

*The Use of T25 Estimates and
Alternative Methods in the Regulatory
Risk Assessment of Non-threshold
Carcinogens in the European Union*

Technical Report No. 83

ISSN-0773-8072-83

Brussels, January 2002

ECETOC Technical Report No. 83

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The Use of T25 Estimates and Alternative Methods in the Regulatory Risk Assessment of Non-threshold Carcinogens in the European Union

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SUMMARY

The regulation of carcinogens in the European Union, under the 'labelling and use' regulations and in the framework of existing chemicals, relies currently on classification using the strength of evidence. It is self-evident that potency, as well as strength of evidence, should be used to determine concentration limits for carcinogenic substances in preparations and for regulating existing chemicals that have carcinogenic properties.

It has been proposed that a simplified method of estimating carcinogenic potency from the results of experimental animal studies should be used for these purposes. The method, proposed by scientists from Norway and the Netherlands, is known as the T25 method. It relies on a simplified method of deriving the dose of the carcinogen that will produce cancer in 25% of the animals that would not have developed cancer spontaneously. A human HT25 is then calculated based on a number of default assumptions. The ratio between the estimated human daily exposure and the HT25 is then used to calculate the expected incidence (= risk) of cancer.

The T25 has also been used in setting concentration limits that trigger labelling for carcinogens in preparations. The T25 estimate is used to assign the chemical to one of three potency classes. The potency class, taken together with the carcinogen classification category, is then used in a scheme to assign a concentration limit for the chemical in preparations. In general, provided the method is used with care, it should provide a satisfactory procedure for assigning concentration limits in preparations.

A workshop was organised by ECETOC in November 2000 to consider these issues. Following the workshop, ECETOC established a Task Force to consider the current proposals and alternatives that had been identified in a preliminary paper drafted by three scientists who attended the workshop.

The Task Force has concluded that the T25 method for risk assessment of non-threshold carcinogens is open to criticism for the following reasons:

- Estimates based on simple proportional linear extrapolation from the T25 should not be used to predict absolute cancer risk, because of the many unverifiable assumptions used in their calculation;
- the estimate is based on unproven methodology, which many believe is flawed;
- the resulting quantitative estimate has a spurious sense of accuracy;
- there is a strong likelihood of misuse and misinterpretation of derived human cancer risk estimates;
- the resulting calculated value will be taken as the 'true' risk in communication with the risk managers and with those exposed;

- the justification of the reliability of the T25 method by comparison of its results with those of the Linearised Multistage model is misleading;
- species differences and mechanistic data are not taken into account.

These concerns can be summarised by stating that the risk estimates produced by this and similar methods appear precise but almost certainly do not reflect the real risks. This may cause confusion.

In addition to the T25, several possible alternative methods were considered by the Task Force. Of these, the Task Force recommends a 'margin of exposure' method, based on the weight of evidence from all suitable relevant carcinogenesis bioassays. For each bioassay, the maximum likelihood estimate of the benchmark dose at a 5% risk level is calculated, and a representative value of these estimates converted by allometric scaling to a human benchmark exposure level. The derivation of this and the final decision as to whether the standard is exceeded, should be informed by other data, such as those relating to metabolism, pharmacokinetics, mechanisms of action, the shape of the dose response curve and human experience.

The human benchmark exposure level is divided by the realistic worst-case exposure of workers, consumers and the public exposed through the environment, and the resulting margin of exposure compared with agreed standards, likely to be 10^4 , 10^5 and 10^6 , respectively, as a basis for judging the acceptability, or otherwise, of the carcinogenic risk.

1. INTRODUCTION

Within the European Union (EU), chemical substances and preparations are classified as regards general systemic toxicity on the basis of their potency. In this context, potency is ideally represented by the position and shape of the dose-effect or dose-response curve, but the value of a particular point on the curve (e.g. LD50 or NOAEL in a multiple dose study) is often used as a surrogate. Though there are many disadvantages in the use of such surrogates, the practice is well established and it would not be practical to change it.

In contrast to the situation for general systemic toxicity, the classification of chemical substances for carcinogenic, mutagenic or reproductive effects has been on the basis of the strength of evidence that the chemical presents this hazard to human beings, rather than its potency. In many cases, a distinction is justified on the grounds that the effects of such chemicals are stochastic. An individual exposed to such a chemical has a probability of expressing the effect that is a function of the exposure, but the effect itself is 'all-or-none'. While there is a continuous (linear) dose-response relationship in a group of exposed individuals of the same species, the dose-effect relationship in a single individual would be a discontinuous step-function and different individuals would have different dose-effect relationships in which the position of the discontinuity would vary randomly, or stochastically. In this context, linear means a relationship in which there are no discontinuities. It does not imply a straight-line relationship; for this the term 'rectilinear' is used.

New and existing chemical substances are required to undergo a process of regulatory risk assessment and where the hazard of carcinogenicity exists, this should be taken into account in the risk assessment. Where it is believed that there is a threshold dose or exposure below which carcinogenesis will not occur, the traditional 'margin of safety' method can be used. In this approach, the threshold is divided by the actual exposure to give a margin of safety' and a decision is made on the adequacy of this margin for workers, consumers or the public. Where a threshold cannot be established, there may be objections to the use of a conventional 'margin of safety' approach, since it has been argued that there is no true no effect level at which the risk in experimental animals is truly zero. It is sometimes assumed that genotoxic carcinogens will have no threshold. However, it is probable that there is, in fact, a threshold for many carcinogens that are genotoxic (though it might be difficult to quantify). Nevertheless, to satisfy these objections, alternative methods have been sought for those cases where no threshold can be identified. It has been proposed (EC, undated b) that the likelihood of developing cancer at a given exposure should be calculated by assuming a rectilinear relationship in humans between exposure and cancer incidence from zero to 25%. This is determined by calculating a dose (HT25) likely to produce cancer in 25% of human by the application of scaling factors (but not safety factors) to an animal T25. This animal T25 is obtained by interpolation or extrapolation on a straight line between the origin and a selected data point for a selected tumour incidence in a selected animal species (usually rodent) carcinogenesis study. The acceptability of the risk estimate based on animal experiments would be determined by the predicted additional tumour incidence in humans.

Particularly for carcinogens, risk assessment, is a refined and developing intellectual exercise and it is not scientifically valid to reduce it to a simple equation or algorithm. A recent report of a Consensus-Building Workshop (Bogdanffy *et al*, 2001) identified the importance of using all relevant scientific information in health risk assessments. Nevertheless, for administrative and regulatory purposes within an iterative framework, a standard method has advantages when the required output is more in the nature of categorisation of the risk and the necessary risk reduction measures rather than quantification of the risk. The output of such a method does not need to produce a risk estimate of high precision, particularly when the accuracy and the underlying scientific basis are uncertain. The fact that the proposed 'T25' method produces a risk estimate appearing to have high precision could lead to misunderstanding as to both the accuracy and reliability of the estimate. Such misunderstandings would be a cause of concern, especially for risk communication and risk management.

