GUIDELINES FOR
SETTING SPECIFIC CONCENTRATION LIMITS FOR CARCINOGENS IN ANNEX I
OF DIRECTIVE 67/548/EEC

INCLUSION OF POTENCY CONSIDERATIONS

Commission Working Group

on the

Classification and Labelling of

Dangerous Substances
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1. EXECUTIVE SUMMARY

The present document gives guidance as to how potency considerations may be included in the setting of specific concentration limits for carcinogens which are classified according to the criteria of Directive 67/548/EEC. As a general procedure, the potency calculations and subsequent assignment of specific concentration limits are only forwarded to the Working Group if they deviate from the general concentration limits. Potency is in this document defined as the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration. Carcinogens are subdivided into three potency groups of high, medium and low potency. For category 1 and 2 carcinogens, those of medium potency will normally be assigned to the general concentration limit of 0.1%. Carcinogens of high potency will normally be assigned a limit of 0.01% and carcinogens of low potency 1%. Category 3 carcinogens will normally be assigned to the medium potency group and given the general concentration limit of 1%, whereas highly potent Category 3 carcinogens will be assigned a specific concentration limit of 0.1% and Category 3 carcinogens of low potency a concentration limit of 1.5% on a case by case basis. The subdivision into the three potency groups is performed based on a tumorigenic dose descriptor. Among several possible descriptors, T25 is selected. T25, the dose giving a tumour incidence of 25% in an exposed human population, or in experimental animals after correction for the spontaneous incidence. Carcinogens of high potency are those with a T25 value which is: \( < 1 \text{ mg/kg bodyweight/day} \), those of medium potency when: \( 1 \text{ mg/kg bw/day} < T25 \text{ value} < 100 \text{ mg/kg bw/day} \), and those of low potency when the T25 value is: \( > 100 \text{ mg/kg bw/day} \). In addition to subdividing carcinogens by the use of the tumorigenic dose descriptor, T25, several other elements bearing on tumorigenic potency (dose-response relationships, site/species/strain/gender activity, mechanism including genotoxicity, mechanistic relevance to humans, toxicokinetics and other elements relevant to potency classification) are taken into consideration, which thereby may modify the potency preliminary evaluation. The examples presented in the Annex are illustrating how the scheme may be applied.

2. INTRODUCTION

2.1 General description of the EU classification system for carcinogens

The Council Directive 67/548/EEC contains rules for the classification of dangerous substances according to the degree of hazard. Annex VI of this Directive (93/21/EEC) illustrates the general principles of the classification of substances. In Chapter 4 of Annex VI criteria are given for the classification of substances as carcinogens in one of the three categories:

**Category 1:** Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.
Category 2: Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:
- appropriate long-term animal studies,
- other relevant information.

Category 3: Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

The EU criteria are based on the strength of scientific evidence that the substance causes cancer. In general, no specific considerations are given to the carcinogenic potency of the substance.

Concentration limits are given above which a substance or a preparation has to be classified as a carcinogen. This can be a specific concentration limit which is given in Annex I or a general limit as mentioned in Directive 88/379/EEC. The general limits are 0.1% for Category 1 and 2 carcinogens, and 1% for Category 3 carcinogens. The present document represents a further development giving guidance for setting specific concentration limits for carcinogens.

It should be noted that specific concentration limits are assigned only in Annex I of Directive 67/548/EEC. In the case of substances not included in the Annex, it is the duty of the producer and importer to provisionally classify and label the substance, and, if the substance is included in a preparation, to apply the general limits of the Directive. This Guidance document has been produced in order that methods normally used to establish specific concentration limits in Annex I are generally known.

2.2 Need for considering potency in setting specific concentration limits for carcinogens

The identification of individual substances on the basis of the strength of evidence for carcinogenicity has resulted in the classification of a large number of chemical carcinogens. The substances that have been identified as carcinogens may also occur as components of a preparation or as impurities. Directive 67/548/EEC and Directive 88/379/EEC set out the general principles governing the classification of substances and preparations. However, the general concentration limits for the three categories of carcinogens according to the Directive 88/379/EEC, do not reflect the potency of a carcinogen in a preparation as such, as they reflect a level of concern for the seriousness of health effects such as carcinogenicity.

The range of acute toxicity values commonly seen for hazardous substances lies approximately in the range from 1 to 2,000 mg/kg; a range of $2 \times 10^3$. For this range of values, a number of general concentration limits are specified (25%, 7%, 3%, 1%, 0.1%) to reflect the variation in acute toxic potency of the preparation. Similar graduated concentration limits are also applied for other health effects, such as corrosivity and irritation.

However, the general classification system for carcinogens does not take into account the wide range of carcinogenic potency that can be observed both in human epidemiological studies and
in animal experiments. As well as the need for a system to reflect this wide range of carcinogen potencies, there are examples of carcinogens where the question of potency as such is of particular concern.

In some cases, it is the high potency of the substances such as dimethylsulfate and hexylmethylphosphoramide or impurities such as TCDD and certain nitrosamines which gives rise to concern and it is possible that a general limit of 0.1% does not adequately express the hazard.

In other cases, substances may be classified as carcinogens although relatively high doses are needed to induce tumours. In such cases the general limit may not adequately express the hazard of a preparation containing such substances, this time by over-estimating the carcinogenicity of the preparation.

Other intrinsic properties of chemical carcinogens may contribute to overall concern, such as the induction of tumours after a very short latency period, or the occurrence of tumours in many different tissue sites. This may be addressed by assigning lower specific concentration limits for such substances, if not addressed directly by the classification.

The assessment of the potency and other relevant characteristics requires expert interpretation of the available data. It is envisaged that carcinogens causing particular concern will be identified during the assessment of data for classification. Potency estimation will aid in this process. Chapter 3 describes the preferred method for evaluating the potency of classified carcinogens.

