Guide values for indoor air: First update of the German risk assessment procedure (basic scheme) [1]

Communication from the Ad-hoc Working Group on Indoor Guide Values of the Indoor Air Hygiene Commission and the States´ Supreme Health Authorities

Abstract

In order to harmonise recommendations on the evaluation of indoor air contaminations by means of guide values, the Ad-hoc Working Group on Indoor Guide Values of the Indoor Air Hygiene Commission of the German Federal Environment Agency and of the States´ Supreme Health Authorities has updated the procedures for toxicologically derived indoor air guide values for individual substances or groups of substances. In general two guide values are proposed by the Working Group. Guide Value II (RW II) is an adverse effect-related value, based on current toxicological and epidemiological knowledge of a substance's effect threshold, usually the LOAEC or a benchmark concentration from human or animal studies. Guide Value I (RW I) represents the concentration of a substance in indoor air for which, when considered individually, there is no evidence at present that even lifelong exposure is expected to have any adverse health impacts.

Individual steps in the derivation of Guide Value II are: i) identification of the pivotal study and the point of departure (PoD), conversion from short-term to continuous exposure by adjustment for ii) study length (subacute – subchronic – chronic) and iii) exposure duration (hours/day and days/week), extrapolation from animal to man by iv) interspecies variability (allometric, toxicokinetic and dynamic factors), consideration of sensitive individuals by v) intraspecies variability (kinetic and dynamic factor), and vi) physiological differences within the population (i.e. children factor), and finally vii) consideration of the quality of database. The quality of the pivotal study is assessed according to the criteria proposed by Klimisch et al. (1997). The assessment factors have been harmonized with recent recommendations by WHO (IAQG 2010) and ECHA (2010) guidance document R 8. RW I is derived from RW II by introduction of an additional factor (usually 10) but can also be derived, if no reliable LOAEC is available, from a "no observed adverse effect concentration" (NOAEC).

A template containing the key information on the chemical and the pivotal study and transparently presenting the assessment factors and derivation of the guide values and a glossary of terms complete the recommendation.

Keywords

Guide values – indoor air – point of departure – assessment factors – data quality

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1 Introduction

In Germany, pollutants in indoor air are evaluated on the basis of differently weighted assessment standards: legally binding *limit values*[2], health-based *guide values or guidelines*, or statistically determined *reference values* [1-3]. This Communication describes the procedure currently applied by German competent authorities to define guide values for indoor air.

Based on a mandate by the Conference of Health Ministers [4], the Ad-hoc Working Group on Indoor Guide Values, which is composed of members of the Indoor Air Hygiene Commission and the States´ supreme health authorities, develops guide values for indoor air uniformly applicable in all federal states of Germany. The assessment of indoor air quality, particularly in the context of adverse health effects and hazards in public buildings such as schools and day-care centres, continues to be an important task for environmental health protection. The Ad-hoc Working Group on Indoor Guide Values therefore considers it necessary to continue to provide guide values for indoor air in the future.

The purpose of setting guide values is to specify existing legal standards. The legal framework for deriving guide values for indoor air pollutants from built environment is found mainly in building regulations, in the form of the respective state building code. Article 3 of the Building Code provides that a building must not pose a potential hazard to the health of the user. Guide values derived in that sense represent *hazard values*.

In justified individual cases, e.g. when impact of pollutants from neighbourhood sources into indoor environments is likely, provisions of the Federal Immission Control Act apply. Unlike the building regulations, this Immission Control Act allows an assessment to be carried out on the basis of a health hazard as well as under the aspect of preventive health protection. The latter served as the basis for the limit values in the Second Federal Immission Control Ordinance for tetrachloroethene in the indoor air of rooms adjacent to dry cleaning shops being the only ones so far to have been laid down in relevant legislation.

For working environments not subject to hazardous substances legislation, the Workplaces Ordinance provides that they must have sufficient fresh air conducive to health (Requirement 3.6: ventilation). This is another area where guide values for indoor air constitute an important assessment standard.