The European Centre for the Ecotoxicology and Toxicology of Chemicals (ECETOC) organised a workshop on 10th November 2000, at which the proposed T25 method for assessment of potency and for quantitative risk assessments was discussed, along with possible alternatives. A report of the proceedings of this workshop has been prepared (Roberts *et al*, 2001).

Following this workshop, a small group¹ met to discuss the issues that surround this proposal and to prepare a draft position paper. Subsequently, an ECETOC Task Force was formed to review and refine this draft and to formulate recommendations. The Terms of Reference for the Task Force were:

- Evaluate comparatively the T25 proposal (EU undated b) for quantitative risk assessment for non-threshold carcinogens and the alternative proposals considered at the ECETOC workshop;
- document the evaluations and make a proposal for the industry-preferred method(s) in a form suitable for submission to the TGD revision process. Ensure that these are available by June/July 2001 for the inaugural ECB sub-group meeting;
- prepare an ECETOC report on the comparative evaluation and the recommendations;
- consider the preparation of a paper on these evaluations for publication in the open literature.

¹ Members of this group are marked with this symbol * in the list of Task Force members.

2. REGULATION OF CARCINOGENS IN THE EUROPEAN UNION

2.1 *Classification, labelling and use regulations*

The current regulations controlling the labelling and use of carcinogens in the EU are summarised as follows:

The 'Dangerous Substances' Directive (EC, 1967)

Carcinogens are classified as follows:

Category 1 - Human carcinogen (R45 or R49).

Category 2 - Probable human carcinogen (R45 or R49).

Category 3 - Insufficient evidence to put in category 2,

- a) but additional data is unlikely to help (R40).
- b) but additional data is needed (R40).

'Marketing and Use' Directive (EC, 1976) and 'Preparations' Directive (EC, 1999)

- Carcinogens in categories 1 and 2 cannot be included in products on sale to the general public.
- Concentration limit for category 3 carcinogens is 1%. At this or higher concentrations, the preparation has to be labelled with R40.
- Concentration limit for category 1 and 2 carcinogens is 0.1%. At this or higher concentrations, the preparation has to be labelled with R45 or R49.

2.2 *New and existing substances regulations*

While the 'Dangerous Substances' Directive requires a risk assessment for new substances (EC, 1967), there will seldom initially be data relating to carcinogenicity on which to base a carcinogenic risk assessment. In contrast, the 'Existing Substances' Regulation (EC, 1993) requires the performance of risk assessments for existing substances and this has to include a risk assessment for carcinogenicity, where appropriate.

A risk assessment for existing substances (EC, 1994, 1996) may reach one of the following three conclusions:

- i) Need for further information and/or testing.
- ii) No need at present for further information and/or testing and no need for risk reduction measures beyond those that are being applied already.
- iii) Need for limiting the risks; risk reduction measures, which are already being applied, shall be taken into account.

The further information required might relate either to the toxic hazard or to exposure. When there is a lack of reliable exposure measurements, exposure may have been estimated by models (such as EASE or Consexpo) using worst-case default assumptions; in consequence the results may be higher than actual exposure. Measurement, rather than estimation of exposure information, may thus alter the conclusion of the risk assessment from i) to ii), above.

Determination of a need for the further toxicological testing of existing chemicals will depend on the degree of concern, which is also the criterion for decision in the case of new substances. This level of concern will depend, in the case of carcinogens, on the potency of the carcinogen as well as on the strength of the evidence that the chemical is indeed a human carcinogen.

The Technical Meeting has implemented a concept arising from the 1st *ad hoc* Sub-group meeting, that a distinction is drawn between iii a) residual risk, and iii b) serious risk (EC, 2000). These subdivisions may not continue to be used, but a distinction between those carcinogens with an acceptable residual risk and those for which further risk reduction measures are required, appears likely to be incorporated in the revision of the Technical Guidance Document (TGD) (EC, 2001).

2.3 Regulatory need for an estimate of carcinogenic potency

The use of the category of a carcinogen to determine its concentration limit in a preparation is inadequate (EC, undated a). It is clearly possible that a potent animal carcinogen might be in category 3 because of mechanistic data or negative epidemiological data, whilst a proven human carcinogen in category 1 might cause cancer only at very high exposure levels. It is self-evident that potency, as well as strength of evidence, should be used to determine concentration limits for carcinogenic substances in preparations.

Similarly, the carcinogenic category (representing the strength of the evidence) alone is insufficient for a risk assessment of a new or an existing substance with carcinogenic properties. An index of potency is also required in this context.

2.3.1 Use of potency in setting concentration limits for carcinogens in preparations

Guidelines have been written (EC, undated a) for using potency in setting concentration limits for carcinogens in Annex 1 of the 'Dangerous Substances' Directive (EC, 1967). In these guidelines, the T25 concept is used to rank the potency of carcinogens. The following three potency bands have been proposed, dependent on the T25 value:

Table 1: Proposed potency bands for ranking carcinogens

Potency	T25 mg/kgbw/day
High	<1
Medium	1-100
Low	>100

On this basis, concentration limits might be set as follows:

Table 2: Concentration limits for carcinogens in preparations

Potency	Category 1	Category 2	Category 3
High	0.01%	0.01%	0.1%
Medium	0.1%	0.1%	1.0%
Low	*	1%	1-5%

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

2.3.2 Use of potency (T25) in carcinogen risk assessment of existing and new substances

In the Netherlands, the Dutch Expert Committee on Occupational Standards has proposed the use of a T25 estimate to assess whether carcinogenesis was the critical endpoint for setting occupational exposure standards (MAC values) (DECOS, 1995). It should be emphasised that T25 is not used by the Dutch Authorities as such for setting occupational exposure limits or for risk assessment.

In the context of the revision of the TGD for risk assessment of new and existing substances, it was decided (EC, 1998) that Norway and the Netherlands should draft guidelines for quantitative risk assessment of carcinogenic substances, based on the tumorigenic dose descriptor T25 as the default descriptor for linear extrapolation.

