The Technical Rules for Hazardous Substances (TRGS) reflect the state of the art, the state of occupational health and occupational hygiene as well as other sound work-scientific knowledge relating to activities involving hazardous substances including their classification and labelling. The

Committee on Hazardous Substances (AGS) compiles or adapts the rules, and they are announced by the Federal Ministry of Labour and Social Affairs (BMAS) in the Joint Ministerial Gazette (GMBI).

This TRGS specifies, within their scope of application, the requirements of the German Hazardous Substances Ordinance (GefStoffV). By complying with these Technical Rules, the employer may therefore assume that the corresponding requirements of the Ordinance have been fulfilled. Should the employer choose a different solution, he must then achieve at least the same level of safety and the same health protection for his employees.

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1 Scope and explanations
2 Definition of terms
3 Limits of risks not associated with a certain substance, as well as exposure-risk relationships (ERR) and substance-specific concentration figures
4 Risk assessment
5 Risk-related concept of measures in accordance with § 10(1) GefStoffV

Annex 1: Substance-specific acceptable and tolerable concentrations and equivalence values
Annex 2: Justification for establishing limits of risks not associated with a specific substance
Annex 3: Guide for the quantification of substance-specific exposure-risk relationships
1 Scope and explanations

(1) This TRGS applies to activities with carcinogenic substances of Category 1A or 1B according to the CLP Regulation and Category 1 or 2 according to TRGS 905 or with substances, preparations or procedures according to § 2(3) No. 3 GefStoffV (TRGS 906). In accordance with the Hazardous Substances Ordinance (GefStoffV), the employer must ensure that the occupational exposure limits (according to § 2(8) GefStoffV) are complied with during activities with hazardous substances (§ 10(2) GefStoffV). No occupational exposure limit can currently be derived for the vast majority of carcinogenic substances.

(2) This TRGS contains a risk-related concept of measures in accordance with § 10(1) of the German Hazardous Substances Ordinance (GefStoffV), which stipulates the requirement of reducing the risk to a minimum according to § 7 GefStoffV. For this concept of measures, limits of risks not associated with a specific substance were defined following an inter-disciplinary discussion (see Annex 2). On this basis, substance-specific concentration values are derived that must then be used by the employer as assessment criterion for risk assessment and for the implementation of measures to reduce exposure to carcinogenic substances.

(3) This TRGS contains the following:
1. Definitions and justifications for risk limits not associated with a specific substance with respect to activities involving carcinogenic hazardous substances,
2. A graduated concept of risk control measures not specific to a certain substance that is based on the amount of risk present, and
3. A guide for the quantification of substance-specific exposure-risk relationships and risk concentrations after exposure to carcinogenic hazardous substances at the workplace.

(4) On the basis of the overall concept described in Paragraph 2, exposure-risk relationships are derived and substance-specific concentration figures are listed in Appendix 1 Table 1 and corresponding biomonitoring values are entered in Table 2. If it is not possible to derive an exposure-risk relationship for a particular carcinogenic hazardous substance, and a substance-specific TRGS is available, the substance or the substance group may be entered in Table 1 and the protective measures of this specific TRGS must be applied.

(5) For certain carcinogenic substances, it may be possible to derive occupational limit values based on occupational medicine or toxicological data, which are then published in TRGS 900.

2 Definitions of terms

(1) The ERR of a carcinogenic substance refers to the relation between the substance concentration (inhalation) and the statistical probability of developing cancer. The ERR derived from experimental or epidemiological studies forms the basis for the extrapolation in the area of low risks, which generally cannot be proved in practice by animal experiments or observed epidemiologically. The reference period for the risk is the entire lifetime (lifetime risk). The risk is the statistical probability of developing workplace-related cancer during the entire lifetime. The method for deriving exposure-risk relationships and their extrapolation is described in Annex 3 to this TRGS.
(2) The acceptable risk is a value not associated with a specific substance that expresses the statistical probability of developing cancer, at an interim level of 4:10000 and at the latest from 2018 at a level of 4:100000.

(3) The acceptable concentration is a substance-specific value. It refers to the concentration of an airborne substance at the workplace, which corresponds to the acceptable risk according to the ERR. Any occasion when this value is exceeded is associated with a low, acceptable risk.

(4) The tolerable risk is a value not associated with a specific substance, which expresses the statistical probability of developing cancer at a level of 4:1000.

(5) The tolerable concentration is a substance-specific value. It refers to the concentration of an airborne substance at the workplace, which corresponds to the tolerable risk according to the ERR. Any occasion when this value is exceeded is associated with a high, intolerable risk.

(6) The equivalence value for the acceptable or tolerable concentration is the concentration of a carcinogenic substance or of its metabolite in body fluids, which corresponds to the air concentration of the substance at the workplace, where the acceptable or tolerable risk is reached after exclusive exposure by inhalation. Such substance-specific equivalence values in biological material are also derived on the basis of ERR. They permit the use of the complementary information about the individual body burden relating to substances at the workplace which can be determined by biomonitoring.

(7) The background concentration is a predefined location factor and should be regarded as a concentration in the ambient air in the context of the risk assessment (see Number 4.1). It cannot be influenced by the company and may vary both in regard to location and time.

3 Limits of risks not associated with a certain substance, as well as exposure-risk relationships (ERR) and substance-specific concentration figures

3.1 Limits of risks not associated with a certain substance

(1) The following limits of risks not associated with a certain substance for activities involving carcinogenic hazardous substances have been defined:

Acceptable risk:
- interim level of 4:10000,
- at the latest from 2018 a level of 4:100000,

below which a low, acceptable risk exists. Above these limits a medium risk will be tolerated if the measures specified in the catalogue of measures are complied with. The second risk limit adopted is the

Tolerable risk: of 4:1000,

above which there is a high risk that is evaluated as intolerable.

(2) The risks refer to a working lifetime of 40 years and exposure for 8 h every working day.

(3) The justification for the definition of the risk limits are contained in Annex 2.
3.2 Definition of substance-specific concentration figures

The substance-specific acceptable and tolerable concentrations can be derived on the basis of the substance-specific ERRs derived in accordance with Annex 3. Before the adoption of the concentration figures in the TRGS 910, the following parameters must be determined and taken into account by the AGS.

3.2.1 Non-carcinogenic effects

If a carcinogenic substance also has acute or chronic, non-carcinogenic effects, these effects are taken into account. If the limit concentration for a non-carcinogenic effect of a substance lies in the medium risk area, this value is adopted and explained accordingly as a tolerable concentration in Annex 1.

3.2.2 Background concentration

If quantitative information about the background concentration is available during the definition of acceptable and tolerable concentrations, it is necessary to check whether the background concentration lies within the range of the acceptable and/or tolerable concentrations.

3.2.3 Exposure situation

(1) With regard to the adoption of the acceptable and tolerable concentrations in Annex 1, the currently available data regarding company-specific/standard industry procedures and processes is taken into account. In order to help the identification of problem areas, companies are therefore required to provide the exposure values defined according to §10(3) No. 1 GefStoffV concerning company-specific/standard industry procedures and processes in a suitable form to the AGS Management Board, e.g. according to the publication of Alker et al. (2000)\(^1\). The substances for which it is necessary to derive an ERR can be found in the operation list of the UA III, published on the BAuA homepage.

(2) Acceptable and tolerable concentrations can be adopted directly in Annex 1, if the state of the art determined by the AGS on the basis of accessible information sources or the communicated exposure values suggests that it will be possible to comply with the tolerable concentration.

(3) If the state of the art is not in compliance with the tolerable concentration, the AGS shall decide whether the values should be adopted in the TRGS 910 after the preparation of a substance-specific TRGS.

(4) If the state of the art determined on the basis of accessible information sources lies below the acceptable concentration or if a documented technical status (e.g. previous TRK value) lies below the tolerable concentration, it must be noted that no increase in the exposure above this standard may occur (requirement of reducing the risk to a minimum).

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3.2.4 Assessment period

Acceptable and tolerable concentrations are defined as shift mean values (time weighted averages) over a reference period of 8 hours. If a different assessment period is determined for a specific substance, e.g. week, month or year, this requires a special note.

3.2.5 Limit of detection

If the acceptable concentration cannot be determined by measurement, it is set at the limit of detection. For further information, please see the publication of Hahn, et al.²

3.2.6 Short-term values

1. The following procedure applies when assessing exposure peaks.

2. The tolerable concentration is supplemented by short-term values which restrict the upward concentration fluctuations around the shift mean value both in terms of their duration and their frequency. The assessment of exposure peaks is carried out according to the Short-Term Value Category II in TRGS 900, and their result is indicated as an excursion factor (EF). A minimum period between the short-term value phases is not defined. The EF is included in the TRGS 910 in addition to the tolerable concentration, and the factor 8 is taken as a default.

3. The acceptable concentration is exclusively defined as a shift mean value; shorter assessment periods are not necessary from a technical point of view and so are not defined.

3.2.7 Reduction of the acceptable concentration in 2018

A reduction of the acceptable concentration to an acceptable risk of 4:100000 is being checked on a substance-specific basis, taking the following factors into account:

1. Limit of detection,

2. Endogenous formation rate,

3. Background concentration.

A reduction is carried out if the above-mentioned factors do not argue against such an action. If the reduction is initially not carried out due to the limit of detection or the background concentration, the possibility of a further reduction is monitored continuously. The aim is to achieve a reduction down to an acceptable risk of 4:100000.

4 Risk assessment

The employer must carry out a risk assessment in accordance with § 6 GefStoffV. The requirements of TRGS 400 must be taken into account in the process. In the case of substances with acceptable and tolerable concentrations (assessment criterion according to § 10(1) GefStoffV) corresponding to Annex 1 of this TRGS, the workplace exposure must be assessed using these concentrations and the necessary measures must be taken in accordance with the stipulations of the Hazardous Substances Ordinance, particularly taking Number 5 of this TRGS document into account. The employer must also define any activities where respiratory protection must be worn due to increased short-term exposure in the medium risk area. In addition, the following special points must be taken into account, if applicable:

1. Consideration of the background concentration: In the context of the risk assessment, the background concentration can be determined and taken into account by the employer. Measurements must be made according to the criteria in the TRGS 402 or comparable procedures. When selecting the sampling location, it must always be ensured that the measurements are not influenced by emissions caused by the company or companies, in case that various companies are working together (e.g. building sites). The workplace-related exposure by inhalation is based on the difference between the substance concentration measured at the workplace and the background concentration.

2. Assessment of the exposure, taking into account the performance characteristics of measurement procedures: With regard to assessment of the exposure taking into account the performance characteristics of measurement procedures, please see TRGS 402 Annex 3 No. 3.1.

3. Taking dermal or oral exposure into account – biomonitoring: In the case of skin-resorptive substances, dermal uptake may make a considerable contribution to the occupational exposure. In the case of possible skin contact with such substances, measuring exposure by inhalation exclusively is not sufficient when assessing the cancer risk at the workplace. Substances that are accidentally ingested orally at the workplace are also not recorded in a measurement of exposure by inhalation. Biomonitoring is therefore more suitable in order to determine the overall exposure by oral, dermal and inhalation route, insofar as an appropriate procedure is available. In order to assess the measurements from biomonitoring, the “substance-specific equivalence values in biological material with regard to the acceptable or tolerable concentration” listed in Annex 1 Table 2 must be used.

4. Exposure to multiple carcinogens: In the event of exposure to multiple carcinogens, they are assessed in the present ERR concept as individual substances and a cumulative or additive approach does not take place at present. Activities with simultaneous exposure to multiple carcinogens, with the exception of welding, reconstruction, maintenance and laboratory workplaces, should be notified to the AGS.

5. Reduction of the acceptable concentration: After reducing the acceptable concentration, the employer must carry out a new risk assessment if the activity no longer lies in the low risk area but in the medium risk area due to this reduction. When selecting the additional measures that then need to be taken according to the concept of measures in Number 5, it is also possible to proceed according to the principle of appropriateness. As the reduced acceptable concentration is often the result of continuous improvement processes in the companies, all companies concerned are advised to base all long-term planning and investment decisions on the final acceptable risk starting as soon as the concept of risk-based measures is introduced.
5 Risk-related concept of measures in accordance with § 10(1) GefStoffV

(1) In the risk concept, three different risk areas emerge on the basis of the acceptable and tolerable risks:

1. Low risk area (the exposures lie below the acceptable concentration)
2. Medium risk area (the exposures lie between the acceptable and tolerable concentrations) and the
3. High risk area (the exposures lie above the tolerable concentration).

(2) The aim of the risk concept is to ensure that exposures lie below the acceptable concentration. According to this concept, the employer must prioritise the various measures to be taken. The higher the concentration of a carcinogenic substance at the workplace, and so the risk, the more urgent is the necessity to take additional operational risk-reduction measures.

(3) The need for risk-reduction measures which increases with the risk, and its relationship to the three risk areas is depicted in the chart below:
The area of low risk includes the area up to the acceptable risk. In this area, the need to carry out additional measures is low.

The medium risk area covers the area between the acceptable and the tolerable risk. In this area, the need for additional measures increases considerably as the respective concentration approaches the tolerable concentration.

The high risk area begins above the tolerable risk. In this area, there is a direct necessity for additional measures in order to return at least to the medium risk area.

(4) The employer must determine which risk area the respective exposures should be allocated to and must take the measures allocated to the respective risk areas in accordance with Table 1. These measures are divided into 5 measures groups:

1. Substitution
2. Technical measures
3. Organisational measures
4. Respiratory protection
5. Administrative measures at the company
(5) Preventive occupational medical examination comply with the German Ordinance on Occupational Medical Prevention (ArbMedVV) and the Occupational Health Rules (AMR) published on the same subject.
### Table 1: Special measures in the event of exposure to carcinogenic hazardous substances depending on the respective risk areas

<table>
<thead>
<tr>
<th>1. Substitution</th>
<th>I. Low risk</th>
<th>II. Medium risk</th>
<th>III. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checking a possible substitution</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Implementation of the substitution (substance and processes), types of use that minimise exposure, see also TRGS 600, Annex 3</td>
<td>Yes, if appropriate.</td>
<td>Yes, mandatory if appropriate (if technically feasible, with due regard to scientific findings and appropriateness).</td>
<td>Yes, mandatory measure of high priority according to the result of the substitution check.</td>
</tr>
<tr>
<td>Explanation</td>
<td>The employer must regularly check the possibility of substituting the substances with substances causing a lower health risk; see TRGS 600</td>
<td>The result of the substitution check must be documented in the risk assessment.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Technical measures</th>
<th>I. Low risk</th>
<th>II. Medium risk</th>
<th>III. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical measures</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Explanation</td>
<td>Regular reviews must be conducted to ensure that the exposure status does not deteriorate; no additional measures are required.</td>
<td>The employer is obligated to take state-of-the-art technical measures, giving due consideration to appropriateness.</td>
<td>The employer is obligated without fail to take state-of-the-art technical measures.</td>
</tr>
<tr>
<td>Spatial isolation according to § 10(3)</td>
<td>Yes, if appropriate</td>
<td>Yes</td>
<td>Yes, preferably through construction measures</td>
</tr>
<tr>
<td>Explanation</td>
<td>Isolating a working area through construction measures is designed to prevent exposure of employees working in other working areas to carcinogenic substances released.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Reducing quantities relevant to exposure

<table>
<thead>
<tr>
<th></th>
<th>Yes, if appropriate</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Explanation**
Reducing the quantities of substances used which are relevant to exposure is a means of minimising the resulting exposure. Regardless of the actual exposure level and the corresponding risk area, the employer shall always ensure that only minimum quantities of substances relevant to exposure are used.

### Warning and safety symbols in accordance with § 10 GefStoffV

<table>
<thead>
<tr>
<th></th>
<th>Yes, if appropriate</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

3. **Organisational measures**

<table>
<thead>
<tr>
<th></th>
<th>I. Low risk</th>
<th>II. Medium risk</th>
<th>III. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Basic) Hygiene measures</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Explanation</strong></td>
<td>Regardless of the actual exposure level and the corresponding risk area, the employer shall always take the measures stipulated in § 8 GefStoffV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimising the duration of exposure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Explanation</strong></td>
<td>The employer must perform the optimisation specific to substances and activities with the aim of achieving a minimum duration of exposure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimising the duration of exposure is desirable. Internal company agreements may be made for this purpose.</td>
<td>Minimising the duration of exposure is mandatory. Internal company agreements may be made for this purpose.</td>
<td></td>
</tr>
<tr>
<td>Minimising the number of exposed employees</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Explanation</strong></td>
<td>Minimising the number of persons exposed is desirable.</td>
<td>Minimising the number of persons exposed is mandatory. The employer must perform the optimisation specific to substances and activities with the aim of achieving a minimum number of persons exposed and a minimum duration of exposure.</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Risk transparency and risk communication</strong></th>
<th><strong>Yes</strong></th>
<th><strong>Yes</strong></th>
<th><strong>Yes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Explanation</strong></td>
<td>The employer must determine the exposure level and the allocated risk area and must also inform the employees of these details in their advisories and instructions.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Operating instructions, advisories and instructions, training</strong></th>
<th><strong>Yes</strong></th>
<th><strong>Yes</strong></th>
<th><strong>Yes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Explanation</strong></td>
<td>The employer must ensure that the employees have access to written operating instructions, that they are trained with respect to the methods and processes (training) to be used with respect to safety when handling the relevant hazardous substances, and that they are verbally instructed about all hazards and protective measures with reference to the operating instructions. A general advisory session on occupational health and toxicology must take place in the context of the advisories and instructions.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 4. Respiratory protection

<table>
<thead>
<tr>
<th></th>
<th>I. Low risk</th>
<th>II. Medium risk</th>
<th>III. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory protection</td>
<td>_</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Explanation</td>
<td></td>
<td>The employer must provide the employees with respiratory protection. In the case of activities with exposure peaks, it is strongly recommended to wear respiratory protection during the period of increased exposure.</td>
<td>The employer must provide the employees with respiratory protection which must in turn be worn by the employees. When wearing cumbersome respiratory protection: see requirements, No. 5</td>
</tr>
</tbody>
</table>

### 5. Administrative measures by the operator

<table>
<thead>
<tr>
<th></th>
<th>I. Low risk</th>
<th>II. Medium risk</th>
<th>III. High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan for action in accordance with § 6(8)1 No. 4b GefStoffV</td>
<td>_</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Explanation</td>
<td></td>
<td>In the context of the risk assessment, the employer must set up a plan for action in which it describes in detail how it is planned to achieve a further reduction in exposure, through which measures, in which periods of time and to which extent.</td>
<td>The documentation of the risk assessment must be submitted to the competent authority on request in accordance with § 18(2) GefStoffV.</td>
</tr>
<tr>
<td>Communication with the supervisory authority</td>
<td>_</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Explanation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. It is urgently recommended to inform the competent supervisory authority – by communicating the plan for action – if the tolerable concentration will foreseeably be exceeded for a period of longer than 3 months.

2. In the case of activities where cumbersome respiratory protection must be worn in the long term, an application should be submitted to the competent authority for exceptional treatment in accordance with § 7(5) GefStoffV in conjunction with § 19(1). A long-term use of cumbersome respiratory protection in the meaning of this TRGS document is deemed to be present if it is foreseeable that respiratory protection must be worn for a total of longer than 120 hours within a period of 3 months for activities within a particular company.

Cumberose respiratory protection is deemed to include all respiratory protection appliances suitable for carcinogenic substances, with the exception of filter devices with fan support and fresh-air and compressed-air hose devices with a hood or helmet.

The documentation of the risk assessment and the plan for action must be submitted together with the application, and should explain how the concentrations will be reduced below the tolerable concentration within 3 years.
Annex 1  Substance-specific values for carcinogenic substances classified as category 1A or 1B according to CLP Regulation or TRGS 905

1  Substance-specific acceptable and tolerable concentrations

Abbreviations used, numbers and explanations

Column “substance identity”
CAS no.  Registration number of the "Chemical Abstract Service"
EC no.  Registration number of the "European Inventory of Existing Chemical Substances" (EINECS)

Columns "Acceptable and tolerable concentration"
Fibre conc.  Fibre concentration in fibers (F) per m$^3$
Weight conc.  Weight concentration in mass per m$^3$
Vol. conc.  Volumetric concentration
E  Respirable fraction
A  Alveolar fraction

Column “Notes”:
a)  Acceptable concentration associated with the risk 4:100000: not yet assigned at present
b)  Acceptable concentration associated with the risk 4:10000

c)  The acceptable concentration lies between the risk 4:10000 and 4:100000: not yet assigned at present
d)  Acceptable concentration was defined on the basis of the limit of detection, Number 3.2 Paragraph 5
e)  The acceptable concentration is associated with the endogenous formation rate, and a further reduction does not take place

Column “EF”

Excursion factor (EF) 1 to 8 according to Number 3.2 Paragraph 5

Column “Remarks”
(1) According to the state of the art, it is possible to fall below the acceptable value; on this subject, see also concept of measures according to Number 5 Table 1 No. 2.

(2) The tolerable concentration was according to the criteria in Number 3.2 Paragraph 1 defined on the basis of the basic of a non-carcinogenic effect. If the value is exceeded, the same measures shall apply as when the occupational exposure limit is exceeded.

E  Inhalable fraction
H  Skin-resorptive

Justifications for the definition of substance-specific concentration values and exposure-risk relationships are published at:
Table 1: List of substance-specific acceptable and tolerable concentrations

<table>
<thead>
<tr>
<th>Substance identity</th>
<th>Acceptable concentration</th>
<th>Tolerable concentration</th>
<th>Remarks</th>
<th>Date Month/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>0.07 mg/m³ b)</td>
<td>0.15 mg/m³ 8 (1) (2), H</td>
<td>09/2014</td>
<td></td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>0.26 mg/m³ 8 H 01/2010</td>
<td>1.2 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminium silicate fibres</td>
<td>10.000 F/m³ b), d)</td>
<td>100.000 F/m³ 8 see also TRGS 558</td>
<td>05/2010</td>
<td></td>
</tr>
<tr>
<td>Arsenic compounds, classified as C1A, C1B</td>
<td>0.83 µg/m³ (E) b)</td>
<td>8.3 µg/m³ (E) 8 see TRGS Metals (in preparation)</td>
<td>09/2014</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td>10.000 F/m³ b)</td>
<td>100.000 F/m³ 8 see also TRGS 517 and TRGS 519</td>
<td>06/2008</td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>0.2 mg/m³ b)</td>
<td>0.6 ppm 1.9 mg/m³ 8 H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzo(a)pyrene in certain PAH</td>
<td>70 ng/m³ (E) b)</td>
<td>700 ng/m³ (E) 8 see TRGS 551, H</td>
<td>03/2011</td>
<td></td>
</tr>
<tr>
<td>Substance identity</td>
<td>Acceptable concentration</td>
<td>Tolerable concentration</td>
<td>Remarks</td>
<td>Date Month/Year</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Name</td>
<td>EC no.</td>
<td>CAS no.</td>
<td>Vol. conc.</td>
<td>Weight conc. or Fibre conc.</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>203-450-8</td>
<td>106-99-0</td>
<td>0,2 ppm</td>
<td>0,5 mg/m³</td>
</tr>
<tr>
<td>Cadmium and Cd-compounds, classified as C1A, C1B</td>
<td>231-152-8</td>
<td>7440-43-9</td>
<td>0,16 µg/m³ (A)</td>
<td>b)</td>
</tr>
<tr>
<td>Hexavalent chromium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>203-458-1</td>
<td>107-06-2</td>
<td>0,2 ppm</td>
<td>0,8 mg/m³</td>
</tr>
<tr>
<td>DimethylNitrosoamine</td>
<td>200-549-8</td>
<td>62-75-9</td>
<td>0,075 µg/m³</td>
<td>b)</td>
</tr>
<tr>
<td>Epichlorohydrine</td>
<td>203-439-8</td>
<td>106-89-8</td>
<td>0,6 ppm</td>
<td>2,3 mg/m³</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>200-849-9</td>
<td>75-21-8</td>
<td>0,1 ppm</td>
<td>0,2 mg/m³</td>
</tr>
<tr>
<td>Hydrazine</td>
<td>206-114-9</td>
<td>302-01-2</td>
<td>1,7 ppb</td>
<td>2,2 µg/m³</td>
</tr>
<tr>
<td>4,4’-Methylene dianiline</td>
<td>202-974-4</td>
<td>101-77-9</td>
<td>70 µg/m³</td>
<td>b)</td>
</tr>
<tr>
<td>2-Nitropropane</td>
<td>201-209-1</td>
<td>79-46-9</td>
<td>0,05 ppm</td>
<td>180 µg/m³</td>
</tr>
<tr>
<td>Substance identity</td>
<td>Acceptable concentration</td>
<td>Tolerable concentration</td>
<td>Remarks</td>
<td>Date</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>EC no. 201-167-4</td>
<td>CAS no. 79-01-6</td>
<td>Vol. conc. 6 ppm</td>
</tr>
</tbody>
</table>

Notes:
- b)
2 Substance-specific equivalence values in biological material for acceptable and tolerable concentrations

Abbreviations used, numbers and explanations

* Extrapolation on the basis of the EKA correlation (exposure equivalents for carcinogenic substances, EKA) is not permissible
# Extrapolation is being checked

Column “Assay material”

\(B\) Whole blood
\(B_E\) Erythrocyte fraction of whole blood
\(P/S\) Plasma/serum
\(U\) Urine

Column “Sampling time”

a) Not fixed
b) End of exposure or end of shift
c) For long-term exposures: after several shifts
d) At the beginning of the next shift
e) Time after end of exposure: ... hours
f) Before the last shift of a working week
### Table 2: List of substance-specific equivalence values in biological material for acceptable and tolerable concentrations

<table>
<thead>
<tr>
<th>Substance identity</th>
<th>Parameter</th>
<th>Equivalence value for</th>
<th>Assay material</th>
<th>Sampling time</th>
<th>Date Month/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>EC no.</td>
<td>CAS no.</td>
<td></td>
<td>Acceptable concentration</td>
<td>Tolerable concentration</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>201-173-7</td>
<td>79-06-1</td>
<td>N-(2-carboxamideethyl)valine</td>
<td>-</td>
<td>400 pmol/g globin</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>203-466-5</td>
<td>107-13-1</td>
<td>N-(2-cyanoethyl)valine</td>
<td>6500 pmol/g globin</td>
<td>650 pmol/g globin</td>
</tr>
<tr>
<td>Benzene</td>
<td>200-753-7</td>
<td>71-43-2</td>
<td>Benzene S-phenylmercapturic acid Trans, trans-muconic acid</td>
<td>2.4 µg/L 0.025 mg/g creatinine 1.6 mg/L</td>
<td>#</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>203-450-8</td>
<td>106-99-0</td>
<td>3,4-Dihydroxybutylmercapturic acid (DHBMA) 2-Hydroxy-3-butenylmercapturic acid (MHBMA)</td>
<td>2900 µg/g creatinine 80 µg/g creatinine</td>
<td>600 µg/g creatinine 10 µg/g creatinine</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>200-849-9</td>
<td>75-21-8</td>
<td>N-(2-hydroxyethyl)valine</td>
<td>3900 pmol/g globin</td>
<td>#</td>
</tr>
<tr>
<td>Hydrazine</td>
<td>206-114-9</td>
<td>302-01-2</td>
<td>Hydrazine</td>
<td>62 µg/g creatinine 47 µg/L</td>
<td>*</td>
</tr>
<tr>
<td>Trichloroethene</td>
<td>201-167-4</td>
<td>79-01-6</td>
<td>Trichloroacetic acid</td>
<td>22 mg/L</td>
<td>12 mg/L</td>
</tr>
</tbody>
</table>
### 3 Directory of CAS numbers

<table>
<thead>
<tr>
<th>CAS no.</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-32-8</td>
<td>Benzo(a)pyrene</td>
</tr>
<tr>
<td>62-75-9</td>
<td>N-Nitrosodimethylamine</td>
</tr>
<tr>
<td>71-43-2</td>
<td>Benzene</td>
</tr>
<tr>
<td>75-21-8</td>
<td>Ethylene oxide</td>
</tr>
<tr>
<td>79-01-6</td>
<td>Trichloroethene</td>
</tr>
<tr>
<td>79-06-1</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>101-77-9</td>
<td>4,4'-Methylendianiline</td>
</tr>
<tr>
<td>106-89-8</td>
<td>Epichlorohydrine</td>
</tr>
<tr>
<td>106-99-0</td>
<td>1,3-Butadiene</td>
</tr>
<tr>
<td>107-06-2</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>107-13-1</td>
<td>Acrylonitrile</td>
</tr>
<tr>
<td>302-01-2</td>
<td>Hydrazine</td>
</tr>
<tr>
<td>1332-21-4</td>
<td>Asbestos</td>
</tr>
<tr>
<td>7440-43-9</td>
<td>Cadmium</td>
</tr>
<tr>
<td>12001-28-4</td>
<td>Crocidolite (see asbestos)</td>
</tr>
<tr>
<td>12001-29-5</td>
<td>Chrysotile (see asbestos)</td>
</tr>
<tr>
<td>12172-73-5</td>
<td>Amosite (see asbestos)</td>
</tr>
<tr>
<td>77536-66-4</td>
<td>Actinolite (see asbestos)</td>
</tr>
<tr>
<td>77536-67-5</td>
<td>Anthophyllite (see asbestos)</td>
</tr>
<tr>
<td>77536-68-6</td>
<td>Tremolite (see asbestos)</td>
</tr>
<tr>
<td>132207-32-0</td>
<td>Chrysotile (see asbestos)</td>
</tr>
<tr>
<td>132207-33-1</td>
<td>Crocidolite (see asbestos)</td>
</tr>
</tbody>
</table>
Annex 2 to TRGS 910

Justification for establishing the limits of risk not associated with a specific substance and the concept of graduated risk reduction measures

1 Definitions of the term “risk”

For the purpose of the present TRGS, the term risk shall mean the likelihood of health damage occurring as a result of exposure to carcinogenic hazardous substances. The risk or likelihood of damage occurring increases with an increasing dose of the dangerous substance or the exposure concentration of a carcinogenic substance. Following intensive toxicological, epidemiological and socio-political discussions, the workplace exposure is divided into three areas through the definition of two risk limits that are not associated with specific substances:

1. In the low risk area (area below the acceptable risk), the occurrence of damage is only possible, and the risk involved is assessed as “acceptable”.
2. In the medium risk area, an occurrence of damage is not only possible but already sufficiently likely; the risk involved is assessed as “undesirable” (tolerable if further measures are taken).
3. In the high risk area (above the tolerable risk), an occurrence of damage is sufficiently likely; the risk involved is assessed as “not acceptable” (intolerable).