Several approaches to the expression of carcinogenic potency have been suggested in the literature (see Sanner et al. 1996). In this document potency is defined as the magnitude, with respect to dose, of the carcinogenic activity of a chemical in the species under consideration. Inherent in this definition are a dose descriptor (defined here as the dose needed to induce tumours) and other elements bearing on carcinogenic potency including dose-response relationships, site/species/strain/gender activity, mechanisms including genotoxicity, other mechanistic information relevant to humans and toxicokinetic properties of the substance (see Chapter 4).

2.3 Descriptors of tumorigenic dose

Many substances have been identified as carcinogens from rodent bioassays and classified according to the strength of this evidence. As pointed out above (section 2.1) such classification is not aimed at scaling potency differences, but some means of addressing potency is needed if the application of a specific concentration limit is to be considered.

Accurate and reliable potency estimates based upon human data have preference above those based on animal data. However, as reported by Allen and colleagues (Allen et al., 1988), there are several difficulties in evaluating human data, such as e.g establishing reliable human exposure doses and to differentiate problems with mixed exposures. Therefore, in most cases, human data are unlikely to be helpful in spite of the obvious species relevance. There are several approaches available for determining potency of carcinogens or dose descriptors from animal
data. An approach that utilises T25 is favored (see below), but several other approaches are also worthy of comment.

'TD50'
In an attempt to measure tumorigenic potency from experimental data Sawyer devised the TD50 concept, which was defined as a daily dose rate required to halve the probability of remaining tumorless at the end of a standard life-span (Sawyer et al., 1984). It is based upon two important assumptions: that there is linearity between dose and the hazard to tumour onset and that tumour onset times are observable. The measurement is complicated by premature deaths due to causes other than tumorigenesis and the non-observability of the time of tumour onset. The latter leads to an assumption that if an animal dies and is found to have a tumour, then the time of death was the time of tumour onset. Consequently, the measure of tumour incidence is confounded with mortality and biased TD50 estimates can occur (Portier and Hoel, 1987). If, on the other hand, tumours do not significantly alter survival, then TD50 values become related to the rate-of-death-with-tumour, rather than the tumour incidence rate (Meier et al., 1993). This undermines the objective of the carcinogenic study, which is to evaluate tumour incidence (McKnight and Crowley, 1984). The list of carcinogens for which a TD50 was determined has been extended substantially due to the use of this concept by others (Peto et al, 1984; Gold et al, 1984).

'TI'
Bailer and Portier (1993) introduced another approach to determine a TD50 value, referred to as the tumour incidence (TI) value. In this TI method tumour-onset times are no longer a prerequisite, as was the case in the TD50 concept (Bailer and Portier, 1993). In later studies a power-function was incorporated into the model as an estimate of the shape of the dose response curve, because the low dose element is particularly important in human exposures, but seldom addressed in experimental carcinogenesis (Meier et al., 1993). This lead to a different ranking as compared with the TD50 estimate rankings. The TI01 power value was favored by these authors because of the shape inclusion, the measure was always less than the MTD and that it had a low correlation with MTD. The latter two reasons cause TI01 to be favored over TI50 (or TD50).

'TDx'
Another method commonly used by Sweden and Norway, is the TDx value (Nordic Council of Ministers, 1986). This TDx is defined as the lowest lifetime daily dose (in mg per kg bodyweight) able to induce a statistically significant increase in tumour incidence of x percent. With the small numbers of animals normally used, this x-value would in general at least be 10 (TD10) in order to be statistically significant. The use of this concept is supported by the notion, that the differences between the TD10 and TD100 are small compared to the large differences in carcinogenic potency which has been found between high and low potency substances in animals.

'T25'
The T25 estimate of potency, which is quite alike the TDx method, is defined as the daily dose (in mg per kg bodyweight) inducing a tumour incidence of 25 % upon lifetime exposure, and is...
based upon the assumption of a linear dose response relationship between and above the experimental doses (excluding the zero-dose). The T25 method could be viewed as a "normalized" TDx method where the tumour response has been set to 25%.

The use of T25 values for potency ranking has several advantages in comparison to the TD50 and TI methods. First, it does not require (complex) computer modelling after establishment of a significant increase in tumour incidence. Also, T25 values are much more likely to be within the range of the experimental data and the use of data from the lowest dose giving a significant response, should in most instances reduce the problem of intercurrent mortality to an acceptable degree. Finally, the data profile needed for calculating a T25 value has to be less specific, e.g. time to tumour data are not needed. Thus, although it is recognized that T25 potency estimates may be less elaborate than some of the other methods for determining potency values (some of which have been shortly discussed here), the above arguments favor its use in potency ranking. It is recognized that the potential loss of precision does not match the many order of magnitude differences in carcinogenic potencies which have been found between high and low potency substances in animals.

It is proposed, therefore, that T25 values should be calculated for the purpose of setting specific concentration limits. It is, however, acknowledged that alternative estimates of potency may be more appropriate for use in risk estimation.

2.4 Procedure

When the carcinogenic hazard of a substance is assessed consideration should also be given to the potency if there is reason for concern (see Section 2.1). The available data from animal and human studies are evaluated to establish the tumorigenic dose descriptor, T25, as described in Chapter 3. A preliminary conclusion as to whether the substance shows high, medium or low potency is taken based on the T25 data. In some cases, such a potency evaluation will not be appropriate (see Section 2.5).

The preliminary potency evaluation may be modified after due consideration of a number of other elements. This may include dose-response relationships, site/species/strain/gender activity, mechanisms including genotoxicity, mechanistic information relevant to humans, toxicokinetic as well as other elements (See Chapter 4).

In this way specific concentration limits are then set taking into account all relevant considerations.

2.5 Cases where potency evaluations are difficult or unfeasible

The process for evaluating potency described in the following sections presupposes the availability of certain types of data. These may not always be available.
The testing strategy which is part of the hazard assessment of new notified substances opens the possibility for classification of substances as carcinogens without necessarily carrying out a carcinogenicity bioassay. In such cases, no direct estimate of carcinogenic potency based on a T25 value is possible.

In some cases, groups of substances are classified as a simple entry in Annex I. While there is often good reasons for including a group of substances as a single entry, the expected potency of the individual substances within the group may vary. In these cases a potency evaluation may be difficult.