In response to this decision, the Commission Working Group on the Technical Meetings for Risk Assessment for Existing Substances produced 'Guidelines for Quantitative Risk Characterisation of Non-Threshold Carcinogens in the Framework of Existing Chemicals following Council Regulation (EEC) 793/93 (EC, undated b). This document assumes that, where there is an established threshold for (non-genotoxic) carcinogenesis, conventional 'margin of safety' approaches may be used for risk assessment. For so-called non-threshold carcinogens, the T25 procedure is proposed.

The document goes into considerable detail about the application of the HT25 concept to human exposure of workers in the workplace, of consumers and of the public through the environment; it is implicit that there are cancer risk estimates for these three groups that are societally acceptable. Several worked examples are included that provide risk estimates to two significant figures. As an illustration, the figures for workers, consumers and the public through the environment, for a polycyclic aromatic hydrocarbon, are calculated at 5.2×10^{-4} , 1.5×10^{-7} and 7.3×10^{-9} for each of these groups respectively. The document makes it clear that all such calculations should be accompanied by a free-text comment that indicates the uncertainty and any possible bias in the risk estimates.

Despite this provision of a comment, concern has been expressed that the numbers will inevitably become dissociated from the comment and will give a false impression of both the accuracy and precision of the risk assessment. In many cases, there is considerable uncertainty about the exposure data and about the shape of the dose-response curve at low doses.

3. CRITICAL REVIEW OF THE PROPOSED T25 METHOD

3.1 Method of calculation

Indices of carcinogenic potency have been described and reviewed over many years. For example, the Carcinogenic Potency Database (Gold *et al*, 1998) uses the TD50 as the index of potency.

The T25 method proposes that the risk for humans should be calculated from an estimate of a 'human' T25, (HT25), derived by the application of scaling factors (but not safety factors) to experimental rodent data (Dybing *et al*, 1997). The most sensitive tumour site that is relevant for humans is chosen, and benign as well as malignant tumours are included. The animal T25 is estimated by interpolation or extrapolation on the straight line from the origin of a plot of % induced tumours (in excess of control) versus dose to the tumorigenic dose point that results in the lowest value for T25. This is stated to be normally the lowest significantly tumorigenic dose (witnessing to the normal sub-linearity of the dose-response relationship), but in some cases it might be a higher dose. The document makes sensible provision for situations in which there is more than one dataset and other eventualities.

In general, a method should be favoured that uses all the data from a study (e.g. using the Linearised Multistage (LMS) model or something similar, referred to below as the 'benchmark dose' (BMD) method), rather than the cancer incidence at one dose only. Therefore, the use of a BMD, or a TD_x, (calculated from all doses of the experimental data using a reasonable model) is preferable to the calculation of the T25 using only the cancer incidence at one dose. Sanner *et al* (1997) have argued that the T25, calculated as proposed by them, has the advantage of transparency, in that it can be reproduced at any time without sophisticated computation. However, the simplicity of the calculation has little advantage when the selection of the study and the tumours to be used as the endpoint requires such sophisticated scientific judgement.

3.2 Application of the T25 method

3.2.1 Determination of concentration limits in preparations

The method proposed by the Commission Working Group (EC, undated a) has been used for several chemicals and found to be a practical approach for determining concentration limits of carcinogens in preparations, thus enabling labelling decisions for the preparations containing them to be made. If it is used with care, it is considered that it should provide an adequate method for this purpose and provide common criteria for the hazard assessment of preparations containing carcinogens.

3.2.2 Carcinogen risk assessment of existing (and new) chemical substances

The regulatory requirement to carry out risk assessments (including for carcinogenicity when appropriate), for existing chemicals that have been prioritised, clearly requires a specified method. Moreover, because the outcomes of the risk characterisation process based on sufficient data are limited (for existing substances) to a binary distinction between those for which there is a need iii b) and those for which there is no need iii a) for further risk reduction methods, the method of risk assessment must be capable of making such a decision. If, therefore, a distinction is to be made between risks that are found either to be acceptable or not acceptable, the procedure must be capable of differentiating accordingly.

In the proposed method, scaling factors are used to convert the animal T25 to the corresponding human dose descriptor HT25. The human dose is calculated from available exposure data (or predicted from models) and the corresponding human lifetime cancer risk is obtained by using rectilinear extrapolation. In practical terms this involves dividing the exposure dose by the coefficient HT25/0.25. The estimated risks are accompanied by a 'commentary' addressing possible modifying factors and areas of uncertainty.

Primary concerns and criticisms of this approach focus on both the tumour data analysis from carcinogenicity bioassays and on the specific assumption of a linear dose-response relationship between the experimental tumour incidence range and zero.

3.3 Tumour data analysis

A major criticism of the T25 proposal is the simplified way in which the tumour data derived from animal bioassays are used in calculating the carcinogenic potency for chemicals.

The manner in which tumour data from rodent bioassays are prepared and analysed is currently under review by the US Food and Drug Administration (FDA, 2001). The Society of Toxicologic Pathologists (STP) is also considering recommending modifications to the Peto Analysis criteria for assessing carcinogenicity in rodent bioassays.

The tumour data from chemical carcinogenicity bioassay studies should be prepared and analysed in the same carefully considered way as is proposed for pharmaceutical carcinogenicity assessment, so that the maximum useful scientific information is derived for subsequent use in a risk assessment.

The method proposed in the T25 document is an oversimplification of the use of tumour data from rodent studies. This could lead to misleading conclusions in deriving estimates of chemical carcinogen potency for the following reasons:-

- The calculation of the T25 dose is dependent on the incidence of tumours in a single site at a single dose. Single data points are subject to considerable stochastic variability and greater confidence would result if all the available data were used.
- Bias in the analysis of tumour data can be introduced by using crude tumour incidence data, without adjusting for differences in mortality across groups. This potential source of confounding has been completely ignored in the present T25 proposals.
- The possibility of using an alternative procedure that does not require data on tumour lethality and cause of death (which is often not available and is another controversial area currently under discussion by the STP) is ignored. The suggestion has been put forward by leading statisticians that tests such as the poly-k test should be investigated further. Extensive studies have indicated that this test performs well under actual study conditions. This is neither mentioned nor discussed in the T25 document.
- No allowance is made for the use of the statistical decision rule tests which tests for significant differences in tumour incidence between the control and treated group at the 0.05 level for rare tumours and at the 0.01 level for common tumours (Haseman, 1983).
- The proposed method involves the calculation of the T25 for the most sensitive tumour site that is relevant for humans. The selection of the most sensitive tumour is not straightforward. In absolute terms, an increase in numbers of a tumour with a low background incidence may be greater than the increase in number of a tumour with a high background incidence, but in the latter case, the percentage reduction in animals free of that tumour may be higher than the percentage reduction in the former case.
- No guidance has been given with respect to determining the relevance of animal tumours for human carcinogenicity and to the estimation of human risk. Examples that are irrelevant are tumours of the rat forestomach and Zymbal's gland, for which there are no human equivalents.
- The quality of data from rodent studies can be highly variable, depending on age, number of dose groups selected, and details of mortality (as with Peto analysis information on tumour lethality, or otherwise). This should be included in a 'weight of evidence' approach in considering potential for carcinogenicity, in a categorical approach.
- No account is taken of important factors, such as time to development of first tumour, and relationship between dose for tumour induction and toxic or even lethal doses. (e.g. dimethyl sulphate, for which inherent toxicity has caused problems in carcinogenicity studies; Schlögel and Banasch, 1970).
- No account is taken of existing different cancer susceptibilities between rodent species (e.g. butadiene, to which the mouse is much more sensitive than the rat (Hazleton Laboratories Europe, 1981; NTP, 1984)).
- Supportive studies providing data regarding mechanism of tumour formation and its relevance for species other than the rodent (especially for humans) seem to have little impact on the analysis.