Finally, guide values also provide significant support when it comes to the question under rent law whether a flat can be used without any health risks.

Although people spend much of their lives indoors, there are, overall, only few legally binding principles in place for the evaluation of indoor air quality. However, it should be kept in mind that the majority of indoor environments are used privately and, contrary to public buildings, statutory regulations on indoor air cannot be enforced for

[2] Terms printed in italic are explained in Annex A: Definition of Terms

private buildings. Moreover, the setting of rigid limit values would make it difficult if not impossible in practice to take the many and varied indoor conditions (air change, room size, sink effects, secondary contamination, etc.) into account. The concept of guide values circumvents this hurdle.

2 General principles

The Ad-hoc Working Group on Indoor Guide Values considers it to be an important goal of its work to derive indoor air guide values by using a procedure as uniform and comprehensible as possible. To this end, it formulated a definition of guide values and developed and published a methodology for their derivation, which it refers to as ‘basic scheme’ [5]. This Communication refines the basic scheme and updates it to reflect current knowledge.

In deriving indoor air guide values, the Working Group uses extrapolation factors (also referred to as “assessment factors” [6]) in certain cases. These extrapolation factors represent reliable assumptions (“conventions”) in the absence of sufficient knowledge. Deviating from these factors is possible if there is evidence in individual cases which makes doing so justifiable or even necessary. Performing a reasoned selection of the data that are to be used as a basis for deriving guide values is one of the key tasks of the Working Group.

The results of the work of the Ad-hoc Working Group are published in *Bundesgesundheitsblatt* and made available on the Internet at http://www.umweltbundesamt.de/gesundheit/innenraumhygiene/richtwerte-irluft.htm.

2.1 Definitions

According to the illustrative list given by the Ad-hoc Working Group in 2007 and the specific distinction it drew on that occasion with regard to *inter alia* working areas in which hazardous substances are handled [1], the term “indoor environment” covers private rooms in which people live or spend time, certain workplaces in buildings as well as the passenger compartments of motor vehicles. VDI Guideline 6022 Part 3 defines rooms intended or suitable for people to stay in not just temporarily to be all rooms in which people regularly spend more than two hours per day or more than 30 days a year [3].

For evaluation of air pollutants in these indoor environments, the Ad-hoc Working Group defines two graduated guide values [5]. In keeping with the requirements under the building code when defining indoor air guide values the Working Group derives a concentration at and above which harmful effects on human health cannot be excluded with sufficient probability in the case of sensitive room users. This concentration is termed Guide Value II (Richtwert II, RW II), or “hazard value’”, and is defined as follows:

Guide Value II (RW II)

Guide Value II is an effect-related, substantiated value that is based on toxicological and epidemiological knowledge of a substance's effect threshold and takes extrapolation factors into account. Guide value II is usually a long-term value, but can also be derived as a short-term value and is in this case marked as such (RW II_K).

Guide Value II represents the concentration of a substance in indoor air at and above which action needs to be taken immediately because this concentration is apt to endanger the health of sensitive persons including children, particularly when they stay in these spaces constantly for long periods of time. The need for action must be understood as meaning a need to consider immediately whether, e.g., remedial measures should be taken to reduce exposure. It may be necessary to recommend the closure of the rooms concerned.

The use of guide values as benchmarks presupposes that a measurement be performed under normal conditions of use. If Guide Value II is found to be exceeded, a control measurement should be carried out immediately to confirm this finding. Where possible and appropriate in individual cases, the internal exposure of room users may be determined.

In addition, the Ad-hoc Working Group derives a concentration level below which adverse health effects are not expected to occur. This concentration is termed Guide Value I (Richtwert I, RW I), or "precautionary value", and is defined as follows:

Guide Value I (RW I)

Guide Value I represents the concentration of a substance in indoor air which, when considered individually, is not expected to cause adverse health effects in sensitive persons even in the case of lifelong exposure, according to current knowledge. Concentrations above this value are deemed to be associated with a hygienically undesirable exposure above usual levels. For precautionary reasons, there is also need for action in the concentration range between RW I and RW II. RW I can serve as remediation target value. It should not be merely complied with, i.e., concentrations should remain below RW I if possible.