Classification of a substance in category 3 may be done on the basis of "insufficient evidence". The quality of the available data will in such cases determine whether a potency assessment is still possible.

In cases where no further evaluation is carried out, the general concentration limits of Directive 88/379/EEC apply, and no specific concentration limits are given in Annex I of Directive 67/548/EEC.

When it is difficult or not possible to evaluate the potency of a carcinogen by determination of the T25 value (i.e. in the case of a non-systemic contact carcinogen), the potency may still be evaluated on a case by case basis, with particular reference to the elements mentioned in Chapter 4.

3. DETERMINATION OF THE CARCINOGENIC POTENCY

3.1 Determination of the T25 value

In this section guidance is given on how T25 is calculated, what data are needed and what assumptions are made.

The T25 is the chronic dose rate in mg per kg body weight per day which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard study period of that species.

T25 may either be incidentally obtained from the experiments or calculated from other tumour incidences using linear intrapolation or extrapolation (e.g. in case of a net 15% incidence, multiply by 25/15%).

**Determination in practice**

This T25 is calculated in principle from the data that are also used in the classification of the carcinogen.
The data for calculating T25 should preferentially be from lifetime oral (feed or gavage) or inhalation studies in mammals according to Annex V guidelines. However, if the test is not according to the guidelines, the following set of criteria should generally be met in order to be used for calculation of a T25 value: a) Animals on test were mammals, b) administration was begun early in life (preferable from time of weaning, but up to 100 days is acceptable for rats, mice and hamsters), c) route of administration was diet, drinking water, gavage or inhalation, d) the substance was bioavailable for systemic absorption, e) test agent was administered alone, f) exposure was chronic, with no more than 7 days between each dose, g) duration of exposure was at least one-fourth of standard study period for that species (see Table 1), h) duration of experiment was at least half of the standard lifespan for that species, i) research design included a control group, j) research design included at least 10 animals per group, k) pathology data were reported for the number of animals with tumours rather than total number of tumours, and l) results reported were original data.

In the absence of such a total data set, data from experiments fulfilling as many of these conditions are preferred. The assumptions made by using experiments not fulfilling Annex V guidelines should be specified and justified by toxicological considerations.

In order to create a common denominator for all carcinogens and to overcome species- and sex-dependent physiological variables, the T25 value should be expressed in mg/kg bodyweight/day. To enable a conversion of feed, drinking water or air concentration of carcinogens to this dose descriptor, the factors given in Tables 1 and 2 should be used unless these data are provided by the study itself.

In an experiment which is terminated before the standard lifespan, the number of tumours found will be reduced, and the dose rate \( d \) needed to give 25% of the animals tumours (after correction for spontaneous incidence) will then be greater than the true T25. For this reason, one should estimate the true T25 as \( f^2 d \), where \( f = (\text{duration of experiment})/(\text{standard lifespan}) \) (Peto et al., 1984). This is in accordance with experimental results (Druckrey, 1967). An experiment lasting for 18 months in rats with the standard lifespan of 24 months will then be corrected by \((18/24)^2 \times d = 0.56 \times d\). If animals are dosed 5 days per week, the dose giving 25% of animals tumours will be corrected by \((5/7) \times d = 0.71 \times d\) to arrive at the true T25 value. If dosing is terminated at \( w \) weeks (\( w < \) the standard lifespan of 104 weeks) (see Table 1) and the animals are observed until termination at 104 weeks, the dose giving tumours in 25% of the animals is corrected by \( w/104 \). If dosing is terminated at \( w \) and the animals observed until \( w \) weeks, the dose giving 25% of the animals tumour is corrected by \((w/104)(w/104)\).

It is assumed that a carcinogen is 100% bioavailable by the relevant route if specific data do not indicate otherwise. This means that carcinogenicity data generated by the inhalation route for gases and vapours can be converted to an oral dose using a standard set of conversion factors (Table 1). In the case of respirable particles tested by the inhalation route, conversion to mg/kg bw/day is possible using inhalation volume, disposition and concentration of particles. For illustrative purposes Table 2 shows the exposure values giving 1 mg/kg/day for lifelong exposure based on the default values in Table 1.
Table 1: Default values for dose calculation, experimental period, weights, and intake by diet, water, and inhalation

<table>
<thead>
<tr>
<th>Experimental animal</th>
<th>Sex</th>
<th>Standard experimental period (years)</th>
<th>Weight (g)</th>
<th>Food/day (g)</th>
<th>Water/day (ml)</th>
<th>Inhalation volume (l/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Male</td>
<td>2</td>
<td>30</td>
<td>3.60</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
<td>25</td>
<td>3.25</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>2</td>
<td>500</td>
<td>20.00</td>
<td>25</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
<td>350</td>
<td>17.50</td>
<td>20</td>
<td>6.0</td>
</tr>
<tr>
<td>Hamster</td>
<td>Male</td>
<td>2</td>
<td>125</td>
<td>11.50</td>
<td>15</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2</td>
<td>110</td>
<td>11.50</td>
<td>15</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Taken from Gold et al 1984.

If more than one T25 can be calculated from the available animal data, then the lowest T25 and which is relevant for humans i.e. the T25 of the most sensitive species or most sensitive site, is chosen. If there is a significant increase of tumours at more than one site, the number of tumour bearing animals may in certain cases be chosen in deriving the T25 value.

The number of tumours per animals is in general not used for deriving a potency descriptor value, because this parameter is highly variable and is not always presented.