3.4 Assumption of a linear dose-response relationship and the risk assessment

The T25 estimate is based on a methodology that was first proposed as a 'screening test' to determine whether carcinogenicity was the critical effect for exposure limit setting. Many believe that this methodology is flawed because of the assumptions – often unstated – that are an integral part of the method. For example, it relies on the assumption of a straight-line dose response curve from the high experimental doses to zero, and thus fails to take account of the more likely non-rectilinear dose-response relationship for both genotoxic and non-genotoxic carcinogens (French and Williams, 2001). There is growing evidence from an understanding of biological mechanisms, that dose-responses, including those for genotoxic carcinogens, are not rectilinear. Caution has to be exercised in particular when using limited high dose animal data (obtained for hazard identification, in which there are confounding factors of toxicity and metabolic saturation) for risk calculation purposes at low exposures.

The estimate of risk provides a spurious sense of accuracy. One reason is that the proposal makes several conservative assumptions (e.g. use of most sensitive tumour type as basis for T25 calculations) and assuming a rectilinear dose response relationship), and neglects factors (such as the greater variability in susceptibility in human populations compared to inbred rodent strains) on the grounds that the method is sufficiently conservative to accommodate this. This combination of conservatism and neglect of factors renders the resulting risk estimate uncertain.

For example, in illustration 3 (EC, undated b), the risk of exposure of workers to an alkene halide is given as 1.1×10^{-3} . The authors assert that to give an estimate of risk with confidence intervals would imply that there were sufficient data to draw a statistical conclusion, which is not appropriate. In a strictly mathematical sense, this is correct. However, the true risk in this example could be hundreds or thousands of times lower than 1.1×10^{-3} . In the same illustration, the estimated risk for man exposed via environment is 7.7×10^{-8} . In this case, the estimate has required extrapolation over an even greater dose range; the error is thus likely to be even greater. Providing an estimate to two significant figures, without any numerical statement about its uncertainties, is equally or more misleading than using confidence limits.

The risk estimates, if used as though they are accurate estimates of human risk from exposure to the chemical of concern, will mislead risk managers and members of the public. For example, the resulting calculated value will be taken as the 'true' risk in communication with the risk managers and with those exposed. Experience of this particular phenomenon has occurred in the USA, where the single figure estimate has been taken as the 'gold standard' without any attempt to deal with the uncertainties. If numerical estimates are to be used. It is imperative for regulations to be based on sound scientific procedures to avoid this error and to provide an estimate of the likely bounds of risk.

The justification of the reliability of the T25 method, is that it provides similar risk estimates to those derived from the LMS model, formerly used in the USA. However, this claim does not add any support to the validity of the calculated risk estimates. Instead it reflects the fact that the basic principles of both procedures are similar in that a) the risk estimates are made from the same animal cancer data, and b) it reflects a similarity in the mathematical expression of dose response in the LMS method as compared with a simple straight line extrapolation through zero in the T25 method.

3.5 *General criticism*

The proposed method of risk assessment for carcinogens distinguishes carcinogens for which no threshold can be determined from the rest, presumably on the assumption that a 'margin of safety' (MoS) approach will be used where a threshold can be determined. The proposal states that 'it is at present prudent to regard substances inducing tumours by genotoxic mechanisms as non-threshold carcinogens'. There is a great danger that it will be assumed that carcinogenic substances that are genotoxic in short-term tests induce tumours by a genotoxic, non-threshold mechanism. This assumption can be criticised on several counts:

- The criteria for distinguishing between these two types of carcinogens are poor. Usually they are based on the presence or absence of genotoxicity in a battery of in vitro and in vivo tests, with genotoxic carcinogens being considered as having a non-threshold dose response. However, for the majority of chemical carcinogens, the evidence that genotoxicity is the sole or prevailing mechanism of tumour induction, is absent. Most of the evidence is based on experimental systems using short-term endpoints other than cancer.
- The absence of a threshold for carcinogens that produce tumours by genotoxic mechanisms is largely unsubstantiated. Experimental verification of the existence of a threshold has to rely on trying to establish that no increase in cancer has occurred in a particular experiment; in practice this is impossible (Purchase and Auton, 1995). Thus, the claim of a threshold has to rely on mechanisms of carcinogenic action. Recent understanding of the mechanisms of carcinogenic action provides good evidence that steps in the carcinogenic process do indeed have a threshold or produce an effect similar to a threshold, e.g. a "hockey stick like" dose-response curve at lower doses. For example, DNA repair mechanisms, including the effect of tumour suppressor genes, can cause significant deviation from linearity in the response to genotoxins.
- The distinction between these two methods for risk assessment is confusing both to those who have to manage the risks and to those members of the public who might be exposed to the risk (Purchase and Slovic, 1999). An integral part of risk management is the communication of risk, and the use of a '2-track' method is confusing.

3.6 Conclusion

The risk estimates produced by calculation of a T25 (whether as proposed or from a model dose-response relationship fitted to actual data) look precise but are almost certainly wrong. The method does not meet the requirement of providing accurate information for the decision required in risk assessment of existing substances.

It is not possible to provide a scientifically reasoned estimate of the bounds of risk from such a simplistic method as that proposed (EC, undated b). It is for this reason that, for risk assessment to be used in the regulatory context, ECETOC (in line with other researchers) proposes different approaches that do not rely on scientifically indefensible risk estimates (ECETOC, 1996). The Task Force considered a variety of alternative approaches and their conclusions regarding these are set out in Appendix 1.