Regarding the measures that should be taken in a given case where guide value I or II is exceeded, the reader is referred to Section 4.3, Use of guide values in risk management, of the guidance issued by the Ad-hoc Working Group [1].

The Guide Values are expressed as a rule in milligram per cubic metre (mg/m^3), as done by the European Chemicals Agency [6]. They are indicated following rounding to the first significant digit.

2.2 Selection of the critical effect endpoint

As a first step, for each substance all relevant effect endpoints must be considered and the most sensitive toxic endpoint (critical effect) identified. If a carcinogenic effect proves to be the most sensitive endpoint, the toxicological assessment should be carried out on the basis of this carcinogenic effect. The procedure to be applied in this case will be described in a separate communication.

For assessment of a substance's carcinogenic potential, the Ad-hoc Working Group generally follows existing legally binding European classifications [7], unless other findings suggest otherwise. An overview of categories used in the EU and by other organizations to assess the carcinogenic potential of a substance or group of substances is provided in Annex B.

For substances which have a threshold mode of action for the most sensitive toxic endpoint, guide values are also derived, on the basis of this principle, if they are classified as suspected carcinogens (classification as "EU category 2 carcinogen" since 1 December 2010 [7] – see Table B1 in the Annex). Such substances include, for example, ones which are respiratory irritants in the lower dose range that is of interest here. Only a significantly higher minimum concentration in air that irritates the respiratory tract for a longer period of time can potentially lead to the development of a tumor as a result of long-term (local) inflammation [8]. The derivation of guide values for such substances, therefore, is intended to prevent inflammation and the potential consequences described. The establishment of guide values for suspected carcinogens of this kind has proved its value in practice.

3 Data used as a basis

3.1 Selection of pivotal study

Choosing the pivotal study, also referred to as critical study or reference study, is a key step in the derivation of guide values for indoor air. To minimize uncertainty in this derivation, the basic scheme preferably uses human studies as a starting point, in line with national and international standard practice. In the absence of suitable human data, animal studies should be used.

The studies most suitable for transfer to the indoor human exposure situation are those with a dosing period as long as possible, i.e., long-term inhalation studies. Since studies of corresponding duration are often unavailable, studies with shorter dosing periods can also be used. The Ad-hoc Working Group considers a study with repeated exposure to be the minimum requirement, i.e. at least a sub-acute study or a developmental or reproduction toxicity study. An acute study, in contrast, is not normally suitable in the opinion of the Ad-hoc Working Group, especially since sufficiently sound factors for extrapolation from an acute study do not exist (see Section 4.1).

In the absence of inhalation studies, oral studies can be used by applying route-to-route extrapolation (see Section 4.2). This presupposes, however, that the primary

effect of the relevant substance is an adverse systemic effect and that respiratory tract irritation is not to be expected. If a feeding study points to an irritating effect on the respiratory tract, an additional factor may have to be applied.

In order to perform route-to-route extrapolation, it is essential to have knowledge of and to consider the similarity of the critical effect and the toxicokinetics in inhalation and oral exposure [9, 10]. Physiologically based pharmacokinetic (PBPK) models can be suitable for and be taken into account in dosimetric extrapolation of route-to-route and interspecies differences.

3.2 Quality of pivotal study

The Ad-hoc Working Group evaluates the quality of the study it uses as a basis for deriving guide values. The quality of this study should be as high as possible. The Ad-hoc Working Group classifies the quality of pivotal studies as follows:

- Studies meeting categories 1 and 2 of the Klimisch criteria [11] are deemed to be of good and satisfactory quality, respectively (see Annex, Table B2).
- In the case of studies of sufficient quality but showing considerable data gaps, derived guide values are accompanied with the advice “with reservation” and marked as “provisional”.
- If data quality is insufficient, guide values cannot be derived. The Ad-hoc Working Group may choose to formulate advice describing the situation.