Table 2: Exposure medium concentrations giving a dose of 1 mg/kg/day for standard lifespan exposure. In the case of inhalation, the calculations are based on 6 hour exposure 5 days a week. The calculations have used the default values given in Table 1

<table>
<thead>
<tr>
<th>Experimental animal</th>
<th>Sex</th>
<th>Food (mg/kg)</th>
<th>Water (mg/l)</th>
<th>Air (mg/m3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Male</td>
<td>8.3</td>
<td>6.0</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7.7</td>
<td>5.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>25.0</td>
<td>20.0</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>20.0</td>
<td>17.5</td>
<td>13.6</td>
</tr>
<tr>
<td>Hamster</td>
<td>Male</td>
<td>10.9</td>
<td>8.3</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>9.6</td>
<td>7.3</td>
<td>8.1</td>
</tr>
</tbody>
</table>
3.2. When to use T25

At present, experience in obtaining T25 is only available for substances administered by oral administration or inhalation. For studies involving i.e. a non-systemic contact carcinogens it is difficult to calculate the T25 value, the potency grading should be made on a case by case basis.

3.3. Human data

As already indicated the use of human data for T25 calculation has several drawbacks (see Section 2.3). Therefore, and because in most instances also animal data are available for determining a T25, these data are evaluated together on a case by case basis.

3.4. Provisional evaluation of potency classification

A preliminary potency evaluation applying the T25 value is made at this stage.

T25 values can be used to place substances classified as a carcinogen into arbitrarily selected ranges that define potency. As such, it is possible to identify carcinogens of high and low potency. For the purpose of assigning specific concentration limits, it is proposed that:

* Carcinogens of high potency: T25 value ≤ 1 mg/kg bodyweight/day
* Carcinogens of medium potency: 1 mg/kg bodyweight/day < T25 value ≤ 100 mg/kg bodyweight/day
* Carcinogens of low potency: T25 value > 100 mg/kg bodyweight/day.

The leading principle for deriving the 1 and 100 mg/kg bodyweight/day is that the majority of the carcinogens are expected to fall into the medium potency range. This is illustrated from the fact that the majority of the calculated TD50-values (Gold et al, 1989) fall into the medium potency range. Thus, for 492 carcinogens for which Gold et al (1989) have calculated TD50, the median was 9.4 mg/kg/day, the 25th percentile 1.24 mg/kg/day and the 75th percentile 70.9 mg/kg/day (Krewski et al 1990). In a comparison of T25 values with TD50 for a set of 110 carcinogens the log plot had a slope of 1.05 (linear slope 1.72) and a correlation coefficient of 0.96. (Dybing et al. 1997).

4. ELEMENTS THAT MAY MODIFY THE PRELIMINARY POTENCY EVALUATION

There may be a need to modify the preliminary potency evaluation. The following additional elements should be considered when allocating the potency group. It should be noted that several
of the elements are not independent and may be interrelated. Some of these factors may have been taken into account in deciding the classification as a carcinogen. Where such considerations have been made, care should be taken to prevent redundancy of such information.

Under the heading of each section \textit{Starting assumptions} are given. If the conditions which are described in Section 4 are fulfilled, then this would not lead to a modification of the potency allocation.

\subsection{4.1 Dose-response relationships}

\textbf{Starting assumption:} A linear relationship is assumed.

A supralinear dose-response relationship may indicate higher relative potency at lower doses. This could move substances near potency borders into a higher potency group. A related problem arises when the tumour frequency is very high at the lowest dose tested. In such cases a maximal tumour response may already have been reached and the calculated T25 might be higher than that which would have been found if lower experimental doses had been used. In such cases substances near the potency borders may likewise be moved into a higher potency group.

A sublinear relationship may indicate lower relative potency at lower doses than at higher doses. This could move substances near the potency borders into a lower potency group.

Tumours occurring only at doses close to the appearance of general toxicity may indicate that lower doses are disproportionally less potent than higher doses, this could move substances near the potency borders into a lower potency group.

\subsection{4.2 Site/species/strain/gender activity}

\textbf{Starting assumption:} Benign and malignant tumours are assumed or observed to occur in one tissue site of both sexes of rats and mice.

Potent carcinogens tend to be effective in common, multiple tissue sites and across species and genders. Thus, substances near the potency borders may be moved to a higher potency group for carcinogens expressing this behaviour.

Low potency carcinogens tend to only be active in a single specific tissue site in a single gender of a single species or only at a single site with a high spontaneous tumour incidence. Thus, substances near the potency borders may be moved to a lower potency group for carcinogens expressing this behaviour.

Data on malignancy of the tumours should also be taken into consideration on a case by case basis.
4.3 Mechanisms including genotoxicity

Starting assumption: Carcinogen has genotoxic activity.

It is recommended to use information on mechanism including genotoxic activity as one element in conjunction with the other elements.

Genotoxic substances are defined here as substances that fulfill the criteria as Category 3 mutagens.

In contrast to genotoxic carcinogens, some non-genotoxic (epigenetic) carcinogens may induce their effects by increasing the number of cell divisions in a target organ. Lack of genotoxic activity in appropriate, well-performed tests may indicate a lower carcinogenic potency and may thus move a substance near the potency borders to the next lower potency group, normally from intermediate to low.

If a NOAEL is identified from the experimental data and the underlying mechanism(s) support a threshold, reference to the NOAEL may be used for setting a specific concentration limit for the carcinogen.

4.4 Mechanistic relevance to humans

Starting assumption: Classified carcinogens based on animal studies are assumed to cause cancer induction in humans.

For experimental carcinogenic substances where the available studies of mechanisms are so convincing that the substance obviously does not represent a cancer hazard for humans, the substance should not be classified for carcinogenic properties. Examples of this are substances which only induce renal tumours in male rats shown to be due to alpha-2µ-globulin nephropathy or liver tumours in rodents shown to be due to peroxisome proliferation. However, in cases where mechanistic information indicate a lesser sensitivity in humans than in experimental animals, this may move substances near the potency borders to a lower potency group than the tumour dose descriptor in itself may indicate.

4.5 Toxicokinetics

Starting assumption: Toxicokinetic behaviour is assumed to be similar in animals and humans.

In most instances, data will not be available allowing a comparison of the toxicokinetic behaviour of a carcinogen between humans and the test animal. Thus, in the absence of
comparative data, it is assumed that the carcinogen shows similar toxicokinetic behaviour in humans and in test animals.