4. RECOMMENDATION AND CONCLUSION

For the reasons given above, a regulatory risk assessment must not rely on scientifically indefensible mathematical calculations of risk estimates for humans, such as the T25 method (or any variation of this procedure), the TD10 of the EPA or the LMS model. For regulatory purposes, a method must be used that avoids publication of unsubstantiated, and in most cases exaggerated, cancer incidence rates to the public. In addition, such approaches require the definition of a societally acceptable risk. Any such risk imposed on a human population will be highly debatable and cannot be scientifically justified. Moreover its acceptability by the public will be questionable.

In reaching its conclusions, the Task Force considered the following to be determinants of their recommendation:

- Data and theory are in general not good enough to support quantitative risk assessment.
- T25 method involves inherently conservative assumptions (such as dose-response linearity) and choices (such as the choice of the most sensitive tumour site and the dose level that gives the lowest T25 estimate) and, based on this conservatism, ignores potentially important factors such as differences in susceptibility. This is an inherently inaccurate process but yields a result of high precision. This causes difficulty and potential confusion in risk communication.
- While it may be argued that all the data are used qualitatively in selecting the study and tissue in which tumours are to be counted to yield a T25 value, the calculated result is conditioned by only a small proportion of the available data. It will not be possible from the result to tell whether the totality of the available data has received appropriate consideration.
- The simplicity and transparency of the T25 method is delusory: only the final calculation is simple. The selection of the study, the tissue in which tumours are counted and the qualifiers that are applied to the point estimate of risk are complex scientific judgements requiring considerable toxicological expertise and these processes are not inherently transparent.
- Risks or 'margins of exposure' (MoE) should be calculated for all suitable studies in order to obtain a 'weight of evidence' appreciation of the need for risk management.
- MoE is conceptually similar to the MoS approach used for risk assessment of threshold phenomena.

4.1 Recommended method

The Task Force considered that a MoE method was the most suitable method for the risk assessment of non-threshold carcinogens. The basic principles and some discussion of the various judgements to be applied to it are set out below (See Figure 1). Background discussions are presented in Appendix 2.

The process begins with a decision that the substance under consideration produces tumours in adequate studies in rodents, that the weight of evidence is that it is genotoxic and that there are no adequate grounds to determine a threshold dose or exposure, below which the carcinogenic pathogenic process will not lead to induction of tumours.

Studies (necessarily including rodent carcinogenesis bioassays) are identified and those that are considered relevant and of adequate quality and sensitivity selected for use in the risk assessment. Apart from carcinogenicity bioassays, the following data may be contributory:

Animal/microbial

- physiologically based pharmacokinetic (PBPK) data
- absorption, distribution, metabolism, excretion (ADME) data
- toxicological data
- mechanistic data

Human

- epidemiology
- health effects and biomonitoring data

For each animal carcinogenicity study *i*) the maximum likelihood estimate (MLE) of a benchmark dose (BMD) for a 5% risk level is calculated using a widely accepted model for the dose-response relationship. The choice of the model will not normally be critical in the context of the relatively imprecise nature of the whole process and other data, such as exposure data, but the choice of model should be justified. The BMD is scaled to a human benchmark exposure level (ⁱE_b) using appropriate allometric scaling factors (Sanner *et al*, 1997; ECETOC, 2002)), modified by available PBPK and metabolism data. Particular care should be taken with route-to-route extrapolations. The reasons for deviating from standard scaling factors should be carefully documented. A value for the human benchmark exposure level (E_b) to be used in the MoE calculation should be chosen after careful consideration of the individual estimates (ⁱE_b) in the light of the characteristics of the corresponding study. This consideration will normally exclude clear outliers and lead to a choice within the lower two thirds of the range of other reliable values, the degree of conservatism necessary being a matter of expert judgement.

The realistic worst-case exposure levels for workers (E_w) should be estimated, as it is estimated in existing chemical risk assessments for any other health endpoint. The MoE should be calculated as $M_w = E_b/E_w$. The same process should be adopted for consumers and the public exposed through the environment. The MoE would be compared with a standard to determine the conclusion of the risk assessment.

The central standards for different exposure groups are likely (by analogy with other situations) to be in the ratio 1:10:100 for workers, consumers and the public through the environment, respectively. International consensus will be required to agree acceptable standards for the MoE for these three groups, but it is likely that 10^4 , 10^5 and 10^6 would be the favoured values. It is envisaged that each standard would be associated with a range (e.g. $10^4 \pm 20\%$). If the MoE were within the corresponding standard's range, toxicological, mechanistic and dose-response curve shape information and any available human data could determine whether the MoE was considered to be greater or less than the standard.

The conclusion of the risk assessment would be based on the MoEs calculated for each exposure group from all relevant adequate studies and a weight-of-evidence approach adopted to decide whether the MoE is greater or less than the standard. If the decision, based on adequate data, was that it was greater than the standard, conclusion 2 would result and the residual risk with existing control measures would be considered acceptable and additional risk reduction measures would not be required. If it were close to or below the standard, conclusion 3 would follow and allocation to any subdivision being judged on risk-benefit considerations. Conclusion 1 would be appropriate if there were serious uncertainty about the human benchmark exposure level or the reasonable worst-case exposure level and the MoE was inadequate when calculated from conservative estimates of these values.