The risk levels for the specified risk limits (acceptable risk and tolerable risk) can only be socio-politically established rather than scientifically substantiated. Numerous criteria have to be taken into account. Apart from risk perception, these are, for example, severity of health damage, the possible extent of damage (type of damage and/or number of persons affected), relation to comparable other risks at the workplace, direct benefit and actual and possible risk reduction measures.

2 Risk comparison

Various risks at the workplace and for the general population were taken as the starting point of the consultations.

2.1 Known risks at the workplace and for the general population

(1) The known risks of a fatal accident at workplaces differ considerably (Alz: working lifetime [40 years]):

<table>
<thead>
<tr>
<th>Industry</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture</td>
<td>3:1000 /Alz</td>
</tr>
<tr>
<td>Building industry</td>
<td>2:1000 /Alz</td>
</tr>
<tr>
<td>Mining</td>
<td>3:1000 /Alz</td>
</tr>
<tr>
<td>Retail</td>
<td>4:10000 /Alz</td>
</tr>
</tbody>
</table>

(2) The risk of contracting cancer by the seven most important airborne environmental carcinogens was calculated for the general population as 1:1000 for urban
populations and 2:10000 for rural populations in 1992 by the LAI (Working Group on Immission Control of the German Länder).

(3) The maximum permitted concentrations of carcinogenic substances are regulated by several government standards concerning food and environmental matters. These concentrations have not always been stipulated with respect to an acceptable risk; however, their calculation corresponds to the following risks that are related to the lifetime (Lz) of the general population:

- Arsenic in drinking water (10 µg/l) 5:10000 /Lz
- Dioxin in food (2 pg Teq/kg) 3:10000 /Lz
- Diesel soot (5 ng BaP/m³) 2:10000 /Lz
- Cadmium in airborne particles 2:100000 /Lz.

The natural radiation dose is associated with an additional cancer risk of 1:1000 with respect to the lifetime (70 years).

2.2 Risk limits in existing regulations for the workplace and for the general population

(1) The Dutch Occupational Safety and Health Act contains a list of air limit values including limits for carcinogenic substances. The risk level associated with these limit values normally must not exceed 1:10000 per year. If possible, a risk level of 1:1000000 per year should be achieved below which no special, additional protective measures would be required. (After conversion to 40 years of working life, these risks correspond to 4:1000 – corresponding to the tolerable risk under discussion here and an acceptable risk of 4:100000 = acceptable risk).

(2) The provisions prevailing in Switzerland with respect to activities involving materials containing asbestos and benzene are based on a substance-specific approach combined with practical considerations. There, the acceptable risk with respect to the lifetime is calculated as 4:100000 for asbestos and 6:10000 for benzene.

(3) For the German general population, the Expert Committee for Environmental Issues (SRU) specified an acceptable risk for a graduated reduction of concentration values in the amount of the “internationally discussed risk level of 1:100000”. The conference of the Ministers of Health agrees with the SRU, indicating that a lifetime risk of 1:100000 for individual substances is the goal of a gradual reduction of environmental concentrations.

(4) The following risks are used as an assessment criterion, among others, with respect to rules governing carcinogenic pollutants:

1. An overall risk of 4:10000 for exposure to multiple substances and as a first step of minimising the risk caused by carcinogenic air pollutants (without smoking/passive smoking) by the LAI in 1992.
3. An additional lifetime risk of 1:1000000 applicable to limit values of carcinogenic substances in accordance with the drinking water ordinance 2001.
The last two points expressly do not account for the special sensitivity of children to genotoxic carcinogenic substances.

(5) In accordance with the Radiation Protection Ordinance, a maximum annual additional radiation dose of 20 mS is permissible, the additional dose relating to the working life is limited to 400 mS. This results in an additional cancer risk of 2:100.

2.3 Considerations relating to the background risk of cancer

The lifetime risk of contracting lung cancer is in the range of 5:1000 to 1:100 for non-smokers that are not exposed to additional factors which cause cancer, such as passive smoking or exposure to carcinogens at work.

3 Establishing the risk limits

(1) The isolated establishment of risk limits is considered impractical. For this reason, an accompanying concept of graduated measures is proposed that consists of three levels of activities:

1. Below the acceptable risk,
2. Between the acceptable risk and the tolerable risk, and
3. Above the tolerable risk,

which account for the various additional cancer risks.

(2) The acceptable risk is defined as the risk at the workplace which does not call for any additional protective measures by the government due to the low remaining additional substance-associated cancer risk. By contrast, employees should not be exposed to values above the threshold set by the tolerable risk. The two risk limits or three different risk areas proposed by these definitions are in line with the national and international discussion and open up the possibility of a concept of suitably graduated measures. Since exposure to carcinogens is associated with very serious potential health hazards, it cannot be accepted unless the mechanism of action of individual substances has been found to have a threshold below which there is no health risk. With respect to the graduated measures proposed, in the future it will be possible to control substances depending on their significance, and governmental risk control measures thus can be distinguished from measures for lower risks that do not require any additional government action and can be imposed by the employers at their own discretion. At the same time, the measures to be taken have been identified.

(3) When establishing the risk limits, analogous provisions stipulated in other countries and for other control subjects were accounted for. They have been described in Number 2 hereof.

(4) In comparison to the general population, the same proportion of particularly sensitive groups of the population or children, elderly or chronically ill people is not to be expected at workplaces. This narrowing-down of the target group for protective measures which is characterised by a lower possible extent of damage compared to the general population and the possibility to provide preventive occupational medicine check-ups, including counselling concerning specific risks, is to be accounted for.
(5) The tolerable risk should be below the background risk for developing cancer described in Number 2.3, so that the additional risk posed by carcinogens at work is lower than the background risk that is generally applicable.

(6) A factor of 100 was considered necessary to describe the difference between the tolerable and acceptable risks in order to make a clear distinction between the risk limits in view of the inevitable inaccuracies regarding the derivation of substance-specific exposure-risk relationships and the determination of actual exposure at workplaces.

(7) It is proposed to target a risk of 4:100000 as an acceptable risk.

(8) With respect to the considerations outlined above and the acceptability criteria to be observed, it is assumed that the level of protection achieved for employees with respect to the acceptable risk is equally differentiated and comparable to that of the general population.

(9) In view of the fact that achieving a value at this level makes very high demands on many activities and processes and many areas, a graduated approach is proposed:

(10) During an introductory phase, this limit will be temporarily set to a value of 4:10000. Depending on the experience with the implementation of the concept of risk-based limit values for carcinogenic substances, the temporary values are to be replaced with final values concerning the acceptable risk no earlier than five and no later than ten years after the introduction of the concept, i.e. between 2013 and 2018.

(11) AGS will monitor the further development of exposure to carcinogens at work in order to achieve a binding reduction of the acceptable risk to 4:100000 as soon as possible, but in any case no later than after 10 years. As the final value is often the result of continuous improvement processes in the companies, all companies concerned are advised to base all long-term planning and investment decisions on the final acceptable risk starting as soon as the concept of risk-based measures is introduced.

(12) Substance-specific, additional risks of contracting cancer through occupational exposure in excess of 4:1000 will be considered unacceptable (intolerable). In some branches of industry, workplace exposure exceeds the airborne concentration corresponding to this tolerable risk. If necessary, AGS will work out adequate protective measures for these highly contaminated workplaces in order to reduce occupational exposure.
Annex 3 to TRGS 910

Guide for the quantification of substance-specific exposure-risk relationships and risk concentrations after exposure to carcinogenic hazardous substances at the workplace

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Search for substance-specific human and/or animal studies investigating carcinogenic effects

Check the minimum criteria for risk quantification
(e.g. in terms of there being sufficient information on exposure and confounder factors in epidemiological studies or in terms of the human relevance of tumours in test animals)

Yes

Minimum criteria fulfilled?

Yes

Point of departure (POD) calculated for the assessment, e.g. as BMD_{10} or T25

No

Taking into account their weight of evidence, is it possible to use aggregated data?

No

No ERR can be derived, search for other risk reduction strategies by risk management

Yes

Threshold plausible and determinable based on data?

No

Occupational exposure limit (OEL) (analogous value)

Sub-linear dose-response?

Yes

Occupational exposure limit (OEL) (analogous value)

No

Linear extrapolation

Mode of action genotoxic or unknown?

Yes

Approximation via the “break function”

No

Comparison carried out (cancer risk vs. non-carcinogenic effects) and regulatory relevant concentrations selected related to:
- High risk: > 4 : 1000
- Medium risk: < 4 : 1000 / 4 : 10000 / 100000
- Low risk: < 4 : 10000 / 100000 or
- Occupational exposure limit (OEL) (analogous value)

Check on way of implementation by risk management

Diagram of the derivation of an exposure-risk relationship (ERR) based on the present Guide

Start
by order from the risk management

Numbering in black circular fields corresponds to the section numbers in the Guide
1 **Scope of risk quantification**

1.1 Preliminary remark: Principles of risk quantification where data are limited

The present Guide is intended to provide the basis for describing exposure-risk relationships for carcinogenic substances according to harmonised rules including the option of a justification for reference values for the defined risk or occupational exposure limits for these substances. For this purpose, criteria are established to assess the suitability of available data on a substance and procedures are recommended to determine exposure-risk relationships from these data in the best possible way. This Guide represents an update to a concept that has previously been agreed in the Committee on Hazardous Substances (AGS), published and used in practice for assessment (AGS, 2008).

The protection of workers from the risks related to exposure to carcinogenic chemicals (carcinogens) at the workplace is in particular regulated by EU Directive 2004/37/EC (Carcinogens Directive) and the German Hazardous Substances Ordinance (Gefahrstoffverordnung, GefStoffV). Under the Carcinogens Directive, “carcinogen” is defined as a substance that meets the criteria for classification as a Category 1A or 1B carcinogen set out in Annex I to Regulation (EC) no. 1272/2008. The same risk management is to be applied to carcinogenic substances (“carcinogens”) of Categories 1A and 1B both within the meaning of the Carcinogens Directive and according to GefStoffV. According to these provisions, it is thus irrelevant whether a substance was identified and classified as carcinogenic on the basis of epidemiological findings (Category 1A) or of animal studies (Category 1B). Since cancer is considered to be a particularly serious disease and the Carcinogens Directive assumes that an exposure level below which no health hazard occurs cannot be determined, legislation provides for particularly far-reaching preventive measures for these substances.

Because of their direct relationship to humans, data from human studies should primarily be used for describing exposure-risk relationships. However, the existence of such data, in particular in view of carcinogenic effects, should represent an exception, as at the same time they document insufficient (occupational) safety. With the existing data and particularly in the case of older studies, there are uncertainties in epidemiology in assessing exposure since no measured values are generally available for historical exposures and person-related exposure assessments can be systematically biased. Moreover, the possible impact of confounders must always be checked in epidemiological observation studies (non-interventional studies). In contrast, animal studies can be carried out under controlled conditions and well-defined exposure conditions, but have the disadvantage that animal studies are designed with limited numbers of animals. The resulting restrictions in the statistical power of the dose-response relationship established should be taken into account correspondingly. When extrapolating findings from animal studies, the species differences must also be considered with regard to dose equivalents and modes of action.

The question of the regulation for carcinogenic hazardous substances arises irrespective of the suitability of the database. Risk management involves establishing a

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3 In the current version of GefStoffV dated 26 November 2010 (German Federal Law Gazette (BGBl.) I S 1643), revised by Article 2 of the law from 28 July 2011 (German Federal Law Gazette (BGBl.) I S 1622), the categories in accordance with Appendix IV of Directive 67/548/EEC are used (Category 1 for proven human carcinogens, category 2 for carcinogens identified in animal studies). This is to be adjusted in a new version of GefStoffV in 2015.
limit value using the available, often not sufficiently reliable exposure-risk relationships. Therefore, uncertainties should be determined and specified for every decision that has been taken. Even the conclusion that the available data are not sufficient to establish a quantitative exposure-risk relationship may be drawn. Given that findings on the modes of action can also be included in the selected exposure metrics and in the assessment of the form of the observed exposure-risk relationship, and that they are to be taken into account for the risk extrapolation, this results in a number of assessment criterion with different reliabilities.

The scientific community has been discussing minimum doses known as thresholds (or “practical” thresholds) for carcinogenic substances, i.e. exposure ranges below which a hazard is considered to be unlikely – for example because of effective biological protective and repair mechanisms. However, this is controversial, and the methods applied to provide evidence and define such thresholds are problematical (Lutz, 2000; Neumann, 2006a; b; c). Such findings can currently be used for regulatory purposes only if they are adequately verified. This involves the definition of quantitative limits specifying the exposure level for these thresholds in addition to plausibility considerations (for example on the assumed mode of action). Quantitative risk assessment together with conventions on risk acceptance are therefore of special importance when establishing limit values for carcinogenic substances. “Risk” is understood to mean the absolute lifetime risk exceeding the background risk after a given exposure (for a more accurate definition see Section 1.4 and Glossary).

To understand risk assessments based on the present Guide it is important to know the general conditions and scientific limits, specify them and accept the assessment made on the basis of the specific data until better data are available. Whereas neither a “real” risk nor a “real” limit value can currently be established by the scientific community, risk managers must accept the scientific assessment as the currently best possible derivation and thus as “presumably real” in order to be able to take action. Since exposure-risk relationships and limit values are derived as anticipated expert opinions and as a precaution, this assumption is possible not least from a legal point of view.

The present Guide deals with the scientific-methodological conventions to be used to bridge knowledge gaps in the area of acceptable and risk-relevant (still temporarily tolerable) exposures to carcinogenic substances. The purpose of this Guide is not to weigh economic interests and a social benefit of technology up against health risks to workers (e.g. no cost-benefit considerations; see Cherrie et al. (2011)). Differentiations are not made between different tumour types, for example based on curability or on the degree of severity of the disease (level of suffering of affected persons); for more information refer to discussion in Morfeld in (2010) and Kalberlah et al. (2011)).

The members of the working group “Risk derivation” are however aware that the selection of many standards (e.g. definition of adverse effects, confidence interval used as a basis, inclusion or exclusion of specific extrapolation models and interpretation of the term of precaution) implies that judgements are formed from a scientific understanding that is not only based on scientific justification.
1.2 Validity

(1) The rules of this Guide only refer to risk quantification for carcinogenic substances as this is to be applied for the implementation of the risk assessment in accordance with the German Hazardous Substances Ordinance (GefStoffV). These rules are then to be specially applied when the assumed mode of action or the data situation does not permit the derivation of a toxicological threshold and therefore no health-based occupational exposure limit (OEL) for carcinogenic substances in accordance with § 2(7) of GefStoffV can be established.

However, rules are also prepared for the derivation of limit values (OEL) for “threshold carcinogens” (see Section 5.3).

(2) For this purpose, this Guide is to help assess exposure-risk relationships according to uniform and transparent methods. The main focus is on the extrapolation of risks into the low dose range where data are limited. Risk management measures in accordance with the Technical Rule for Hazardous Substances (TRGS) 910 can be based on the risk determined in this way.

The result of this risk quantification does not only include a point estimate of the risk, but also shows the exposure-risk relationship over a wide range. The Guide can thus be used as a three-range “traffic light model” (two evaluation points instead of one limit value) and the exposure-risk relationships can help to establish “process- and substance-related criteria” (VSK; verfahrens- und stoffspezifische Kriterien) which are announced pursuant to § 20(4) of GefStoffV.

(3) It is not the purpose of this Guide to justify the levels of risks deemed dangerous or “acceptable” in terms of social and health policy. However, these reference values (“tolerable risk”, “acceptable risk”) are specified in order to enable links in terms of methodology to be presented within this Guide.

This Guide will thus not answer the question of what is the right risk level at which to set the “acceptable concentration” or “tolerable concentration” for carcinogenic substances. It will however be possible to include evaluation points relevant to regulations in the established exposure-risk relationship (e.g. for concepts of measures associated with a given risk level). Comparisons between the potencies of carcinogenic and non-carcinogenic effects will also be carried out and the methodology used will be explained in this Guide.

All risk assessments are based on cancer incidences from animal studies that recorded both the animals that developed cancer and those that died, as well as from human data, where preference was also given to cancer incidences over mortality data. The question of curability of tumour diseases is consciously not considered as part of the risk assessment.

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4 See Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin – BAuA) research project F2010, 2005
(4) The method of this Guide is not designed to predict actual cancer incidence rates for a real workplace situation or to make projections as to the frequencies of developing cancer in the exposed population.

The misuse of risk quantifications (e.g. to project the number of exposure-related deaths) must be avoided. Exposure-risk modelling, extrapolation to low risks and the assumed exposure scenario are subject to specific conventions that are required for a harmonised procedure under the given regulatory conditions, but are not necessarily adequate for other purposes. Thus, the risk quantifications determined in accordance with this Guide do not need to be suitable for example for calculating a compensation claim according to the Occupational Disease Ordinance.

Accordingly, the concentration values (acceptable and tolerable concentrations) listed in TRGS 910 as well as the exposure-risk relationship (ERR) on which these are based may not be used as a basis for legislation governing occupational diseases, and they therefore have no direct relevance to the corresponding procedures for the identification of occupational diseases. The scientific evidence that underpins the derived ERR and the justification documents published on the website of the Federal Institute for Occupational Safety and Health (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin – BAuA)\(^5\) can however be used to make individual decisions in relation to a procedure for the identification of occupational diseases in specific cases. In such cases they should be separately assessed, taking the individual case into account, in compliance with the applicable legislation governing occupational disease.

(5) Exposure assessments for individual workplaces are not covered by this Guide. A standard exposure scenario for a workplace is assumed only (“nominal risk”, see Section 4.5).

(6) Reference to substances: Different methods exist internationally in terms of whether a risk quantification should only apply for one individual tested substance or whether it can be applied to a substance group for which the same mode of action can be assumed (including when the substances of this group were not all necessarily tested). No definition of this kind is provided in this Guide. However, this Guide does set out to examine and substantiate the procedure on a case-by-case basis, and the procedure is to include both the qualitative aspect (“same mode of action within one group”) and the quantitative aspect (comparison of the bioavailabilities and potencies within the group).

An obvious example for this question is the possibility for metals of only assessing the defined individual compound that was actually tested, or to only exclude cases from a group under consideration where there is a scientific justification – a procedure frequently applied in Germany (e.g. “lead and its inorganic compounds with the exception of...”). There is currently no gener-

ally applicable rule governing the procedure to apply. An ERR generally refers to the correspondingly classified substance according to the CLP Regulation, including the substance identification to be found therein.

1.3 Importance of default assumptions

(1) The methods proposed in this Guide often have a default character, i.e. they are to be applied by default if no substance-specific information justifies deviation from the default. However, if more qualified, substance-specific data are available, deviation from the standard assumptions is possible. If this is the case, the justification must be documented (see Section 9).

Findings of low relevance are not always adequate to justify deviation from the default. Additional findings may also be misused for a risk quantification carried out according to a deviating method: the margin of discretion left open here ("deviation is possible") allows the maintenance of the default and is limited by the required justification.

(2) In general, assessments with the relatively highest probability (for example: geometrical mean and maximum likelihood estimate) are used to establish the default.

Defining (reasonable) worst case assumptions for all parameters has been expressly avoided. The selection involves a difficult deliberation process, which has to be transparent. The differentiated procedure was selected against the background of the relative uncertainty resulting from the extrapolation steps that need to be taken here. At present, there is no procedure (e.g. probability calculation) that is suited to reduce this uncertainty. Combinations of multiple worst case assumptions would lead to a risk quantification with a very conservative character. The result cannot be validated and increasingly becomes a matter of speculation as the number of such assumptions increases. The convention specified above is selected in the present Guide to focus the discussion of a justification on actual risk assessment rather than on a suitable estimate of the range of uncertainty that cannot objectively be defined in more detail.

(3) Assessment of the data for individual substances and the resulting conclusions (for example about the mode of action to be assumed and degree of deviation from the default value in the individual case) are not covered by this method.

The substance-specific procedure – if it deviates from the default procedure formulated here – is based on standards that must be substantiated for each individual substance.

1.4 Definition and classification of the risk concentration

(1) This Guide deals with the methods of calculating a risk concentration. The risk concentration calculated under specific assumptions for the purposes defined in the introduction is a concentration value (unit:

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6 In the previous version of this Guide, the following term was used in a non-specific way: “cancer risk figure”, instead of “risk concentration”.

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mg/m³, µg/m³ or ng/m³) for the exposure-related lifetime risk in the scenario of exposure over the entire working lifetime (for defined exposure scenario see Section 4.5). The lifetime risk refers to the likelihood that a person will develop a specific type of tumour or cancer if mortality from other causes is about equally high as in a non-exposed population. The corresponding risk can also be referred to as a (statistical-mathematical) estimate of the excess risk or as additional risk or extra risk since the background incidence was specifically taken into account here (see Section 3.35 (3); 3.36; Glossary entry for these terms). Multiple risk concentrations are usually used for one substance, which correspond to excess risks of differing levels.

A number of scientists believe that the validity of the excess risk determined in animal studies for an excess risk in humans is so low that they reject a risk quantification made on this basis because of too much uncertainty. However, for the assessment of occupational exposure to carcinogenic substances, the majority of the authors of this Guide support using the risk concentration with the assignment of an excess risk. They expressly refer to the definition (explicit specification of the conditions of the calculated risk and uncertainty) and distinction from risk that can actually be observed in humans.

The term lifetime risk indicates that the inclusion of the total period up to old age is considered, the same distribution of lifetimes being used as a basis as in a general population or in the control group of a carcinogenicity study (Becher and Steindorf, 1993). In the practice of quantitative risk assessment, however, derivation of the risk generally refers to a specific age, i.e. about 2 to 2.5 years in animal studies and 70 to 90 years for epidemiological data (e.g. 89 y.: Goldbohm et al. (2006); 85 y.: Attfield and Costello (2004); Rice et al. (2001); SCOEL (2003); Sorahan et al. (1998); Stayner et al. (1998; 2000); 80 y.: HEI-AR (1991); 75 y. Stayner et al. (1995); Steenland et al. (2001)). The statistical life expectancy of men who are currently 20 years old is 77 years and the corresponding figure for women is 82 years (Robert Koch Institute (RKI), 2011). Based on the life table method, the cancer risk should therefore be calculated at least up to an age of 80 years.

Risk management can be based not only on risk concentrations, but also on the ALARA principle (ALARA: “as low as reasonably achievable”). The ALARA principle on its own is considered to be inadequate to establish regulatory priorities in handling carcinogenic substances in a differentiated way. In principle, the ALARA principle can be followed in parallel. However, this Guide does not specify this risk management instrument.

The present concept identifies the risk concentrations defined in (1) with assigned excess risk rather than a margin of exposure (MoE; see e.g. (ECHA, 2012b)); in this way, the nominal risk can be quantified for a wide range of an exposure-risk relationship.

The procedure of identifying a quantified risk instead of an MoE is also used because it is desirable that the same (assumed) nominal risk is regularly used as a defined level of protection on which to base measures and the comparison with an OEL (non-carcinogenic effects). An MoE is insufficient for this purpose.

As a final step of risk characterisation in the chemicals assessment with an
MoE, a quantification is carried out (the margin between a prevalence – for example as a benchmark dose at 10% – and the exposure level is calculated) and assessed, i.e. it is interpreted as “sufficient” or “not sufficient”. There have been no rules to date as to how non-linearity to be assumed in the dose-risk relationship via the mode of action should be reflected in this risk characterisation via the measure of the margin.

(3) This approach based on the risk concentration as an assessment criterion differs from the concept of the European Food Safety Authority (EFSA). The EFSA concept results in a point estimate (sufficiently safe dose or concentration specified), whereas the present concept defines the exposure-risk relationship with validity over an exposure range.

While the risk concentration is based on the average risk (sensitive persons are implicitly protected, but with a deviating individual residual risk, if the risk for moderately sensitive persons is sufficiently low), the EFSA concept tries to explicitly consider the protection of sensitive groups of persons by means of safety factors. If the safety factors are sufficiently high, no residual risk is identified, which is similar to assuming a threshold (see EFSA, 2005), even though such a risk can still be present.

The guides for compiling a Chemical Safety Report (CSR) under the chemicals policy (REACH) either define a risk concentration for specifying a DMEL (derived minimal effect level) (here intended procedure) or, alternatively, apply the method according to EFSA (modified). The EFSA procedure was originally designed to describe a margin required between prevalence in the experimental scenario and exposure level after ingestion rather than for the workplace (different safety factors), but it can be adjusted accordingly. There are currently no supportive statistical data or rules for the levels of the safety factors used in the modified EFSA procedure (interspecies variability, intraspecies variability and further individual differences in cancer defence mechanisms). Society would have to agree on conventions used (e.g. 1% risk for sensitive persons notified). Standards would also have to be established for deviating from the default procedure for a specific substance when more qualified information is available (differentiated procedure for different modes of action). The value (DMEL) routinely calculated according to the modified EFSA procedure can however be identical with the result calculated according to the ERR concept. There is currently no social consensus on a tolerable and/or acceptable (nominal) risk level for the application of the risk concentration being used and transformed into a DMEL within the framework of REACH and/or the ECHA guidelines on REACH. For critical analysis of the EFSA concept and the standards for the DMEL derivation, see Püringer (2010; 2011).

1.5 Database

(1) If human data are available for risk quantification, these must primarily be checked for their suitability for risk quantification and used, if appropriate, but the data quality (incidence data; course of exposure) is to be considered. Risk quantifications on the basis of epidemiological data and animal studies must be compared with each other (plausibility check).

(2) The procedure according to this Guide takes into account that only...
data from animal studies can be used as a basis for risk quantification in most cases; the definitions used in this Guide thus apply to data from animal studies, although human data are treated in the same way unless another procedure is described in the specific quantification step.

(3) Non-positive epidemiological study results are generally not evidence of the absence of a potential risk. They must be interpreted with due caution and their suitability for the question concerned taken into account (statistical power, exposure level and quality of exposure classification).

Literature: (Ahlbom et al., 1990; Wald and Doll, 1985)

Negative epidemiological data can only be used for plausibility checking of a positive finding from an animal study in exceptional cases; namely when the absence of the relevant tumours is documented in a very wide number of highly exposed persons. For the classification of the relevance of human data compared with animal studies see also Lavelle et al., (2012) and Goldbohm et al. (2006).

1.6 Data quality

(1) If a minimum quality is guaranteed (see Section 8), risk quantifications can generally be made. Limited quality and a resulting uncertainty must however be documented in the particular step of risk quantification.

Studies with a quality that is possible or desirable today cannot always be assumed as a basis for risk quantification. In addition to assessment uncertainties due to a lack of data quality of this kind, there are certain uncertainties resulting from the evidence level in each case (the number and extent of the extrapolation step). These uncertainties are inherent in the process of risk quantification if knowledge is incomplete. Depending on the data, the degree of the resulting total uncertainty may not be clear cut. Therefore a criterion must be defined from which the total uncertainty is so great that the resulting statement is to be considered speculative and can thus no longer be used (see Section 8). The particular individual step of risk quantification and Section 1.3 of this Guide – additionally – establish how uncertainties should be handled.

2 Discussion of the predominant mode of action

2.1 Mode of action as a central theme for risk quantification

(1) Information on the predominant mode of action or the predominant modes of action of the observed carcinogenic effect of a substance is useful both for determining the point of departure (Section 3) and for extrapolation into the low risk range (Section 5). For this purpose, the following factors must be characterised: a) the type of possible genotoxic effects, b) the type of non-genotoxic events as impact parameters on the multi-factorial process of carcinogenicity, c) the respective importance of these factors for the mode of action of carcinogenicity.
and the uncertainty of the relevant conclusion. The results must be documented in an appropriate way (Section 9).

2.2 Mutagenicity and genotoxicity

Preliminary remarks: The terms mutagenicity and genotoxicity are used for adverse effects on the genetic material of the cells but they are not synonyms: Mutagenicity refers to permanent, hereditable changes (mutations) in offspring or in the amount and structure of the DNA of cells. The more general term genotoxicity covers all damage that does not yet represent mutation in itself, but that has the potential to develop into this in the event of further processing. See the Glossary (Section 10.1) for further information and definitions (mutagenicity, clastogenicity, aneugenicity and genotoxicity).

In a regulatory context, findings from genetic toxicity tests are used as an indicator for possible carcinogenicity for the purposes of classification, where no data on carcinogenicity is (yet) available from animal studies. Where positive carcinogenicity studies do exist, they also play an important role in the evaluation of the mode of action in terms of the extrapolation of dose-response relationships for tumour risks.

Regulatory guides (“Guidance Documents”, including (ECHA, 2012a; EFSA, 2005; SCHER/SCCP/SCENIHR, 2009)) emphasise the importance of mechanistical information in the “cancer risk assessment”. For non-genotoxic cancer risk factors (“tumour promoters”), it is assumed that there are thresholds under which they do not induce any (adverse) effects. For non-genotoxic carcinogens and for types of genotoxicity that are induced via protein-mediated mechanisms (e.g. some causes of aneuploidy), it is possible – supported by the relevant mode of action evidence – to deviate from a linear extrapolation into the low dose range (ECHA, 2012a; EFSA, 2005).

Earlier assessment concepts were based on the assumption that every mutation induced by DNA-reactive substances or metabolites increased the risk of carcinogenicity, and therefore that a linear extrapolation into the low dose range was justified. However, ECHA (2012a) and SCHER/SCCP/SCENIHR (2009) have since been discussing whether individual DNA changes could be retained without any consequence whatsoever, if their frequency is less than those with which the same changes also occur as background damage, or when repair systems can eliminate additional damage and “completeness can be assumed for this process”. In these cases too, provided that they are supported by experimental findings, it is possible to deviate from a linear extrapolation into the low dose range (ECHA, 2012a; EFSA, 2005).

This type of deviation from a linear extrapolation is, however, only justified when concrete (e.g. experimental) data is available that also supports such a deviation in quantitative terms (for procedure see Section 5).

A phenomenological justification alone is generally insufficient to assume non-linearity or a threshold for mutagenic substances (along the lines of: “no mutagenicity observed at low concentrations”; “sub-linear course for mutations confirmed via modelling of the data”). In this case, comprehensive analyses of DNA change without consequences or of the plausibility of complete repairs should be presented as part of the justification. This should however only be possible in exceptional cases, so that in terms of a basis, a non-linearity (sub-linearity) should be used more as a dose-response model rather than a threshold.
Furthermore, it must be taken into consideration that thresholds are not necessarily within the high dose range; they may in fact be at a dose so low that the linearity assumption may still be appropriate for the relevant extrapolation range.

Finally, it should be emphasised that it is frequently the case that multiple modes of action can occur at the same time and in combination with each other (for procedure, see Section 5).