In situations where the bioavailability of a carcinogen is higher in humans than in animals, this may move substances near the potency borders into a higher potency group, whereas if the bioavailability is lower in humans than in animals, substances near to the potency borders may be moved into a lower potency group.

If the net metabolic activation (activation vs detoxication) rates of a carcinogen are higher and/or detoxication rates lower in humans than in animals (assessed in vivo or in vitro), this may move substances near the potency borders into a higher potency group. Conversely, if the net metabolic activation rates are lower and detoxication rates higher in humans than in animals, substances near the potency borders may be moved into a lower potency group.

If target doses as determined by physiological-based kinetic modelling are higher in humans than in animals, this may move substances near to the potency borders into a higher potency group. Conversely, if target doses as determined by physiological-based kinetic modelling are lower in humans than in animals, substances near the potency borders may be moved into a lower potency group.

4.6 Other elements relevant to potency evaluation

Other types of information may be utilized in deriving a final allocation of a carcinogen to a potency group. Structure-activity considerations may give important indications on the potency, by examining the potency of structurally related carcinogens. Alkylating activity is normally only considered as an indication of potential genotoxicity. In the case genotoxicity data are scarce or inadequate, strong alkylating activity may move substances near the potency borders to a higher potency class.

4.7 Finalizing potency evaluation

This stage of the evaluation is concluded by a reassessment of the preliminary potency evaluation carried out in Section 3.4. To illustrate the proposed scheme, some examples have been evaluated. In Annex, each of these examples are presented describing how the T25 values are derived, giving information on other potency elements and how these elements are used for allocation of potency class.
5. ASSIGNING SPECIFIC CONCENTRATION LIMITS

On the basis of the guidance described in Chapters 3 and 4 a final potency evaluation has been made. From this final potency evaluation specific concentration limits for carcinogens can be derived.

In cases where potency evaluation is not carried out, the general concentration limits of Directive 88/379/EEC apply, and no specific concentration limits is given in Annex I of Directive 67/548/EEC.

5.1 Specific concentration limits for Category 1 carcinogens

Category 1 carcinogens showing high potency will normally be given a specific concentration limit an order of magnitude lower (0.01%) than the general limit of 0.1% (see Table 3). Highly potent Category 1 carcinogens can be assigned a specific concentration limit lower than 0.01% on a case by case basis following in depth consideration of all the available data. Category 1 carcinogens that are assigned to the medium potency range will normally have a general concentration limit of 0.1%.

Due to the relative insensitivity of epidemiological studies, it is envisaged that carcinogens of low potency will not normally be identified in human studies. It is anticipated that Category 1 carcinogens will not be assigned to the low potency range, and that these carcinogens will generally attract a concentration limit not higher than 0.1%

5.2 Specific concentration limits for Category 2 carcinogens

Category 2 carcinogens showing high potency will normally be given a specific concentration limit of 0.01%; those showing low potency a specific limit of 1%. Highly potent category 2 carcinogens may be assigned a lower specific concentration limit than 0.01% on a case by case basis following in depth consideration of all the available data. Category 2 carcinogens that are assigned to the medium potency range will normally have a general concentration limit of 0.1%.

5.3 Specific concentration limits for Category 3 carcinogens

Category 3 carcinogens showing high potency will normally be assigned a specific concentration limit of 0.1%. Category 3 carcinogens that are assigned to the medium potency range, will have a general concentration limit of 1%. Category 3 carcinogens showing low potency will normally be assigned a specific concentration limit of 1-5% on a case by case basis. The limit of 5% may be considered in certain cases, such as for substances with a very high T25 value or when toxicokinetic data indicate that target dosed of the carcinogen in humans will be much lower than in the animal species showing the carcinogenic effect. Such an effect should only be considered for substances that do not show any genotoxic effects.
Table 3: Proposed scheme for subdividing carcinogens in three potency classes

<table>
<thead>
<tr>
<th>EU CATEGORY</th>
<th>POTENCY GROUP</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARCINOGENS OF HIGH POTENCY</td>
<td>(7)(^a) 0.01%</td>
<td>(7)(^a) 0.01%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>CARCINOGENS OF MEDIUM POTENCY</td>
<td>0.1%</td>
<td>0.1%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>CARCINOGENS OF LOW POTENCY</td>
<td>-(^b)</td>
<td>1.0%</td>
<td>1-5%(^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Specific concentration limits may be considered on a case-by-case basis if another limit than the default limit is to be used.

\(^b\) Classified human carcinogens will generally be of high or medium potency in order to be recognized as such.

\(^c\) The limit of 5% may be considered in certain cases, such as for substances with a very high T25 value or when toxicokinetic data indicate that target dosed of the carcinogen in humans will be much lower than in the animal species showing the carcinogenic effect.

6. REFERENCES


ANNEX

Illustration of the use of information which affect the potency classification

The three illustrations presented here are aimed to demonstrate how additional information with bearing on the potency should be assessed when allocating a substance with a T25-value close to the border between two potency groups to another potency group than that suggested by the T25-value itself. The illustrations do not represent real chemicals and any similarities is fortuitous.

Since the guideline for setting specific concentration limits is applicable both for Category 1, 2 and 3 carcinogens, the classification is not discussed. Only information relevant for the potency is presented in the illustrations.

Further details about how to calculate T25 is available in the publication “T-25, a simplified carcinogenic potency index. Description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity.” Pharmocol Toxicol 80: 272-279, 1997 by Dybing E, Sanner T, Roelfzema H, Kroese D, and Tennant RW. In this publication the calculation of T25 is illustrated for a gavage study, a diet study, and an inhalation study.
ILLUSTRATION 1.

POLYCYCLIC AROMATIC HYDROCARBON
PAHX

1. CA Name: XXXX
   CAS No: xxx-xx-x

FORMULA

C_mH_yy Mol. wt: xxx.x

2. EU classification: Category x

3. Effective dose level in humans: Not applicable. Exposure to complex mixtures of polycyclic aromatic hydrocarbons have been shown to cause cancer in humans. No data on exposure to individual polycyclic aromatic hydrocarbons is available (lack of sufficient evidence for carcinogenicity in humans).