4.2 Conclusion

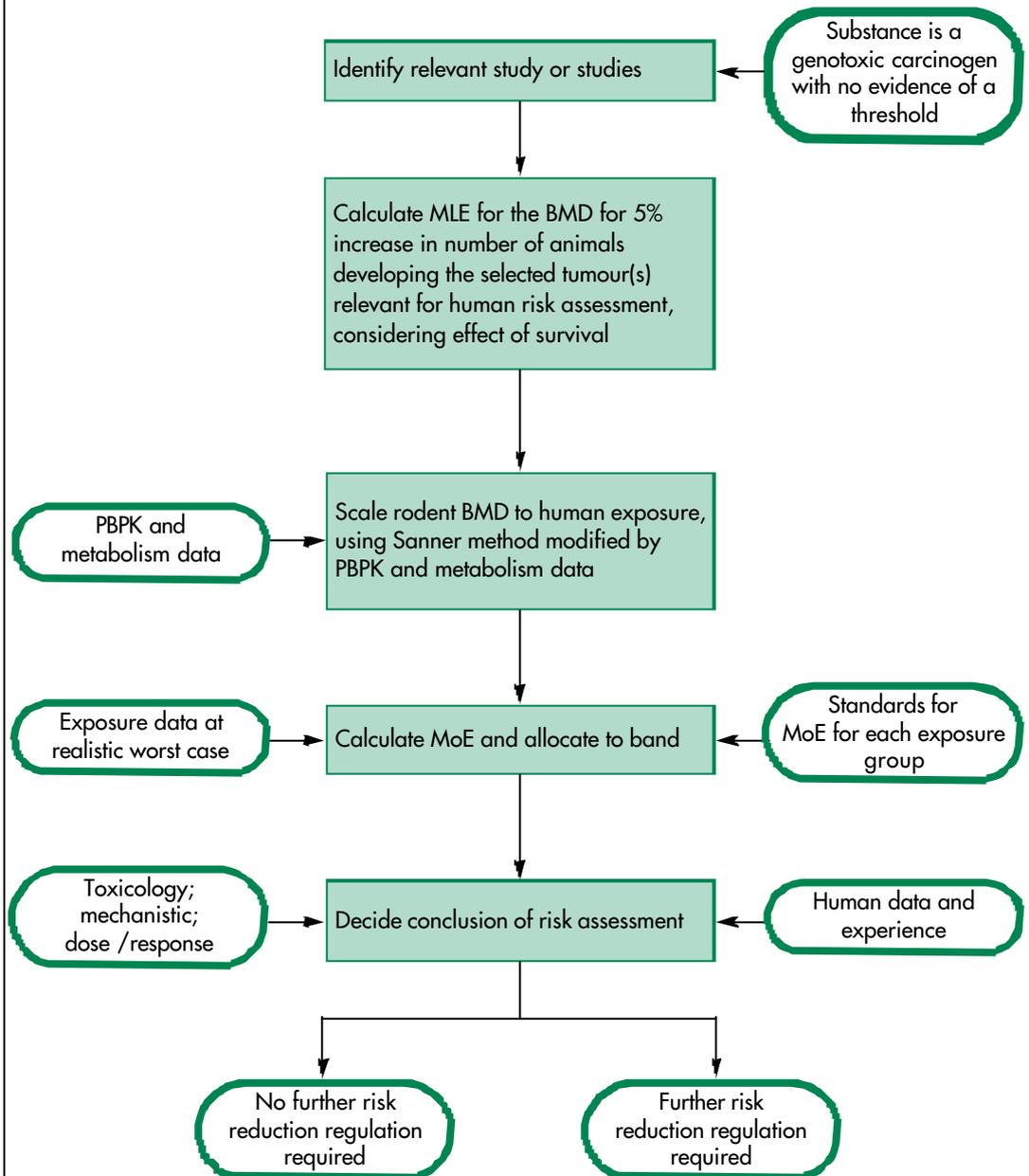
Risk assessment for carcinogenicity is necessary to meet the requirements of the 'Existing Chemicals' Regulation in the EU, even where there is no established threshold for the effect. In such cases, the risk assessment should be done by calculating a MoE, comparing exposure with the maximum likelihood estimate of the BMD for a specified risk level of e.g. 5%. ECETOC does not regard the risk level specified as critical, provided acceptable values for the MoE are set.

The values of MoEs for workers, consumers and the public that would lead to the various conclusions of the risk assessment is a societal decision that is not discussed in this document, but 10^4 , 10^5 and 10^6 are predicted to be values that would command considerable agreement.

This proposal is consistent with the approach advocated by other bodies (Bogdanffy *et al*, 2001).

In the case of carcinogens that are accepted to have a threshold, a MoS is calculated as part of their risk assessment. In such cases, the MoS is numerically identical to a MoE using the no effect level rather than the BMD, as the comparator for human exposure. It would thus be possible to use the terms MoE in both cases; this might facilitate risk communication.

Figure 1. The basic process



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APPENDIX A. DISCUSSION OF ALTERNATIVES TO THE T25 METHOD

This appendix provides a brief outline of possible methods of providing information for risk managers that will allow them to decide which carcinogens require action under the EU regulations in order to differentiate between the conclusions iii a) and iii b). It aims to provide only an indication of the principles of available alternative methods and to communicate the opinion of ECETOC as to the best method in principle. The details of any method recommended in the Technical Guidance Document (EC, 1996) would have to be developed in the appropriate forum, especially in respect of any numerical (default) values for the approaches considered and proposed.

Variations on the T25 method proposed by Sanner *et al* (1997)

Alternative TD values, such as TD10, could be used. The initial calculation of the T25 (or whatever other value is preferred) based on animal data could be obtained from a dose-response curve derived from a suitable mathematical model and converted into the human T25 using the methodology proposed by Sanner *et al* (1997). This would provide better use of the available animal experimental data, but still assumes the rectilinear dose-response relationship over the whole range of doses. The problem of the precision of the risk estimate could be overcome by expressing cancer incidences in a band e.g. $>10^{-3}$, $10^{-3} - 10^{-5}$, $10^{-5} - 10^{-7}$, $10^{-7} - 10^{-9}$, $<10^{-9}$. This would avoid the problems arising from the absence of expression of uncertainty and inappropriate communication of the single figure risk, but the calculated point estimate would almost certainly be available in the public domain and could not only give rise to confusion but also give the impression that the actual risk is being concealed.

'Margin of safety' (MoS) method

The basis of this approach is the application of standard safety factors to the observed cancer NOEL derived from animal studies. The NOEL (no observed effect level) is defined as the dose level at which no increased incidence of tumours is detected. It is used to deduce a virtually safe human exposure value (DOH, 1991).

The NOEL will depend on the size of the experiment and the dose choices and would be expected to vary between similar experiments. For this reason, a decision would have to be made as to whether to use as the rodent 'NOEL' a single observed NOEL, the highest NOEL from the available experiments that was not an LOEL, the lower confidence limit of a benchmark dose or simply a small fraction (e.g. 1%) of a dose that produced a small tumour incidence, or some other figure.

However such 'NOEL' were derived, the following default factors could be used for occupational exposure of workers, if there is no indication of or scientific justification for a sub-linear dose response curve in the low dose region:

- factor of 10 to allow for animal to human extrapolation;
- factor of 10 to allow for inter-individual differences;
- further factor of 10 to allow for the severity of the effect (cancer).

The 'MoS' method would therefore (in this example) derive a human acceptable dose, which is a factor 10^3 lower than the 'NOEL' for carcinogenesis. Further factors could be applied for consumer exposure and public exposure through the environment. If there is a valid indication of a clear sub-linear dose-response curve, smaller safety factors are appropriate.

The main advantages of this method are that:

- It is simple and transparent and compatible with existing standard setting procedures.
- Existing widely accepted uncertainty (safety) factors are used.
- It cannot be misapplied to derive quantitative cancer risk estimates.
- It is readily applicable to all carcinogens (whether or not they are defined as genotoxic).
- Factors can be modified according to current knowledge (e.g. of toxicokinetics).