Examples

For arsenic, a threshold is to be assumed due to the observed mode of action. However, as this type of assumed threshold can currently not be quantified, and as this seems to be located at very low exposure levels, a linear extrapolation of the ERR takes place for carcinogenic effects.

A non-linearity in the dose-response relationship within the low-concentration range (in vitro) has been identified by Doak et al. (2007) among others in relation to mutations by alkylating substances. The study investigated substances that were very well examined. However, for some of these substances the linearity assumption was confirmed. The authors assume a homoeostasis due to DNA repairs at a low exposure that could be effective in different ways.

A non-linearity for mutagenic effects has also been described in reference to ethyl methanesulfonate (impurity in an AIDS medication) (Gocke and Müller, 2009; Gocke and Wall, 2009; Müller and Gocke, 2009).

Further information see sources such as Greim and Albertini (2012).

(1) It must be examined whether interaction of a direct nature in terms of the mode of action, of the substance with the genetic material is substantiated or to be assumed based on other information. Secondary genotoxicity that is of an indirect nature in terms of the mode of action (e.g. via oxidative stress, interference with the mitotic process, inhibition of topoisomerase, inhibition of the DNA repair enzymes, etc.) is to be distinguished from primary genotoxicity (direct DNA interaction such as intercalation or adduct formation and mutations caused by the parent substance or metabolites). In the case of indirect (secondary) genotoxicity, non-linearity of the exposure-risk relationship can be established with a higher degree of probability.

In the case of primarily genotoxic substances, differentiation is also made between those that are direct DNA-reactive and those that are only DNA-reactive following bioactivation. However, according to new international nomenclature, the term “indirect” is not used in reference to a bioactivation, but as a synonym for secondary genotoxicity. This differentiation into primary and secondary mechanisms of genotoxicity is also customary in the relevant scientific literature. Differentiation is made between “direct DNA reac-

7 A draft ERR justification document is available, in which the mode of action is explained. At the point in time that this Guide was approved, the document had not yet been approved by the Committee on Hazardous Substances (AGS).
tive versus non-direct DNA reactive mechanisms” (Dearfield et al., 2011; ECHA, 2012a), that is substances with the DNA itself as the target or with non-DNA target molecules.

**Examples**
- of primary (directly) genotoxic substances include aflatoxin, alkylating agents, nitrosamine and Polycyclic Aromatic Hydrocarbons (PAHs), which modify the DNA and have a mutagenic effect either directly or following bioactivation.
- of secondary (indirect) genotoxic substances are (hydro)quinones and redox-active metals, which induce oxidative stress, spindle poisons (vincristine) or topoisomerase inhibitors (doxorubicin, etoposide) and inhibitors of DNA repair enzymes (including arsenic, cytosine arabinoside).

The quality and verification of the assessment of genotoxic properties must be characterised (differentiation according to in vivo/in vitro findings, compatibility of the available study results, impact of the dose range in the available test and information about gaps).

In vivo and in vitro tests with multiple doses are generally not designed to derive “no effect levels”; they are instead used to identify a genotoxic potential (hazard). However, the order of magnitude at which effects can still be measured can, in individual cases, provide a valuable source of information for risk derivation, including the question of whether and to what extent genotoxicity is expected within the low dose range, and it can (where applicable) support the type of extrapolation. For some forms of genotoxicity (e.g. aneuploidies), minimum concentrations of dangerous substances that are required to cause cancer can be assumed. Findings from valid in vivo genotoxicity tests are particularly valuable for drawing conclusions about the mode of action.

(2) **Information on genotoxicity (type of genotoxicity and quality and verification of the findings) can be essential for the specificity on the target organ in which tumorigenicity was observed.**

In the assessment of genotoxicity tests, it must be considered that up to 80% of the substances that are negative in carcinogenicity tests in rodents are positive in one or several in vitro tests (Kirkland et al., 2005; Matthews et al., 2006). Cytogenetic tests with mammalian cells (chromosome aberration tests, micronucleus tests and the mouse lymphoma test) in particular show a high level of sensitivity but only a low level of specificity (irrelevantly positive) and therefore only have limited validity in terms of extrapolation of the findings to the in vivo situations to be assessed. There are numerous reasons depending on the in vitro test system used and the class of substances, and these are presented in the reviews (Dearfield et al., 2011; Kirkland and Müller, 2000). Mutagenicity tests in bacteria (Ames test) and mammalian cells (HPRT test) result in a much better specificity for rodent carcinogens.

(3) **The relevance of in vitro genotoxicity test results must be examined on the basis of the conditions used in the tests (e.g. comparison of the dose-response relationships of genotoxicity and cytotoxicity and high**
dose effects) and of the structure of the tested substance. If necessary, structure-effect relationships should be included. In unclear cases, the results of valid in vivo tests are decisive for systemically acting carcinogens. For locally acting carcinogens, negative in vivo tests are conclusive only if it has been demonstrated that the target organ can be reached.

2.3 Meaning of germ cell mutagenicity

(1) The topic of “germ cell mutagenicity” itself is not covered by this Guide. However, where germ cell mutagenicity is present, somatic cell mutagenicity can also be assumed.

All currently known germ cell mutagens also have a mutagenic effect in somatic cells in vivo. Substances that are mutagenic in somatic cells can induce heritable damage if they themselves or their active metabolites reach the genetic material in the germ cells. Conversely, this suggests that substances that do not induce any mutations in somatic cells in vivo are also not germ cell mutagens.

Non-classification according to Muta. 1A, 1B or 2 (according to CLP Regulation (EC) no. 1272/2008) has no relevance for the question of the carcinogenicity mode of action.

2.4 Non-genotoxic events

(1) Information on non-genotoxic effects with a potentially causal impact on the process of carcinogenicity must be recorded and described and the dose range determined must be compared with the carcinogenic doses. This mainly includes cytotoxicity (e.g. irritation, inflammation and necrosis), induced cell proliferation, receptor-mediated processes, protein binding, direct hormonal effect, indirect impact on hormonal feedback systems, organ specificity and sex specificity. Toxicokinetic information (e.g. enzyme induction, saturation and/or new metabolites specifically at high doses) are relevant for the process of carcinogenicity in this context.

(2) The quality and verification of the assessment of non-genotoxic properties must be characterised (differentiation according to in vivo/in vitro findings, compatibility of the available study results, impact of the dose range in the available test and information about gaps).

(3) Information on non-genotoxic events (type of effect and quality and reliability of the findings) must be assessed particularly for its relevance in the target organ in which tumorigenicity was observed.

(4) The consideration of whether genotoxicity plays “no” role or a “inferior” role in the carcinogenic process involves weighing up aspects that are not clearly defined. The following represent qualitative criteria at least in terms of assuming an inferior genotoxicity:

• There are positive findings on primary genotoxicity in vivo.

• Secondary (or also primary) genotoxicity exists in vitro at low concentrations (in comparison to cytotoxicity; micromolar and poss. nanomolar range).
• The existing data with negative findings for genotoxicity are not of high quality (default assumption, because the relevance of the positive information cannot be excluded).
On the other hand, where the following apply it can be assumed that there is no genotoxicity (instead of inferior genotoxicity) or that genotoxic influence can be seen as “not sufficiently likely”:
• The genotoxicity was only found in vitro and not in suitable in vivo studies (negative in vivo studies).
• There is no in vitro data available showing (primary or secondary) genotoxic effects from studies carried out in a qualified way using very small doses.
• Only secondary genotoxicity was observed in vivo, and only in high concentrations/doses.
• The assumption that there is no genotoxicity corresponds to the information on the mode of action,
• The database is good and does not indicate a mechanism that is influenced by genotoxicity.
When deliberating this issue, a decision can be made in favour of “no” genotoxicity in case of doubt in reference to suspected carcinogens (carc. Cat. 2 in accordance with CLP Regulation (EC) no. 1272/2008). However, for substances that are clearly carcinogens (carc. Cat 1A or 1B according to CLP Regulation) a decision of “no” genotoxicity must be supported by an unquestionable database.

The background for this decision guidance is the information contained in the rationale behind the MAK (maximum concentration at the workplace) values for carcinogens in group III, 4, according to which carcinogens are summarised there for which “genotoxic effects play no or at most a minor part” (DFG (German Research Foundation)), 2012). In contrast to the DFG, this Guide differentiates in relation to the subsequent procedure (e.g. possible threshold for “no role” or “break function” for “inferior role”).

2.5 Relevance of different impacts in a multifactorial process
(1) According to a weight-of-evidence approach, the relevance of primary and/or secondary genotoxicity (see Section 2.2) and of non-genotoxic events (see Section 2.4) to the process of carcinogenicity must be assessed. The central factor(s) of impact on cancer is (are) to be described and its (their) assumed relevance to humans substantiated.
(2) A distinction of the assumed modes of actions differentiated according to tumour site and/or dose range may also be a result. The existence of several (possible) modes of action must be identified.
(3) The occurrence of pre-malignant effects (like the formation of foci in the liver) must be examined and their dose-response relationship described, if possible.
(4) Background rates and the occurrence of spontaneous tumours in the control group are to be assigned to the discussion of the mode of ac-
2.6 Targeted conclusion

(1) After all the information has been recorded, the following statements can be made:

- Postulated mode of action
- Key events (observed; agreement with mode of action)
- Dose-response relationship
- Time-related association
- Intensity of the association; consistency of the data for this conclusion; specificity of the association
- Biological plausibility
- Other possible modes of action
- Confidence in the assessment
- Data gaps; uncertainties

(2) The following questions must specifically be answered:

- Is the weight of evidence sufficient to identify a mode of action in an animal study?
- Where the basic assumption that findings from animal studies can be extrapolated to humans is being deviated from: Can the human relevance of the mode of action be ruled out with sufficient likelihood on the basis of fundamental qualitative differences in key events between animals and humans?
- And: Can human relevance of the mode of action be ruled out with sufficient likelihood on the basis of quantitative toxicokinetic and/or toxicodynamic differences between animals and humans?
- How great is the level of trust placed in the generated mode of action assessment (uncertainties should be specified)?

There may also be a sub-linearity or (in exceptional cases) a threshold for genotoxic events. Genotoxic events must be differentiated from this point of view (see TGD, Risk Characterisation, Section 4.14.3.4; Butterworth, 2006).

Non-genotoxic events cannot always be associated with a threshold either; for example, a value cannot always be specified for such a threshold in the case of some receptor-mediated processes (see TGD, Risk Characterisation, Section 4.14.3.3; Butterworth, 2006).

As far as data for an exposure-risk relationship in the experimental range are required to determine the relevance of the different statements, there is an actual interdependence between tasks according to Section 3 (risk quantification) and tasks according to Section 2 of this Guide (in particular 2.5 and 2.6: Exposure-risk relationship). Accordingly, the items of this Guide cannot be dealt with in a strict chronological order.
The items mentioned under 2.6 are based on considerations by WHO (International Program on Chemical Safety, IPCS) and are explained in detail in Boobis et al. (2006). Examples of the procedure in the discussion of the mode of action can be found in Kirman et al. (2004), Cohen et al. (2003), and Preston and Williams (2005). The basic method for recording the mode of action is explained in Meek et al. (2003) and Seed et al. (2005). In various publications (e.g. Streffer et al., (2004), Hengstler et al., (2006), Bolt and Huici-Montagud, (2008), and Foth et al., (2005) similar differentiations of the mode of action are stipulated as those stipulated for the method applied here. These differentiations are described in more detail in Section 5.1 of this Guide.

Neumann (2006a; b; c) substantiates why it is impossible to find a definite threshold for a carcinogenic effect and recommends avoiding the term completely. However, since there are no alternatives that can be communicated better (Dieter and Konietzka, 2006), the term will continue to be used in the present Guide with the above restrictions of its meaning.

3 Risk quantification in the range of observed cancer incidences

3.1 Selection of animal species, sex and tumour site(s)

(1) If tumour data are available for several of the customarily used animal species, preference is to be given to the species reacting most sensitively.

(2) The extent to which quantitative extrapolation to humans can be assumed must be considered for the selection of the animal species and the types and sites of tumours observed there. Extrapolation can be assumed in particular if a tumour site is identical in a species comparison and/or findings on the mode of action support the occurrence of a specific type of tumour (or a specific tumour site).

Animal studies are carried out against the background that qualitative and quantitative extrapolation to humans is possible in principle (if necessary, considering extrapolation and/or correction factors). Thus, preference must always be given to the animal model with the closest relationship to humans. If it is not known which animal model is closest to humans in a particular case, a conservative approach should be selected. This basically applies even if discrepancies were demonstrated in the individual case: The human metabolism of 1,3-butadiene seems to be more like that of the less sensitive rat than that of the more sensitive mouse. If risk quantifications based on epidemiological data are compared with those based on animal studies, agreement of the cancer risk for mice and humans is higher for 1,3-butadiene (Roller et al., 2006). This possible contradiction in the case of 1,3-butadiene means that a) particular importance is to be attached to human data (see Section 1.5(1)), b) conservative extrapolation steps such as assuming linearity in the low risk range should not be abandoned too hastily because of supposed mechanistic evidence, and c) the relative sensitivity of
test animals compared with humans must be examined further.

(3) A tumour site observed in an animal study which deviates from observations based on human epidemiological studies does not generally militate against its human relevance (see references under 3.1 (6)). The resulting risk quantification must however be regarded as less reliable.

(4) If increased tumour incidences were obtained in both sexes, the data for the sex with the higher tumour rate must generally be used. If the tumour rates are about the same in both sexes, the data can be added for both sexes to increase the statistical validity.

(5) If tumours were found in several organs, the data on all organs for which a statistically and/or biologically increased tumour incidence was observed at a specific dose and/or a statistically significant dose-response relationship (possibly only as a trend) was evident are to be used.

The tumour site selected is generally that which leads to the lowest exposure-risk relationship (most cautious risk concentrations). Deviations from this are possible in individual, substantiated cases (see 3.1 (6)).

There are numerous typical forms of tumours whose spontaneous incidence is high and sometimes also considerably varies in specific rodent strains and whose relevance to humans is not known (see 3.1 (6)). If their frequency is increased as a function of the dose compared with the current and mean historical control, an exposure-related effect can generally be assumed.

(6) Whether or not specific tumour sites (if necessary, with a restriction to specific animal species or strains) are taken into account must be considered on a case-by-case basis. If specific tumour sites are not considered, a justification must be provided. The following references may provide answers to the question of the (qualitative and/or quantitative) extrapolation to humans:

- Extrapolation (including quantitative extrapolation) is generally assumed when the substance is also genotoxic and a genotoxic mode of action is assessed as relevant for the carcinogenicity.
- If the bioavailability of the substance or its metabolites in the target organ can be assumed or can be shown therein, this further supports the hypothesis of extrapolation to humans. The substance concentration (observed or to be assumed) in the target organ is also to be included in the consideration of quantitative extrapolation.
- Where the genotoxicity is not relevant or is of limited relevance, mechanistic findings regarding the mode of action compared across species (e.g. cytotoxicity, endocrine activity) can be used for estimating the extrapolation.
- No (qualitative or quantitative) extrapolation can be assumed for \(\alpha_{2U}\)-globulin-induced renal tumours of male rats.
- If the genotoxicity does not play a dominant role in the mode of action, it is particularly necessary to weigh up each individual case where
there are the following tumour sites:

- Liver tumours after PPARα stimulation (“peroxisome proliferation”)
- Leukaemias of the Fischer rat
- Phaeochromocytomas of the Fischer 344 rat
- Thyroid tumours in rats
- Leydig cell tumours
- Liver tumours in the B6C3F1 mouse
- Forestomach tumours
- Mesotheliomas of the tunica albuginea and/or tunica vaginalis (male rats)
- Harderian gland (nictitating membrane gland in the canthus) and Zymbal’s gland (ear sebaceous gland)

- For a more detailed discussion of the relevance of these tumour sites, and for assessment of individual cases, see Section 8.3.

  The strictly qualitative species comparison is relevant for classifications, but not for determining the exposure-risk relationship considered here or for establishing a risk concentration.

- Even without genotoxicity, all other sites and types of tumours and tumours in animal species or strains other than those mentioned are generally quantitatively transferrable, but sometimes with considerable uncertainties.

- If tumour incidences were obtained both a) in sites with questionable human relevance and/or questionable quantitative extrapolation and b) in sites with definite quantitative extrapolation, preference is generally to be given to the latter ones for risk quantification.

  It must be checked whether other types of tumours have occurred that cannot be attributed to spontaneous pathology with a relevance to humans that is not in question or not significantly so. When carrying out risk quantification, these are generally to be prioritised over the data for unreliable sites, even when they are not observed in the comparatively low concentration.

  A more detailed discussion on this differentiation can be found in Section 8.3.

The tumour incidences in the various organs named under (5) and (6) must generally be quantified separately and compared with each other. In the standard case, risk quantification is based on the tumour site with the lowest T25 (a dose or concentration at which cancer occurs in an additional 25% of the animals). The different background rate is taken into account in the T25 calculation. In some exceptional cases, however, different tumour sites must be combined (example: asbestos – mesotheliomas and lung tumours). In such cases, the relevance of the total incidence for risk quantification must be substantiated.

With the T25 procedure, based on a concentration with a significantly increased tumour incidence, a dose at which the incidence for this tumour in an animal study is 25% after lifetime exposure is determined by linear inter-
polation (i) taking into account the background incidence, (ii) if applicable, with correction of a non-lifetime study period, and (iii) assuming complete absorption (see also Glossary).

Calculation of a T25 or BMD for several tumour sites, sexes and with or without benign tumours in later steps allows extrapolations to be made into the low risk range based on several PODs in parallel and together with a differentiated mechanistic discussion. Aggregations of findings are useful particularly if the question of the differentiation of various dose-response relationships (e.g. because of the homogeneity of the reactions observed) is of minor importance. It may thus be appropriate to aggregate the findings over different tumour sites if a carcinogen has a uniform mode of action. The EU TGD points out: “For a substance inducing more than one type of tumours, the determination of a dose-descriptor value is from each relevant tumour type rather than from the number of tumour bearing animals. If several relevant data sets on tumour incidences are available, dose descriptors values should be derived for all these.” (Section 4.14.2.3; EC, Technical Guidance Document, 2005). Different background rates of tumours in different organs are arguments against aggregation of several tumour sites.

McConnell et al. (1986) argue in favour of a differentiated consideration of the possibilities of aggregating tumours for cancer risk calculations. U.S. EPA interprets this evaluation: “The incidence of benign and malignant lesions of the same cell type, usually within a single tissue or organ, are considered separately and are combined when scientifically defensible.” (A list of cases in which aggregations can be made is included in McConnell et al. (1986)).

The principle of adding up the total number of tumour bearing animals irrespective of the tumour site is thus not supported.

Some older studies were designed in such a way that only suspected target organs were evaluated. Such selective studies can nevertheless be used for risk quantification if they reveal carcinogenic effects. Multiple tumours (multiplicity) are usually reported additionally in such studies if they are observed.

(8) If several types of tumours were found in one organ/tissue, a combined consideration should generally be chosen. In certain substantiated cases (e.g. human relevance of only one type of tumour), an individual approach is appropriate.

(9) If benign and malignant tumours are observed in one organ, their incidences are generally added. Different types of tumours found in one animal are not added since the total incidence (related to the organ > 100%) may be exceeded. If there is evidence that, for example, the malignant degeneration of a benign tumour in humans is unlikely, no addition is required based on a scientific justification.

3.2 Selection of a point of departure

(1) The point of departure (POD: point of departure for further steps of risk assessment) is a defined exposure level with risk assignment to the concentration-risk function for a substance. The POD is at or close to the exposure level (concentration range) for which data on cancer
incidences are available from epidemiological observations or animal studies. For the POD, the risk as cancer incidence in percent is compared with the relevant concentration (mg/m$^3$). The POD is a normalised value. “Normalisation” is to be regarded as the conversion to lifetime (occupational) exposure (see Section 4.4), if applicable route-to-route extrapolation to the route of inhalation (see Section 4.2) and consideration of the background incidence (see Sections 3.35 (3); 3.36) in the prescribed way. The POD is a starting point for extrapolation or for comparison; depending on the level of comparison, the T25 is thus to be specified as a human equivalent (hT25) or to be applied at the level of animal studies. The boundary conditions for using a T25 must always be specified precisely.

(2) If data of sufficient quality are available from observations, the POD is to be identified as the benchmark concentration or benchmark dose. The central estimated value (BMD) rather than the 95-percent confidence interval (BMDL)$^8$ is to be used here. $^9$The POD is a starting point for extrapolation or for comparison; depending on the level of comparison, the benchmark dose is thus to be specified as a human equivalent (hBMD)$^{10}$ or to be applied at the level of animal studies. The boundary conditions for using a benchmark dose must always be specified precisely.

The criteria of sufficient data quality for modelling according to the benchmark approach must be defined separately (see Section 3.4). The relation between BMD and BMDL also indicates the quality of the applied modelling (quality of adjustment of the model function to the available experimental data). For the calculation of the BMDL, this factor can thus be used (apart from other criteria) for assessing the question of whether the benchmark approach should be applied at all in a particular case.

Selecting the BMD instead of the BMDL may imply a certain error (since it cannot be ruled out that the exposure-risk relationship is more appropriately described by the BMDL). However, selection of the BMD seems to be justified: 1) because of analogy to the T25 where data are not accurate (T25 is also a central estimated value without confidence interval), 2) because of the possible low error (if there is a large deviation between BMD and BMDL the benchmark approach would not be appropriate, 3) since a conservative extrapolation procedure is selected anyway in most cases because of linearisation in the range below the BMD as the POD.

For conversion of a benchmark dose to equivalent human exposure see Section 4.

(3) The benchmark response (BMR)$^{11}$ at the POD is generally to be established at 10% for reasons of comparability. A BMD$_5$ can divergently (only) be used as the POD if the BMD$_{10}$ is still in the observed range. A

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$^8$ For terminology on the benchmark procedure see Glossary and EPA, 2000
$^9$ BMD (benchmark dose) or BMDL are used below even if airborne concentrations are referred to in the specific case (BMC; BMLCL).
$^{10}$ For relevance of the term human equivalent and for conversion see Section 4
$^{11}$ For abbreviations in the benchmark approach, see Glossary
BMD$_1$ can only be used as the POD if the BMD$_5$ is still within the observed range.

In many cases, there are only minor deviations for the assumed risk if the T25 is compared with the BMD$_{10}$ after correction (linear conversion) of the risk level (see Annex to EC, Technical Guidance Document, 2005). There may however be deviations depending on the course of the concentration-risk relationship. Therefore, and because of the more complete description of the derived course of the concentration-risk relationship in the experimental range, preference is to be given to the application of the benchmark approach. For examples see Section 5.2.

The present Guide continues to use modelling between the BMD$_{10}$ and BMD$_{0.1}$ (response of 10% or 1 per mille) in cases in which there is mechanistically substantiated non-linearity together with a good database (see Section 5.2). If the reasons for non-linearity are not sufficient, modelling with the benchmark method is carried out only for the experimental range up to a BMD$_{10}$ as the POD. Earlier, the U.S. EPA used the linearised multistage (LMS) model. This procedure is almost identical with modelling by means of the multistage model in the experimental range and a continuation of the modelled function into the low risk range (e.g. if there is a BMR of 1:1000). With the EPA concept, the 95 percent confidence interval is however included.

(4) If a sufficiently qualified benchmark concentration cannot be specified, the T25 is to be used as the POD for the calculation according to the method of Sanner et al. (2001)/Dybing et al. (1997)

The calculation formula for T25 is provided in the Glossary.

In cases in which the benchmark approach cannot be used, preference is given to the T25 as the POD over similar other values because

- this corresponds to the method of risk quantification in various EU provisions on risk assessment,
- the "Steinhoff" method discussed earlier in Germany is compatible with the T25 as the POD,
- although it is not related to a normalised percentage (25%),
- the LED(10) in the U.S. EPA (2005a) in turn requires using the benchmark approach although this is not always adequately qualified.

The U.S. EPA ED(10) approach is also based on benchmark modelling (without consideration of the confidence interval) and its method is identical with the derivation of the BMD$_{10}$. Since the difference between the T25 and ED$_{10}$ is linearly taken into account when calculating a reference MoE according to EU/TGD, the ED$_{10}$ may be used as the POD in the EU MoE approach.

(5) Specification of a POD is not formally required for extrapolations into the range of regulatory interest that is below the observed incidences for which continuation of the concentration-response relationship already present in the range of observation is assumed (continuous function; see Section 5.2). It should nevertheless be specified for comparison.
BMD$_{10}$ or T25 must be calculated for all tumour sites relevant to humans (for selection of tumour sites and species see Section 3.1).

For benchmark modelling with poorer data quality (see Section 3.3), it is appropriate to calculate both the T25 and the BMD$_{10}$ to identify the effects of the uncertainty of the specific decision: The PODs established according to the respective procedures may be close together or show clear discrepancies. The specific information must be documented.

*For examples see section 5.2 (case B)*

### 3.3 Application of the benchmark approach

The models to be selected for curve fitting should be consistent with the mechanistic considerations about carcinogenicity. Therefore, the multistage model (or function), which corresponds to the multistage model of carcinogenicity, is often used. However, the gamma function also corresponds to this mechanistic understanding. Multistage or gamma function are thus the preferred models for modelling with the benchmark approach in the experimental range. Other models should, however, also be considered if the data can be adjusted in a clearly better way. In view of a recommendation by the EFSA, the “quantal linear” model of the BMDS (benchmark dose software) should not be selected for quantal data (applicable for case numbers for carcinogenicity)\(^{12}\).

A range of software products are available for benchmark modelling. The BMDS software from the U.S. EPA\(^ {13}\) is particularly worthy of mention. Alternatively, it is also possible to use PROAST from the Dutch National Institute for Public Health and the Environment\(^ {14}\). However, the cut-off criteria and rules for application in the following only relate to BMDS. If PROAST is used for the modelling, the parameters and cut-off criteria used must be documented.

With the BMDS software, a key criterion for selecting the best model is the lowest AIC value (AIC: Akaike’s Information Criterion for the assessment of regression adjustment).

Where there are major discrepancies between permitted results, an average of these values (BMD and/or BMDL) is to be established (particularly relevant for PROAST). This calculation of averages is first carried out unweighted, until additional benchmarks are established for a weighting (Davis et al., 2011; EFSA, 2009).

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\(^{13}\) [http://www.epa.gov/ncea/bmds/](http://www.epa.gov/ncea/bmds/)

If the benchmark approach for the quantification of effect thresholds is used for non-carcinogenic effects, the BMDL\textsuperscript{15} should normally be used for the assessment rather than the BMD. The decision as to the model selection is implemented in the same way as the procedure in the case of carcinogenic effects (see (1)).

3.4 Minimum criteria of data quality for application of the benchmark approach

(1) In general, data for at least the control group and two dose groups should be available in order to implement the benchmark approach.

In Annex XI to the EU TGD, there are some examples in which the T25 is compared with the BMD\textsubscript{05}. Three dose groups were required for this purpose. However, this criterion is not required, as an insufficient database is sufficiently recorded via other criteria. Due to the insufficient quality of the statistical evaluation that is to be expected, poor modelling with permissible models leads indirectly to a decision against the benchmark approach.

(2) If the tumour incidence is identical, or differs only slightly in all dose groups (plateau effect), application of the benchmark approach is not appropriate.

The plateau effect is also normally already taken into account by the poor model fit and therefore does not necessarily represent an explicit criterion. However, it does represent helpful information, as it enables an exclusion to be made on the basis of the visual assessment.

(3) If there is only one dose group outside the control for which the effect level is clearly above the BMR, application of the benchmark approach is not appropriate.

In this case only two points are present, resulting in a linear link (T25 approach). If the dose group is near to the BMR sought, and if the result is significant, the relevant point can be used directly as a POD instead of the T25 response. This does not exclude the possibility that in the end a “break function” may be used for the extrapolation – based on this POD, in the case of qualified information pointing to a sub-linearity (see Section 5.2).

(4) Benchmark models, that deliver a too small p value (p < 0.05) are to be discarded. Models for which the BMD/BMDL is > 10 are also to be discarded (high uncertainty of the BMD). Models whose “scaled residuals” in the BMR range are outside –2 to +2 are unsuitable. If multiple permissible benchmark calculations remain, these are only suitable if the range of the selected BMDL is ≤ 10 (models qualified in the same way indicate a wide range of possible answers and therefore do not allow for a definite statement).

This last criterion has no statistical justification nonetheless corresponds to the approach of the EFSA.

A “goodness of fit” test is carried out as part of the benchmark modelling in accordance with BMDS. As part of this process, the “log-likelihood” values

\textsuperscript{15} For abbreviations in the benchmark approach, see Glossary
are compared:

A) “reduced” vs. “full model”. This test checks whether a dose-response relationship even exists. The p-value must be ≤0.05.

B) “fitted model” vs. “full model”. This test checks whether the model estimates the course of a curve sufficiently accurately. In accordance with the EFSA procedure the p-value must be > 0.05 for the “fitted model”.

(5) The following factors are considered for the suitable benchmark modellings remaining following checking of the selection criteria in accordance with (4): when BMDS is used, the model with the minimum BMDL is juxtaposed with the model with the lowest AIC value, a check is also carried out to ascertain whether a multi-stage or gamma model provides a suitable modelling, and a check is also furthermore carried out to identify whether the visual adjustment leads to a plausible result; the various factors relating to the selection are then weighed up and a justification for the selection is provided.

If there are uncertainties in relation to the selection, the protocols for the BMDS calculation should be checked in detail to ascertain whether artificial limitations have developed by parameter fixation (e.g. no p value identified) which make it more difficult to assess the results.

(6) In cases of doubt, where the data quality is limited, the procedure set out in section 3.2 (7) should be followed. This means that the decision is between T25 and the benchmark process. The justification for the finally selected procedure must be documented.

For an example see Section 5.2 (case B)

(7) Doses can thus only be omitted for the modelling if multiple doses characterise a plateau effect or reduced incidences are actually observed in the high dose range or the course is substantiated by an incidence of nearly 100%.

A plateau effect, specific changes at doses near to the maximum tolerated dose or an incidence of approximately 100% do not allow for further differentiation, which means that this information can distort the exposure-risk relationship. In this case the information for this group (high dose range) can be disregarded. However, the omission of dose groups leads to a reduction in the degree of freedom for the modelling.

(8) BMD calculations in which the p value is not quantified are no longer used.

A non-quantified p value can be detected from a note in the BMDS protocol: “p= not applicable”

3.5 Procedure in the case of human data

The relevance attached to epidemiological observational studies in the quantification of occupational cancer risks as compared with animal studies has already been discussed in Section 1.1 and in the explanations of the data to be used as a basis (Section 1.5 (1)). For the risk term applied here see Section 1.4.
The following references on the procedure require an adequate epidemiological database (for minimum criteria see Section 8.6 of this Guide).

