to which is assigned the standard phrase R 45, which denotes carcinogenic substances in category 1 and category 2, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(k) Preparations shall be regarded as:

suspect for humans owing to their possible carcinogenic effects and assigned at least the symbol and indication of danger 'harmful', if they contain a substance producing such effects to which is assigned the standard phrase R 40, which denotes carcinogenic substances in category 3, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 in Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(l) Preparations shall be regarded as:

mutagenic and assigned at least the symbol and indication of danger 'toxic' if they contain a substance producing such effects, to which is assigned the standard phrase R 46 which denotes mutagenic substances in category 1, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(m) Preparations shall be regarded as having to be treated as mutagenic and assigned at least the symbol and indication of danger 'harmful' if they contain a substance producing such effects to which is assigned the standard phrase R 46, which denotes mutagenic substances in category 2, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(n) Preparations shall be regarded as:

suspect for humans because of their possible mutagenic effects and assigned at least the symbol and indication of danger 'harmful' if they contain a substance producing such effects to which is assigned the standard phrase R 40, which denotes mutagenic substances in category 3, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(o) Preparations shall be regarded as:

teratogenic and assigned at least the symbol and indication of danger 'toxic' if they contain a substance producing such effects, which is assigned the standard phrase R 47, which denotes teratogenic substances in category 1, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(p) Preparations shall be regarded as:

having to be treated as teratogenic and assigned at least the symbol and indication of danger 'harmful', if they contain a substance producing such effects to which is assigned the standard phrase R 47, which denotes teratogenic substances in category 2, in a concentration equal to or exceeding:

— either the concentration specified in Annex I to Directive 67/548/EEC for the substance under consideration, or

— the concentration specified at point 6 of Annex I (Table VI) to this Directive where the substance or substances under consideration do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits.

(q) Preparations shall be regarded as:

having specific effects on health not further defined and assigned at least the symbol and indication of danger 'harmful' if they contain a substance which does not yet appear in Annex I to Directive 67/548/EEC but to which is provisionally assigned the standard phrase R 40 denoting such substances in a concentration exceeding that specified at point 6 of Annex I (Table VI) to this Directive.

6. For preparations covered by this Directive:

(a) No account shall be taken of substances whether or not listed in Annex I to Directive 67/548/EEC, whether existing as impurities or as additives, if their concentration by weight is less than:

— 0,1 % for substances classified as very toxic or toxic,

— 1 % for substances classified as harmful, corrosive or irritant,

unless lower values have been specified in Annex I to Directive 67/548/EEC.

(b) Dangerous substances not listed in Annex I to Directive 67/548/EEC but used as constituents of a preparation in a concentration by weight higher than that given at point (a) of this paragraph shall be given concentration limits characterizing the health hazards.

Some substances may have more than one property harmful to health, e.g. harmfulness/irritation, corrosiveness/harmfulness, corrosiveness/sensitization: each of these properties must therefore be characterized by its specific concentration limit.

These concentration limits shall be determined in accordance with Annex I to this Directive by the manufacturer or any other person who places such a preparation on the market.

Article 4

The classification of dangerous preparations according to the degree of hazard and the specific nature of the risks involved shall be based on the definitions laid down in Article 2. The preparations shall be classified according to the greatest degree of hazard in accordance with Article 7 (1) (d).

Article 5

1. Member States shall take all necessary measures to ensure that the preparations envisaged by this Directive cannot be placed on the market unless they comply therewith.

2. If there is any doubt with regard to the compliance referred to in paragraph 1, Member States may request information on the composition of the preparation and any other pertinent information.

3. To this end, the manufacturer, or those responsible for placing the preparation on the market, shall hold the data used for the classification and labelling of the preparation at the disposal of the authorities of the Member States.

Article 6

1. Member States shall take all the necessary measures to ensure that:

(a) dangerous preparations are not placed on the market unless their packaging meets the requirements of Article 15 (1) of Directive 67/548/EEC with respect to their strength, leak-tightness and fastening systems;

(b) containers which contain dangerous preparations offered or sold to the general public do not have:

— either a shape and/or graphic decoration likely to attract or arouse the active curiosity of children or to mislead consumers,

6. Carcinogenic/mutagenic/teratogenic effects

For substances which produce such effects and for which specific concentration limits do not yet appear in Annex I to Directive 67/548/EEC and for those which, in accordance with point 3.1.1 of Annex III to Directive 83/467/EEC, are provisionally assigned the phrase R 40, the concentration limits laid down in Table VI shall determine, where appropriate, the classification of the preparation and the compulsory R phrase to be assigned to it.