4. Effective dose level in animals: PAHX has been shown to be carcinogenic when administered to mice by the oral route, after skin painting and after subcutaneous injection.

MICE Mice, groups of 50 males and 50 females received 0.4 mg PAHX by gavage on 5 days per week. The control groups (50 males and 50 females) received only the solvent by gavage. Treatment started at 6 weeks of age and the surviving mice were sacrificed 104 weeks after start of the experiment. The treatment had no effect on the body-weight or survival of the animals. Animals that died spontaneously or that became moribund were examined for occurrence of tumours. The treated mice developed pulmonary carcinomas (treated males 98% [49/50], females 80% [40/50]). No such tumours were found in the control groups. In addition the following tumours were increased; mammary carcinoma (treated females 76% [38/50] and hemangioendothelioma (treated males 50% [25/50], treated females 44% [22/50]). No such tumours were found in the control animals.

Remarks on study:
   species, strain, sex: mouse, xxx, male
   route: oral, gavage
   tumour: pulmonary carcinomas
   duration: 104 weeks
   note: gavage administration five times per week
20

Lowest dose with a significant increased tumour- incidence.

<table>
<thead>
<tr>
<th>Control</th>
<th>0/50 (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 mg/gavage</td>
<td>49/50 (98%)</td>
</tr>
<tr>
<td>net %:</td>
<td>98%</td>
</tr>
</tbody>
</table>

note:

Daily dose per kg bodyweight during the exposure period.
Bodyweight is not specified (def.)\(^1\) default 30 g
i.e. 0.4 x 1000/30 x 5/7 = 9.5 mg PAHX/kg bodyweight/day

Dose at this incidence of lung carcinomas when administration started after 6 weeks and exposure is for 24 months.
24/24 x 24/24 x 9.5 mg PAHX/kg/day = 9.5 mg PAHX/kg bodyweight/day

T25 after 24 months.
T25 = 25/98 x 9.5 mg/kg bodyweight per day = 2.4 mg/kg/day.

The T25 dose descriptor in mouse is: 2.4 mg/kg/day.

5. **Dose-response relationship:** Tumour frequency is very high at the only dose tested in mice.

6. **Site/species/strain/gender activity and degree of malignancy:** Only studied in mice. Tumours at different sites in both males and females.

7. **Genotoxicity:** Starting assumption.

8. **Mechanistic relevance to humans:** Starting assumption.

9. **Toxicokinetics:** Starting assumption.

10. **Other elements relevant to potency classification:** Starting assumption.

11. **Allocation of potency class:** Medium potency based on the T25 tumorigenic dose descriptor in mice. Moved to high potency due to the very high tumour incidence at the only dose tested and the formation of tumours at different sites.

12. **References:**

\(^1\) (def.): In case bodyweights, feed consumption data etc. are not specified, the default data set is used.
Table 1. Potency elements which affect the classification.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>EU category</th>
<th>T25 in human studies mg/kg/day</th>
<th>T25 in animal studies mg/kg/day</th>
<th>Dose-response relationships</th>
<th>Site/ species/ strain/ gender activity and degree of malignancy</th>
<th>Genotoxicity</th>
<th>Mechanistic relevance to humans</th>
<th>Toxicokinetics</th>
<th>Other elements relevant to potency classification</th>
<th>Changes in potency class&lt;sup&gt;A&lt;/sup&gt;</th>
<th>Allocation of potency class</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAHX</td>
<td>x</td>
<td>NA&lt;sup&gt;B&lt;/sup&gt;</td>
<td>2.4</td>
<td>Tumour frequency is high at the lowest dose tested in mice.</td>
<td>Tumour at different sites in mice, both sexes</td>
<td>SA&lt;sup&gt;C&lt;/sup&gt;</td>
<td>SA</td>
<td>SA</td>
<td>SA</td>
<td>Moved from medium to high</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>A</sup>Change from potency class based on T25 dose descriptor alone.

<sup>B</sup>Not applicable.

<sup>C</sup>Starting assumption.
**ILLUSTRATION 2.**

**ALKANE SULTONE AS**

1. **CA Name:** XXXX  
   **CAS No:** XXX-XX-X

**FORMULA**

\[ \text{C}_x\text{H}_y\text{O}_z\text{S} \quad \text{Mol. wt: } xxx.x \]

2. **EU classification:** Category x

3. **Effective dose level in humans:** Not applicable (lack of sufficient evidence for carcinogenicity in humans).

4. **Effective dose level in animals:** Two studies in rats, tumour induction has been found after oral administration.

**EXPERIMENT 1**

Rats, groups of 50 males and 50 females received 0, 5 mg, and 10 mg AS per kg bodyweight by gavage 5 times per week for 18 months. Treatment started at 6 weeks of age and the surviving rats were sacrificed at 24 months after start of experiment. The treatment had resulted in a reduced body-weight and survival of the high dose animals compared with the control animals. Animals that died spontaneously or that became moribund were examined for occurrence of tumours. The results are shown in table 1.

Table 1. Tumour frequency in rats after administration of AS for 18 months by gavage.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>0 mg/kg Males</th>
<th>0 mg/kg Females</th>
<th>5 mg/kg Males</th>
<th>5 mg/kg Females</th>
<th>10 mg/kg Males</th>
<th>10 mg/kg Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant gliomas of the brain</td>
<td>2/50 (4%)</td>
<td>0/50 (0%)</td>
<td>14/50 (28%)</td>
<td>16/50 (32%)</td>
<td>25/50 (50%)</td>
<td>23/50 (46%)</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>-</td>
<td>0/50 (0%)</td>
<td>-</td>
<td>20/50 (40%)</td>
<td>-</td>
<td>38/50 (76%)</td>
</tr>
<tr>
<td>Adenonomas and adenocarcinomas</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20/50 (40%)</td>
<td>-</td>
<td>38/50 (76%)</td>
</tr>
</tbody>
</table>

Remarks on study:
- **species, strain, sex:** rat, XXX, females  
- **route:** oral, gavage  
- **tumour:** brain gliomas  
- **duration:** 18 months dosing, experiment terminated after 24 months  
- **note:** gavage administration five times per week

**Lowest dose with a significant increased tumour incidence.**

the malignant gliomas is used since no indications was given concerning the frequency of malignant mammary tumours.