(1) The selection of epidemiological studies should be based on the following procedure:

- The available epidemiological evidence should be identified by means of a well-structured, systematic literature search and reviewed for its quality and suitability for risk assessment. Principles established for the selection of occupational epidemiological studies for carrying out a meta-analysis should be considered here. It must be decided in each individual case whether several studies are combined to a pooled estimator for an assessment in a meta-analysis or whether individual studies are assessed separately in order to specify a range of potential risk scenarios.

Literature: Blair et al. (1995); Roller et al. (2006), Section 5.2; see the discussion on meta-analysis for granular biopersistent particles (Gebel, 2012; 2013; Morfeld, 2013).

- In general, analytical study designs with an individual exposure estimate are to be selected for risk assessment. Both cohort and case control studies can be used for risk assessment.

Study designs used in occupational epidemiology can be classified in the following descending order of evidence: (1) cohort study; (2) case-control study (CCS); (3) cross-sectional study (CS); (4) ecological or correlational study

Quantitative exposure data are more often available from cohort studies, whereas a CCS generally guarantees a better consideration of confounding factors (for further details on the special strengths and weaknesses of study designs see Ahrens et al. 2008). When justified, in exceptional cases, e.g. a CCS embedded in a cohort with more specific or detailed information on exposure and/or the effect end point, a CCS can be more appropriate for a risk assessment than the underlying cohort study.

(2) Target parameters are taken into account as follows:

- In general, preference is to be given to measures with reference to cancer incidence over those to cancer mortality unless incidence and mortality are regarded as almost identical because high lethality is involved in a specific type of cancer (as e.g. in the case of lung carcinoma).

- The information density of the strata decreases, the more finely the considered end points are classified. It must thus be considered in each individual case whether different end points can be combined in an appropriate way to increase the statistical power (i.e. combination of various related tumour entities into one group) even if causal factors may differ in detail, e.g. in the case of head-neck tumours or myeloproliferative diseases.
• It must be decided in each individual case whether “early” end points (such as biological markers), which can be attributed as necessary early stages in the causal chain to an examined target disease, may be included in the assessment of the available studies. This is particularly useful when these early clinical effects can be seen as warning signals.

This factor is generally taken into account as a subsidiary point within the assessment, i.e. to assist in the selection of a POD for weight-of-evidence assessments or when selecting an extrapolation method. Warning signals can justify the introduction of preventive measures.

(3) The following approach can be taken when calculating the acceptable and tolerable concentrations:

• A cumulative measure of exposure is generally used for calculating the risk-related concentrations (working lifetime of 40 years with average exposure). An alternative measure of exposure can only be used as a basis for decisions if it is substantiated with the mode of action.

• A point estimator for every exposure category (e.g. median and geometric mean) is the preferred specification for use.

If merely an exposure range was reported (e.g. 1–9 ppm-years), the range mean (5 ppm-years in the example) can be used as a basis for the calculation. Concentrations specified in mg/m³ should be converted to substance-specific ppm. The calculations of the acceptable and tolerable concentrations are based on 240 working days/year and an inhaled volume of e.g. 10 m³ per working day, which is estimated to be 8 hours (the inhaled volume depends on the workload; 10 m³ refers to slight to moderate physical activity).

(See Section 4.6 and van Wijngaarden and Hertz-Picciotto, (2004)).

• Subsequently, the cumulative concentrations specified in ppm-years must be converted to the long-term mean after 40 years.

• Depending on the database, direct measures of absolute risk (e.g. cumulative risk) or – if these were not reported – measures of the relative risk must be related to exposure. Measures such as SMR, SIR, RR or OR will generally be available. For the calculation of the lifetime risk of the exposed persons, these relative risk increases can be multiplied by an estimated value for the lifetime risk of the reference group, e.g. the general population, unless the detailed life table method is used.

RKI (2011) is one example of an appropriate source for a uniform selection of the background risk for the reference cohort.

• The risk measure reported for the exposure range (RR/SIR, etc.) can be correlated with the cumulative exposure value in a regression analysis, which allows extrapolation into the high or low risk range and statements to be made about the risk per unit increase (1 ppm) of exposure. In this way, the lifetime risk can be assessed in relation to a specific exposure level or an assumed occupational exposure limit.
After subtraction of the risk of the non-exposed persons (e.g. general population) an estimated value of the exposure-related excess risk is obtained.

Restrictions of the validity of the results are to be discussed.

A procedure in analogy to Roller et al., (2006) and Goldbohm et al., (2006) has therefore been suggested.

Bias, possible residual confounding and misclassification, for example, may restrict the validity of the results. Risk estimators that were adjusted for confounder effects should be used. Calculations of adjusted vs. non-adjusted risks should be compared with each other, if possible, since adjustment depends on the model and this allows for an assessment of the intensity of possible confounding.

Inconsistent or non-existing dose-response relationships can often be observed in epidemiological studies. However, the data can also be considered in cases in which the test results only suggest the existence of a cause-effect relationship. Deviations from an expected dose-response relationship and their possible causes and consequences for risk extrapolation are to be discussed.

It must be considered that the described procedure ignores variations of the risk among individuals due to different susceptibility. It should also be assumed that the composition of the investigated cohorts in reference to their morbidity and associated exposures is different from the general population (Healthy Worker Effect), which means that the results are not necessarily representative for other populations. However, these considerations are of subordinate importance against the background of assessing the risk of occupational exposure and the establishment of limit values to improve occupational safety.

If semi-quantitative exposure specifications and no other epidemiological data are available, the attempt may be made to establish classification criteria for exposure levels – where necessary by contacting the authors of the original publications – and thus make a quantitative exposure assessment.

Adjustment of the rate of inhalation and the respiratory volume/day from the environment to the workplace. Based on the assumption of a study involving environmental exposure of humans (with 20 m³ of respiratory volume/day), a conversion to an exposure duration of 8 h per day at the workplace must be carried out. A respiratory volume of 10 m³ is then assumed for this shortened timeframe (conversion by a factor of 2).

(➔ For reference to identical respiratory volume/d when calculating from animal study, see Section 4.2)
(5) Deviations from the default are possible in the following cases:

- In order to be able to check the consistency of the results under different conditions, measures of exposure deviating from cumulative exposure (intensity, duration, exposure peaks or threshold) may also be considered depending on the mode of action if specific estimators were documented in the assessed literature.

- In general, cross-sectional studies and ecological studies should at best be used to supplement qualified epidemiological data and/or data from animal studies (weight-of-evidence approach). Taken independently as a basis they do not generally enable sufficiently qualified risk quantification.

(6) For extrapolation into the low-risk range, see procedure for toxicological data from animal studies (see Section 5). Human data should, if possible, be used to check the plausibility of the extrapolation factors in extrapolating animal studies to humans.

3.6 Handling of background incidences

(1) In compliance with the standard procedure in the T25 and benchmark approaches (according to the U.S. EPA or PROAST software), the “extra risk” calculation is generally to be used.

From a toxicological point of view, there is no well-founded scientific justification for the convention of selecting the extra risk, although it is accepted as a standard procedure, since (i) the deviations are generally slight if there is a low background rate, (ii) there is an agreement with many older unit risk calculations, (iii) this ensures an agreement with the T25 approach, and (iv) this ensures an agreement with the traditional procedure in the multistage approach.

3.7 Risk quantification by specifying the T25

(1) If a POD is established by specifying the T25 value according to the method of Sanner et al. (2001) and Dybing et al. (1997), no modelling of the dose-response relationship in the experimental range is required. The T25 is determined by linear interpolation. This procedure is to be used regularly if a qualified benchmark calculation cannot be made.

For a detailed definition of the T25 see Glossary.

(2) If only the route of inhalation is relevant (applies to occupational exposure limits), the T25 value is expressed as airborne concentration (mg/m³ or ppm).

For further adjustment of the T25 to the exposure pattern at the workplace see Section 4.2.

(3) Details on the procedure used in this T25 approach are available in the cited literature (ECHA, 2012b). The most important items are:

- The lowest dose group showing a significantly increased tumour incidence is selected as the point of departure.
The criterion of significance is to be established either on a statistical basis (Fisher’s exact test to compare the dose group with the control group) or a biological basis. In analogy to the FDA (2001), levels of significance of $p < 0.05$ are to be used for rare tumours or tumours with a spontaneous incidence $\leq 10\%$, and $p < 0.01$ for tumours with a spontaneous incidence higher than 10%. If necessary, both the experimental control group and the historical control data are to be employed for comparison (for historical control incidences see e.g. Derelanko and Hollinger, (2002)).

- The spontaneous incidence in the control group is subtracted from the tumour incidence in the treated group.

  If there is high mortality in the considered dose group, the resulting greater uncertainty of the T25 value must be discussed, or the next lower dose group must be selected, since mortality rates are generally not corrected. High mortality may also mean that the study can no longer be used for risk quantification (see Section 8, minimum criteria).

- T25 values are generally calculated separately for species, sex and organ/type of tumour (see Section 3.1 (6)).

  The types of tumours/organs/sexes can be combined if there is a justification to support this (see Section 3.1(6)).

- A shorter exposure period compared with the standard lifespan of the test species and a reduced observation period are corrected.

  The shorter exposure period ($w_1$ in weeks) compared with the standard lifespan ($w$ in weeks) of the test species and a reduced observation period ($w_2$ in weeks) is corrected by multiplication with the factor $(w_1/w)x(w_2/w)$ (see Section 4.5);

- Exposure patterns deviating from the selected standard values are considered.

  Linear conversion is used for this, for example for doses/day, exposure days/week and exposure period/day in the case of inhalation.

- The lowest T25 value regarded as relevant to humans (with regard to species/organ/type of tumour) is used for risk quantification (see also Section 3.1).

  This does not fully agree with the usual procedure according to EU. The T25 value was originally designed as a dose of the substance related to body weight and was thus specified in mg per kg body weight and day (mg/kg x d). If several studies are available in which gavage was not used in every case, but animals were for example exposed via the drinking water, diet or inhalation, conversion of exposure to the body weight-related dose has been suggested to be used as the common basis of comparison (EC, 1999). However, in the present case, a concentration must be specified, e.g. in mg/m³.

  If no route-to-route extrapolation is permitted (see Section 4.4), the specific (oral or dermal) point of departure may not be used for a T25 inhalation value.

(4) The T25 is converted to a human equivalent (hT25) by means of the factors specified in Section 4.
4 Extrapolating data from animal studies to humans

4.1 Consideration of species differences

(1) In the derivation of risk concentrations, this Guide generally assumes the same sensitivity of test animals and humans for carcinogenic effects after inhalation exposure. There is no reliable verification of this assumption; since it has only limited scientific validation, it has the character of a convention.

Roller et al. (2006) demonstrated for many carcinogens that the sensitivity of humans in inhalation studies is usually higher than that of test animals. The authors thus concluded: “The results suggest that species extrapolation based on equivalent exposure without taking toxicokinetic or toxicodynamic species differences into special account generally does not lead to an overestimation of the risk for humans.” This finding supports the statement made in Section 4.1 (1). Roller et al. (2006) go even further on the basis of their findings and propose that identical sensitivity should also be assumed “if mechanistic data, for example, suggest lower human sensitivity.”

(2) Substance-specific data showing a clear deviation from the average (e.g. from pharmacokinetic models) can be used for substantiating a risk quantification deviating from the default.

This procedure allows deviation from the default if there is a “clear deviation from the average.” What importance is attached to mechanistic or kinetic findings suggesting lower human sensitivity with sufficient likelihood is a matter to be decided on in the individual case (expert judgement).

4.2 Procedure based on an animal inhalation study

(1) Substances tested in an animal inhalation study are generally exposed for 6h/day. Taking into account the increased level of physical activity among humans (assumed inhaled volume of 10 m³ over an 8-hour working day), a conversion factor of two (rat → human; mouse → human) can generally be selected in order to calculate the equivalent exposure level for humans. This factor applies for systemic effects.

This assumption complies with a convention selected in the REACH Guidance Document. The procedure deviates (valid as at: 2012) from the methodology in accordance with the Announcement on Hazardous Substances 901 (BekGS 901) (Committee on Hazardous Substances (AGS), 2010).

It is assumed in relation to systemic effects (REACH Guidance Document R.8) that the respiratory minute volume can be converted between species in proportion to the body weight using the appropriate scaling factors (human: 0.2 l/kg body weight x min. at rest; rat: Respiratory minute volume 0.2 l/min, 250 g, accordingly: 0.8l/kg x min. At a scaling factor of 4: 0.2l/kg x min: identical to human at rest; mouse: Respiratory minute volume 0.042 l/min, 30 g, accordingly: 1.4 l/kg x min. At a scaling factor of 7: 0.2l/kg x min: identical to human at rest).
Differentiations according to water solubility (> 1g/l; readily water soluble substances) are not carried out here (contrary to the older version of this Guide).

For example, a T25 (rat) of 10 mg/m³ after 6-h exposure/d corresponds to an hT25 (humans; 8h/day) of 5 mg/m³. This adjustment also takes place for other species of test animal.

The procedure according to Section 4.2 (1) represents a previous determination (valid as at October 2013). Further verifications were requested and these can be used at a later date (with quotable justification) for a deviating extrapolation, following their completion.

(2) The factor of two should also be used to take into account interspecies differences in the pulmonary or alveolar minute ventilation in the case of local effects (in the upper or lower respiratory tract) where the daily exposure duration is 6h/day for the animal study and 8h/day for humans with an increased level of physical activity, and when no formal calculation of the HEC takes place. The species differences are already sufficiently taken into account with the HEC calculation (see Section 4.3).

With this assumption, a convention is adopted from the relevant REACH guidance document. The procedure deviates (valid as at: 2012) from the methodology in accordance with BekGS 901 as of (Committee on Hazardous Substances (AGS), 2010).

\[
\text{corrected } N(\text{L})\text{OAEC} = \text{inhalatory } N(\text{L})\text{OAEC} = \frac{\text{exp.cond}_{\text{rat}}}{\text{exp.cond}_{\text{human}}} \\
= \text{inhalatory } N(\text{L})\text{OAEC} = \frac{6 \text{ h/d}}{8 \text{ h/d}} \times \frac{6.7 \text{ m}^3}{10 \text{ m}^3} \times (8 \text{ h}) \quad \text{(for workers, in case of 8 h exposition)}
\]

Figure 1: Conversion from an exposure period of 6 to 8 hours and from a respiratory volume at rest of (6.7 m³/ 8h) to increased activity (10 m³/ 8h) in accordance with ECHA, (2012b), figure R 8-2

The procedure according to Section 4.2 (2) represents a previous determination (valid as at October 2013). Further verifications were requested and these can be used at a later date (with quotable justification) for a deviating extrapolation, following their completion.

(3) If there are species differences in absorption, these must be considered in the interspecies extrapolation for the quantification of the dose...
for systemic effects.

4.3 Interspecies extrapolation for locally acting particles and aerosols

(1) For particles or aerosols, the estimated human equivalent concentration (HEC) is calculated based on the data from the animal experiment (rat experiment). The inverse for the HEC/C_T factor corresponds to the interspecies extrapolation factor, and C_T is the exposure concentration in the animal experiment, for which a corresponding transformation is sought. In general, HEC/C_T is calculated using the following formula:

\[
\frac{\text{HEC}}{C_T} = \left( \frac{\text{AgV}_T}{\text{AgV}_H} \right) \times \left( \frac{\text{ELR}_H}{\text{ELR}_T} \right) \times \left( \frac{\text{NF}_H}{\text{NF}_T} \right) \times \left( \frac{\text{DF}_T}{\text{DF}_H} \right)
\]

\[
C_T \quad \text{exposure concentration; entry as mass concentration [mg/m}^3]\]
\[
\text{AgV} \quad \text{Weighted daily respiratory volume}
\]
\[
\text{ELR} \quad \text{Average elimination rate (dependent on the clearance rate)}
\]
\[
\text{NF} \quad \text{Normalisation factor (reference tissue)}
\]
\[
\text{DF} \quad \text{Deposition fraction (percent/100)}
\]
\[
T \quad \text{Animal (rat)}
\]
\[
H \quad \text{Human}
\]

A detailed description of the HEC model and the criteria for selecting the framework conditions for using the HEC model and for calculating the deposited dose using the MPPD (Multiple-Path Particle Dosimetry Model) software are provided in the “Gutachten zur biologischen Plausibilität von HEC und MPPD” (Report on the biological plausibility of HEC and MPPD), July 2011\(^\text{16}\) (FoBiG, 2011).

- \( \text{AgV}_T/\text{AgV}_H \)
  The ratio \( \text{AgV}_T/\text{AgV}_H \) delivers the value of 0.008 in a standard case. The consideration of the different exposure durations/day in accordance with Section 4.2 is omitted, as the different respiratory minute volumes and different exposure durations (8h for humans; 6h for rats as standard) are already taken into account in the factor \( \text{AgV}_T/\text{AgV}_H \).

The calculation was based on an exposure duration of 6h/d (rat) or 8h/d (human) and a respiratory volume of 0.077 m\(^3\)/d (rat) or 10 m\(^3\)/d (human). For the rat figure, the averaged value was corrected by a factor of 5/7 (exposure days/week), and the figure for humans was corrected by the value 240/365 d/year (Hartwig, 2012). This results in \( \text{AgV}_H = 6.57 \text{ m}^3/\text{d} \) and \( \text{AgV}_T = 0.055 \text{ m}^3/\text{d} \). This results in \( \text{AgV}_T/\text{AgV}_H = 0.00837 \) (rounded up to 0.008). Provided that qualified data are available for the rats in the animal experiment carried out as part of the key study, the study-specific information can be used here.

\(^{16}\) Available at www.baua.de with this title
The ratio for the normalisation factors is determined with $\frac{NF_H}{NF_T} = 150$ in a standard case. The deposited dose is thereby normalised to the surface of the respiratory tract (alveolar plus tracheobronchial region), if a better normalisation measure cannot be applied in the individual case.

For the purposes of the calculation, surface areas of 4090 cm² (alveolar region) and 35 cm² (tracheobronchial region) were established for a rat lung and surface areas of 627000 cm² (alveolar region) and 3200 cm² (tracheobronchial region) were established for a human lung (Oberdörster, 2010) and the resulting value was rounded. Due to the inexact allocation of the effect to the alveolar region (only) or the tracheobronchial region (only), the entire area (of minimum quantitative relevance) appears to be a suitable measure of the characteristics of the relationships between the species. This does not mean that other criteria (e.g. regional surface areas of parts of the lung, number of macrophages, volume of macrophages, or lung weight) cannot offer better normalisation measures in individual cases. However, these generally lead to an interspecies difference in a similar order of magnitude. Differentiations according to rat strains are not generally required in order to ensure overall accuracy.

The ratio of the deposition fractions ($\frac{DF_T}{DF_H}$) should be calculated in each case via modelling with the Multiple-Path Particle Dosimetry Model (MPPD-Modell, here: Issued: 2011, Version 2.11). The results are largely determined by the particle size distribution.

A table explaining the selection of the settings in the MPPD model 2.11 program is attached in Annex 10.3. The standard settings recommended in the table are to be adopted for rats and humans. In reference to humans, data that correspond to the characterisation “light activity” and breathing through a combination of mouth and nose are recommended for exposure conditions.

Background information for the selected modes of action is also provided in the Help function for the modelling software (MPPD, 2011), which is available free of charge.

As a general rule, the standard settings indicated in the table should not be deviated from as
- The model validation is not approved for some changes.
- For the ERR calculations there is only justification for a rough orientation to the range of differentiated conversion options
- It is not clear that an alternative dose metric, for example, delivers an improved calculation of the deposition fraction with multiple parallel mechanisms.
- An alternative dose metric (e.g. particle number) does not necessarily lead to alternative and more reliable interspecies extrapolations.

The deposited fractions within the entire tracheobronchial and alveolar region can be read off from the calculation (MPPD) protocol and expressed as a ratio ($\frac{DF_T}{DF_H}$).
The particle mass is used as the dose metric here, taking into account the density of the substance from the animal study. The particle size distribution and dose metric are adopted for humans.

The selection of different particle size distributions for animals and humans is not provided for as part of an ERR derivation. Even in the case that alternative situations could arise at different workplaces, the best available information on effects in relation to defined particle size distributions from animal experiments are to be used.

Where agglomerates exist, it is in some cases suggested to take into account the “agglomerate density” instead of the substance density: As the agglomerate density is only known in a small number of cases, the substance density should generally be used – in order to ensure the comparability of the results from the individual considerations.

Irrespective of this, it should be noted that the agglomerate density cannot be more than 25% less than the substance density. The influence of this difference on the calculation of the deposited dose with the help of the MPPD software is very small.

• **ELR**

The ratio for the elimination rates $\frac{ELR_H}{ELR_T}$ for poorly soluble particles is recorded with the factor 0.15. In the case of particles of medium solubility, this factor is doubled to 0.3 and where the level of solubility is even higher, the ratio of the elimination rates is not taken into account ($\frac{ELR_H}{ELR_T} = 1$).

The factor for poorly soluble substances is derived from the elimination half life for granular bio-persistent particles (GBP) in the alveolar region of 60 d (rats) and 400 d (humans). An elimination rate ($= \ln(2)/\text{elimination half life}$) of 0.0116/d for rats and 0.00173/d for humans can be calculated (Hartwig, 2012). This calculation method involves uncertainties, particularly in the case of substances that are not assigned to the GBP. However, it can be used as a conservative benchmark and seems to be more suitable than the alternative of calculating via MPPD.

In the case of more easily soluble particles, a clearance via solubility (e.g. in the acidic environment of the lysosomes following endocytosis) is to be taken into account in addition to the mechanical elimination. However, there is evidence to support a longer retention of soluble (metal) particles in the alveolar region (e.g. for protein binding). Where a corresponding macrophage clearance is carried out, this can in part lead to species differences. For this reason, the influence of the different elimination rates at higher solubility level are taken into account with less weight (0.3 instead of 0.15). When the level of solubility is very high, no differentiation between the elimination rates is assumed as standard.

However, it is not currently possible to provide a generalised statement about what should be understood as easy solubility or medium solubility within the target tissue (based on definitions of water solubility in the ECHA...
guidance, for example). In order to reach a decision, the information should be factored in in each individual case and the decision should be explained. For example, zinc oxide (relatively low water solubility of 1.6 mg/l) is eliminated from the lungs very quickly (Pauluhn et al., 2003), which means that species differences can be disregarded in the clearance. The half-lives of sodium pertechnetate (easily soluble) and tetraphenylarsonium pertechnetate (medium solubility) in the lungs of volunteers do not differ from each other (Kopunec et al., 1996; Walker et al., 2001).

From the above factors, a factor $HEC/C_T$ is calculated:
$$HEC/C_T = \frac{AgV_T}{AgV_H} \times \frac{NF_T}{NF_H} \times \frac{ELR_T}{ELR_H} \times \frac{DF_T}{DF_H}$$  \hspace{1cm} (1)

The following results for poorly soluble particles:
$$HEC/C_T = 0.008 \times 150 \times 0.15 \times \frac{DF_T}{DF_H} = 0.18 \times \frac{DF_T}{DF_H}$$  \hspace{1cm} (2)

for particles of medium solubility:
$$HEC/C_T = 0.008 \times 150 \times 0.3 \times \frac{DF_T}{DF_H} = 0.36 \times \frac{DF_T}{DF_H}$$  \hspace{1cm} (3)

for very easily soluble particles:
$$HEC/C_T = 0.008 \times 150 \times \frac{DF_T}{DF_H} = 1.2 \times \frac{DF_T}{DF_H}.$$  \hspace{1cm} (4)

(2) The application of the interspecies extrapolation factor $HEC/C_T$ has no effect on the level of the variability factor (intraspecies and interspecies variability), which is (only) taken into consideration in the case of non-carcinogenic effects (see Section 6.2).

(3) The dosimetry model MPPD 2.11 and the $HEC/C_T$ calculation is not applied as standard in the following cases:

- In the case of particle sizes greater than > 3 µm, practical experience has shown that the modelling uncertainties are too great, and therefore the current version of the MPPD (2.11) should not be used for such sizes.  
  **Empirical values are available for particle sizes > 3 µm, which are better covered by earlier MPPD versions (in particular MPPD 2.01).**

- When data from animal studies is not based on rat studies (and instead on mice or dogs, for example).  
  *In such cases, the RDDR model of the U.S. EPA (1994) can be applied for the mouse, which calculates (less reliable) depositions. The MPPD software can still be used to calculate human data. There is no suitable dosimetry model available for other species that could be applied in standard cases.*

- When clear “overload” phenomena are decisive for the observed effects.
In this case the interspecies factor can be used as without “overload” if the effects can be attributed at least in part to the specific toxicity of the substance. However, the resulting value does include additional uncertainties. ERR modelling using the MPPD model in the “overload” range should not be used for pure particle effects (see GBP, granular biopersistent particles without known substance-specific toxicity).

- When observed effects clearly do not correlate with the deposited or retained dose.

For example, if particles clearly cause effects in the tracheobronchial region in animal studies, but such effects are not seen in the alveolar region even though relevant or even higher deposition occurs in the alveolar region, then the standard normalisation selected here and the selected deposited fraction within the entire lower respiratory tract are unsuitable. No standard procedure can be provided in this Guide for this case (procedure must be substantiated on a case-by-case basis)

- When formal calculation with the model leads to an overall HEC/C_T factor of below 0.05 (interspecies extrapolation factor > 20).

The intended cut-off criterion is not well substantiated by data. However, it can be shown that the individual assumptions in the dosimetric model, in particular in the normalisation and in the dose metric, are associated with considerable uncertainties. For this reason, a cautious approach was selected, which is clearly focussed on:

a) existing extrapolation practice for poorly soluble particles, and
b) on the overarching understanding that animals and humans are presumed to be sensitive to carcinogenic effects to an approximately equal level taking into account toxicokinetic differences.

No standard procedure can be provided in this Guide for this case (procedure must be substantiated on a case-by-case basis)

4.4 Procedure based on an animal study with oral administration

(1) If there is no study-specific information on a relevant dose related to body weight, and only concentrations in the diet or water have been reported, the following default values can be used for conversion (ECHA, 2012b).
Table 1: Standard values for consumption of food and water and body weight of different species of test animal according to EFSA (2010).

<table>
<thead>
<tr>
<th>Experimental animal</th>
<th>Sex</th>
<th>Body weight (kg)</th>
<th>Food consumption per day(^a) (g)</th>
<th>Water consumption per day(^a) (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Male</td>
<td>0.03</td>
<td>3.6 (120)</td>
<td>5 (167)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.025</td>
<td>3.25 (130)</td>
<td>5 (200)</td>
</tr>
<tr>
<td>Rat</td>
<td>Male</td>
<td>0.5</td>
<td>20 (40)</td>
<td>25 (50)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.35</td>
<td>17.5 (50)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>Hamster</td>
<td>Male</td>
<td>0.125</td>
<td>11.5 (92)</td>
<td>15 (120)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.110</td>
<td>11.5 (105)</td>
<td>15 (136)</td>
</tr>
</tbody>
</table>

\(^a\) In brackets the daily food or water consumption is given in g or ml per kg body weight per day, as appropriate.

(2) A dose administered in an animal study (unit: mg per kg body weight and day; mg/kg x d) is transformed into a human equivalent dose by applying an allometric scaling factor. As a default, conversion is carried out via allometric scaling based on the basal metabolic rate \([\text{body weight}_{\text{human}} / \text{body weight}_{\text{animal}}]^{0.25}\). The following rounded factors are obtained:

- Dog, monkey 2
- Rat 4
- Mouse 7

If an oral study is used as a basis, consideration of a scaling factor is no conservative extrapolation step, but instead represents biologically substantiated data adjustment in the default case (see TGD, Section 4.14.2.4, and Table 11 (scaling factors based on default weights); EPA, (2005a); Kalberlah and Schneider (1998)).

(3) In the next step, the human equivalent dose is to be transformed into an airborne concentration. Differing route-specific absorption rates must be corrected in a route-to-route extrapolation. However, there are reasons for avoiding “route-to-route extrapolation”, in particular where the following apply:

- pronounced first pass effect;
- in the case of inhalation exposure, local tumours in the respiratory tract are expected (especially relevant to locally acting, but also persistent substances as well as metal compounds);
- local tumours after oral administration play a role relevant to assess-
ment (e.g. forestomach tumours in rodents);

- organ concentrations deviating considerably in the critical target organ are expected after inhalation and relevant to assessment (e.g. often decisive in studies with administration by gavage).

The limits of route-to-route extrapolation were specified, for example, when the German OEL concept, formally known as “ARW” (Arbeitsplatz-Richtwerte, workplace guidance values) concept was developed by the Committee on Hazardous Substances (AGS) (AGS, 2006; 2010).

(4) If no route-to-route extrapolation can be made based on a study with oral administration and if no inhalation studies or findings from inhalation of the carcinogen by humans are available, risk quantification is generally not possible (see Section 8).

4.5 Procedure for studies with a shorter exposure and/or observation period

(1) If exposure was stopped before the end of the study (longer observation period after the exposure period), a correction calculation must be carried out. Assuming an experimental period of 100 weeks, this means for example:

actual exposure: 50 ppm in the diet for 70 weeks and observation period for 30 weeks;

calculated exposure: $50 \text{ ppm} \times \frac{70}{30 + 70} = 35 \text{ ppm}$ throughout the entire experimental period.

If all animals of a dose group die prematurely, the exposure period and lifespan of the animal showing the greatest longevity is used as a basis for conversion.

*Source:* (Gold et al., 2005)

If an exposure period of about 100 weeks in an animal study is converted to a human equivalent, this equivalent exceeds the proportion of a working lifetime of about 40 years. Even if lifetime exposure is back-calculated to exposure over a working lifetime in further steps, it is a conservative approach to use the observations after this longer exposure period as a basis for the quantifications.