If several suitable studies are available, guide values are calculated for all studies, where appropriate, using the extrapolation factors described in Section 4, and either the lowest value or the value obtained in a process known as “weight of evidence” is selected.

3.3 Point of departure in the derivation of indoor air Guide Value II

Having regard to the hazard orientation required under the building code, the Ad-hoc Working Group generally uses the lowest tested concentration at which an adverse effect was observed in a test conducted under specific conditions (lowest observed adverse effect concentration - *LOAEC*) as the *point of departure*, or reference point. In evaluating whether a given effect is to be regarded as adverse, the Ad-hoc Working Group uses criteria proposed by different organizations [12-15] (see Annex, Table B3). When choosing the LOAEC it must be assessed whether the likelihood and severity of the potential effect are still acceptable.

If a reliable LOAEC is unavailable or cannot be estimated from a LOEC or NOAEC as detailed below under “Procedure”, a benchmark dose (BMD) approach may be applied [6, 16].

Procedure. The Ad-hoc Working Group usually uses the LOAEC as point of departure (initial concentration) for the derivation of Guide Value II.

If only a LOEC (lowest observed effect concentration) is available instead of a LOAEC or if adverseness cannot be reliably assessed, the Ad-hoc Working Group multiplies the LOEC with a factor of 3 to estimate a LAEC (lowest adverse effect concentration), provided that the study in which the available LOEC was determined is valid.

If neither a LOAEC nor a LOEC is available, but a NOAEC (no observed adverse effect concentration) is, the Ad-hoc Working Group multiplies the NOAEC with a factor of 3 to estimate an LAEC, provided that the study in which the NOAEC was determined is valid. Given the uncertainties which this step involves, the Guide Value II derived on this basis is designated as provisional (also see Section 3.2). If the available dataset is suitable for estimation of a BMD, the $BMDL_{10}$ may be used as the starting point for further derivation [17]. When doing so, the conditions under which the $BMDL_{10}$ was estimated must be described and evaluated.

3.4 Point of departure in the derivation of indoor air Guide Value I

By derogation from the procedure previously applied, the Ad-hoc Working Group will in future generally use the NOAEC as the starting point for the derivation of Guide Value I. If a NOAEC cannot be determined at all or not reliably, a NAEC (no adverse effect concentration) should be estimated based on the LOAEC.

How far apart from the LOAEC the NAEC should be primarily depends on the spacing between the dose steps chosen in the relevant study. At dose steps with a factor of 5 to 10, a factor of 10 is usually applied to extrapolate a NAEC from a LOAEC (e.g. [8, 13]). At dose steps with a factor of 2 to 3, a smaller factor, e.g. of 3, is justifiable for LOAEC-NAEC extrapolation (e.g. [18]). In its guidance document, the ECHA recommends the application of an assessment factor of normally at least 3 to up to 10 in exceptional cases [6].

If BMD estimates are available, the $BMDL_5$ can be used as NOAEC [6, 16]. The datasets produced in epidemiological studies are often significantly larger than those of animal experiments, so that a $BMDL_1$ can be derived on the basis of these studies. This was done by the EFSA for example, which for lead used a $BMDL_1$ derived on the basis of large-scale human studies as NOAEC [19].

According to the previous version of the basic scheme, the setting of Guide Value I was also meant to ensure sufficient protection against odour nuisance [5]. The basic scheme left open in what way odour perception should be taken into account.

Procedure. The Ad-hoc Working Group uses the NOAEC as starting point for the derivation of Guide Value I, if a reliable NOAEC is available.

If information regarding the NOAEC is absent or uncertain, a NAEC is estimated on the basis of the LOAEC by dividing it as a rule by a factor of 10. If the LOAEC was observed to cause only a minor effect and the dosage regime warrants the conclusion that the NAEC could be close to the LOAEC, the Ad-hoc Working Group considers it justifiable to calculate the NAEC by dividing the LOAEC by a factor of 3.

If the available dataset is suitable for estimation of a BMD, the $BMDL_1$ or $BMDL_5$ may be used as the starting point for further derivation. When doing so, the conditions under which the relevant BMDL was estimated must be described and evaluated.