Control: 0/50 (0%)

5 mg/kg gavage: 16/50 (32%)
Daily dose per kg bodyweight during the exposure period.
gavage: 5 mg AS/kg bodyweight, five times per week: i.e. 5 x 5/7 = 3.6 mg/kg/day.

Dose at this incidence of gliomas when administration started after 6 weeks and exposure is for 18 months.
18/24 x 24/24 x 3.6 mg AS/kg/day = 2.7 mg AS/kg bodyweight per day

T25 after 24 months.
T25 = 25/32 x 2.7 mg/kg bodyweight per day = 2.1 mg/kg/day.

The T25 dose descriptor in rats is: 2.1 mg/kg/day.

EXPERIMENT 2.
Rats, groups of 50 males and 50 females received 0, 2.5 mg, and 5 mg AS per kg bodyweight by gavage 5 times per week for 104 weeks. Treatment started at 6 weeks of age and the surviving rats were sacrificed at 104 weeks after start of experiment. The treatment had no effect on the body-weight or survival of the animals. Animals that died spontaneously or that became moribund were examined for occurrence of tumours. The results are shown in table 2.

Table 2. Tumour frequency in rats after administration of AS for 104 weeks by gavage.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>0 Males</th>
<th>mg/kg</th>
<th>2,5 Males</th>
<th>mg/kg</th>
<th>5 Males</th>
<th>mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Cerebrum, Malignant glioma</td>
<td>2/50 (4%)</td>
<td>0/50 (0%)</td>
<td>9/50 (18%)</td>
<td>12/50 (24%)</td>
<td>20/50 (40%)</td>
<td>22/50 (44%)</td>
</tr>
<tr>
<td>Cerebellum, Malignant glioma</td>
<td>0/50 (0%)</td>
<td>0/50 (0%)</td>
<td>6/50 (12%)</td>
<td>10/50 (20%)</td>
<td>18/50 (36%)</td>
<td>20/50 (40%)</td>
</tr>
<tr>
<td>Mammary gland, adenocarcinoma</td>
<td>-</td>
<td>0/50 (0%)</td>
<td>-</td>
<td>6/50 (12%)</td>
<td>-</td>
<td>12/50 (24%)</td>
</tr>
</tbody>
</table>

Remarks on study:
- species, strain, sex: rat, xxx, females
- route: oral, gavage
- tumour: cerebral gliomas
- duration: 104 weeks
- note: gavage administration five times per week

Lowest dose with a significant increased tumour incidence.
Gliomas were found both in cerebrum and cerebellum and their incidence was presented separately. The incidence of gliomas of the cerebrum in females (highest incidence at low dose) was used.
Control: 0/50 (0%)
2.5 mg/kg gavage: 12/50 (24%)
net %: 24%

Daily dose per kg bodyweight during the exposure period.
gavage: 2.5 mg AS/kg bodyweight, five times per week: i.e. \(2.5 \times \frac{5}{7} = 1.8\) mg/kg/day.

**Dose at this incidence of gliomas when administration started after 6 weeks and exposure is for 24 months.**

\[
\frac{24}{24} \times \frac{24}{24} \times 1.8\ \text{mg AS/kg/day} = 1.8\ \text{mg AS/kg bodyweight per day}
\]

**T25 after 24 months.**

\[
T25 = \frac{25}{24} \times 1.8\ \text{mg/kg bodyweight per day} = 1.9\ \text{mg/kg/day}.
\]

**The T25 dose descriptor in rats is: 1.9 mg/kg/day.**

*The T25 dose for experiment 2 is used as it is the lowest T25 and furthermore this experiment seems to have a higher quality and is better described than the first experiment which is an older study.*

5. **Dose-response relationship**: Starting assumption.


7. **Genotoxicity**: Starting assumption.

8. **Mechanistic relevance to humans**: Starting assumption.

9. **Toxicokinetics**: Starting assumption.

10. **Other elements relevant to potency classification**: Strong alkylating activity. The figures for gliomas of the cerebrum and cerebellum may represent different animals (unfortunately not specified) therefore, the number of animals at risk of developing gliomas could be higher than the incidence used for the present T25 calculation. The T25 value calculated here may be numerical too high.

11. **Allocation of potency class**: Medium potency in accordance with default situation based on the tumorigenic dose descriptor from animal studies. The fact that it is an alkylating agent and the likelihood that T25 calculated represents a too high number provides justification for allocation of AS in the high potency class.

12. **References:**
### Table 2. Potency elements which affect the classification.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>EU category</th>
<th>T25 in human studies mg/kg/day</th>
<th>T25 in animal studies mg/kg/day</th>
<th>Dose-response relationships</th>
<th>Site/species/strain/gender activity and degree of malignancy</th>
<th>Genotoxicity</th>
<th>Mechanistic relevance to humans</th>
<th>Toxicokinetics</th>
<th>Other elements relevant to potency classification</th>
<th>Changes in potency class&lt;sup&gt;A&lt;/sup&gt;</th>
<th>Allocation of potency class</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>x</td>
<td>NA&lt;sup&gt;B&lt;/sup&gt;</td>
<td>1.9 The calculated T25 may be an overestimate</td>
<td>SA&lt;sup&gt;C&lt;/sup&gt;</td>
<td>Only tested in rats. Gliomas in cerebrum and cerebellum and mammary adenocarcinomas</td>
<td>SA</td>
<td>SA</td>
<td>SA</td>
<td>Strong alkylation activity</td>
<td>Moved from medium to high</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>A</sup>Change from potency class based on T25 dose descriptor alone.

<sup>B</sup>Not applicable.