TABLE VI

Substance	Classification of the preparation and standard risk phrase	
	At least T	At least X_n
At least T with R 45 for carcinogenic substances of category 1 or 2	≥ 0,1 % R 45 obligatory	
At least X_n with R 40 for carcinogenic substances of category 3		≥ 1 % R 40 obligatory
At least T with R 46 for mutagenic substances of category 1	≥ 0,1 % R 46 obligatory	
At least X_n with R 46 for mutagenic substances of category 2		≥ 0,1 % R 46 obligatory
At least X_n with R 40 for mutagenic substances of category 3		≥ 1 % R 40 obligatory
At least T with R 47 for teratogenic substances of category 1	≥ 0,5 % R 47 obligatory	
At least X_n with R 47 for teratogenic substances of category 2		≥ 5 % R 47 obligatory
At least X_n and R 40 provisionally in accordance with point 3.1.1 of Annex III to Directive 83/467/EEC		≥ 1 % R 40 obligatory

APPENDIX 3

DEFINITIONS

CARCINOGEN: a substance which causes cancer in specific situations.

CANCER: a malignant neoplasm with autonomous growth and certain pathological characteristics with include atypia, invasive growth and, frequently, metastasis.

CARCINOGENIC, MUTAGENIC, TERATOGENIC HAZARD IDENTIFICATION: the detection of the inherent property of a chemical which enables it to produce a cancer, a mutagenic or teratogenic effect under appropriate conditions.

CARCINOGENIC, MUTAGENIC OR TERATOGENIC POTENCY: the magnitude, with respect to dose, of the carcinogenic, mutagenic or teratogenic activity of a chemical in the species under consideration.

CARCINOGENIC, MUTAGENIC OR TERATOGENIC RISK: the probability that a certain population under specified conditions of exposure will develop an increased incidence of cancer, mutation or teratogenic effect.

HAZARD ASSESSMENT: used to indicate the quantitative evaluation of hazard. This involves a combination of the potential of a chemical to harm man or the environment, and the potential for exposure to a chemical.

MUTAGEN: a substance which can generate a mutation in a particular cell or organism. In the current context attention needs only be focused on mutagens causing heritable effects, i.e. those which cause mutations to mammalian germ cells in vivo.

POTENTIATION: the provocation or enhancement of an effect of one agent by the presence of another agent.

PREPARATION: a mixture or solution composed of two or more substances.

"PREPARATION SPECIFIC CONCENTRATION LIMIT": term proposed by ECETOC. Once a *"Specific Concentration Limit"* is established each carcinogenic, mutagenic and/or teratogenic substance should be further considered in the context of the particular preparation. Factors relating to physical properties and the potential for interaction should be considered and could be overriding in determining the "Preparation Specific Concentration Limit".

RISK: the probability that the potential hazard of a substance is realised under specific conditions.

RISK PHRASES

R 40 : Possible risks of irreversible effects.

R 45 : May cause cancer.

R 46 : May cause heritable genetic damage.

R 47 : May cause birth defects.

"SPECIFIC CONCENTRATION LIMIT": term used in the Dangerous Preparations Directive for a concentration level above which a substance in a preparation turns that preparation into a "dangerous" one, thus attracting appropriate classification and labelling. This limit might technically satisfy the requirements for inclusion in Annex 1 of the Dangerous Substances Directive (67/548/EEC).

TD_{50}: the chronic dose rate in mg/kgbw/day which would halve the "actuarially" adjusted percentage of tumour-free animals at the end of a standard experiment time, mostly the "standard life span" for the species. "For each species, the reported TD_{50} value is the most potent from among sites that a published author evaluated as positive".

TERATOGEN: a chemical which can induce non-heritable structural or functional damage to the the developing embryo/foetus when the mother is exposed during pregnancy.

SUBSTANCES: chemical elements and their compounds as they occur in the natural state or as produced by industry, including any additives required for the purpose of placing them on the market.

APPENDIX 4

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