The procedure to be applied for health assessment of odours or odourous substances will be described in a separate communication.

3.5 Time scaling of the initial concentration

If the exposure conditions in the chosen pivotal study differ from the timeframe of the guide value to be derived, the initial concentration must be corrected for time differences (referred to as “time scaling”) [6]. The guide values derived by the Ad-hoc Working Group are normally geared to continuous exposure. In continuous 24-hours exposure there is no recovery whatsoever, whereas an exposure design based on 6-hour exposure includes an 18-hours period of recovery [6]. Exposure conditions of 24 hours per day will most likely be found in population-based studies, whereas the exposure duration in occupational studies will mostly be 8 hours per day on 5 days per week. In so-called chamber exposure studies, subjects are sometimes exposed for even shorter periods (e.g. 2 or 4 hours). Animal inhalation studies often have an exposure duration of 6 hours per day over 5 days per week, and in developmental or reproduction toxicity studies exposure can last, e.g., 6 hours on the relevant gestational days.

To correct the initial concentration for time differences, for occupational studies WHO uses an adjustment factor of 168 hours/40 hours = 4.2 [8] and ECHA uses a factor of 24 hours/8 hours = 3 [6]. For animal studies ECHA gives an adjustment factor of 24 hours/6 hours = 4, but points out that this factor may underestimate the health risk for continuous exposure [6].

Procedure. The Ad-hoc Working Group adjusts the initial (PoD) concentration to reflect continuous 24 hour/7day exposure as appropriate according to the exposure conditions of the underlying study.

If in the case of repeated dose studies it can be assumed that a certain effect such as sensory irritation is mainly driven by the exposure concentration and not the total dose, the Ad-hoc Working Group dispenses with time-scaling of the initial concentration.

4 Selection of extrapolation factors

In line with international standard practice, the basic scheme provides default values for the selection of extrapolation factors. The previous version of the basic scheme points out that deviation from these default factors is possible if further findings so warrant. Since the basic scheme was first developed, the discussion on the use of certain extrapolation factors in regulatory toxicology has moved on. Today, a more differentiated view is taken of factors applied to account for the study duration and for interindividual and interspecies variability [6, 20, 21].

In Germany, the Committee on Hazardous Substances (AGS), in its TRGS 901 (technical rules on hazardous substances 901 as recast by BekGS 901 which presents criteria for derivation of occupational exposure limits), proposed a standard procedure for selecting certain extrapolation factors [22]. Extensive guidance on standardized extrapolation factors can be found in “Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health”, which was issued by ECHA for chemical safety assessment under the REACH Regulation [6].

The AGS and ECHA guidance has since been taken into account by the Ad-hoc Working Group in its work to derive indoor air guide values. As a result, some differentiations of the basic procedure have been made in practice. In light of this, the Ad-hoc Working on Indoor Air Guide Values has reviewed the basic scheme concept and modified it to reflect current knowledge. The sections below provide a description of the various extrapolation factors needed to derive the guide values and the rationale on which they are based.

4.1 Duration of study

The indoor air guide values defined by the Ad-hoc Working Group are normally long-term guide values (see Section 2.1). In the absence of a long-term (chronic) study, at least a study with repeated exposure (see Section 3.1) must be available as a starting point.

For extrapolation from a subacute or subchronic study to a long-term exposure situation, both BekGS 901 [22] and ECHA [6] suggest a factor of 6 (subacute – chronic) and 2 (subchronic – chronic). Current evaluations of studies (e.g. [23]) support the selection of these extrapolation factors.

ECHA believes that time-scaling is not appropriate for certain endpoints, such as sensory irritation, where the endpoint is mainly driven by the exposure concentration, and not by the total dose [6]. ECHA does not, however, give detailed procedural guidance on this subject.

Procedure. The Ad-hoc Working Group normally uses an extrapolation factor of 6 (subacute – chronic) or 2 (subchronic – chronic) to account for the study duration.

Where guide values are derived on the basis of developmental toxicity studies these extrapolation factors are not applied because such studies are already concerned with a specific sensitive time window.

When guide values are derived on the basis of sensory irritation studies it should be considered on a case-by-case basis whether the application of an extrapolation factor to account for the study duration is appropriate.

4.2 Interspecies differences

If a sound human study is not available, the Ad-hoc Working Group uses results from animal studies, preferably inhalation studies. In agreement with the World Health Organization [24], the previous version of the basic scheme [5] provided a total default factor of 10 for the overall assessment of interspecies differences with regard to both toxicodynamics and toxicokinetics. This view no longer holds. At the end of the 1990s, WHO suggested that the interspecies factor be divided into a factor of 4 for toxicokinetics and of 2.5 for toxicodynamics [20]. ECHA goes further, recommending a fundamentally different approach between oral exposure and inhalation exposure studies [6].

When an oral study is used as starting point, ECHA recommends applying, instead of the above factor for the toxicokinetic component, internationally accepted factors known as allometric scaling factors (e.g., mouse: 7; hamster: 5; rat: 4; guinea pig: 3) to account for differences in metabolic rate, plus a factor of 2.5 for differences in toxicodynamics [6, 22]. In the absence of route-specific information, it recommends that 50% absorption should be assumed for oral exposure and complete absorption for inhalation exposure [6] (see Annex C).

In contrast to this, ECHA and AGS believe that applying an allometric scaling factor is unnecessary in the case of inhalation studies, since the respiratory rate directly correlates with the basal metabolic rate. In the case of systemic effects following inhalation exposure, they thus consider a factor of 1 for interspecies differences as adequate [6, 22]. To account for remaining uncertainties, ECHA proposes an extrapolation factor of 2.5 for differences in toxicodynamics [6]. This extrapolation factor can also be applied in the case of, e.g., local effects, including specific effects on the respiratory tract caused by local metabolism. It can be dispensed with if sufficient data and studies with several species are available.

An additional extrapolation factor may be necessary to account for, e.g., possible differences in absorption rate between animal and humans.

Procedure. The Ad-hoc Working Group generally follows the approach taken by ECHA and AGS as described above and considers a value of 1 as interspecies factor for inhalation studies as adequate. It must be verified in this context whether the assumption of an identical rate of absorption between animal and humans following inhalation is correct. An extrapolation factor of 2.5 to account for differences in toxicodynamics should be used if, for example, only one mammalian species was tested in the study selected.

If an oral animal study is used as the starting point, the relevant species-specific allometric scaling factor should be applied to account for differences in metabolic rate as well as a factor of 2.5 for differences in toxicodynamics. In addition, in the absence of route-specific information, 50% absorption should be assumed in the case of oral exposure and complete absorption in the case of inhalation exposure.

4.3 Intraspecies differences

For most effect endpoints, sufficient information on interindividual variability is not available. The World Health Organization normally applies a factor of 10 to account for intraspecies variability, for both occupational and animal studies. In agreement with WHO's approach, the Ad-hoc Working Group too normally applied a total factor of 10 for interindividual variability. In the case of larger population or occupational studies, reducing or dispensing with this factor is, in general, conceivable if it can be assumed that the study conditions are sufficiently representative of sensitive groups of individuals.

Nasal irritation represents a specific exposure-response situation. Evaluation of data from human studies on irritating effects of a number of volatile organic compounds on the respiratory tract showed that the sensitivity of the majority of the subjects (97.5%) deviated from the average by less than a factor of 5 [25]. Accordingly, the Danish National Research Centre for the Working Environment suggested that a factor of 5 should be used in risk assessments to account for interindividual variability in irritation [21]. The Ad-hoc Working Group has followed this suggestion in the assessment of a number of respiratory irritants.

The Ad-hoc Working Group uses an additional extrapolation factor of 2 to protect especially sensitive groups of individuals, particularly children. This factor is considered necessary because of the fact that compared with adults, breathing rates per kg of body weight are about twice as high in children and up to three times as high in newborns [26, 27]. ECHA considers it justified to employ, additionally to the above standard factor of 10 for intraspecies differences, another factor of up to 10 to account for particular vulnerability in the embryonic or early childhood phase [6].

Procedure. The Ad-hoc Working Group takes intraspecies differences into account by applying an assessment factor of 5 for the endpoint irritation and of 10 for other endpoints. As suggested by ECHA [6], it may choose to reduce this extrapolation factor to 2 if reliable human studies are available.

In addition, the Ad-hoc Working Group generally applies an extrapolation factor of 2 to account for physiological differences, particularly the higher respiratory minute volume per kg of body weight which children have compared to adults. In the case of reproduction toxicity studies, this so-called children factor can normally be omitted since these studies already focus on a sensitive group.

Remarks

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Annex A: Definition of Terms

Adverse effect: Change in morphology, physiology, growth, development or life span of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences [13].

BMD (benchmark dose): The BMD procedure is based on the statistical analysis of dose-response data from animal and epidemiological studies, and, unlike the LOAEC/NOAEC approach, it considers the complete shape of the dose-response curve. The BMD procedure determines the dose that is associated with a predefined benchmark response (BMR, e.g. 10% increase in the incidence or prevalence of an effect of interest) [16, 28].

BMDL (benchmark dose level): Lower 95% confidence limit of the benchmark dose with an incidence of x%.

Extrapolation factor: protective factor, also referred to as assessment factor (AF). Standardised = default factor: Pragmatic, numerically expressed exposure factor which does not change with the substance considered (e.g. inhalation rate, size of skin surface) and which is used in calculations as standard value in the absence of relevant data.

Guide value: An assessment value derived on the basis of suitable information on toxic effects and dose-response relationships gained from epidemiological or animal studies. It may be defined for different levels of protection; see Hazard value (Guide Value II); Precautionary value (Guide Value I).

Guideline: A legally non-binding, health and hygiene-based assessment value for a substance or group of substances. It is derived in cases where available systematic practical experience indicates that the likelihood of complaints and adverse health effects increases with increasing concentration of the substance or group of substances but where the available knowledge is, overall, insufficient to derive a guide value [3]. Guidelines exist for, e.g., carbon dioxide, TVOCs and fine particulate matter in indoor air. In a broader sense, guidelines also include the values set by supraregional organizations and bodies such as the World Health Organization’s guidelines, e.g. the WHO Air Quality Guidelines. As stressed by the WHO again and again, these guidelines should be transformed into national limit or guide values in accordance with the respective legal frameworks [8, 13, 24].

Hazard value: See text under “Guide Value II”

Klimisch criteria: See Table B2 in Annex B.

Limit value: A legally binding value which is defined taking into account health criteria as well as economic and technical aspects. It must be complied with and, with a view to measurement error and other factors, concentrations must be sufficiently ensured to remain below it. Limit values are either assessment values laid down in legislation or administrative limits laid down in, e.g., the German states´ technical building (TB) regulations, in technical rules for hazardous substances (TRGS) or in administrative provisions [2]. For indoor air, Germany so far has only one limit value that is

applicable nationwide (for tetrachloroethene (2. BImSchV)) as well as technical building provisions on PCP and PCBs which vary from federal state to federal state.

LO(A)EC: Lowest observed (adverse) effect concentration. The lowest observed adverse effect concentration is defined as the lowest exposure concentration with a biologically and/or statistically significant increase in the frequency or severity of an adverse effect among an exposed population relative to a non-exposed group [29].

NO(A)EC: Highest concentration of a substance in a test at which no statistically significant (adverse) effects were observed. While some effects may occur at the NOAEC compared to a suitable control group, these are regarded neither as adverse nor as leading to adverse effects [6].

POD (point of departure): The dose-response point that marks the beginning of a low-dose extrapolation. This can be the lower bound on dose for an estimated incidence or change in response level from a dose-response model or a NOAEC or LOAEC for an observed incidence or change in level of response.

Precautionary value: See text under “Guide Value I”

Reference value: A reference value characterizes the respective bound on the range of concentrations generally present in an environmental medium, the so-called background pollution. Reference values provide no indication of possible health risk. According to an international convention, the (upper) reference value is defined to be the 95^{th} percentile of the concentration of a substance in the environmental medium studied for a given reference population [1].