<sup>C</sup>Starting assumption.
**ILLUSTRATION 3.**

**CHLORINATED ALKANE**

**CA**

1. **CA Name:** Xxxx  
   **CAS No:** xxx-xx-x

**FORMULA**

\[ C_{x_x}H_{y_y}Cl_{z_z} \text{ Mol. wt: } x_x \]

2. **EU classification:** Category x

3. **Effective dose level in humans:** Not applicable (lack of sufficient evidence for carcinogenicity in humans).

4. **Effective dose level in animals:** CA has been tested by oral administration in mice and rats.

**MICE** Mice, groups of 50 males and 50 females, received CA by gavage 5 times per week for 104 weeks. The mice were started on treatment at 6 weeks of age and the surviving mice were sacrificed at 104 weeks after start of experiment. The dose levels were 0, 200 and 400 mg/kg. Survival rates and weight gains were comparable for all groups except high dose females which had a decreased survival. Highly significant increases in hepatocellular carcinoma were observed in both sexes (Table 1).

**Table 1. Tumour frequency in mice after oral administration of CA for 104 weeks.**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>MALES</th>
<th></th>
<th>FEMALES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>200</td>
<td>400</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0/50</td>
<td>15/50</td>
<td>35/50</td>
<td>0/50</td>
</tr>
<tr>
<td></td>
<td>(4%)</td>
<td>(30%)</td>
<td>(70%)</td>
<td>(0%)</td>
</tr>
</tbody>
</table>

**Remarks on study:**
- **species, strain, sex:** mouse, xxx, females  
- **route:** oral, gavage  
- **tumour:** liver carcinomas  
- **note:** gavage administration five times per week

**Lowest dose with a significant increased tumour incidence.**

Hepatocellular carcinoma in low-dose females.  
Control: 0/50 (0%)  
200 mg/kg: 22/50 (44%)  
net %: 44%
Daily dose per kg bodyweight during the exposure period.
gavage: 200 mg/kg bodyweight, 5 times a week (5/7) i.e. 143 mg/kg/day

Dose at this incidence of hepatocellular carcinoma when administration started after 6
weeks and exposure is for 24 months.
104/104 (exposure) x 104/104 (observation) x 143 mg CA/kg/day = 143 mg/kg/day.

T25 after 24 months.
T25 = 25/44 x 143 mg/kg/day = 81.3 mg/kg/day.

The T25 dose descriptor in mice is: 81.3 mg/kg/day.

RATS Rats, groups of 50 males and 50 females, received CA by gavage 5 times per week for 104 weeks.
The rats were started on treatment at 6 weeks of age and the surviving rats were sacrificed at 104
weeks after start of experiment. The dose levels were 0, 50 and 100 mg/kg. Survival rates and
weight gains were comparable for all groups except high dose females which had a decreased
survival. Increases in hepatocellular carcinoma were observed in both sexes and significant
increases in kidney carcinomas were observed in males (Table 2).

Table 2. Tumour frequency in rats after oral administration of CA for 104 weeks.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>MALES mg/kg</th>
<th>FEMALES Mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>0/50 (0%)</td>
<td>2/50 (4%)</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney carcinomas</td>
<td>0/50 (0%)</td>
<td>4/50 (8%)</td>
</tr>
</tbody>
</table>

Remarks on study:
species, strain, sex: rats, xxx, male
route: oral, gavage
tumour: kidney carcinomas
note: gavage administration five times per week

Lowest dose with a significant increased tumour incidence.
Kidney carcinomas in male rats:
Control: 0/50 (0%)
100 mg/kg: 12/50 (24%)
net %: 24%

Daily dose per kg bodyweight during the exposure period.
gavage: 100 mg/kg bodyweight, 5 times a week (5/7): i.e. 71.4 mg/kg/day
Dose at this incidence of tumours when exposure was for 24 months.
104/104 (exposure) x 104/104 x 71.4 mg CA/kg/day = 71.4 mg/kg/day.

T25 after 24 months.
T25 = 25/24 x 71.4 mg/kg/day = 74.4 mg/kg/day.

The T25 dose descriptor in rats is: 74.4 mg/kg/day.


7. Genotoxicity: No genotoxic activity.

8. Mechanistic relevance to humans: Short-term doses higher than those used in the carcinogenesis study cause necrosis and cell proliferation. Histopathology at end of carcinogenesis study showed evidence of chronic liver damage.

9. Toxicokinetics: CA metabolism was calculated to be slower in humans than in rodents, exposure to equivalent doses of CA would lead to lower target concentrations in humans.

10. Other elements relevant to potency classification: No specific information available.

11. Allocation of potency class: Medium potency in accordance with the default situation based on the tumorigenic dose descriptor from animal studies. The lack of genotoxic activity, the mechanism and the toxicokinetics suggest low potency. CA is placed in the low potency class.

12. References:
Table 3. Potency elements which affect the classification.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>EU category</th>
<th>T25 in human studies mg/kg/day</th>
<th>T25 in animal studies mg/kg/day</th>
<th>Dose-response relationships</th>
<th>Site/species/strain/gender activity and degree of malignancy</th>
<th>Genotoxicity</th>
<th>Mechanistic relevance to humans</th>
<th>Toxicokinetics</th>
<th>Other elements relevant to potency classification</th>
<th>Changes in potency class&lt;sup&gt;A&lt;/sup&gt;</th>
<th>Allocation of potency class</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>x</td>
<td>NA&lt;sup&gt;B&lt;/sup&gt;</td>
<td>74.4 (rats) 81.3 (mice)</td>
<td>SA&lt;sup&gt;C&lt;/sup&gt;</td>
<td>SA</td>
<td>No genotoxic activity</td>
<td>Necrosis and cell proliferation in short-term experiments. Chronic liver damage</td>
<td>Metabolic activation faster in rodents than in humans</td>
<td>SA</td>
<td>Moved from medium to low</td>
<td>Low</td>
</tr>
</tbody>
</table>

<sup>A</sup>Change from potency class based on T25 dose descriptor alone.

<sup>B</sup>Not applicable.

<sup>C</sup>Starting assumption.