(2) If the experimental period is shorter than the lifespan, another correction of the experimental period to the lifespan is generally carried out using the correction factor $f_2$ with $f = \frac{\text{experimental period}}{\text{standard lifespan}}$ (e.g. experiment stopped after 100 and standard lifespan is 104 w: correction factor $= (100/104)^2 = 0.92$). The following standard lifespans are assumed: Mouse, rat, hamster: two years; dog: eleven years, monkey (macaque): 20 years

*Dybing et al. (1997)* select a corresponding approach for their T25 concept (see also Section 3.7(3)):

Shorter exposure ($w_1$) compared with the total study period ($w_2$ weeks):
correction factor \( f = \frac{w_1}{w_2} \)

Shorter experiment \((w_1)\) compared with the total lifespan \((w_2\) weeks):  
Correction factor \( f = (\frac{w_1}{w_2})^2 \)

This “standard lifespan” is not a very conservative convention. In divergence from this standard, it may be necessary to assume a prolonged lifespan especially for lung tumours on rats. In rats, exposure-related lung tumours occur especially at the age of more than 2 years. The spontaneous rate for lung tumours is low in rats; it is about 1 to 2% after 2.5 years, or somewhat higher or lower depending on the strain. The observation period should definitely be more than 2 years for quantitative risk assessment. McConnell and Swenberg (1994) state, for example: “Following the 24-mo exposure period, the animals were held for lifetime observation (until ~20% survived).” This implies that 24 months are not a lifetime observation, but that a specific criterion (here 20% survival rate) can be used for the definition of “lifetime” (longer than 24 months) for pragmatic reasons.

(3) If the exposure concentration is reduced during the study, the time-weighted mean is generally used for the exposure level.

The simple approach of a cumulative dose metric over the entire lifespan (according to Druckrey; see below) does not consider that a carcinogenic substance is specifically able to induce one or several stages of carcinogenicity. If an early stage of carcinogenicity is affected, exposures at the beginning of life are especially critical. Persisting substances can maintain a persistent systemic load even after early discontinuation of treatment.

The Guidelines for Carcinogen Risk Assessment” (2005) of the U.S. EPA point out (17): “For chronic exposure studies, the cumulative exposure or dose administered often is expressed as an average over the duration of the study, as one consistent dose metric. This approach implies that a higher dose administered over a short duration is equivalent to a commensurately lower dose administered over a longer duration. Uncertainty usually increases as the duration becomes shorter relative to the averaging duration or the intermittent doses become more intense than the averaged dose. Moreover, doses during any specific susceptible or refractory period would not be equivalent to doses at other times. For these reasons, cumulative exposure or potential dose may be replaced by more appropriate dose metric when indicated by the data.”

For the multistage and Moolgavkar models, there are for example mathematical proposals of adjustment for intermittent and short-term exposures occurring in arbitrary periods of life (Chen et al., 1988; Crump and Howe, 1984; Yamasaki, 1988). However, these seem to be too complex for routine use.

According to Druckrey’s rule, tumorigenicity is the result of a total dose effective over the entire lifetime \((d \times t = \text{const.})\). This description applies to many genotoxic substances. However, it does not consider depot effects, i.e. constant effects of poorly soluble or otherwise biopersistent substances after inhalation or injection (such as metal compounds, asbestos and wood dust). Druckrey’s rule may also underestimate the late sequelae of high, tis-

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17 [http://www.epa.gov/IRIS/cancer032505.pdf](http://www.epa.gov/IRIS/cancer032505.pdf)
sue-damaging doses acting for a short period because, for example, increased cell proliferation rates increase the sensitivity of target tissues, establish genotoxic lesions and promote the migration of stem cells into target tissue. However, Druckrey’s rule is the primary basis of linear dose extrapolation and also of usual time extrapolation.

**Literature:** Chen et al. (1988); Yamasaki (1988); Crump and Howe (1984); Dybing et al. (1997)

(4) Studies in which the exposure period is less than half of the standard lifespan are not suitable for risk quantification. The observation period should generally not be below 18 months in a study with mice and not below 2 years in a study with rats.

In a rough estimate, half of the standard lifespan approximately corresponds to the ratio between lifespan and working lifetime in humans. For example, an exposure period of 1 year (rat) is generally sufficient for a quantitative application of the specific tumour findings. However, if the observation period is short, it is likely that the risk is underestimated to a relevant degree.

4.6 Standardisation of the daily exposure period

(1) The following standard assumptions apply to occupational exposure:

Exposure period during working lifetime: 40 years; duration of workday: 8 hours; weekly working days: 5 d, annual working time: 48 weeks; body weight: 70 kg; inhaled volume: 10 m$^3$/workday (8 h). Deviating exposure patterns are generally converted linearly to these standard assumptions. If information from the general population is available, the following exposure parameters are assumed unless otherwise specified: Exposure period: 75 years; body weight: 70 kg; food intake/day: 1.4 kg, water intake/day: 2 litres, inhaled volume: 20 m$^3$/day (24 h).

For conversion on the basis of an animal study, care must be taken to avoid duplicate calculation: According to Section 4.2 (1), conversion from 6 h/d (resting conditions; animal study) to 8 h/d (light activity; workplace) is carried out via a factor of 2.

(2) If an animal study is extrapolated to humans, the experimental exposure period (per day/per week) is generally specified and is converted linearly to the above-mentioned duration (occupational exposure).

This approach is based on the biological model assumption that the cumulative dose (c x t) of an effect is the dose metric determining the risk. This procedure is selected (for the default case) although it is known that this is a conservative step of simplification in most cases. The levels of the parameters have been adopted from the EU Technical Guidance Document (see Section 4.14.2.5 and Table 12 there).
5 Extrapolation to lower risk levels

5.1 Definition of the procedure according to the mode of action

(1) If, based on the information in Section 2, a mode of action determined essentially by direct genotoxicity was established for carcinogenicity, linear extrapolation is carried out in the default case.

In the current context, a linear extrapolation will not to be scientifically verified and it represents a conservative convention. With certain substances it is possible that sub-linear courses may be present at very low exposure levels, even in the case of direct genotoxicity. In such cases, the database is generally not sufficient to describe the sublinearity in more detail or to name the substances for which there would be a scientific justification for assuming such a sublinearity with simultaneous genotoxicity. When the database is limited in this way, linear extrapolation is therefore used.

(2) If, based on the information in Section 2, it was demonstrated that the mode of action is only characterised by non-genotoxic events and if a dose-response relationship with a threshold can be identified for the parameter(s) to be determined, this threshold must be calculated.

For the distinction between “no” genotoxicity and “inferior” genotoxicity, see Section 2.4.

(3) If no mode of action is known or sufficiently reliable, linear extrapolation is carried out in the default case.

In reality, sublinear courses may be present at very low exposure levels in many cases. In such cases, the concentration as of which the risk increases disproportionately (“break point” in the approximation method selected here) can often not be specified with sufficient reliability, such that with a correspondingly limited database a linear extrapolation also takes place.

(4) In cases in which the mode of action is essentially known, but a) direct genotoxicity is of no predominant importance, b) there is no definite threshold for carcinogenicity, or c) a threshold cannot be quantified on the basis of the available data, a sublinear dose-response course into the low-risk range is generally assumed.

However, linear extrapolation is carried out if no data are available that enable the sublinearity to be estimated (i.e. when the concentration range in which the slope becomes steeper for the risk of developing cancer is not clear).

The explanations in Section 2.6 must be considered for the term “threshold”. In principle, a NOAEL for carcinogenic effects (no observed significantly increased incidence above background) is not considered quantitatively equivalent to a threshold.

(5) If assignment to (1) to (4) is unclear, it must be examined via various methods of parallel risk quantification (see Section 5.2) whether differences are obtained for the results and how relevant the establishment of a mode of action actually is. If the dose-risk courses are close together, it may not be necessary to establish the predominant mode
of action in order to nonetheless quantify the risk without any relevant errors. The uncertainty in risk quantification must be documented. If different risk quantifications still lead to comparable risk concentrations for exposures with an increased risk (e.g. in the case of additional lifetime risks down to the per mille range), although considerable deviations occur at lower risks, the range in which specific exposure-risk courses are valid must be defined.

(6) Risk extrapolation into the low risk range using the model function showing the best adjustment to the data for the experimental range is generally not the suitable procedure. For example, supralinearity may be found in the experimental range, but sublinearity in the low risk range.

This statement is inconsistent with the convention, introduced in Section 3.2 (3) and 5.2 (2), to use the benchmark method instead of the linearised multistage model as a mechanistically substantiated basis for the experimental range and the low risk range if sub-linearity has been proven. This modelling is used for extrapolation because it describes sublinearity in a simple way. However, it cannot be concluded that the “correct” slope was found in the low risk range by means of this procedure.

5.2 Extrapolation to lower risk levels for non-linear courses

(1) Based on information corresponding to Section 5.1 (4), 1st section, a non-linear exposure-response course is assumed with sufficient likelihood. In this case, a plausible setting is defined for this non-linear function.

(2) If the database is sufficiently qualified to use the benchmark approach, it is assumed that the benchmark modelling maps even the non-linearity sufficiently accurately in the risk range $\geq 1:1000$. This also applies when the general methodological validity range only covers the experimental range of the risks greater than, for example, 1% or 5%. Linear extrapolation is carried out between the $BMD_{0.1}$ (1:1000) and the origin or background level.

Reference to the BMD instead of the BMDL is therefore justified, a) because orientation to the BMD is the maximum likelihood estimate; b) because according to Section 5.1 (4), there must be additional reasons supporting a non-linear course, which means that modelling that ought to be regarded as mathematically possible using the BMDL is considered unlikely for these, for example mechanistic reasons; and c) because based on quality criteria benchmark modelling is regarded as accurate only if the differences between the BMD and the BMDL are small. If a BMD is used as the basis instead of a BMDL, a relevant underestimation of risk is not to be expected (even if “in reality” the BMDL should reflect the risk more correctly). This procedure is also similar to the method of the T25, for which a confidence interval is also not factored in.

The following examples (Cases A and B) show a distinction between a case with non-linearity (Case A) and linearity (Case B). In Case A, additional mechanistic evidence supporting non-linearity would be necessary. If this cannot be provided, the $BMD_{1.0}$ is the POD, below which there would be lin-
ear extrapolation.

**CASE A**: Good database refers to non-linear relations.

<table>
<thead>
<tr>
<th>Concentration (mg/m³)</th>
<th>Number of animals</th>
<th>Number of tumours</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
<td>Course indicates clear non-linearity;</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>1</td>
<td>good database; e.g. mechanistic evidence of</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
<td>0</td>
<td>non-linearity</td>
</tr>
<tr>
<td>200</td>
<td>50</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>50</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

Result; graphically:

![LogProbit Model with 0.95 Confidence Level](image-url)
Result in figures; explanation:

<table>
<thead>
<tr>
<th>Model</th>
<th>BMD_{10}</th>
<th>BMDL_{10}</th>
<th>BMDL_{0.1} = 1 per mille</th>
<th>BMD_{0.1} = 1 per mille</th>
<th>T25</th>
<th>T25/250 = 1 per mille</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>151</td>
<td>111</td>
<td>22</td>
<td>40</td>
<td>235</td>
<td>0.94</td>
</tr>
</tbody>
</table>

**Comment 1:** Difference 40/0.94 shows that the BMD (1 per mille) indicates a clearly lower risk than the T25 approach, which would not be suitable for this database.

**Comment 2:** The slight difference between 151 and 111 (or 40 and 22) shows that there is no relevant difference between the BMD and BMDL if there is a good database.

**Comment 3:** The log probit model was used. This model was selected due to the lowest AIC value (AIC = 100.87).

**CASE B: Moderate database allows non-linear or linear relations**

<table>
<thead>
<tr>
<th>Concentration (mg/m³)</th>
<th>Number of animals</th>
<th>Number of tumours</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
<td>Course does not rule out non-linearity, although linearity also possible; moderate database (criteria met according to Guide 3.1)</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>50</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>50</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>
Result; graphically:

![Multistage Cancer Model with 0.95 Confidence Level](image)

09:28 02/21 2013

Result in figures; explanation:

<table>
<thead>
<tr>
<th>Model</th>
<th>$\text{BMD}_{10}$</th>
<th>$\text{BMDL}_{10}$</th>
<th>$\text{BMDL}_{0.1} = 1$ per mille</th>
<th>$\text{BMD}_{0.1} = 1$ per mille</th>
<th>T25</th>
<th>Linear: $\frac{T25}{250} = 1$ per mille</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>99</td>
<td>58</td>
<td>0.56</td>
<td>1.1</td>
<td>231</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Comment 1: Difference 0.92/1.1 shows that BMD (1 per mille) indicates almost the same risk as the T25 approach since linearity is possible (see graph).

Comment 2: There is no substantial difference between the BMD and BMDL.

Comment 3: The multistage model (2 degrees of freedom) was used. This model was selected due to the lowest AIC value ($\text{AIC} = 98.86$). Note: Due to the comment in Section 3.3 (1) that the “quantal-linear” model is not to be used, this has been excluded here.
If the T25 was used as the POD for cancer, it is assumed for the case of substantiated non-linearity that a non-carcinogenic effect decisively contributes to cancer (e.g. irritation to the respiratory tract or cytotoxicity in the kidneys) at higher doses and that it can be described quantitatively as an enhancing mechanism. There are four steps to determine the assumed exposure-risk course.

- **Step 1:** A human equivalent threshold (TC*; as airborne concentration) is determined for this non-carcinogenic per se enhancing effect by considering usual extrapolation factors.

  The extrapolation of data on non-carcinogenic effects is carried out following the OEL concept (Committee on Hazardous Substances (AGS), 2006; 2010).

- **Step 2:** Based on the T25 normalised and converted to the human equivalent (hT25), the cancer risk $10^p$ is calculated for concentration $TC^*$ linearly to the origin or background level.

- **Step 3:** The concentration $TC^*$ is then pragmatically assigned a cancer risk ten times (order of magnitude: $10^{(p-1)}$) lower than following linear extrapolation.

- **Step 4:** Finally, linear extrapolation is carried out from the point “$TC^*$ and $10^{(p-1)}$” up to hT25 on the one hand and down to the origin on the other (or to the background level). The sub-linear exposure-risk course approximated in this way can be used to determine the nominal risk for every point between the origin (or background level) and the hT25, with the “break point” of the function at the extrapolated threshold ($TC^*$) representing the start of the enhancing mechanism.

With this “hockey stick” approach, gaps in knowledge are bridged. It is generally known when a non-linear course is to be assumed for the exposure-risk relationship, although further parameters that can quantitatively describe the non-linearity of the cancer are frequently not known. The unknown degree of “sagging” of the sub-linear function is replaced by a reduction factor at the extrapolated threshold for the effect enhancement.

The following Figure 2 basically shows the above-mentioned steps for a case in which there is an hT25 for cancer, including sufficient data are available to determine a threshold ($TC^*$) for an enhancing effect (for explanation see text):
5.3 Extrapolation with an assumed threshold phenomenon

(1) If a minimum dose or threshold is assumed for carcinogenicity (Section 5.1(2)), this threshold dose must be quantified on the basis of available experimental data including specific extrapolation factors. It is assumed that neither direct genotoxicity nor other modes of action without any threshold play a role in this case.

(2) To establish the threshold dose, special care must be taken to record early evidence (indicators) in particular of the specifically relevant critical change. For example, in the case of nephrotoxicity relevant to

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cancer, initial early damage to the kidneys manifest in the form of specific proteinuria would have to be reported. The dose-response relationship, LOAEL and NOAEL are to be established for this effect, which although not carcinogenic itself is regarded as decisive for carcinogenicity.

(3) If no differentiated experimental findings are available on early lesions that are regarded as decisive for the carcinogenic effect, this can be compensated for by conservative extrapolation factors. From this point of view, establishing an irritation threshold for a non-carcinogenic substance, for example, requires lower extrapolation factors than establishing an irritation threshold for a substance for which irritation is an important parameter for the mode of action in cancer.

(4) For this reason, an additional factor of (generally) 10 is considered in addition to the usual extrapolation factors. Against the background of cancer as a possible secondary effect, this method aims to ensure that the threshold is indicated or undershot with a particularly high level of reliability. According to the terminology in Section 5.2, this conservative threshold is therefore at TC*/10, with TC* referring to carcinogenic rather than to cancer-enhancing effects.

Extrapolations to calculate the TC* are based on the OEL concept (Committee on Hazardous Substances (AGS), 2010).

If the “usual” NOAEL is considered to be a value that may well be associated with an effect level of 5% (even if an effect was no longer observed in an experimental system), a definitely lower effect level will have to be associated with the resulting NAEL via this factor of 10 (e.g. effect level of 0.5%).

This procedure is consistent with the concept of the individual extrapolation factors as a specific percentile of a distribution (e.g. 90th percentile for the intraspecies factor): Selecting an additional extrapolation factor is equivalent to increasing the intraspecies factor, for example, to include a higher percentile (e.g. 95th percentile) of different sensitivities, but it is generally included (not related to an individual factor such as intraspecies factor, interspecies variability factor or time factor, but to the total distribution, i.e. multiplied individual factors).

In individual cases it may be that the factor 10 is not required or that its full scope is not required, because the exposure level under consideration for TC* already offers a high level of protection against adverse effects in connection with the level of effect to be assumed in this case. In this case a smaller factor can (with explicit justification) be used to calculate the conservative threshold, or an additional factor of this kind can even be completely dispensed with.

(5) For the purpose of extrapolating the threshold value to be assumed, the risk course is taken into consideration up to the risk at 1% (benchmark response 1%) alongside the modelled function (as BMD), in conjunction with the benchmark approach for cancer risks. This implies that the quality standards for using the benchmark approach are observed (see Section 3.3) and mechanistic findings must be consistent with the modelled course of the exposure-risk relationship. Pragmatically, a “zero” risk is assumed at a BMD*01/10 (corresponding
to a benchmark response from a per mille).

Recommendations for quantification of the exposure-risk relationship in the range above the assumed threshold are made in this Guide only if benchmark modelling was applied. If no benchmark modelling is carried out, the threshold is calculated according to Section 5.3 (4), although no general statement is made about the course of the exposure-risk relationship above this threshold (an individual consideration may be required).

The following graph of the extrapolation procedure is obtained for a case in which benchmark modelling is able to reproduce cancer in a qualified way. The calculated threshold ($\text{BMD}_{01}/10$) must then be converted to a human equivalent (workplace scenario) before being used for regulatory purposes.

![Diagram of the procedure for determining a threshold for carcinogens when a qualified benchmark modelling is available for $\text{BMD}_{01}$.](image-url)

Figure 3: Diagram of the procedure for determining a threshold for carcinogens when a qualified benchmark modelling is available for $\text{BMD}_{01}$. 
6 Regulatory-toxicological relevance

The determination of evaluation points (level of the tolerable risk or acceptable risk) and the measures of when they are maintained or exceeded fall within the scope of risk management decisions (see Committee on Hazardous Substances (AGS) risk concept\textsuperscript{19}). These decisions are to be made in a higher-level context (outside this Guide) but they must take into account scientific findings. The regulatory-toxicological references of individual elements (largely consisting of the present Guide and the OEL concept presented in BekGS 901) of the overall concept to each other and individual relevant points (e.g. endogenous exposures, exposure peaks) are documented here in Section 6.

6.1 Tolerable and acceptable concentrations

(1) Based on the exposure-risk relationship, the evaluation points for tolerable risk (nominal risk of 4:1000) and acceptable risk (4:10000 up to 2013 and 4:100000 from 2013 to 2018 at the latest) are generally assigned to corresponding tolerable and acceptable concentrations. In special cases, tolerable and/or acceptable concentrations can be assigned to other risk levels:

- Special case 1: A health-based limit value for a non-carcinogenic effect of a carcinogenic substance (OEL-analogous value, see 6.2 (1)) derived using the BekGS 901 method is lower than the tolerable concentration derived according to the present Guide for the carcinogenic effect. In this case, the concentration for the non-carcinogenic effect is identified as a tolerable concentration (see Section 6.2).

- Special case 2: In the case of a carcinogenic substance that is also formed endogenously, a deviating acceptable concentration can be calculated that is associated with a risk other than the acceptable risk named above (see Section 6.3).

- Special case 3: If the minimum criteria for cancer risk quantification are not fulfilled, point estimates of an overly speculative character may be obtained (see Section 8.7).

6.2 Derivation of a reference value following the BekGS 901 method.

(1) In addition to a risk quantification for carcinogenic effect according to the ERR concept, a value for the protection against non-carcinogenic effects is also regularly calculated for carcinogens, for the purpose of making comparisons. This reference value is described as an “OEL-analogous value”\textsuperscript{20} in the ERR justification document. This makes it clear that the value was determined for the most critical, non-carcinogenic toxicological end point according to the methodology of

\textsuperscript{19} \url{http://www.baua.de/de/Publikationen/Broschueren/A82.html}

\textsuperscript{20} The term “OEL-analogous value” should only be used for justification documents (ERR); it should not be used as an isolated term in lists with a regulatory function (in particular not in the German Technical Rule for Hazardous Substances (Technische Regel für Gefahrstoffe, TRGS) 900), and not in risk management.
the relevant OEL concept (Committee on Hazardous Substances (AGS), 2010), for the purpose of comparison noted above. In the case of particles with a local effect on the respiratory tract, the “human-equivalent concentrations” (HEC) method is added to the OEL concept.

The HEC concept was presented in Section 4.3 in relation to the derivation of carcinogenic effects. It can also be used for non-carcinogenic effects in the lower respiratory tract (tracheobronchial region (TB) and pulmonary region (PU)). The same default assumptions apply as for carcinogenic effects. However, it is to be expected that deviations from the default will rather be justified. For example, it is easier to assign effects to solely the PU region or solely the TB region (more well substantiated deviation in the normalisation) or it is possible to more clearly differentiate between whether the deposited or retained concentration is relevant for the effect (for example, it is justified to use the deposited dose instead of the retained dose as a basis where there are effects due to soluble substances that already take effect when there is acute exposure).

(2) The OEL-analogous value becomes the (health-based) tolerable concentration if it is below the value that was calculated following the ERR concept for the risk 4:1000. In this case, the value corresponding to the risk of 4:1000 is not identified as the result of the ERR derivation.

A health-based OEL (Committee on Hazardous Substances (AGS), 2010) should not be exceeded, even when it relates to a carcinogenic substance for which higher concentrations would be tolerated based on the risk of 4:1000. The range of the “medium risk” (see measure concept) defined in Annex 1 becomes smaller. This value is then substantiated, using a health-based approach, via non-carcinogenic effects. The concentration corresponding to the cancer risk of 4:1000 must, however, still be reported in the ERR justification document. This would also be the case if the OEL-analogous value equated to a risk of 3:100000 for example. In this case, an acceptable level would already be reached based on the background of carcinogenic potency, but not against the background of the non-carcinogenic effects. An extension of the high-risk range, and potentially the low-risk range, occurs; this means that a cancer risk in the already acceptable level was calculated below the health-based tolerable concentration.

The rather differing consequences according to the relevant regulatory area when a value calculated according to the OEL concept or ERR method is exceeded is accepted and the term “tolerable concentration” is always used to describe the transition into the range of higher risks.

(3) If the OEL-analogous value is above the tolerable level of 4:1000, it is documented as part of the comparison, but it does not assume any regulatory meaning and it is not identified in the result for the ERR derivation. However, it must be taken into account that non-carcinogenic effect concentrations can also have an effect on the level of the excursion factor (Section 6.4) for short-term exceedances of the tolerable concentration.
6.3 Endogenously-formed carcinogens

(1) The maximum concentration at the workplace for substances or their metabolites that also occur endogenously is based on the already existing endogenous exposure. In this context, the mean additional exposure at the workplace should not result in exceedance of the standard deviation (SD) from the time-concentration-integral (c x t product, the “area under the curve”, AUC) for the mean endogenous exposure in the adult general population. The resulting value is considered as an acceptable concentration, provided the concentration extrapolated based on the carcinogenic potency, following the formal scheme, would lead to identification of a lower concentration.

Exposures to carcinogens formed endogenously at the level of the acceptable or tolerable concentrations calculated according to the present Guide can lead to risks, such as are already posed by the endogenous exposures of the substance. The risk from the endogenous exposure can even be higher than the underlying acceptable risk, for example. The endogenous exposure must therefore be taken into account in the comparative assessment. In the past, endogenous exposures have already served as a benchmark for a corresponding assessment of potential workplace exposure for numerous carcinogenic substances (isoprene, ethanol and acetaldehyde).

It has not been conclusively determined in this Guide whether the resulting value can be valid as an OEL in accordance with the endogenous exposure at the acceptable level.

6.4 Risk concentration as shift mean value and exposure peaks or shortened exposure duration

(1) The concentrations derived from the exposure-risk relationship (ERR) represent shift mean values (unit: mg/m³, or ppm). These can be exceeded for short phases within the shift (short-term value phase), provided that the shift mean value is maintained. As with substances with non-carcinogenic effects, the shift mean is allowed to be exceeded four times a day for up to 15 minutes on each occasion, using an excursion factor. The highest excursion factor is 8, as otherwise it is no longer possible to adhere to the product of multiplying the shift length by the limit value.

(2) In principle, the dose-time product (AUC) is a decisive factor for genotoxic carcinogens, as the probability of DNA damage depends on the sum of the reactive metabolites effective across the time period. As a peak in concentration must offset periods with a correspondingly reduced concentration (in order to maintain the shift mean value), it is in principle guaranteed that the daily total exposure is independent on the concentration peak. However, this is only the case when the con-

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21 TKC: Tolerable concentration (based on cancer risk calculation); TNKC Tolerable concentration (based on non-carcinogenic effect / OEL-analogous value); AKC: acceptable concentration; EF_{carc}: excursion factor; KZC_{carc} resulting short-term concentration for carcinogenic effects (like STEL_{carc}); EF_{noncarc}: excursion factor for non-carcinogenic effects; KZC_{noncarc} resulting short-term concentration for non-carcinogenic effects (like STEL_{noncarc})
centration peak is so high that the detoxified metabolism pathways still conform themselves to a linear kinetics. It must therefore be ensured that a linear kinetics is present for the concentration that corresponds to the excursion factor. This can be estimated for example based on the dose-incidence relationship and by referring to relevant toxicokinetic studies. In most instances, due to the relatively low concentrations corresponding to the tolerable risk, this will be the case; a value of 8 therefore frequently results as $EF_{\text{carc}}$.

(3) The short-term peak concentration in the case of exposure to carcinogenic substances can only be derived on the basis of genotoxic effects after short-term exposure in exceptional cases. This would constitute a possible reason for deviating from the default formulated under (2) and can lead to substantiated deviations in $EF_{\text{carc}}$. An additional reason for the deviation from the default factor 8 is the presence of an amplification effect. In this case too, it would be necessary to clarify whether the concentration on its own or the concentration-time product (the AUC) is of primary importance for this effect. If the AUC is decisive, the concentration peak is irrelevant, unless the kinetics in this range is no longer linear (see (2)). If it is not possible to conclusively clarify whether the AUC is decisive, a concentration dependency should be taken as the default assumption and the EF is calculated in the same way as for non-carcinogenic effects (see (4)).

As the acceptable concentration normally equates to less than 1/10 of the TKC even for carcinogens with amplification effects, but the EF can be no higher than 8, it is not necessary to identify an EF for the acceptable concentration (2018).

(4) Excursion factors for non-carcinogenic effects are quantified within the scope of this Guide according to the method, as provided for by the DFG for determining short-term values. As part of this process, differentiation is made between substances with locally active (irritant) and systemic effects.

(5) A differentiation is made between the following cases and the following rules for determining the $EF_{\text{carc}}$ is determined:
Table 2: Queries for selecting an excursion factor for short-term exposure (deviation from daily mean) in the case of carcinogenic effects in connection with possible non-carcinogenic effects.

<table>
<thead>
<tr>
<th>If</th>
<th>and if</th>
<th>then</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. TNKC ≥ TKC ?</td>
<td>KZC_{noncarc} ≥ KZC_{carc}</td>
<td>→ EF_{carc} decisive</td>
</tr>
<tr>
<td>b. (b1) TNKC ≥ TKC ?</td>
<td>KZC_{noncarc} &lt; KZC_{carc}</td>
<td>KZC_{noncarc} due to irritation: EF = KZC_{noncarc}/TKC</td>
</tr>
<tr>
<td>c. (c1) TNKC &gt; TKC ?</td>
<td>KZC_{noncarc} &lt; KZC_{carc}</td>
<td>KZC_{noncarc} due to systemic effect and KZC_{carc}/KZC_{noncarc} ≤ 2 : EF_{carc} decisive</td>
</tr>
<tr>
<td>c. (c2) TNKC &gt; TKC ?</td>
<td>KZC_{noncarc} &lt; KZC_{carc}</td>
<td>KZC_{noncarc} due to systemic effect and KZC_{carc}/KZC_{noncarc} &gt; 2 : EF_{carc} decisive</td>
</tr>
<tr>
<td>d. TNKC = TKC ?</td>
<td>KZC_{noncarc} &lt; KZC_{carc}</td>
<td>→ EF_{noncarc} decisive</td>
</tr>
<tr>
<td>e. TNKC &lt; TKC ?</td>
<td></td>
<td>→ No EF_{carc} to be identified; EF_{noncarc} decisive</td>
</tr>
<tr>
<td>f. No TNKC determined?</td>
<td></td>
<td>→ EF_{carc} decisive</td>
</tr>
</tbody>
</table>

Example for a:
TNKC: 2 ppm  EF_{noncarc} 4  KZC_{noncarc} : 8 ppm
TKC: 1 ppm  EF_{carc} 8  KZC_{carc} : 8 ppm  → decisive EF = 8

Example for b1:
TNKC: 2 ppm  EF_{noncarc} 1  KZC_{noncarc} 2 ppm
TKC: 1 ppm  EF_{carc} 8  KZC_{carc} 8 ppm  → decisive EF = 2

Example for c1:
TNKC: 2 ppm  EF_{noncarc} 2  KZC_{noncarc} 4 ppm
TKC: 1 ppm  EF_{carc} 8  KZC_{carc} 8 ppm  → decisive EF = 8
In the example c1, the TKC of 1 ppm is to be maintained at the workplace. The decisive EF equates to 8, because the concentration in the blood resulting from the $KZC_{c_{arc}}$ is to be maintained for the non-carcinogenic effect. In the case of a half-life of 1 hour (shortest possible half-life time for EF 2), the concentration peak is 20% higher than the steady-state concentration in the blood, and for an EF of 8, it is 140% higher than the steady-state concentration (DFG 2011\textsuperscript{22}). The steady-state concentration in the case of exposure to TKC is, however, only half as high as for exposure to TNKC. $C_{\text{max}}$ for $KZC_{c_{arc}} = (0.5 \times \text{steady-state TNKC}) \times 2.4 = 1.2 \times \text{steady-state TNKC}$, i.e. $C_{\text{max}}$ is equally high in both scenarios. In the case of longer half-lives, the influence of the peak concentration is even smaller.