The disadvantages are that:

- It relies on the derivation of a NOEL. A NOEL cannot be assumed to be a no effect level, the existence of which is controversial in the case of carcinogens, since it implies a threshold of effect.
- It assumes that current safety factors are correct and appropriate. In reality they are always somewhat arbitrary.

A variation of the margin of safety (MoS) approach

This approach was described by Dr K Crump at the ECETOC workshop (Roberts *et al*, 2001) and is based on the concept that there should be one risk assessment method for all carcinogens (one-track approach), regardless of whether or not a threshold can be determined

The T25 for all carcinogens (whether genotoxic or not) is calculated and converted to a human HT25. Guidelines for developing an 'advisory exposure level', are applied by the use of adjustment factors (Crump, 1996). For example, one adjustment factor could be used to reduce the T25 into the low dose uncertain risk level and one adjustment factor could be used to account for mechanistic information. A third adjustment factor could be used to account for the quality of the database and a further adjustment factor could be used to account for variations in human susceptibility.

The advantages of this method are:

- It does not rely on the derivation of a NOEL.
- A single method, based on the same principle as is used for other forms of chemical toxicity.
- Can be applied to all chemical carcinogens.
- Communication of the result of the calculation is relatively easy.
- Calculations are transparent.
- Use of calculated risk values of dubious validity and the need to communicate them are avoided.

The disadvantage is:

- The selection of the adjustment factors will be somewhat arbitrary.

Margin of exposure (MoE) method

This method is discussed in detail in the main body of this document. Its main advantages are that:

- No calculation of risk expressed as number of cases per unit of exposed population is made. This is important as all scientists acknowledge that the calculated value is inaccurate because of the unverifiable assumptions incorporated into the methodology and because it removes the danger of communicating false information about risks to the risk managers and public.
- Method of calculating the MoE is transparent.
- Decisions can be made by the regulatory system on a similar basis to those derived from calculation of risk.

The disadvantage is:

- Definition of the appropriate margin of exposure for regulatory action will require as careful justification as the choice of societally acceptable risks.

A categorical approach

Essentially, this is a modification of the MoE approach in which the decisions regarding safe exposures are made generically. The approach would involve the development by consensus of three tables (for workers, consumers and the public exposed through the environment) relating acceptable exposures to the category and potency of the carcinogen, thus:

Table 3: Acceptable exposure of workers to carcinogens

Potency	Category 1	Category 2	Category 3
High	W1H	W2H	W3H
Medium	W1M	W2M	W3M
Low	W1L	W2L	W3L

Workers signified by 'W'; 1,2,3 refers to categories H,M,L to potencies

W1H to W3L are daily exposures (mg/person/day or mg/kg/day) that would be considered acceptable. Similar tables would be developed for consumers, with exposures C1H to C3L, and for the public with exposures P1H to P3L. While this would appear to require determination of 27 arbitrary values, in practice a relationship W:C:P would be agreed as scaling factors between the three tables. This would reduce the number of values to be determined to 11. The number could be further reduced if it was considered that there is diagonal symmetry in the tables. There would be no need to distinguish between threshold and non-threshold carcinogens.

The decisions regarding the values are not necessarily more difficult than the allocation of occupational exposure limits for carcinogens.

The advantages of this method are:

- Single method is applied to all chemical carcinogens.
- Communication of the method of assessment is easy and transparent.
- Avoids the use of calculated risk values of dubious validity and the need to communicate them.

The disadvantage is:

- The consensus values for acceptable exposure will be difficult to achieve and open to criticism.

APPENDIX B. DISCUSSION OF THE BACKGROUND TO ASPECTS OF THE PREFERRED METHOD

The endpoint for calculating the benchmark dose (BMD)

The Task Force considered that the endpoint for calculating the BMD for a particular risk level (e.g. 5%) should be the increase in the number of animals exhibiting the specific tumour type(s)² considered to be the most sensitive to the carcinogenic action amongst the tumours that are relevant to humans, i.e. excluding tumours generally recognised to be irrelevant to human risk. The most sensitive type of tumour should be identified using the Haseman (1983) rule for statistical significance. This allows some flexibility in the interpretation of the significance limit for common (endocrine or hepatic) tumours, by using the rule that $p < 0.01$ for these, rather than the more usual limit of < 0.05 .

The Task Force suggests the use of a 5% risk level³, which is commonly calculated. The lower 95% confidence limit of the 5% effect level BMD is often considered to be comparable to the classical NOAEL. The choice of a 5% response in the BMD method influenced by the discriminating power of the animal experiment. If the control shows a response of 0 in 50 animals, a statistically significant ($p < 5\%$) difference based on the Fisher exact test (one sided) starts at 5 in 50 animals, an incidence of 10%. If more dose groups are used, a trend test can detect a significant difference at lower incidences, but only by considering simultaneously the other dose groups. It is quite evident that the discriminating power of a standard rodent carcinogenicity experiment usually is not better than 5%.

It has been recommended by Murrell *et al* (1998) that both the point estimate of the BMD 5% and the lower confidence limit should be quoted in order to make possible a quality check on the data. To enable a consistent method to be used even when data was of lower quality, the Task Force agreed with Murrell *et al* (1998) that the maximum likelihood estimate of the BMD should be used because the lower confidence limit is very dependent on the variability in the study data. Standards should be set accordingly.

Margin of Exposure and Modifying Factors

The acceptability of the MoS or MoE might be determined by many aspects.

In some cases, tumour formation is associated with cytotoxic effects in the target organ and cytotoxic effects occur before tumour formation. It has been shown that the cytotoxicity is a threshold type of effect or the cytotoxic dose-effect relationship is sub-linear. In this case, a small MoS or exposure is acceptable.

2 The tumour type would normally be all tumours (malignant and benign) in a particular tissue or organ. The % decrease in animals free of relevant tumours in all organs and tissues was rejected on the grounds of the instability of this metric.

3 The decision depends, *inter alia*, on the typical ratio of the BMDs for (say) 1%, 2%, and 5% risk levels. If the ratio is typically 1:2:5, it makes no difference which risk level is used provided the standards are set accordingly. This would be true for a rectilinear dose-response relationship over this range. Examination of the ratio for a variety of constructed dose-response curves indicated that, where the relationship is concave upwards, the BMD for a 5% risk level might only be twice the BMD for a 1% risk level.

In other cases, there is an absence of increased specific tumour mortality in occupationally exposed workers. Although precise exposure levels might be not available, it is quite possible to subdivide workers in low, middle and high exposure groups on the basis of specific jobs with exposure to carcinogenic compounds. If by means of Poisson regression analysis or by Cox regression analysis (IARC, 1987) it can be shown that the regression coefficient of exposure predicting an increased the tumour incidence is equal to zero with more than 95% significance, this should be accepted as a strong argument for accepting a small MoS.