Annex B: Categories

Table B1: Comparison of categories used to classify carcinogenic substances [7, 31]

EU category (from 1.12.10)*	Description EU	EU category (until 30.11.10)	DFG category**	Description DFG	Example
1A	Proven to have carcinogenic potential for humans	1	1	Carcinogenic for humans as sufficiently indicated by epidemiological studies	Benzene
1B	Presumed to have carcinogenic potential for humans based on animal evidence	2	2	May be regarded as carcinogenic for humans based on evidence from animal studies or the like	Penta-chloro-phenol
2	Suspected human carcinogens based on evidence from animals and humans but which is not sufficiently convincing for placement in Category 1A or 1B	3	3	Cause for concern due to proven or potential carcinogenicity. Cannot be finally evaluated because of insufficient information. Provisional classification.	Naphthalene
			3a	Substances which could be placed in categories 4 or 5 subject to a MAK value yet to be determined	Dichloro-methane
			3b	Evidence from in vitro or animal studies, further studies necessary.	PCBs
			4	Non-genotoxic effect mechanism. No or very small cancer risk if MAK value is complied with.	Tetrachloro dibenzo dioxin
			5	Genotoxic substances. Very small contribution to cancer risk if MAK value is complied with.	Styrene

* EU (2008), Table 3.6.1 [7]
**DFG (2011), Chapter III [31]

Table B2: Criteria by Klimisch et al. [11]

Klimisch criterion	Short description	Explanation
1	Reliable without restriction	"Studies or data…which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method".
2	Reliable with restrictions	"Studies or data…(mostly not performed according to GLP) in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable".
3	Not reliable	"Studies or data…, in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment".
4	Not assignable	"Studies or data…, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)".

Table B3: Example of the ranking of effect thresholds [30]		
Rating	**Effect level**	**Effect**
0	NOEL	No observable effect
1	NOAEL/LOEL	Enzyme induction or other biological changes compatible with possible effect mechanisms, with no pathologic change and no change in organ weights
2	NOAEL/LOEL	Enzyme induction and subcellular proliferation or other changes in organelles compatible with possible effect mechanisms, but no other apparent effects
3	NOAEL/LOEL	Hyperplasia, hypertrophy or atrophy, but no change in organ weights
4	NOAEL/LOEL	Hyperplasia, hypertrophy or atrophy with changes in organ weights
5	LOAEL	Reversible cellular changes including cloudy swelling, hydropic change or fatty changes
6	(LO)AEL	Necrosis or metaplasia with no apparent decrement of organ function
7	(LO)AEL	Slight, reversible changes in organ function

Annex C: Calculation methods

1. Route-to-route extrapolation

For route-to-route conversion of, e.g., a LOAEL based on an oral dose [mg/kg bw day] into an inhalation exposure LOAEC [mg/m^3], the Ad-hoc Working uses the following factors:

Difference in bioavailability (fb) →
% $absorption_{oral}$ / % $absorption_{inhal}$

Since uncertainty is high for the inhalation route and the risk may be underestimated compared to the oral route, a figure of 100% is assumed for bioavailability via inhalation unless information is available that suggests otherwise. The extrapolated LOAEC is calculated as follows:

LOAEC [mg/m^3] = fb x $LOAEL_{oral}$ [mg/kg bw d] x 70 [kg bw]/20 [m^3/d]
(Formula 1)

2. Conversion of ppm into mg/m^3

In some studies, exposure is expressed as ppm. Unless otherwise indicated in the study itself, ppm is converted to mg/m^3 according to the formula:

C [mg/m^3] = ppm x [molar mass in g/mol] / [molar volume in l/mol]
(Formula 2)

mg/m^3 = ppm x molar mass / 24.1 l; according to TRGS (technical rules for hazardous substances), the molar volume must be standardized at a temperature of 20 C and a pressure of 101.3 kPa and then amounts to 24.1 litres.