**Example for c2:**

| TNKC: 1.5 ppm | $EF_{\text{noncarc}}$ 2 | $KZC_{\text{noncarc}}$ 3 ppm |
| TKC: 1 ppm | $EF_{\text{carc}}$ 8 | $KZC_{\text{carc}}$ 8 ppm |

decisive EF = 3

In example c2, $EF_{\text{carc}}$ is not sufficient as the ratio of $KZC_{\text{carc}}$ to $KZC_{\text{noncarc}}$ is too great. With the figures from (DFG 2011: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mbpeakexpd0051/pdf), an EF of 4 would lead to the same $C_{\text{max}}$. For the purpose of simplicity, the ratio of $KZC_{\text{noncarc}} / TKC$ is used as a relevant EF.

**Example for d:**

| TNKC: 1 ppm | $EF_{\text{noncarc}}$ 2 | $KZC_{\text{noncarc}}$ 2 ppm |
| TKC: 1 ppm | $EF_{\text{carc}}$ 8 | $KZC_{\text{carc}}$ 8 ppm |

decisive EF = 2

If an EF of 8 is appropriate, longer excursion time periods than up to 15 minutes can instead be tolerated, with a correspondingly reduced EF (e.g. for 30 minutes: EF 4 instead of 8), provided that the figure obtained by multiplying the EF and the excursion period is adhered to.

6.5 Simultaneous exposure to multiple carcinogens

This Guide does not currently supply a method for risk quantification for the combined effect of multiple carcinogenic substances at the workplace.

7 Intraspecies extrapolation

(1) No intraspecies extrapolation is carried out. The main focus is therefore the average individual risk as additional lifetime (occupational) risk. Risk management applies a low average risk as a benchmark, which means that the risk for sensitive groups of people is lower and this group is thus indirectly taken into account. Whereas in the case of non-carcinogens, sensitive persons are (more or less) explicitly protected from health effects via an intraspecies factor (as a default factor for variabilities), this Guide suggests ensuring this protection in the

\textsuperscript{22} http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mbpeakexpd0051/pdf
case of carcinogens by selecting an appropriately lower average individual risk (considered to be acceptable or tolerable). If an appropriate intraspecies factor for a carcinogenic effect could be determined, direct conversion (to the risk for sensitive groups of persons) would be possible.

It is a frequently applied convention to disregard the intraspecies factor for carcinogens (ECHA, 2012b). There are only insufficient data that can adequately reproduce the wide range of sensitivities in this multifactorial process of carcinogenicity.

It is currently unforeseeable when adequate data about carcinogenic effects will be available to establish a scientifically based default value for intraspecies variability. The level of a specific factor would therefore be extremely unreliable due to this insufficient database. A provisional evaluation of data from animal studies did not reveal a clearly higher variability of outbred strains compared with inbred strains with reference to cancer. It is not possible to simply link enzyme activities and their variability to the variability in cancer.

A few assessment methods, (see EFSA (2005) and Section 1.4 (3)) specify an intraspecies factor of 10 for carcinogens, but this has no effect on the level of protection, i.e. level of the proposed limit value. EFSA (2005) proceeds from the assumption that the intraspecies variability for carcinogenic effects is identical with that for other effects.

The U.S. EPA (2005b) also considers an intraspecies factor for cancer, but expressly only for infants, who have a special sensitivity that is generally, however, not reproduced in animal carcinogenicity studies. As a specific object of protection, “child health” is not decisive for the workplace in this context.

However, sensitive groups of persons are explicitly taken into account for the quantification of non-carcinogenic effects that are considered as factors causing or enhancing carcinogenicity (see Section 5.2 (2) and 5.3 (4)).

8 Minimum criteria for risk quantification

8.1 Classification of the substance to be assessed

(1) Quantitative estimates of the exposure-risk relationships should generally be carried out for carcinogens that are classified in carcinogenicity Categories 1A or 1B in accordance with CLP Regulation (EC) no. 1272/2008.

The question of whether carcinogenic substances without formal classification (EU) should also be evaluated according to ERR criteria is to be decided individually in each case. This consideration is relevant, for example, for substances classified by IARC or by U.S. EPA or national committees, or for substances recommended for classification. This Guide does not cover the revision of the classifications. For a substance that has no legal classification, however, an ERR can only be of decisive importance for regulatory handling if the substance is simultaneously classified as a clear carcinogen in TRGS 905. Otherwise, the ERR approach is used for the purpose of
making comparisons, in order to range the cancer risk in terms of non-carcinogenic effects.

(2) Substances classified in carcinogen Category 2 can also be assessed if they are considered in each individual case (Regulation (EC) no. 1272/2008). This is particularly the case if this classification was not based on the (limited) quality of the study or the (insufficient) reporting or on questionable human relevance, but mechanistic uncertainties were decisive (e.g. possible threshold mechanism and questionable genotoxicity in the case of otherwise definite findings of cancer).

For a substance suspected of being carcinogenic (Category 2 according to CLP Regulation), however, an ERR can only be of decisive importance for regulatory handling if the substance is simultaneously classified as a clear carcinogen in TRGS 905. Otherwise, the ERR approach is used for the purpose of making comparisons, in order to range the possible cancer risk in terms of non-carcinogenic effects.

The question of whether substances suspected of being carcinogenic but without formal classification (EU) should also be evaluated according to ERR criteria, for the purpose of comparison, is to be decided individually in each case. This Guide does not cover the revision of the classifications.

(3) Carcinogens that were classified in Categories 4 or 5 according to the national assessment proposal of the MAK Commission (DFG, 2012) can generally be assessed quantitatively.

Even in this case, however, an ERR can only be of decisive importance for regulatory handling if the substance is simultaneously classified as a clear carcinogen in TRGS 905.

8.2 Information on carcinogenicity after inhalation

Tumorigenicity data for the route of inhalation are required for deriving an exposure-risk relationship at the workplace; this includes data assessable via route-to-route extrapolations (see Section 4.4). For example, if cancer incidences are only available after oral, dermal or parenteral administration without the possibility of qualified route-to-route extrapolation, no relevant quantification can be made.

8.3 Tumour sites without or with limited quantitative extrapolation

If specific tumour sites occur in specific animal species (possibly also sex-linked or combined with other substance properties), these findings are regarded as not transferable or not transferable quantitatively. The specific restrictions must be considered when examining the minimum criteria (see Section 3.1(6)).
The following types of tumours in rodents are examples of those (frequently or occasionally) having no or restricted quantitative extrapolation to humans:

- **Kidney tumours following α-2u-globulin-induced nephropathy in male rats**

  Kidney tumours following α-2u-globulin-induced nephropathy in male rats are a species- and sex-specific phenomenon and can be induced by a large number of non-genotoxic substances that bind to this protein.

  *This effect has no relevance to humans (Capen et al., 1999).*

- **Liver tumours after PPARα stimulation (“peroxisome proliferation”)**

  These tumours are rodent-specific to a high degree. In some types of animals, particularly rats and mice, simulation of the peroxisome proliferator activating receptor α (PPARα) – largely located in the liver peroxisomes – induces a complex enzyme pattern, which acts as a second pathway for the fatty acid catabolism. The consequences include oxidative stress, a strong increase in peroxisomes, organ hyperplasia, increases in and – in some cases – persisting cell proliferation. The development of liver tumours is also a possibility. The human liver only generates a small amount of this receptor. Many types of animal, including receptor-deficient transgenic mice do not display the phenomenon of peroxisome proliferation. In most cases, there is no relevance to humans (IARC, 2000).

- **Leukaemias of the Fischer rat**

  Mononuclear (large granular lymphocyte; LGL) leukaemias occur very frequently in Fischer rats. Developments start in the spleen and exhibit strongly fluctuating levels of incidence (approx. 15–25%, or up to 50% in smaller cohorts of 50 animals). The historical control data should be taken into account when assessing such tumours. The occurrence of this type of tumour on its own is not generally sufficient to assess the test substance as carcinogenic. In the case of a genotoxic substance, however, human relevance cannot generally be ruled out. In these cases, it should be checked whether mononuclear leukaemias were the only increased tumour type with which a quantitative risk assessment can be carried out.

- **Phaeochromocytomas of the Fischer rat**

  Phaeochromocytomas are benign or malignant tumours that mostly developed from the chromaffin cells of the renal medulla but can also occur ectopically (paragangliomas, developmentally separate epithelium germs?). In humans, in whom these tumours seldom occur, catecholamines can easily be released, resulting in blood pressure crises and other metabolic and cardiovascular events. These tumours occur relatively frequently in rats, both
spontaneously and in association with exposure. In the case of a quantitative risk assessment, mean historical rates and ranges of variation have to be taken into account, and the (very frequently age-related) hyperplasias have to be differentiated in the diagnosis. This tumour is apparently more likely to be formed in male rats than in female rats. According to an analysis by Greim et al. (2009), metabolic alterations such as hypoxia, oxygen utilisation disorders, and disorders of the Ca homeostasis or the hypothalamic endocrine regulation have a triggering or amplifying effect. In animal experiments, these conditions may be caused by the test substance; however, in most cases they result from high-dose phenomena with a limited relevance for workplace exposure. This is true particularly if there is a non-genotoxic mechanism of action and only the male sex is affected.

- **Thyroid tumours in rats**

  Substances that induce the glucuronidation path (phase II enzyme) in the liver may also lead to a more rapid elimination of thyroid hormones from the blood and, as a result, to a stimulation of the thyroid tissue via the central feedback system (Goldstein and Taurog, 1968; Hill et al., 1989; McClain, 1989). Liver hypertrophy or other signs of a general enzyme induction are not always observed. This is demonstrated by the example of tert-butyl alcohol (NTP, 1995), which led to thyroid hyperplasia in mice of both sexes and to an increased incidence of adenomas in females. Partial glucuronidation of this substance was detected in rabbits (Kamil et al., 1953).

  In humans, the glucuronidation path is generally affected less than in rats. Moreover, triiodothyronine ($T_3$) and thyroxine (tetraiodothyronine; $T_4$) are bound in the plasma with a high affinity to a transport protein and have a considerably longer half-life than in the rat (Döhler et al., 1979; Larsen, 1982; Oppenheimer, 1979). Thus, an increased concentration of glucuronidating enzymes is of less consequence for the $T_3/T_4$ metabolism of humans. Moreover, serum TSH is considerably higher in male rats than in female rats and many times higher in humans, who do not reveal a gender difference in the TSH levels (Chen, 1984). The male rat is typically disposed to benign and malignant thyroid tumours, whereas in humans thyroid carcinomas are not observed even after high TSH stimulation (Refetoff et al., 1993). Based on all this data it is concluded that thyroid carcinomas that are induced non-genotoxically in rats via this mechanism are of limited importance for humans (Capen et al., 1999).

- **Leydig cell tumours**

  Leydig cell tumours occur with a considerably higher frequency in rodents than in humans. The adenome from the cells of the interstitium is the most frequent of all tumours occurring among rats; spontaneous incidence in Fischer rats can be as much as 100%; the corresponding figure is approx. 1 to 2% for Long Evans rats (McConnell et al., 1992). The relevance of these tumours to humans is low, particularly if a substance is not genotoxic (Cook et al., 1999).
• **Liver tumours in the B6C3F₁ mouse**

These tumours have a high background rate. According to Maronpot (1999), liver adenomas occur in about 30% of the ♂ animals and in 15% of the ♀ animals; hepatocellular carcinomas occur in 20% of the ♂ and 10% of the ♀ animals. There are doubts about whether the criteria are fulfilled for assessing the substance as carcinogenic for humans particularly if the substance is not genotoxic and this type of tumour is the only one that occurs with an increased incidence (Gamer et al., 2002). Also the absolute level of the dose and the administration mode (by means of gavage?) are to be included in the consideration of the relevance to humans of liver tumours in the B6C3F₁ mouse.

• **Foregut tumours**

Particularly in the case of non-genotoxic substances, relevance of these tumours to humans may be considerably restricted because of different anatomical conditions. For genotoxic substances, their suitability as a basis for a quantitative risk calculation must be decided on a case-by-case basis and depends on whether other tissues are also affected. The local potential for irritation and the administration mode (feeding vs. gavage) should be taken into account in the assessment. In the case of inhalation studies, it should also be checked whether it is possible for the animals to ingest the substance orally when cleaning their fur (animals kept in isolation or group exposure in chambers?), after condensation of the substance on their fur.

• **Mesotheliomas of the tunica albuginea and/or tunica vaginalis (male rats)**

These are tumours, which in rare cases can also occur in humans. Throughout its life, a rat has an open connection between its scrotum and abdominal cavity, so that the testes covered by the tunica albuginea and peritoneal mesothelium can migrate through the peritoneal mesothelium-clad inguinal canal into the abdominal cavity and back out again. With some rat strains, particularly Fischer rats (McConnell et al., 1992; Mitsumori and Elwell, 1988), mesotheliomas occur relatively frequently. However, if a substance is genotoxic, human relevance cannot be completely ruled out simply because humans have different anatomical conditions.

**Examples:**

Ethylene oxide (EO) is a mutagen and distributes itself fairly evenly around the body. EO has led to mesotheliomas of the tunica albuginea in male rats. However, as other tumours also increased, these were included in the risk quantification. Acrylamide (drinking water study) represents a further example for these mesotheliomas of the tunica albuginea (IARC, 1994).
• **Harderian gland (canthus) and Zymbal’s gland (ear sebaceous glands)**

These glands do not appear in humans; however, an exposure-based tumour increase in these glands of test animals should be used for quantitative risk assessment, unless other tumours are more suitable.

**Example:**

Dichlorobenzidine has led to Zymbal’s gland carcinomas in two investigations (Pliss, 1959; Stula et al., 1975). Other tumour types were also observed, including bladder tumours and adenocarcinomas of the mamma in male animals. However, Zymbal’s gland tumours were the most frequently occurring, meaning that they could be considered in a quantitative risk assessment.

### 8.4 Lack of studies

If no long-term animal studies or qualified human studies are available for a substance, the nominal cancer risk can generally not be quantified. Quantification may be justified in individual cases on the basis of considerations by analogy and restricted substance-specific studies. Evidence of a comparable genotoxicity also belongs to the studies regularly required for this estimation An appropriate scientific justification must be submitted for this purpose.

### 8.5 Quality of the animal study and the reporting

(1) Publication with detailed reporting is generally assumed. The following information should be included: Species, strain and sex of the exposed animals and control, number of exposed animals/exposure group/sex incl. control, doses or airborne concentration and analytical detection method for the specified exposure, weight of the animals at the beginning and end of exposure/comparison between exposure groups and control, exposure period and observation period, tumour incidences/group incl. control and historical control data, if applicable, detection method and scope of examinations to identify tumour incidences, mortality during and at the end of the study, concomitant non-malignant effects (control; dose groups) incl. effects related and not related to exposure, change in organ weights (relative and absolute), abnormalities in feed composition and feed consumption, identity of the substance incl. data on purity or data on impurities and additives.

Body weight gain should not be reduced by 10% or more and the life expectancy of the animals should not be markedly reduced for reasons other than tumorigenicity, i.e. the maximum tolerated dose (MTD) should not be exceeded.

If these quality criteria are not met in a study or in reporting, the lifetime risk can generally not be assessed quantitatively based on the specific individual study.

Other substance toxicity must also be expected to occur in test groups with considerably increased tumour incidence. In general, these specific groups can nevertheless be included in the analysis of the exposure-risk relationship.
The minimum criteria described here are criteria which should be fulfilled for an animal experiment at least as regards risk quantification. They do not, however, equate to obligatory criteria that must be fulfilled for the purposes of deciding on the classification.

(2) If the minimum criteria in accordance with 8.5 (1) are not fulfilled for an animal study, it must instead be verified whether a weight-of-evidence approach is possible by looking at multiple studies together (see Section 8.7).

8.6 Minimum criteria for considering epidemiological studies in risk derivation

The minimum criteria described in this context are criteria which should be fulfilled at least as regards risk quantification. They do not, however, equate to obligatory criteria that must be fulfilled for the purposes of deciding on the classification.

(1) The following are key requirements for epidemiological studies (minimum criteria):

- Study hypothesis/specific question formulated before the beginning of the study
- Number of persons studied appropriate for the question/the risk to be detected (statistical power)
- Sufficient diagnostic quality and documentation or – where there is access to the cancer register – sufficient quality of the register and, to the extent possible, characterisation of tumour site and type (ICD)
- Confounders considered
- Avoidance of selection effects (bias) and critical discussion of their possible impacts on study results
- Information allowing a critical assessment of the study results, for example of consistency of dose-response relationships or of robustness of the results (sensitivity analyses, e.g. after exclusion of specific subgroups, stratified according to duration of employment or according to exposure intensity, etc.).

Correlation studies should not be included in an assessment a priori because of their collective assignment of exposure. Nor are case studies without any reference group appropriate for risk derivation. Cross-sectional studies are only suitable for the assessment of acute effects since they are not time-related (monitoring studies with an individual classification of exposure). They are not suitable for assessing a cancer risk unless they are related to a relevant end point.

The German Society of Epidemiology has developed Guidelines and Recommendations for Ensuring Good Epidemiological Practice (GEP) to ensure that a quality standard for epidemiological research is established in Germany, to help avoid dishonesty and scientific bias and to guarantee communication among scientists based on trust (http://www.dgepi.de/infoboard/stellungnahmen.htm). The central requirements for epidemiological studies have been taken from these Guidelines.
The exposure estimate should include information for the following aspects:

- The method and data sources for the exposure assessment
- The assessment rules formulated in advance for the determination of exposure
- Information on the cumulative exposures, or information to enable their calculation, i.e. regarding the duration and intensity of the exposure.
- Information regarding the consideration of co-exposures: Unlike in a study, there are often mixed exposures which make it difficult to assign the risk of developing cancer to a specific agent. Possible co-exposures must therefore be considered.
- Consideration of further extrapolation paths, e.g. dermal absorption of substance in the case of substances that will be absorbed through the skin.

If these aspects are not sufficiently taken into account in a study, it does not meet the necessary minimum criteria for using human data for risk quantification.

Literature: Cordier and Stewart (2005); Ahrens and Stewart (2003); Krohmout (1994); Lavelle et al. (2012)

Human data that comply with the above requirements are only available for a relatively small number of substances. It should therefore be checked in each individual case whether epidemiological studies of poorer quality exist for which, taken in isolation, there is no justification for use in the derivation of dose-response relationships, but that can be used to estimate risks for a certain exposure in a similar order of magnitude where there is consistency with other data – from equally weak human studies or animal studies (weight-of-evidence approach, see Section 8.7).

Particularly in cancer epidemiology, occupational exposures are often determined and assessed retrospectively (exposure assessment) with the risk of an incorrect classification of the exposure. Various methods of exposure assessment have been developed to allow as valid an assessment of occupational exposure as possible. Irrespective of possible combinations and further sources of information, exposure determinations and assessments derived from occupational epidemiological studies are based on measured data, expert assessments, exposure classifications by means of job-exposure matrices (JEMs) or information provided by study participants. All methods of exposure assessment have specific strengths and weaknesses. Regardless of this, all methods can basically be considered in the derivation of exposure-risk relationships if they allow an assessment of cumulative exposure with sufficient certainty.

For further details on the specific strengths and weaknesses of the study designs see Ahrens et al. (2008).
8.7 “Weight of evidence” approach and its limitations

(1) In some cases, where the minimum quality is not met for an individual study, this can be replaced by a weight-of-evidence approach taking into account multiple human studies, multiple animal studies or a combination of both (even if each of these individual studies does not meet the minimum criteria). In vitro data and considerations by analogy, as well as mechanistic studies could be included here, provided they enable quantitative conclusions. This type of “weight of evidence” approach is to be aimed for and to be preferred to an omission of an ERR derivation, provided that sufficient substantiation has been provided for the consideration of each individual case. A key criteria here is whether a POD (point of departure) can be quantified with sufficient reliability.

The following must be established where risk quantification is being carried out based on the weight of evidence:

- What aspects of the minimum criteria for the key studies taken into account are not fulfilled?
- What uncertainties exist as regards usage of the aggregated data?
- What quantitative range, insofar as it can be sufficiently defined, can be determined from the possible risk quantification (range of possible POD)?
- What supporting, positive substantiation made the weight-of-evidence approach possible in quantitative terms?
- What where the principles for compiling the data for identifying a POD (e.g. “geometric mean”, “weighted mean via expert assessment”, etc.)? In general, the aggregation of the data for an estimate should correspond to the “maximum likelihood” and not the “reasonable worst-case” or “worst-case”.

If a POD can be established, an extrapolation, for example, to the acceptable risk is generally possible. The possibility of the minimum criteria or a weight-of-evidence approach being sufficient for identifying a tolerable risk, but not for identifying an acceptable risk is excluded: the (linear or non-linear) extrapolation into the risk range < 4:1000 (i.e.: 4:10000 to 4:100000) is associated with high levels of uncertainty in the case of all substances and has been consented as the convention (which goes beyond purely scientific possibilities) independently of the substance specific database. Furthermore, the frequently more conservative process of linear extrapolation was determined for carcinogens for which no information on the mode of action exists or for which this type of information is not quantifiable; i.e. for substances with a particularly poor database. It can generally be assumed that no (qualified) data from observations exists in the extrapolation range between tolerable concentration and acceptable concentration and that there is therefore regularly uncertainty in the extrapolation. However, with the nature of the convention described above, the question of the minimum criteria only relates to the theme of a quantitative point of departure (POD).
and whether this can be determined in a way that is not overly speculative.

In the case of a weight-of-evidence approach, it must be taken into account that for many substances the amount of experimental studies, epidemiological data, in vitro data and mechanistic findings available is very low. As a consequence of this it may be that no doubts emerge regarding the data quality, and this may mean that (reinforced by an ostensible homogeneity in the small amount of data available) the minimum quality is viewed as having been attained even though additional analyses would have brought up discrepancies and added weight to uncertainties. This bias should be taken into account. In this respect, substantiated, limited contradictions or weak points in a study should not lead to an ERR derivation being halted if it does take place for non-substantiated contradictions (as is generally the case). However, resulting uncertainties should be documented.

If data analysis and weighing up of data reveal that the minimum criteria are not met and a weight-of-evidence approach does not permit an ERR quantification, it is a requirement in accordance with Regulation (EC) no. 1272/2008 that for substances in categories 1A and 1B, no threshold can be calculated in particular for the carcinogenicity (or an OEL). This is because data quality that exceeds the minimum criteria is required in order to calculate a threshold. Where necessary, a “break function” can be established within the framework of a “weight of evidence” approach.

(2) A deeper distinction between “weight-of-evidence assessment possible” and “no quantitative assessment possible” must be decided on and substantiated in each individual case. The following should be checked and assessed as criteria for overall sufficiency in the quality of a POD:

- Heterogeneity of the findings in the individual studies (spread of results, size of the “data cloud”)
- Risk level within the observed range (at POD) in comparison to risk 4:1000
- Consistency of animal and human findings

(3) In relation to carcinogenic substances, ERR derivation is not possible in cases where the minimum criteria are neither fulfilled for the epidemiology nor the animal studies and a weight-of-evidence approach can furthermore not be carried out (no POD – no ERR).

It is possible that the minimum criteria could also not be met for substances in Carc. Cat. 1A (CLP Regulation), as they relate to risk quantification and not to classification.

The inadequate database that makes it impossible to derive an ERR should be documented.

It should be checked whether the derivation of an OEL-analogous value (or an OEL for substances suspected of carcinogenicity) is possible based on the non-carcinogenic effects. The resulting value, where obtained, should
be classified as part of the reporting (in relation to non-quantifiable carcinogenic or potentially carcinogenic effect).

(4) If the database is not sufficient for a “weight of evidence” assessment, a semi-quantitative assessment of the cancer risk should be made.

The inadequate database which only enables semi-quantitative risk estimation to be carried out, should be documented and reference should be made to the relevant uncertainty of semi-quantitative risk assessment. The result of the assessment may, however indicate that no statement (not even a semi-quantitative statement) is possible as regards the cancer risk.

It should be checked whether the derivation of an OEL-analogous value (or an OEL for substances suspected of carcinogenicity) is possible based on the non-carcinogenic effects. The resulting value, where obtained, should be classified as part of the reporting (in relation to non-quantifiable or semi-quantifiable carcinogenic or potentially carcinogenic effect).

(5) An ERR derivation is not possible where the minimum criteria for animal study data are met but those for human data are not met and a higher level of sensitivity among humans in comparison to test animals can furthermore be assumed based on the insufficient human data.

The information listed under points (1) to (4) regarding a weight-of-evidence approach and the commenting required as well as the assessment of the non-carcinogenic effects should be taken into account.

The substance o-toluidine is introduced by way of example. There is insufficient human data available on this substance for the purposes of risk quantification, but there are indications that it may be associated with a substantial cancer risk for humans. Results from qualified animal experiments indicate a low risk of cancer, which does not completely explain the quantitative information from the human data. ERR derivation is therefore not possible.

(6) ERR derivation is possible where the minimum criteria for animal study data are met but those for human data are not met and a higher level of sensitivity among humans in comparison to test animals cannot be assumed based on the insufficient human data (as where human data completely lacking).

This applies as a general rule for carcinogens in Category 1A, 1B and Category 2 (CLP Regulation). It represents a frequently observed database. However, for substances in Category 2 (suspected of being carcinogenic) usage of the ERR in compliance with the regulations necessitates classification in accordance with TRGS 905 (see Section 8.1 (1)).

As a general rule, the possibility of an ERR derivation basically involves the estimation of a threshold to be assumed for carcinogenic effects where there is sufficient data quality for Cat. 1A, 1B substances (CLP Regulation). This results in the identification of an OEL (basis for carcinogenicity).
(7) If the minimum criteria for the assessment of carcinogenic potency are fulfilled for carcinogens in Category 2 (CLP Regulation), the health-based OEL derived based on the non-carcinogenic effects (instead of tolerable and acceptable value based on carcinogenic effect) should then be classified as unreliable in the event that, for exposure at the level of the planned OEL, the cancer risk calculated for it using the ERR method is greater than approx. 4:10000.

In this case it should be assumed that although the substance is “only” a substance suspected of being carcinogenic, a) a qualified statement on the cancer risk is possible, and b) this could still be relevant at the level of the OEL, meaning that an isolated assessment of the non-carcinogenic effects in terms of the calculated (possible) cancer risk is not satisfactory. The comparison between the risks calculated for the tolerable and acceptable concentrations using the ERR method and the risks for the anticipated OEL based on non-carcinogenic effects are to be documented. Due to the legal situation, the assessment of non-carcinogenic effects is relevant.

A similar view can be taken of the situation where a risk assessment is taking place for other substances that are carcinogenic or suspected of being so that are not currently classified according to the CLP Regulation (e.g. substances classified by U.S. EPA or by IARC or nationally outside TRGS 905).

(8) In relation to carcinogens in Category 1A and 1B (CLP Regulation) ERR derivation is possible in the case that the minimum criteria are met for human data but are not met for data from animal studies.

It is generally to be expected that the minimum criteria for human data will be met as regards substances in Category 1A, but that this is unlikely for substances in Category 1B. However, this correlation is not reliable, as the classification criteria are not identical to the criteria for the quantitative risk assessment.

(9) Derivation of an ERR is possible in the case that the minimum criteria are met both for data from animal studies and human data. If the derivations contradict each other in quantitative terms, the risk quantification should be carried out using the weight-of-evidence principle. If a clear weighting is still not possible with this approach, the more cautious assessment should be used.

In this context a weight-of-evidence approach does not necessarily mean a poor database and the averaging of data from human and animal studies; it can also involve selecting the more plausible data pool (human data, animal data). A justification should be provided for the selection.
9 Requirements for documentation

9.1 Justification documents

(1) Agreements on regulations (e.g. limit values and conditions for risk management associated with risk levels) require transparency, the opportunity to make revisions, and therefore appropriate and public documentation. In the present case, publicly accessible justification documents are therefore to be created for deriving substance-related exposure-risk relationships and risk concentrations.

*A standard form with information on completion is enclosed with this Guide as an Annex (see Annex 10.4).*

(2) Justification documents may refer to this Guide as regards their methodology, which means that default factors or individual steps do not have to be substantiated in detail in each individual case if they comply with the information in this Guide. However, an explicit reference should be made (e.g. “the shorter exposure period was taken into account in accordance with the regulations of the Guide, Section 4.5”).

(3) If justification documents are based on published data and all the necessary data are included in the cited source (see also minimum criteria according to Section 8), unambiguous citation of the source is sufficient to describe the database of risk quantification.

(4) The main emphasis of a justification document should be on (a) rationales for the assumed predominant mode of action (see Section 2), (b) deviations from the default procedure proposed in this Guide, (c) selection of the tumour site (including species, sex, etc., see Section 3.1), (d) description of the mathematical calculation, and (e) comparison between the risk for carcinogenic effects and non-carcinogenic effect levels.

Moreover, a justification is required whenever this is explicitly specified in the individual sections of this Guide.

(5) A conclusion section (Section 9 in Annex 10.4) is to be provided as an independent section of the justification so that it can be understood as a summary without having to read the main section.

(6) Reference to third party risk quantifications and the justification given there is sufficient only if the cited reference is consistent with the requirements of this Guide as regards methodology and transparency.

(7) There are special requirements as regards the documents when no risk concentrations can be quantified.

(8) When the benchmark approach or the MPPD methodology (for calculating a human-equivalent concentration, HEC) is applied, the relevant calculation profile should be attached as an annex to the ERR justification documents.
9.2 Processing sequence

In the following Figure 4, the principal links between the methodological elements and work steps are summarised in a flow diagram.
Diagram of the derivation of an exposure-risk relationship (ERR) based on the present Guide

Start by order from the risk management

Search for substance-specific human and/or animal studies investigating carcinogenic effects

Check the minimum criteria for risk quantification
(e.g. in terms of there being sufficient information on exposure and confounder factors in epidemiological studies or in terms of the human relevance of tumours in test animals)

Yes

Point of departure (POD) calculated for the assessment, e.g. as BMD$_{10}$ or T25

Data extrapolated from animal studies to humans (e.g. for an exposure of 8 h/d, 5 d/wk., 48 wk./year and 40 years of working life)

“Mode of action” (MOA) agreed, (e.g. based on genotoxicity, metabolism)

Threshold plausible and determinable based on data?

Extrapolation to the threshold

Sub-linear dose-response?

Approximation via the “break function”

Mode of action genotoxic or unknown?

Linear extrapolation

Yes

No ERR can be derived, search for other risk reduction strategies by risk management

Non-carcinogenic effect investigated and assessed (Bekanntmachung zu Gefahrstoffen (Announcement on Hazardous Substances, BekGS) 901)

Occupational exposure limit (OEL) (analogous value)

No

Taking into account their weight of evidence, is it possible to use aggregated data?

Yes

No

Comparison carried out (cancer risk vs. non-carcinogenic effects) and regulatory relevant concentrations selected related to:
- High risk: > 4 : 1000
- Medium risk: < 4:1000 > 4:10000/100000
- Low risk: < 4:10000/100000 or
- Occupational exposure limit (OEL) (analogous value)

Check on way of implementation by risk management

Numbering in black circular fields corresponds to the section numbers in the Guide
Figure 4: Diagram of the derivation of an exposure-risk relationship (ERR) based on the present Guide; numbering in blue circular fields corresponds to the section numbers in the Guide

10 Annexes

10.1 Glossary

Acceptable/tolerable risk:

The health risk (ibid.) caused by the effects of hazardous substances is a continuum that generally increases with the concentration of the hazardous substance. In the risk concept of the Committee on Hazardous Substances (AGS), this continuum is divided into the following three areas by means of two evaluation points, the acceptable risk and the tolerable risk:

1. If occurrence of damage is only possible, the risk involved is assessed as “acceptable”. Basic worker protection measures are required for this risk (range below the acceptable risk).

2. If occurrence of damage is more than just possible but not yet sufficiently likely (see (3)), the risk involved is assessed as “undesirable”. This risk indicates that there is concern about health damage.

3. If occurrence of damage is sufficiently likely, the risk involved is assessed as “not tolerable”. This risk refers to a health hazard (above the tolerable risk).

The risk levels for the specified evaluation points (acceptable risk and tolerable risk) can only be socio-politically established rather than scientifically substantiated. Numerous criteria have to be taken into account. Apart from societal risk perception, these are, for example, severity of health damage, the possible extent of damage (type of damage and/or number of persons affected), relation to comparable other risks at the workplace, direct benefit and actual and possible risk reduction measures.

The term “acceptable exposure” is also used to distinguish this from a “risk-relevant concentration” (where the tolerable concentration is exceeded).

Additional risk:

Means of calculating the exposure-related lifetime risk as a difference between the risk of the exposed persons and the risk of the non-exposed control group:

\[ P_A(x) = P(x) - P(0) \]

with \( P_A(x) \): Additional risk during exposure \( x \)

\( P(x) \): Lifetime risk of the exposed persons

\( P(0) \): “background risk” (lifetime risk of a non-exposed control group)

The term additional risk is mainly used for data from animal studies, while the term excess risk (ibid.) is preferred for the analogous risk when discussing epi-
demiological data.

Adduct formation:
Here: Binding of a xenobiotic or its metabolite to the DNA. DNA adducts in the nucleus may prevent cell division and/or induce mutations under certain conditions.

AIC (Akaike’s information criterion):
Statistical method to describe the relative quality of adjustment of curve models. Curves that are better adjusted generally result in lower AIC values. Important test in the benchmark approach (ibid.).

AKC:
Abbreviation for: Acceptable concentration, i.e. the exposure concentration considered as remaining constant across the entire working life which is associated with a calculated “acceptable” cancer risk (see “Acceptable/tolerable risk”).

Allometric scaling:
Element of interspecies extrapolation (ibid.) of small test animals to humans. Allometry is understood to mean the determination of the relation of various biological parameters to body size. In mathematical terms, allometric scaling takes into account that in mammals, for example, metabolic activity does not linearly increase with the body weight of the individual animal species. This means that humans seem to be more sensitive to comparable toxic effects than mice, for example, if the dose absorbed is related to body weight.

Alpha2u globulin:
Low-molecular protein, high amounts of which are produced in the liver of adult male rats. Specific light hydrocarbons (e.g. isophorone, 1,4-dichlorobenzene and limonene) bind to alpha2u globulin. The complexes formed in this way accumulate in kidney cells, which may result in cellular destruction with subsequent repair, regeneration and an increased occurrence of renal tumours. This non-genotoxic mechanism of tumorigenicity (see “Genotoxicity”) is considered to be sex-specific and species-specific and of no relevance to humans.

Amplification effect:
Here: Disproportionate increase in the dose-response relationship induced by the toxic effect of a substance/its metabolites on the baseline of a further toxic effect of this substance/its metabolites that already occurs at low doses. For example, the genotoxic effect of trichloroethylene is amplified by the nephrotoxicity induced at higher doses.
Aneugenicity:
Induction of aneuploidy; relates to the effects that cause a change (gain or loss) in the number of chromosomes in cells. An aneugen can cause the loss or gain of chromosomes that result in cells that do not have a whole number multiple of the haploid chromosome set.

A-Staub:
See “Respirable dust”

Attributable risk:
Attributable risk or attributive risk refers to the proportion of persons affected by a disease that can be attributed to a specific risk factor (ibid.). The attributable risk among exposed persons (ARE) can be distinguished here from the attributable risk in the general population (population attributable risk; PAR). Whereas the ARE specifies the fraction of cases developing cancer in the exposed subpopulation, the PAR refers to the specific rate for the total population. Thus, although the PAR may be small for rare exposures, the specific fraction of the relative risk (RR) in the exposed subgroups, e.g. workers in a specific branch of production, may be very high if the level of the RR is correspondingly high, and may be more than 50% at a RR > 2.

Two factors must be known to calculate the attributable risk in the general population (PAR):
• the incidence of the risk factor in the population, and
• the extent to which this risk factor increases the risk of developing cancer.

For example, assuming that the risk of developing lung cancer is ten times higher in smokers compared with non-smokers, and further assuming that the frequency of smoking for men in a population is 40%, this would result in an attributable risk of about 78%, i.e. 78% of the cases of lung cancer among the male population would be said to be caused by smoking. Comparable estimates of the attributable risk among exposed persons (ARE) may be made for occupational exposure on the basis of data for exposure prevalence and by using risk estimates from studies available on a specific exposure.

Mathematical definitions of ARE and PAR:

\[
ARE = \frac{RR - 1}{RR} = \frac{\text{Incidence exposed} - \text{Incidence not exposed}}{\text{Incidence exposed}}
\]

\[
PAR = \frac{P[E=1|x (RR - 1)]}{P[E=1|x (RR - 1) + 1]}
\]

\[
= \frac{\text{Incidence population} - \text{Incidence not exposed}}{\text{Incidence population}}
\]

With probability of \(P[E=1]\) of being exposed, dependent on the population.
Benchmark approach:

Approach of adjusting a mathematical model to the data obtained in a study for the dose-response relationship. Several model functions are available.

The benchmark approach is an instrument to determine a point of departure (ibid.) for quantitative risk assessments. The dose that leads to an effect with a certain likelihood can be estimated for a defined effect frequency or a defined effect measure, i.e. the benchmark response” (BMR). This dose is referred to as a benchmark dose (BMD). A $BMD_{10}$ indicates the dose at which there is a 10% risk that the effect concerned would be likely to occur. The reliability of assessing a dose-response relationship is quantified by specifying a confidence interval. The value of the lower (generally 90 or 95%) confidence interval of the benchmark dose is referred to as the benchmark dose lower bound (BMDL). The quality of adjustment of the results with different model functions can be checked by means of the AIC (ibid.).

Bias:

In epidemiology, the term bias is understood to mean distortion attributable to a systematic error in obtaining the data. Unlike random errors, systematic errors lead to one-sided deviations.

Bioactivation:

Transformation of a xenobiotic, generally due to enzymes inside the body, to a toxic or carcinogenic metabolite.

BMD (benchmark dose):

See “Benchmark approach”.

BMDL (benchmark dose lower bound):

See “Benchmark approach”.

BMR (benchmark response):

See “Benchmark approach”.

Calculation of the sample size:

The planning of every epidemiological study requires calculating the sample size that is necessary to verify or falsify the assumptions used as a basis for the hypothesis to be investigated. Various parameters must be defined for calculating the sample size:
1. **Significance level or probability of type I error:** Identifies the statistical reliability that is used to calculate a possible difference (when comparing several groups) or an increase in risk. The significance level is usually established at a maximum of 5%. The smaller the significance level, the larger the sample size must be. If a significance level of 5% or below is calculated, this means that the difference calculated here will actually occur in at least 95% of all conceivable comparable studies.

2. **Power of probability of type II error:** Establishes in what percentage of all conceivable constellations an actual difference or an existing risk increase is not overlooked. A power of 90% would thus mean that the risk of failing to detect a difference – although there is a difference – is not greater than 10%. It is of course desirable that the power of the study is as great as possible. The greater the power, the larger the sample size must be. In epidemiological studies, the power used should not be smaller than 80%.

3. **Assumptions about the minimum size risk increase:** The smaller the risk to be detected, the larger the sample size must be to detect the risk increase at a given power. Previous studies or plausible assumptions must be used as a basis for establishing this parameter. Risk increases of more than 100% occur relatively seldom under environmental exposure.

4. **Assumptions about the frequency of the critical risk factor in the reference group or reference population:** If several risk factors are to be analysed in a study at the same time, it is suitable to use the rarest risk factor as a basis for the calculation of the sample size. If no exact data are available for the frequency of risk factors, a pilot study should be carried out. Alternatively, information from published studies may be used.

**Cancer risk figure:**

This term was used in the previous version of this Guide as a synonym for “risk concentration” (ibid.).

**Case-control study (CCS):**

The aim of case-control studies is to determine the importance of risk factors (ibid.) for the formation of diseases in quantitative terms. Case-control studies are based on the logical consideration that the incidence of a risk factor promoting the formation of a disease must have been higher in patients affected by this disease before its outbreak than in a reference group of persons not affected. Since searches in case-control studies only start after a disease has developed, i.e. they are directed towards the past, case-control studies are characterised as retrospective studies. A case-control study results in an odds ratio (ibid.) which specifies how many times more frequently the disease develops if the risk factor exists than without it. An odds ratio below 1.0 would indicate a reduced risk and a value above 1.0 would specify an increased risk. An odds ratio of 1.5 corresponds to a risk increase of 50%. However, the specific confidence interval (ibid.) must be calculated to assess the relevance of an odds ratio.
Case-control study nested in cohort: This design is a special case of the case-control study, which is often found in occupational epidemiology. All the cases of a cohort are compared with a random sample of the control persons not affected at the time of the case diagnosis from the same cohort (incidence density sampling); in this way, the optimum conditions of incidental and complete case recruitment and the requirement of random selection of non-affected persons from the same reference population are met.

Cell proliferation

Multiplication of cells in a tissue.

Chi-square distribution:

A continuous probability distribution over the number of positive real figures

Clastogenicity:

Substances that cause chromosome breakages are described as clastogenes. This can be the result of direct DNA damage or an indirect mechanism, e.g. an inhibition of topoisomerases (ibid.) (SCHER/SCCP/SCENIHR, 2009).

Clearance:

Here: Cleaning deposited particles from the airways using a physicochemical solution or mechanical removal. This process can take place in the central airways via the ciliated epithelium (mucociliary clearance), and in the lower airways via ingestion by freely moving macrophages, a type of “phagocyte” (macrophage clearance).

Clitoral gland:

See “Preputial gland”:

CLP Regulation


- **1A**: Substances that are known to be carcinogenic among humans; this classification is generally given due to evidence from human studies.
- **1B**: Substances that are likely to be carcinogenic among humans; this classification is generally given due to evidence from animal studies.
2: Suspicion of carcinogenic effect among humans.

The CLP Regulation sets out an analogous classification scheme, for example for mutagenic and germ cell mutagenic substances. The present Guide uses this classification scheme.

Cohort study:

In epidemiology, a cohort is a group of persons with a common characteristic. This characteristic may be common exposure to a dangerous substance, living in a specific region, having an identical occupation or the like. In a cohort study, the members of a cohort are observed for the occurrence of endpoints over a defined period. These endpoints may be the occurrence of defined diseases or death from defined courses. Since the risk of developing a disease subsequent to exposure is examined in a cohort study, this is a prospective study design. In occupational medicine, the starting point of cohort studies is often shifted back. These studies are often referred to as historical cohort studies or studies with a historical-prospective design.

When epidemiological studies are planned, the required sizes of sample populations must be defined as in the case of animal studies.

Confidence interval:

A confidence interval allows assessment of the range of variation of an estimate (e.g. odds ratio, relative risk and standardised mortality ratio). The interval specifies the range in which 95 of 100 possible estimates would fall if the 95% confidence interval is calculated, or 99 of 100 if the 99% confidence interval is calculated. The 95% confidence interval is commonly used. If an odds ratio (ibid) was estimated to be 1.41 and the confidence interval ranges from 0.95 to 1.67, no significant increase in the odds ratio is found because the 95% range also includes values below 1.0, i.e. the true risk may be slightly increased, unchanged or even slightly reduced.

Confounder:

A variable that distorts the association between the actually investigated impact (e.g. a specific substance at the workplace) and the investigated end point (e.g. carcinogenicity). Confounding is the mixing of confounder effects with the effect of the risk factor to be investigated.

Correlation studies:

See “Ecological studies”

Cross-sectional study:

In a cross-sectional study, a defined group of persons, in most cases a sample of the population, is examined at a defined time. Such a study allows the frequency of characteristics, patterns of behaviour and risk factors (ibid.) to be es-
timed. These frequencies are designated with the epidemiological term “prevalence” (ibid.). Apart from prevalences, means of measured values (e.g. systolic blood pressure and cholesterol level) can also be estimated. When a cross-sectional study is designed, the required size of the population must be calculated for both approaches; see calculation of the sample size.

Survey is a synonym for cross-sectional study. Cross-sectional studies are among the most important instruments for examining the health status of a population. According to the state-of-the-art, surveys must be carried out as representative studies, i.e. on the basis of a representative random sample from the population.

Cytotoxicity:

Damaging substance effect on tissue cells and/or the ability of an agent to reduce the cell vitality (function and cell division), or even to cause cell death.

DALY:

Abbreviation for “disability-adjusted life years” or “disease-adjusted life years”. This is a measure of the total number of a person’s or group of people’s life years (YLL, ibid.) impacted by disability and/or illness or lost due to premature death

Default:

Statistically supported standard value or assumption that is to be used in the absence of substance-specific or species-specific data. A default allows deviations and is a means to describe systems despite incomplete knowledge of their characteristics.

Deposition:

Here: Deposit of inhaled particles in the airways. Deposited particles can be cleared from the airways.

DMEL:

Abbreviation for “derived minimal effect level”

The European REACH Regulation (EC) no. 1907/2006 actually prescribes the derivation of a “health-based” derived no-effect level (DNEL, ibid.) for chemicals with certain characteristics. If a DNEL cannot be established for carcinogens/mutagens, particularly when a toxicological threshold (ibid.) is unknown or implausible, this regulation (as set out in Annex I) allows for “a qualitative assessment of the probability that effects can be avoided when the exposure scenario is applied”. In the REACH guide “Guidance on Information Requirements and Chemical Safety Assessment” (Section R.8), rather than in the REACH Regulation itself, the setting up of a DMEL is recommended, defined as “a reference level which is considered to be of very low concern. DMEL derived in accordance with the guidance should be seen as a tolerable level of effects and
it should be noted that it is not a level where no potential effects can be foreseen.”

The aforementioned REACH Guide recommends numerous possibilities for deriving DMEL values. These include a “linear model” which is largely in agreement with that described in the present Guide, as well as the EFSA concept (ibid.) or physiologically-based pharmacokinetic models (ibid.).

The REACH Guide does not provide any clear specifications as to the protection level or risk level to be aimed for. Its authors limit themselves to the following passage: “Although there is no EU legislation setting the ‘tolerable’ risk level for carcinogens in the society, cancer risk levels had been set and used in different contexts (see APPENDIX R. 8–14 for various values previously applied within and outside the EU). Based on these experiences, cancer risk levels of $10^{-5}$ and $10^{-6}$ could be seen as indicative tolerable risks when setting DMELs for workers and the general Population, respectively."

**DNA polymerases:**

Enzymes that catalyse the synthesis of the genetic substance deoxyribonucleic acid (DNA) based on their components, the deoxyribonucleotides. An existing DNA single strand serves as a matrix for this purpose.

**DNEL:**

According to annex I of European Regulation (EC) no. 1907/2006 on the Registration, Evaluation, Authorisation & Restriction of Chemicals (REACH), the objective of determining damaging effects on the health of humans is “to derive levels of exposure to the substance above which humans should not be exposed. This level of exposure is known as the Derived No-Effect Level (DNEL – the derived level of exposure under which the substance does not lead to any damage to human health)”.

Manufacturers or importers must establish DNEL values for hazardous substances subject to registration when $\geq 10$ tonnes are being produced or imported per year, and these values must be listed in the chemical safety report and safety data sheet. Different DNEL values can be determined for one and the same substance in reference to different groups of people (e.g. consumers, employers, pregnant women, children) and different exposure durations and routes (oral, dermal, inhalative).

The REACH guide “Guidance on Information Requirements and Chemical Safety Assessment” describes the procedure for deriving the DNEL values. The procedure is basically similar to that suggested in the German Announcement on Hazardous Materials (BekGS) 901 for establishing OELs (ibid.) for Germany; however, there are small differences in the extrapolation factors.

In Germany, OELs are the binding health-based limit values for ambient air quality at the workplace. If no OEL (and no MAK value) is available, the substance-specific and scenario-specific DNEL (“inhalative, long-term workers”) can, for example, be applied, in accordance with the German Technical Rule for Hazardous Substances (TRGS) 402 in order to assist in the assessment of whether the affected protective measures are sufficient.
Dose-response relationship:

Functional relationship between dose and effect (effect level) of a pharmacologically or toxicologically active substance. Strictly speaking, dose-response relationships for the end point “cancer” are dose-incidence relationships and describe the tumour rate as a function of the dose (or concentration). These functions are continuous and in most cases asymptotically approach a maximum value for the tumour rate.

For the low dose range – generally inaccessible in animal studies – several courses of curves can be modelled, e.g. using the benchmark approach (ibid.):

- **Linear dose-response relationship**: Curve section can be described by a straight line function.
- **Sublinear dose-response relationship**: The initially slow increase in the tumour rate, for example, increases more than proportionally (“sagging” curve) with a steadily increasing dose.
- **Supralinear dose-response relationship**: Minor increases in the dose in the low dose range lead to a relatively large increase in the tumour rate, for example, whereas dose increases in the upper range only lead to a slight increase in the tumour rate and thus to a flattened curve (“bulged” curve).

These descriptions of the curves provide no information as to whether the functions pass through zero.

Ecological studies (or correlation studies):

These studies compare exposure and disease at the level of groups, i.e no individual information is available on exposure or a disease (or both) (e.g. frequency of performing a specific production process and cancer mortality when two factories are compared). However, since exposure and disease statuses are not assigned individually, ecological studies should generally not be used for deriving exposure-risk relationships for the assessment of occupational exposure limits.

**EF:**

Abbreviation for: Excursion factor (ibid.)

**EFSA concept:**

Strategy of the European Food Safety Authority (EFSA) for the risk assessment of genotoxic (see “Genotoxicity”) and carcinogenic substances. The concept is based on the calculation of a margin of exposure (ibid.). The dose leading to a tumour rate of 10% in an animal study (calculated as the BMDL, ibid., if adequate data are available) is determined as a reference point on the dose-response curve. If the margin of exposure (i.e. the ratio between the dose absorbed via the digestive tract and the BMDL10) is 10000 or higher, the cancer risk for consumers of contaminated food is classified as low and it is suggested that these substances should be treated with low priority. The further the margin of exposure falls below 10000, the more urgently minimising measures must be taken.
Endocrine:

*Relating to the hormonal system.*

Endocytosis:

*Absorption of substances into the cell via invagination and then constriction of the cell membrane.*

Enzyme induction:

*Activation of an increase of the synthesis of specific enzymes in the cells of a tissue. If metabolic enzymes are induced, this may have effects on the detoxification or toxification of absorbed xenobiotics.*

EPA:

*Abbreviation for “United States Environmental Protection Agency”. The EPA is an independent environmental agency within the US Federal Government.*

Epidemiology:

*Epidemiology is the study of the distribution and causes of health-related conditions or events in defined populations (ibid.) and the application of the results of such studies with the aim of avoiding health problems. “Study” refers to observation studies, surveys, hypothesis tests and analytical and experimental studies. “Distribution” involves the evaluation of specific data according to time, location and groups of persons. “Causes” are understood to mean all physical, biological, social, cultural and behaviour-related factors that may have an effect on health. “Health-related conditions or events” include diseases, causes of death, patterns of behaviour such as tobacco consumption, reactions to preventive measures and the provision and use of health services. “Defined populations” are understood to mean groups of humans with identifiable characteristics (age, sex, residence, etc.). “Application of the results ...” explicitly refers to the aim of epidemiology, i.e. to promote, protect and restore health (Porta, 2008).*

ERR:

*See “Exposure-risk relationship”.*

E-Staub:

*See “Inhalable dust”*
Estimate:

Unknown parameters of the population are approached by means of observational values from a sample. Various statistical methods are available for this purpose. Thus population means (see “Population”) are estimated using sample means. The fuzziness of these point estimators is assessed by means of the variability of the relevant characteristic in the population, which was estimated by means of a sample. For a better assessment of point estimators such as estimated relative risks (RR), the point estimators and their variability estimators are combined in confidence intervals which, at a given confidence level of for example 95%, allow rough statements, such as “the RR is between 2.0 and 5.5 at a 95% probability”, to be made.

Excess risk:

The term has several meanings:

(a) It is often defined as the additional risk of developing cancer among exposed persons in relation to the basic risk, also called relative risk difference (RD): \( \text{RD} = \text{RR} - 1 \). It specifies the percentage of risk increase among exposed persons. For example, it is 50% at a relative risk (RR) of 1.5, 100% at a RR of 2.0 and, correspondingly, 900% at a RR of 10.

(b) In this Guide, it is understood to mean the exposure-related lifetime risk, which is generally defined as the difference between the risk of the exposed persons and the risk of a non-exposed reference group (e.g. general population):

\[
P_{\text{excess}} (x) = P(x) - P(0)
\]

with \( P_{\text{excess}} (x) \): excess risk during exposure x

\( P(x) \): Lifetime risk of the exposed persons

\( P(0) \): “background risk” (lifetime risk of a non-exposed reference group)

This definition of the term of excess risk is the one most prevalently used for epidemiological data; it is formally identical with additional risk (ibid.). In animal studies, the term “excess risk” may also be used if the exposure-related lifetime risk was calculated as an extra risk (ibid.), although this is not quite formally correct.

Excursion factor (EF):

Excursion factor by which the shift mean value can be exceeded up to four times per shift for a maximum period of 15 mins in each case. A distinction is made between the \( \text{EF}_{\text{carc}} \) and the \( \text{EF}_{\text{noncarc}} \) which denote carcinogenic and non-carcinogenic effects respectively.

Exposure-risk relationship (ERR):

An exposure-risk relationship (ERR) describes the relationship between a substance-specific risk of a carcinogenic effect and an assumed exposure to this substance. To identify the ERR, an additional risk of developing cancer (i.e. in access of the background rate) from a concentration of a substance in the air is set against exposure during an entire working lifetime. The ERR can be used to
derive substance-specific exposure concentrations for carcinogenic dangerous substances in the air at the workplace, which correspond to the acceptable and tolerable risk (ibid.). As explained in the previous Guide, ERRs are derived on the basis of data from the field of occupational health and toxicology taken from available literature and they are used to implement preventative measures, and measures that minimise risk.

Extra risk:

Means of calculating the exposure-related lifetime risk by means of the risk of the exposed persons and the risk of a non-exposed control group according to the following formula:

\[ P_E(x) = \frac{P(x) - P(0)}{1 - P(0)} \]

with  
\[ P_E(x) \quad \text{Extra risk during exposure } x \]
\[ P(x) \quad \text{Lifetime risk of the exposed persons} \]
\[ P(0) \quad \text{“background risk”} \]

(lifetime risk of a non-exposed control group)

It is thus the ratio of additional risk (ibid.) to the proportion of individuals who do not react in the absence of exposure. For mathematical reasons, the extra risk is calculated in specific dose-response models particularly for data from animal studies; in general, the result hardly differs from that of the additional risk.

Extrapolation factor/safety factor:

An extrapolation factor is physiologically/empirically substantiated. Risk assessment is based on available toxicological data and extrapolations are made to an expected, not experimentally determined value (e.g. lowering of the effect concentration when extending the study period). This quantitative assessment must include a comprehensible interpretation of empirical data.

Additional, more qualitative aspects (data quality, severity of the effect or indicative facts) are considered to provide protection from unknown or scientifical-ly/empirically non-quantifiable risks in accordance with the precautionary principle. A factor used for this purpose is referred to as a safety factor.

Extrathoracic region (ET):

Covers the upper respiratory tract, nose, mouth, pharynx and larynx.

First pass effect:

Substances that are absorbed by the digestive tract enter the liver after absorption via the hepatic portal vein. During their first pass through the liver, they may in some cases be metabolised to such a considerable extent that only a fraction of the substance itself reaches the remaining organs.
Forestomach

Aglandular digestive organ in front of the main stomach of rodents. Forestomach tumours often develop after administration of genotoxic carcinogens (see "Genotoxicity") via the diet or by gavage to rodents. Humans have no forestomach.

Gamma function:

Special mathematical function from which a continuous probability distribution (gamma distribution) is derived

Gavage:

Administration of a substance by means of gavage

Genotoxicity:

A relatively general term for effects on the genetic material. It refers to processes that change the structure and/or the information content of the DNA or the DNA segregation (division of daughter cells) and that are not necessarily associated with mutagenicity (ibid.). Genotoxicity tests therefore also encompass tests that provide information about induced DNA damage, but that do not supply direct evidence of a mutation, for example via effects such as unscheduled DNA synthesis (UDS), sister chromatid exchange (SCE), DNA strand breaks, DNA adduct formation or mitotic recombination, as well as tests for mutagenicity. See source: (SCHER/SCCP/SCENIHR, 2009).

A differentiation is made between the following:

Primarily genotoxic substances: the starting substance and/or metabolite(s) react directly with the DNA and can change the genetic information in this way

Secondarily genotoxic substances: induction of genetic lesions without direct interaction with the DNA. Examples are oxidative damage through the formation of reactive oxygen species or disturbance of DNA repair.

Glucuronidation:

The transferral of residual glucuronic acid from the uridine diphosphate glucuronic acid (“activated glucuronic acid”) to nucleophilic reaction partners such as hydroxyl, amino, sulfhydryl or carboxyl groups. This reaction is catalysed by the UDP glucuronosyltransferases belonging to the phase II enzymes (ibid.). Glucuronidation causes non-polar xenobiotics to become hydrophilic and eliminable.

Harderian gland:

Additional lacrimal gland of the nictitating membrane in the nasal canthus of many animal species. Humans have no nictitating membrane.
hBMD:

Human equivalent benchmark dose (see “Benchmark approach”); calculated from animal data extrapolated to humans.

HEC:

Abbreviation for “human-equivalent concentration”. Within the context of this Guide, this term refers to the fact that for the purposes of interspecies extrapolation (ibid.) for locally effective substances (particularly those causing damage to the lungs), the effect concentrations determined in the inhalation study on animals must be converted to reflect the conditions for humans. This results in a (human-) equivalent concentration for that used in the animal study.

Haemangiosarcoma:

Malignant tumour that starts in the tissue of the interior lining of the blood vessels, in the endothelium.

Homoeostasis:

Maintenance of a steady state in the physiological system.

hT25:

Human equivalent T25 (ibid.); calculated from the T25 determined from animal data by extrapolation to humans.

Hyperplasia:

Enlargement of a tissue or organ by increasing the number of cells (multiple cell division).

Hypertrophy:

Enlargement of a tissue or organ by increasing the cell volumes.

Hypophysis:

Also known as the pituitary gland, the hypophysis produces a number of hormones.

Hypoxia:

Insufficient supply of oxygen to a tissue.

IARC:

Abbreviation for “International Agency for Research on Cancer”, subsidiary of...
the World Health Organization (WHO), headquartered in Lyon, which has the aim of carrying out cancer research and classifying carcinogenic substances.

ICD:

Incidence:
Refers to the incidence of new cases of a specific disease related to a defined period (generally one year) and a defined population. All patients newly affected in a defined region must be recorded to determine the incidence. This is generally possible on the basis of population-related epidemiological disease registries, e.g. the cancer registry and heart attack registry, or by carrying out specifically designed incidence studies. For Germany, incidence can be specified for only a few groups of diseases and for regionally very restricted areas. The only German epidemiological cancer registers that supply reliable incidence data for all age groups across longer time periods are the cancer registers of Saarland and the former GDR, up to 1990. The cancer registries, which have been established on a Federal state level since the nineties under the Federal Cancer Registry Law, are not quite complete, but will in future increasingly provide usable data (see “Dachdokumentation Krebs” under www.rki.de). The German Childhood Cancer Registry, based in Mainz, provides data for malignant tumours during childhood (up to and including the age of 14) for the whole of Germany.

The cumulative incidence (CI) indicates the proportion of persons who have developed a specific disease at a defined time:

\[
CI = \frac{\text{Number of persons who developed the disease within the defined time period}}{\text{Number of persons at risk of developing the disease across the defined time period}}
\]

Inhalable dust (German: E-Staub, “E” for “Einatembarer Staub”):
The mass fraction of a particulate matter that can be inhaled by humans through the mouth and/or nose is described as the inhalable fraction (inhalable dust, E-Staub). While smaller particles (aerodynamic diameter <5 µm) are inhaled almost completely, the inhalability decreases for larger particles (due to the non-inhalable fraction). The size distribution of the inhalable fraction can be taken from the standard DIN EN 481. Inhalable dust can be divided into further particle fractions based on the location they are deposited in the lungs (e.g. alveolar fraction/respirable dust, ibid.).
**Interspecies extrapolation:**

> Here: conversion of results obtained from animal studies to the (average) conditions in humans

**Interstitium:**

> Interstitial tissue (e.g. connective tissue) that is drawn across the organs and divides them from each other. It has a supportive, carrying or cradling function.

**Intraspecies extrapolation:**

> Here: mathematical consideration of differences in sensitivity of the human population in risk assessment

**KZC:**

> Abbreviation for short-term concentration (ibid.)

**Leydig cell tumour:**

> Neoplasm originating from the testosterone-producing Leydig cells of the testis. Whereas Leydig cell tumours very seldom occur in humans, a high spontaneous incidence is observed particularly in aging Fischer 344 laboratory rats.

**Life table method:**

> Statistical method to calculate the lifetime risk of dying from a specific type of cancer. The age-specific mortality rates for a certain type of cancer and for all causes of death are used to calculate the lifetime risk in this method.

**Macrophage clearance:**

> See “Clearance”.

**Macrophages:**

> Freely moving cells located in different areas of tissue and belonging to white blood cells that incorporate microorganisms and other particles and can transport them away (“phagocytes”). The alveolar macrophages of the alveoli are principally referred to within the context of this Guide.

**Mamma:**

> Mammary gland of mammals. Also appears in a rudimentary form in the male sex.
Margin of exposure (MoE):

Margin between the lowest concentration shown by experimental data to cause toxic effects (here: tumours) and the expected or measured concentration to which humans are exposed (at the workplace).

Maximum likelihood estimate:

Statistical method to estimate the highest probability as accurately as possible as a reference for the population on the basis of the available sample.

Maximum tolerated dose (MTD):

Highest dose in an animal study at which no serious toxic effects of a general type occur. The MTD is generally determined on the basis of body weight gain. The MTD should be reached, but not exceeded in animal studies investigating the possible carcinogenic effect of a test substance.

Mesothelioma:

Malignant tumour of the peritoneum, pleura or pericardium. Human pleural mesotheliomas are mainly caused by inhaled biopersistent fibres (asbestos) of specific dimensions.

Mitogen:

A mitogen is a substance that stimulates cell division; “mitogen” means stimulating cell division.

Mitosis:

Nuclear division in which one nucleus produces two daughter nuclei that are genetically identical.

Mitotic process:

See “Mitosis”.

MPPD:

Abbreviation for “Multiple-Path Particle Dosimetry Model” – a calculation model that can be used to estimate the deposition and clearance (removal, dissolution) of inhaled particles in the lungs of rats and humans. It is used to calculate what is referred to as the human-equivalent particle concentration (HEC, ibid.) based on the results from animal studies with inhalation particle exposure. A number of versions of the model are available on the Internet, free of charge.²³

²³ http://www.ara.com/products/mppd.htm
**Multihit model:**

*Dose-incidence model that can be used for the modelling of dose-response relationships (ibid.) of carcinogenic substances and is based on the assumption that several adverse events (“hits”) are necessary for the formation of a tumour.*

**Multistage approach, linearised:**

*Risk estimate approach long propagated by the U.S. EPA. The underlying mathematical model function (multistage model) describes a multistage process that is assumed as a basis for the formation of clinically manifest tumours. It is used for modelling the dose-response relationship (ibid.) down to the low dose range by means of the available experimental data. The risks at low doses are then assessed by means of a straight line, which corresponds to the slope of the model function at zero.*

**Mutagenicity:**

*Refers to the induction of permanent, transferable changes to the quantity or structure of the genetic material of cells or organisms. These changes (mutations) may affect a single gene, a gene segment, a block of genes or chromosomes (SCHER/SCCP/SCENIHR, 2009). Mutations can occur in somatic cells (somatic mutagenicity) and in germ cells (germ cell mutagenicity).*

**Necrosis:**

*Uncontrolled cell death.*

**Nephrotoxicity:**

*Specific toxic effect on the kidneys.*

**Non-linearity:**

*Used synonymously with the term “sub-linearity” here (see “Dose-response relationship”) in reference to the extrapolation to the low risk range, not to be confused with threshold (ibid.).*

**Occupational exposure limit (OEL):**

*In accordance with Section 7 (2) of the German Hazardous Substances Ordinance (GefStoffV), an OEL is “the limit value for the time-weighted average concentration of a substance in the air at the workplace in relation to a specified reference period. It indicates up to what concentration of a substance acute or chronic effects for the health of workers are in general not to be expected.” Occupational exposure limits are shift mean values, generally for an exposure period of eight hours, five days a week across a working lifetime.*

*A prerequisite for deriving an OEL is the existence of a substantiated assumption for a toxicological threshold (ibid.). Particularly in the case of carcinogenic*
substances with a direct genotoxic mode of action, a threshold is hardly known, and for this reason is generally not possible to derive an OEL. In such cases, the risk concept following the Technical Rule for Hazardous Substances (TRGS) 910 is used (see “OEL-analogous value”).

Occupational exposure limits are suggested by the Committee on Hazardous Substances (AGS), decided on by the German Federal Ministry of Labour and Social Affairs and published in TRGS 900. The employer must ensure that they are complied with. If an OEL is exceeded and no effective exposure reduction measures are available, the affected substance must be replaced. Where this is not possible, the GefStoffV prescribes an incremental procedure for the implementation of appropriate (technical, organisational or personal) protective measures.

Odds ratio:

The odds ratio (OR) is a measure of association between two odds. The odds is defined as the ratio of the probability of an event to the probability of no event (of developing a disease under a given exposure or of an exposure with a given disease). For rare diseases, the OR approximately specifies how many times more likely it will be for a disease to develop if a specific risk factor exists than in its absence. Odds ratios are obtained as the result of case-control studies (ibid.). An odds ratio below 1 indicates a reduced risk and an odds ratio above 1 specifies an increased risk. The specific confidence interval (ibid.) must be known to assess the relevance of an increase in the odds ratio. The odds ratio is interpreted as an estimator of the relative risk (ibid.) particularly in case-control studies, since the latter cannot be calculated in case-control studies. The rarer the disease, the better the RR is approximated by the OR.

OEL:

See “Occupational exposure limit”.

OEL-analogous value:

A value for the non-carcinogenic effect of a carcinogen derived from the concept for non-carcinogenic substances.

A value (OEL) derived for the most sensitive toxic, non-cancerous effect according to the procedure set out in the “Kriterien zur Ableitung von Arbeitsplatzgrenzwerten” (criteria for deriving occupational exposure limit values) in BekGS 901 may be within or below the tolerable concentration (see “Acceptable/tolerable concentration”) for the substance examined. If this possibility cannot be excluded, a value of this kind must be derived – alongside the exposure-risk relationship (ibid.) for the risk of developing cancer – following the “OEL concept”, and it must furthermore be taken into account in the management concept. Differentiation should be made between a value of this kind calculated for the non-carcinogenic properties of a carcinogenic substance and a value of this kind for a non-carcinogenic substance (than OEL), notwithstanding the fact that derivation methods are to be applied in the same way. A value of this kind is therefore referred to as an “OEL-analogous value” to differentiate it.
from the OEL.

This differentiation is therefore also necessary because, in contrast to the OEL, an OEL-analogous value does not necessarily protect against damaging effects (tumour diseases). Exposures that exceed these OEL-analogous values do not, however, “merely” hold an increased risk of tumours; they also indicate that there is a risk of the potential short-term occurrence of further, non-cancerous risks to health. If the OEL-analogous value is above the tolerable concentration (see “Acceptable/tolerable concentrations”), the practical significance is comparatively little. Exceedance of the tolerable concentration must still be avoided based on the concept of measures of TRGS 910 due to the associated intolerable cancer risk. However, if there is already reason to suspect adverse effects on health other than tumours even at low concentrations within the workplace, exceedance of these OEL-analogous values triggers the same protective measures as when “classic” occupational exposure limits (ibid) as for non-carcinogenic substances are not adhered to. The term: “OEL-analogous value” is used to describe the procedure and assessment results in the supporting documents for the ERR, but not within the context of risk management. In the latter context, the “OEL-analogous value” becomes the OEL in the case that it is to be applied solely as a decisive factor and in place of an ERR, and it becomes the risk-related tolerable concentration where it is decisive even below the tolerable risk (4:1000) as the upper limit of an occupational exposure.

OR:

\textit{Odds ratio (ibid.)}

Overload:

Overload of the lungs by incorporating a very large quantity of particles, which negatively affect the macrophage clearance (ibid.).

\textbf{p53 protein:}

Gene product (referred to according to its molecular mass), an increased amount of which is produced in cells with damaged genetic material (DNA). It causes an increase in DNA repair, temporary inhibition of cell division and, in certain circumstances, the programmed death of the affected cell (apoptosis). It thereby hinders mutations, i.e. the transfer of genetic damage to daughter cells. For this reason it is also referred to as a “tumour suppressor”.

\textbf{Paraganglion:}

A collection of nerve cell bodies, some with a hormone-producing function. An example is the “chromaffin” (i.e. capable of being coloured in the lab using chromium salt) cells of the adrenal medulla.

\textbf{Parenteral administration:}

Administration of a substance by bypassing the (gastro)intestinal tract (e.g. by
Peroxisome proliferation:

Peroxisomes are cellular organelles that are of central importance in lipid metabolism, for example. Certain substances (peroxisome proliferators, e.g. fibrates and phthalates) are known to produce a marked proliferation of the liver peroxisomes of some vertebrates, particularly of rodents. Peroxisome proliferation is a complex enzyme induction which also leads to oxidative stress in the liver, organ hyperplasia and increased cell proliferation. This can lead to liver tumours. In most cases, there is no relevance to humans. The human liver only expresses the PPARα receptor in very small amounts.

Phaeochromocytoma:

Tumour of the adrenal medulla.

Pharmacokinetic model:

Physiologically based pharmacokinetic models (PBPK models) attempt to describe the behaviour of a substance in the organism and quantify tissue concentrations in test animals and humans.

Phase II enzymes:

Enzymes that bond a relatively large (generally polar) molecule (e.g. glucuronic acid or glutathione) to a xenobiotic or its metabolite. It is normally easier to eliminate a xenobiotic modified in this way from the organism. An example of phase II enzymes (ibid.) is sulfotransferases.

POD:

See “Point of departure”.

Point of departure (POD):

Initial value for further steps of risk assessment (see “T25 approach”).

Population:

In epidemiology, population is understood to mean every human group that can be defined by at least one characteristic. This may be the entire population of a country or region or a group of patients (patient population) characterised by a specific, defined disease.

Power, statistical:

See “Statistical power”
PPARα receptor:

See “Peroxisome proliferation”.

Pre-malignant effects:

Precursors of a malignant neoplasm in a tissue

Preputial gland:

Pheromone-producing gland located in front of the genitals of some mammals (e.g. rats and mice). It is commonly referred to as the clitoral gland in females. Humans do not have anatomical equivalents of the preputial/clitoral glands.

Prevalence:

The total number of patients with a defined disease related to a defined population at a given time or, cumulatively, within a specific observation period of a population. It defines a proportion, which is usually specified as a percentage with values between 0 and 1.

Primary genotoxicity:

See “Genotoxic”.

PROAST:

Benchmark software of the Dutch National Institute for Public Health and the Environment (http://www.rivm.nl/en/Library/Scientific/Models/PROAST). Used by the European Food Safety Authority (EFSA) for benchmark modelling. Diffs to some extent from the BMDS software from U.S. EPA in terms of the modelling, the understanding of the selection of suitable models and the cut-off criteria; however, the differences do not appear to be major. In cases of doubt, the matter should be weighed up taking into account the visual assessment of the data adjustment and the T25 calculation (ibid.).

PU region:

See “Pulmonary region”.

Pulmonary region (PU):

Lower respiratory tract and the section of the lungs in which gaseous exchange takes place. Anatomically speaking, the fine end branches of the bronchia (respiratory bronchioles), the alveolar ducts and the pulmonary alveoli are included in this region.
RDDR:
Abbreviation for “regional deposited dose ratio”. Model of the United States “Environmental Protection Agency” (EPA) calculating the particles deposited in the respiratory tracts of mice, rats and humans following inhalation exposure (see “Deposition”).

REACH:
REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) is the fundamental regulation under the EU chemicals legislation that was introduced to achieve harmonisation throughout Europe. It was finally adopted on 18 December, 2006 and entered into force on 1 June, 2007 (Regulation (EC) No. 1907/2006; Directive 2006/121/EC).

The European Chemicals Agency (ECHA) has published a comprehensive range of Guidance Documents to assist with identifying hazardous characteristics of chemicals and performing risk assessments.

Relative risk:
Factor that specifies how many times more frequently (or less frequently) a specific event (disease or death) occurs in a population compared with a reference population. For example, the relative risk of dying from bronchial carcinoma is up to 25 for cigarette smokers depending on the number of cigarettes smoked daily and the lifetime number of packets of cigarettes smoked, i.e. a heavy smoker has a 25 times higher risk of dying from bronchial carcinoma than a non-smoker. For rare diseases, the relative risk can reliably be assessed on the basis of case-control studies (ibid.) by means of the odds ratio (ibid.). As a rule, this requirement is fulfilled for cancer.

The relative risk (RR) can be defined as the ratio of the incidence among exposed persons (I₁) to the incidence among non-exposed persons (I₀): RR = I₁/I₀

Respirable dust (German: A-Staub, “A” for “Alveolengängiger Staub”):
Respirable dust or the alveolar fraction of a body of particles is understood as the fine fraction of the inhalable dust (ibid.) which can penetrate the deepest regions of the human lungs (pulmonary or alveolar region). An absolute size cannot be specified for these particles; instead a size distribution according to DIN EN 481 is described.

Retention:
Here: The residue of particles deposited in the airways (see “Deposition”) The number of particles retained following inhalation exposure is consistently reduced via clearance (ibid):
Retained dose = deposited dose – clearance
Risk concentration:

In this context, the risk concentration is a concentration value calculated under specific assumptions for the exposure-related lifetime risk in the scenario of exposure over a whole working life. The lifetime risk refers to the likelihood that a person will develop a specific type of cancer if mortality from other causes is about equally high as in a non-exposed population. The risk concentration can correspond to the excess risk (ibid.), the additional risk (ibid.), or the extra risk as the background risk is specifically taken into account here.

Risk factor:

Characteristics of persons or external effects that may lead to a positive or negative impact on the risk of developing a disease/mortality risk. Thus cigarette smoking is a risk factor for the development of bronchial carcinomas, bronchitis, myocardial infarction, gastric and bladder carcinomas, leukaemia, etc. The LDL fraction of cholesterol is a risk factor for the development of arteriosclerotic changes, whereas the HDL fraction of cholesterol as a "positive" risk factor is apparently capable of preventing the development of myocardial infarctions. Some scientists also consider the sex and age of a person to be risk factors. Occupational exposure, environmental factors and socio-economical characteristics have been shown to be strong risk factors for a large number of diseases.

Risk:

According to the socio-political and legal definition (see Section I Art. 2 of EU Directive 98/24/EC), in this connection, risk means the likelihood that cancer will develop under exposure to carcinogenic dangerous substances. The risk or likelihood of occurrence of damage increases with an increasing dose of the dangerous substance or exposure concentration of a carcinogenic substance. The term used on its own does not involve a statement on the level of risk.

Route-to-route extrapolation:

Extrapolation from one route of absorption to another.

The main routes at the workplace are the absorption of substances by the respiratory tract (inhalation) and skin (dermal), whereas in animal studies test substances are often administered via diet or drinking water (orally). Because of the first-pass effect (ibid.), which can be pronounced in some cases, correction factors must sometimes be introduced for transferring the results from feeding, drinking water or gavage studies to workplace conditions.

RR:

Abbreviation for: Relative risk (ibid.).

Safety factor:

See “Extrapolation factor/ safety factor”.
Secondary genotoxicity:

See “Genotoxic”.

Short-term concentration:

Short-term concentrations are potential short-term exceedances of the TKC or the TNKC when maintaining the shift mean value and they are calculated by means of linking with an excursion factor (EF). We differentiate between short-term concentration (KZC) for carcinogenic (KZC_{carc}) and non-carcinogenic effects (KZC_{noncarc}). Also known as STEL (Short-term Exposure Limit (ibid)).

SIR:

Abbreviation for: Standardised incidence ratio (ibid.)

SMR:

Abbreviation for: Standardised mortality ratio (ibid.)

Standardised incidence ratio (SIR):

Number of new cases of a disease observed in a study population in a specific period divided by the number of new cases of a disease that would be expected if the age-specific incidence rates (see “Incidence”) of the study population were the same as the age-specific incidence rates of an external reference population.

Standardised mortality ratio (SMR):

Number of deaths (of a specific cause) observed in a study population in a specific period divided by the number of deaths that would be expected if the age-specific mortality rates of the study population were the same as the age-specific mortality rates of an external reference population.

Statistical power:

Probability at which a statistical test can detect (actually existing) differences (e.g. different tumour rates in exposed versus non-exposed test animals) and differentiate them from random variations. The statistical power for example depends on the sample size (number of test animals in a dose group). This parameter can thus be used to assess the size that a study population should be in order to verify established differences and exclude random effects (see “Calculation of the sample size”).

STEL:

Abbreviation for “Short-Term Exposure Limit”. Exposure peak which can be reached a maximum of four times per shift for a period of no more than 15 mins
in each case.

**Stratification:**

See “Stratum”.

**Stratum (plural: strata):**

In epidemiology: subgroup of a cohort. The classification of a study population into subgroups (e.g. according to age, sex and smoking habits) is referred to as stratification.

**Sub-linearity:**

See “Dose-response relationship”

**Sulfotransferases:**

Metabolic enzymes that belong to the group of phase II enzymes (ibid). They catalyse the conversion of the phosphate group consisting of 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to nucleophilic groups primarily hydroxyl residue) The resulting reaction products are generally more easily soluble and are therefore easier to remove from the organism. In rare cases, sulfation can also cause follow-on reactions leading to very genotoxic metabolites. This bioactivation derived from sulfotransferase is not generally recorded in the standard in-vitro mutagenicity tests (e.g. Ames test).

**Supralinearity:**

See “Dose-response relationship”

**T25 approach:**

Simple risk assessment method recommended by the European Commission for setting specific limits for preparations with carcinogens (Dybing et al., 1997; EC, 2002; Sanner et al., 1997). Based on a concentration with a significantly increased tumour incidence, a dose at which the incidence for this tumour in the animal study is 25% after lifetime exposure is determined by linear interpolation (i) taking into account the background incidence, (ii) if applicable, with correction of a non-lifetime study period, and (iii) assuming complete absorption.

\[ T_{25} = C \cdot \frac{\text{Reference incidence}}{(\text{Incidence at } C - \text{Incidence in the control group})} \cdot \frac{(1 - [\text{Incidence in the control group}])}{1} \]

with:

\[ C = \text{lowest significant tumorigenic concentration or dose (mg/m}^3 \text{ or mg/kg } \cdot \text{d) reference incidence } = 0.25 (25\%) \]
incidence at \( C \) = tumour incidence in % divided by 100

incidence of the control group = tumours in % divided by 100

The T25 value can (if applicable via conversion into a human-equivalent concentration as \( hT25 \)) be described and used as a point of departure for estimating the risk for low doses into the low dose range (see Figure).

Graph of the T25 approach: Calculation of the T25 by means of the incidence of forestomach tumours in rats after exposure to styrene-7,8-oxide (Data from Lijinsky, 1986)

The actual dose-response relationship and the variation of the experimental data are not considered in the T25 approach since only the background incidence and the incidence at an exposure concentration are used for the calculation of the tumorigenic dose 25%.

T25:

Abbreviation for: Tumorigenic dose at which 25% additional incidence is expected. In the experimental system, the T25 is originally specified as a dose (mg/kg x d). In the present Guide transformations into an inhalation concentration are also referred to as T25 or \( hT25 \) (ibid.) (see also “T25 approach”).

T3, T4:

Thyroid tumours: \( T3 = \) triiodothyronine,
\( T4 = \) thyroxine (tetraiodothyronine).
TB region:
See “Tracheobronchial region”.

Threshold, toxicological:
A toxicological threshold for a dose is generally understood to mean a dose or exposure concentration (threshold) below which a specific effect does not occur. The term must not be confused with the “no observed effect level” (NOEL), which specifies a significant observed increase in effect compared with a “background” and depends on the relevant study design.

Just as there are many definitions for the toxicological threshold, it is controversial whether such thresholds exist in individual steps of carcinogenicity induced by chemical carcinogens (Neumann 2006a, b, c). A threshold is generally assumed for “epigenetic”, non-genotoxic carcinogens (e.g. cytotoxic [see “Cytotoxicity”], immune-damaging substances and hormone-like growth stimulators). However, it is also being discussed whether the threshold model can be applied to specific secondarily genotoxic (ibid.) carcinogens (Hengstler et al., 2006). Although there are arguments in favour of such a view, the experimental detection of a threshold seems to be difficult in these cases.

Threshold:
See “Threshold, toxicological”.

TKC:
Abbreviation for tolerable concentration (see “Acceptable/tolerable risk”) that is based on a cancer risk calculation.

TNKC:
Abbreviation for tolerable concentration (see “Acceptable/tolerable risk”) that relates to non-cancerous effects. Corresponds to the “OEL-analogous value” (ibid.)

Tolerable concentration:
Exposure concentration considered as remaining constant across the entire working life which is associated with a calculated “tolerable risk” for the development of an occupational tumour (TKC; ibid. and see Acceptable/tolerable risk).

The term “risk-relevant exposure” is used to distinguish this from an “acceptable concentration”.

If the OEL-analogous value is below the risk of 4:1000, the corresponding concentration can become the (health-based) tolerable concentration based on non-cancerous effects (TNKC; ibid. and see Acceptable/tolerable risk).
Tolerable risk:
See “Acceptable/tolerable risk”

Topoisomerases:
Enzymes that are able to unwind the helically coiled DNA double strand and play an important role in DNA replication and cell division.

Toxicodynamics:
Study of the effect of toxic substances on the organism (see also “Toxicokinetics”).

Toxicokinetics:
Study of the fate of toxic substances in the organism (absorption, distribution, metabolism and excretion) (see also “Toxicodynamics”).

Tracheobronchial region (TB):
Central respiratory tract incorporating trachea and the bronchial system (apart from the respiratory bronchioles, see “Pulmonary region”).

TSH:
Abbreviation for thyroid-stimulating hormone. This messenger, also referred to as the thyrotropic hormone, is formed in the hypophysis (ibid.) and it controls the thyroid gland for growth, iodine uptake and hormone development.

Tunica albuginea:
Term to describe a connective-tissue covering around the spleen, the testis (specifically referred to under “Tunica vaginalis”), the corpus cavernosum in the penis or around the ovaries.

Tunica vaginalis:
Also referred to as “tunica vaginalis testis”, this is a two-layer area of skin that covers the inside of the scrotum and sheaths the testes on male mammals.

U.S. EPA:
See “EPA”.

Unit risk:
According to the concept of the US environmental agency EPA, “unit risk” is understood to be the risk of cancer which arises due to permanent exposure to the
hazardous substance under observation during an entire lifetime in the amount of 1 µg/m³. When converting to the situation at the workplace it should be taken into account that the maximum working time of an individual generally equates to a maximum of 1/6 of their lifetime.

YLL:

Abbreviation for “years of life lost”, that is the years of life lost to premature death. When observing a cohort, YLL is described as the product of multiplying the number of deaths by the remaining average life expectancy (in years) at the point of death.

Zymbal’s gland:

Sebaceous gland in the external auditory canal of rodents. Humans have no Zymbal’s gland.

10.2 Examples of calculation

The examples of calculation reference published documentation and documentation available over the Internet. See in particular:

Example 1: Trichloroethylene – re. Section 5.2 (“break function”)


Example 2: 1,3-butadiene – re. Section 5.1 (linear extrapolation)

### 10.3 Explanations regarding the HEC concept

Table: Information on using MPPD Model Version 2.11

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<th>MPPD 2.11</th>
<th>Rat</th>
<th>Human</th>
<th>Comments/literature</th>
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<td>Human</td>
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**Input Data**
- **Deposition / Clearance**
  - Deposition only

**Calculations**
- Accept settings
- run

**Report results**
- create
  - Set up path, save file
- view
  - View results
- Plot results
  - „Regional Deposition“
  - „Regional fraction“
  - „Regional Deposition“
  - „Regional fraction“
- Possibilities for evaluation of results in graphic format based on preset selection criteria

Calculated deposition: Numerical value for column P
10.4 Documentation template (ERR documentation)

**Position paper:**
Exposure-risk relationship (ERR)
for ##A

##B, 201## (1st draft)
Position paper of the working group ## in the subcommittee UA III:

ERR justification document for ## (as of: ##/##/20##)

1. **ERR (exposure-risk relationship)**
   - **Tolerable concentration** (risk-based; for 4:1000): ## mg/m$^3$; ## ppm
   - **Acceptable concentration** (for 4:10000 up to 2013): ## mg/m$^3$; ## ppm
   - **Acceptable concentration** (for 4:100000 after 2013, 2018 at the latest): ## mg/m$^3$; ## ppm
   - [If applicable: Tolerable concentration (health-based) ## mg/m$^3$ (## ppm)]
   - [Only report if below (health-based) tolerable concentration. If < (risk-based) tolerable concentration, do not document (risk-based) tolerable concentration here]
   - **Excursion factor for short-term exposure**: ##
   - **Reference to skin absorption**: ##

2. **Substance characteristics**
   - **Molecular formula**: 
   - **Structural formula**: 
   - **Molecular weight**: ## g/mol
   - **CAS no.**: ##
   - **Melting point**: #°C
   - **Boiling point**: #°C
   - **Water solubility**: # g/l at 20°C
   - **Partition coefficient (log P$_{OW}$)**: #
   - **Conversion factors**: 1 ppm = ## mg/m$^3$
   - 1 mg/m$^3$ = ## ppm

   Classification according to Regulation (EC) no. 1272/2008 (CLP): ##

3. **Introduction**
   - [Main usage; substance characteristics; mode of action incl. non-carcinogenic effect; information on main points in the risk assessment; distinction]

   A detailed description of relevant toxicological studies can be found in [e.g. Greim (20##) and in ##]. The following information is focused on the studies of key relevance for deriving an ERR.
4. Toxicokinetics/metabolism

5. Toxicity following repeated exposure (ERR-relevant, non-carcinogenic effect)

[Brief, generally only qualitatively; where possible refer to other sources in database. However, should be more detailed and quantitative if relevant for ERR (mode of action, “break function”? or if, in the case of weak carcinogens and higher, non-carcinogenic potency, effects could occur below the tolerable concentration. Can also be associated with acute effects in individual cases. Also to be considered: local effects, high level of sensitising potency, high level of reprotoxicity??]

6. Genotoxicity

In vitro

[further differentiation into primary and secondary genotoxicity; see Section 2.2 of this Guide]

In vivo

[further differentiation into primary and secondary genotoxicity; see Section 2.2 of this Guide]

7. Carcinogenicity

7.1 Data from animal experiments

Inhalation

Oral

Dermal

7.2 Human data

8. Predominant mode of action for carcinogenicity

[See Section 2 of the Guide; address alternative MoA, following this then poss. adjust structure; where applicable, also multiple MoA at the same time, above all ensure qualitative discussion/rationale here]
9. **Derivation of the ERR**

9.1 **Relevant systemic or local non-carcinogenic effect**

[If applicable, comparative derivation of an OEL-analogous “threshold” for non-carcinogenic effects using the OEL concept, or confirmation that local and systemic toxicity of other end points, excluding carcinogenicity and genotoxicity, is irrelevant in the range of the ERR in question.] Value can become the [health-based] tolerable concentration if it is below the (risk-based) tolerable concentration.

9.2 **Exposure-risk relationship in case of carcinogenic effect**

9.2.1 **Cancer localisation with human relevance and quantifiable cancer incidences**

[Justification for selection; explanation of why certain localisations are no longer being considered; information below only covers the localisations that are included in a narrow selection]

**Localisation 1** [replace with specific term]

[Here: quantitative explanation. Specific formulation and/or subdivision according to “mode of action”, assumption 1, assumption 2, etc. corresponding to the argumentation in Section 8; where possible, include figure in explanation, including conversion to human-workplace scenario and, where applicable, route-to-route extrapolation]

**Localisation 2** [replace with specific term]

[Here: quantitative explanation. Specific formulation and/or subdivision according to “mode of action”, assumption 1, assumption 2, etc. corresponding to the argumentation in Section 8; where possible, include figure in explanation, including conversion to human-workplace scenario and, where applicable, route-to-route extrapolation; where applicable, continue with further localisation etc.]

9.2.2 **ERR / risk quantifications and OELs of other organisations**

[If applicable, where there are discrepancies, discuss how these differences came about]

9.3 **Conclusion**

9.3.1 **Summary of the database, data assessment, justification for the selection of studies and derivation logic**

[Justification for the selection from the alternatives in Section 9.2 as criterion for assessment]

9.3.2 **Table of results**

Please see below the results for the additional nominal risks of developing cancer in the case of inhalation exposure across the duration of a working life:
<table>
<thead>
<tr>
<th>Risk/basis</th>
<th>Concentration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Point of departure”: [e.g. T25, BMD10] for species/study</td>
<td>## mg/m³; ## ppm</td>
</tr>
<tr>
<td>4:1000</td>
<td>(tolerable concentration; risk-based)*</td>
</tr>
<tr>
<td>4:10000</td>
<td>(Acceptable concentration up to 2013)</td>
</tr>
<tr>
<td>4:100000</td>
<td>(Acceptable concentration after 2013, 2018 at latest)</td>
</tr>
<tr>
<td>Non-carcinogenic effect relevant in comparison to cancer risk ([OEL-analogous value], associated cancer risk: ## x:1000); for species/study</td>
<td>## mg/m³; ## ppm (tolerable concentration; health-based)*</td>
</tr>
</tbody>
</table>

[*Only report tolerable concentration (health-based) here if below the tolerable concentration (risk-based). Conversely: only report tolerable concentrations (risk-based) here if below tolerable concentrations (health-based). In this case do not report tolerable concentration (health-based) here, only in Section 9.1), insert where applicable in terms of the concentration sequence*]

Where a linear extrapolation takes place during the identification of the acceptable concentration, this generally corresponds to a (conservative) convention and not a procedure based on a scientifically proven procedure (“linear extrapolation principle where knowledge lacking”). This convention character also applies to a limited extent when using a “break function”, in which case additional scientific findings are employed in developing the ERR:

**9.3.3 Discussion; more in-depth explanation of the weight-of-evidence approach**

[Cite missing studies; allocation of the substance-specific uncertainties with the POD derivation; characterisation of the plausibility considerations for the POD including the uncertainties; where applicable, cite span of discussed values; cite principle of averaging (e.g. “geometric mean value for present possible POD”), justification for the procedure (positive reasons)].

**9.3.4 Short-term values for daily mean to be maintained**

[Cite and explain excursion factor following Section 6.4 of this Guide]
9.3.5 Other end points

[Information on key points excluding carcinogenicity and recommended handling; e.g. “(skin) sensitising effect is possible and was not quantitatively assessed in the present context” or “there are insufficient studies available to assess the eco-toxicity” or “cardiovascular effects are described for mixed exposure in relevant concentration, but were not included in the present assessment.”, etc.]

Note: In the case of an OEL-analogous value, if a risk of reproductive toxicity exists (based on the formal classification according to “pregnancy group: Z” for OEL values), this should be specially noted, including when at a low concentration, with the limitation of the additional cancer risk, protection against reproductive toxicity effects exists.

9.3.6 Percutaneous absorption

[Discuss whether, where applicable in addition to the air path, percutaneous absorption makes a relevant contribution to the body burden]

9.3.7 Possibilities for biomonitoring

[Add information about possible opportunities for biomonitoring]

10. Literature

Annex

Detailed calculations and detailed tables
11 Literature

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