Finally, the shape of the dose response should be considered. The preferred model for the shape factor is the Weibull model. Alternatively (i.e. for studies with a control and three dose groups) the LMS model is useful⁴.

In many studies conducted as part of the US NTP it is necessary to correct for decreased survival in the higher dose groups since these studies were usually done in a hazard identification mode employing high dosages. Where there is decreased survival, it is necessary to estimate the Kaplan-Meier tumour probability, dependent on dose and observation period (ten Berge, 1999). The Kaplan-Meier tumour probability might be considered as the true tumour incidence independent of survival except by the tumour of interest. If the shape factor of the Kaplan-Meier tumour probability is 2 or 3 (indicating that the tumour rate is related to the dose level to the 2nd or 3rd power), a small MoS is quite acceptable. In fact, the observed MoS might be raised to the shape factor in order to achieve the virtual MoS.

Scaling

The conversion of a BMD in an animal experiment to the corresponding human exposure should be based on the conventional allometric scaling factors as proposed by Sanner, but where there are data relating to pharmacokinetics or metabolism that indicate the use of further factors, these should be estimated and used.

In considering the adjustment factors that apply between the species in which carcinogenicity data have been generated and humans for whom the data are being applied, a significant factor in species differences in cancer response may be associated with differences in absorption, distribution, metabolism and excretion. Of these qualitative or quantitative differences in metabolism may be expected to give the most striking basis for species differences in response. This would be expected to be particularly the case where differences in metabolism are directly related to metabolic activation to or deactivation of the ultimate carcinogen. Additionally at the high doses used in some carcinogenicity studies the metabolic pathways for the test article (e.g. paracetamol) (Bergman *et al*, 1996) in the test species may differ from those at lower doses due to saturation of the prime metabolic pathway.

⁴ At least one polynomial term should contain the dose to a power > 1 for proving a sub-linear dose response. In applying the LMS-model, a polynomial term with the dose to a power = 1 can often be found, which more or less emphasises that, at low dose levels, the dose-response is rectilinear. In the dose-response analysis of the EPA, the higher dose levels often did not fit, owing to decreased survival, and were not considered. Using only the lower dose levels turned out to provide the best fit with a polynomial term of the dose to the power = 1.

Experimental data or biologically valid PBPK modelling (may be used as a basis for making adjustments between species. PBPK modelling may also be used to explore the relationship of experimental data from gavage-dosed animals to the human exposure in which plasma peaks are not so exaggerated.

In projecting data from in-bred strain animal carcinogenicity studies towards an assessment of human exposure, account should also be taken of the greater heterogeneity in the human population.

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 No. 69 Toxicology of Man-Made Organic Fibres
 No. 70 Chronic Neurotoxicity of Solvents
 No. 71 Inventory of Critical Reviews on Chemicals (Only available to ECETOC members)
 No. 72 Methyl tert-Butyl Ether (MTBE) Health Risk Characterisation
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 No. 79 Exposure Factors Sourcebook for European Populations (with Focus on UK Data)
 No. 80 Aquatic Toxicity of Mixtures
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Joint Assessment of Commodity Chemicals (JACC) Reports

- | No. | Title |
|-------|---------------------|
| No. 1 | Melamine |
| No. 2 | 1,4-Dioxane |
| No. 3 | Methyl Ethyl Ketone |
| No. 4 | Methylene Chloride |
| No. 5 | Vinylidene Chloride |
| No. 6 | Xylenes |
| No. 7 | Ethylbenzene |

- No. 8 Methyl Isobutyl Ketone
- No. 9 Chlorodifluoromethane
- No. 10 Isophorone
- No. 11 1,2-Dichloro-1,1-Difluoroethane (HFA-132b)
- No. 12 1-Chloro-1,2,2,2-Tetrafluoroethane (HFA-124)
- No. 13 1,1-Dichloro-2,2,2-Trifluoroethane (HFA-123)
- No. 14 1-Chloro-2,2,2-Trifluoromethane (HFA-133a)
- No. 15 1-Fluoro 1,1-Dichloroethane (HFA-141B)
- No. 16 Dichlorofluoromethane (HCFC-21)
- No. 17 1-Chloro-1,1-Difluoroethane (HFA-142b)
- No. 18 Vinyl Acetate
- No. 19 Dicyclopentadiene (CAS: 77-73-6)
- No. 20 Tris-/Bis-/Mono-(2 ethylhexyl) Phosphate
- No. 21 Tris-(2-Butoxyethyl)-Phosphate (CAS:78-51-3)
- No. 22 Hydrogen Peroxide (CAS: 7722-84-1)
- No. 23 Polycarboxylate Polymers as Used in Detergents
- No. 24 Pentafluoroethane (HFC-125) (CAS: 354-33-6)
- No. 25 1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0)
- No. 26 Linear Polydimethylsiloxanes (CAS No. 63148-62-9)
- No. 27 n-Butyl Acrylate (CAS No. 141-32-2)
- No. 28 Ethyl Acrylate (CAS No. 140-88-5)
- No. 29 1,1-Dichloro-1-Fluoroethane (HCFC-141b) (CAS No. 1717-00-6)
- No. 30 Methyl Methacrylate (CAS No. 80-62-6)
- No. 31 1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)
- No. 32 Difluoromethane (HFC-32) (CAS No. 75-10-5)
- No. 33 1,1-Dichloro-2,2,2-Trifluoroethane (HCFC-123) (CAS No. 306-83-2)
- No. 34 Acrylic Acid (CAS No. 79-10-7)
- No. 35 Methacrylic Acid (CAS No. 79-41-4)
- No. 36 n-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)
- No. 37 Methyl Acrylate (CAS No. 96-33-3)
- No. 38 Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)
- No. 39 Tetrachloroethylene (CAS No. 127-18-4)
- No. 40 Peracetic Acid (CAS No. 79-21-0) and its Equilibrium Solutions

Special Reports

- | No. | Title |
|--------|---|
| No. 8 | HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances |
| No. 9 | Styrene Criteria Document |
| No. 10 | Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1) |
| No. 11 | Ecotoxicology of some Inorganic Borates |
| No. 12 | 1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0) |
| No. 13 | Occupational Exposure Limits for Hydrocarbon Solvents |
| No. 14 | n-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document |
| No. 15 | Examination of a Proposed Skin Notation Strategy |
| No. 16 | GREAT-ER User Manual |

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction