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Occupational exposure limit values for carcinogens – The German Hazardous Substances Committee's Working Group „AK CM"

G. H. Degen, E. Nies

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Abstract

The tasks of the Working Group „Limit Values and Classification of Carcinogenic and Mutagenic Substances" (AK CM) within the German Committee on Hazardous Substances include the scientific derivation of occupational exposure levels for carcinogens. The present paper illustrates the Working Group's activities and approaches by way of examples and discusses possible consequences and perspectives.

Luftgrenzwerte für krebserzeugende Arbeitsstoffe – aus der Arbeit des „AK CM" im AGS

Zusammenfassung

Zu den Aufgaben des Arbeitskreises „Grenzwerte und Einstufungen für CM-Stoffe" (AK CM) im Ausschuss für Gefahrstoffe zählt es, für krebserzeugende Substanzen wissenschaftlich begründete Arbeitsplatzgrenzwerte vorzuschlagen. Anhand ausgewählter Stoffbeispiele will der vorliegende Beitrag Arbeitsweise und Positionen des AK CM mit Blick auf eine zeitgemäße Grenzwertsetzung für Kanzerogene erläutern sowie mögliche Konsequenzen und Zukunftsperspektiven diskutieren.

1 Subject

Since 2005, the AGS (Committee for Hazardous Substances of the German Federal Ministry of Labour and Social Affairs) has been maintained by three subcommittees which in turn are able to create working groups of their own on a project basis. Against this background, Subcommittee III (responsible for hazardous substance evaluation) launched the AK CM working group, which has responsibility for limit values for CM substances and for their classification. The members of this group were to formulate specific proposals for:

- Classification of individual substances according to their carcinogenic and mutagenic (CM) properties, in accordance with the criteria of the German Hazardous Substances Ordinance and the EU Dangerous Substances Directive, 67/548/EEC [1]
- Definition of and arguments for occupational exposure limits (OELs) for substances classified as carcinogens

The activities of the AK CM concerning the definition of limit values for carcinogens will be discussed below in more detail.

2 Background

With the introduction of the concept for occupational exposure limits under the new German Hazardous Substances Ordinance, under which only *health-based* OELs are now permitted, substances for which toxicological thresholds of action cannot be determined with adequate reliability were deleted from the German lists of limit values. These included substances of which the toxicological and occupational medical effects have not been closely studied, and also the majority of carcinogens. At the present state of knowledge, it is considered virtually impossible to state concentrations, particularly for genotoxic carcinogens, below which chronic harmful effects upon health need not generally be anticipated, as required by the German Hazardous Substances Ordinance. The very existence of threshold doses in this context is frequently called into question (cf. [2 to 4]).

New approaches to the formulation of limit values should consequently be taken. The Ministry in charge therefore instructed the AGS to develop a concept for the deduction of risk-based atmospheric limit values. The "Risk acceptance" project group of the AGS, which was composed of stakeholder representatives from all affected social

groups, soon agreed upon "acceptable" and "tolerable" cancer risks at the workplace, the levels of which were defined at 4:100,000 and 4:1,000 respectively (see Page 287 ff. in the present issue).

Concurrently with this activity, Subcommittee III of the AGS formed the "Risk deduction" working group which submitted a proposal, in the form of a guidance document, for a procedure for quantifying cancer risk figures from animal experiments and/or from epidemiological data. The procedure paid particular attention to the use of default assumptions in order to close gaps in knowledge (cf. Page 295 ff. in the present issue). Even before the "Risk deduction" working group's guidance document became available, the AK CM provided Subcommittee III with the first dose-risk descriptions for selected, comparatively well documented carcinogens. The experience gained with these analyses of such substances was in turn incorporated into the guidance document on risk deduction, in a generalised form or in the form of examples.

The next section presents selected examples of important projects conducted by the AK CM working group.

3 Substance examples

3.1 1,3-Butadiene

Gaseous 1,3-butadiene is the base material used for the manufacture of synthetic rubber and other copolymers. An elevated risk of lymphosarcoma was detected among workers involved in 1,3-butadiene production; greater numbers of leukaemia cases occurred in its processing for the production of synthetic rubber. The causes of these differences have not yet been fully explained. A detailed comparison of the studies conducted in the production of synthetic rubber and monomers can be found in *Roller* et al. [5]. The epidemiological findings are supported by the results of animal experiments.

1,3-Butadiene is a genotoxic carcinogen, and some of its oxidative metabolites are able to react with DNA. The substance has been classified by the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) [6] and other specialist bodies as a human carcinogen; it is therefore logical that legal classification in carcinogen Category 1 (known to be carcinogenic to

man) in accordance with the EU Dangerous Substances Directive, 67/548/EC [1], is binding upon the EU Member States.

Up until 2004, technical guidance concentration (TRK) values of 15 ppm (34 mg/m^3) applied in Germany for the area of treatment following polymerisation and loading, and 5 ppm (11 mg/m^3) for other areas. The value of 5 ppm still applies in Austria and Switzerland.

In particular, the AK CM had the task of critically reviewing the comprehensive epidemiological literature. The working group was not able to draw upon studies from the area of monomer production for quantitative evaluation, due to the lack of sound information on the exposure levels. Conversely, it considered two publications concerning the follow-up of a cohort in North American synthetic rubber production [7; 8] to be particularly relevant. The data contained in these studies on the incidence of leukaemia were regarded as providing a suitable basis for describing the dose-effect relationship.

Graff et al. [7] had divided the cumulative exposure of the workers studied into quartiles, but had not stated any medians or geometric means. The AK CM countered this deficit by taking the class midpoint of the four exposure categories as a basis and dividing it by 35 working years in order to estimate the corresponding long-term mean value of the exposure (see **table**).

Table:

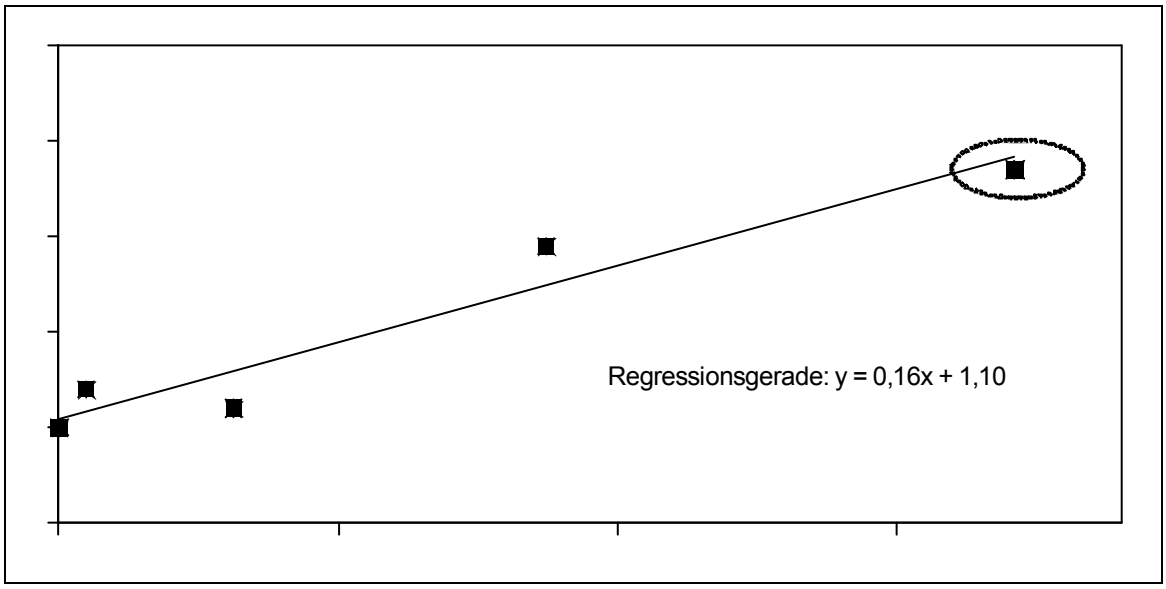
1,3-Butadiene: Relationship between long-term exposure and relative leukaemia risk (data from the North American Cohort Study [7]).

Cumulative exposure in ppm x years		Long-term mean, 35 years, in ppm
Range (according to [7])	Class midpoint	
0	0	0
> 0 to < 33.7	16.85	0.48
33.7 to < 184.7	109.2	3.12
184.7 to < 425	304.9	8.71
≥ 425.0	600*	17.1

**estimated*

If the long-term mean values calculated in this way are now compared to the relative cancer risks also documented by *Graff* et al. [7], the risk increase per exposure unit is expressed by the slope of the straight line of regression (**figure**). In this specific case, the result is a slope of 0.16, or 0.2 when rounded. This means that at an average exposure increase of 1 ppm for the entire working life, the relative risk of contracting cancer increases by 0.2.

Figure:
Calculation of the long-term mean for 1,3-butadiene (North American Cohort Study). Regressionsgerade = linear regression line



The background leukaemia risk for the male population in the United States and other industrial countries is around 1% [9]. If this value is multiplied by the rise in the relative risk of 0.2 per ppm 1,3-butadiene determined as described above, the result is an "excess working life risk"[1] of 0.2% (2:1,000) after 35 years' workplace exposure to a long-term mean value of 1 ppm.

Linear extrapolation ultimately produces a "tolerable" concentration (cancer risk of 4:1,000) at a level of 2 ppm and an "acceptable" concentration (cancer risk of 4:100,000, see Page 287 ff.) of 0.02 ppm 1,3-butadiene under full-shift daily working exposure over 35 years[2].

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1 The excess risk is a measure of the difference between the risk for the exposed group and that for a non-exposed peer group (such as the wider population).

2 The guide produced by the AGS "Risk deduction" working group at the end of the AK CM's discussions of 1,3-butadiene recommends that 40 years be assumed for the working life rather than 35 years. In view of the general uncertainties associated with the risk assessment however, this discrepancy is negligible.

3.2 Acrylonitrile

Acrylonitrile is liquid at room temperature and serves as an important base material for chemical syntheses, primarily for the manufacture of polyacrylonitrile, which is widely used in the textile industry, particularly in the form of synthetic fibres.

More recent studies were unable to provide unequivocal confirmation of epidemiological indications of an elevated lung-tumour rate among persons experiencing occupational contact with acrylonitrile. In inhalation experiments with rats, acrylonitrile caused tumours in the Zymbal gland (an organ not present in the human body) and in the central nervous system. Feeding studies also confirmed the carcinogenic potential of the substance, which the MAK Commission and the European Commission classify as a confirmed animal carcinogen. Whether genotoxic processes play a crucial part in triggering tumours is still the subject of debate; some metabolic products are at any rate mutagenic (cf. [10]). Up until 2004, a technical guidance concentration (TRK) of 3 ppm acrylonitrile (7 mg/m^3) applied in Germany. In Switzerland and Austria, the occupational exposure limit at workplaces is 2 ppm.

A literature survey conducted by the AK CM identified several scientific studies dealing with quantification of the cancer risk presented by acrylonitrile. Linear extrapolation shows the lifetime risks for 0.1 mg/m^3 (0.05 ppm) as determined by several authors using several different methods to be in a quite narrow range of 1.6×10^{-4} to 2.7×10^{-3}. The experts in the working group ultimately agreed to base deduction of "acceptable" and "tolerable" workplace concentrations upon the well-documented calculations of *Felter* and *Dollarhide* [11].

Felter and *Dollarhide* had modelled the dose-effect data mathematically from a rat inhalation study. From the incidence of astrocytomas (tumours of the astrocytes, a supporting tissue of the brain) in female animals (which respond with somewhat greater sensitivity than their male counterparts), they were thus able to determine the atmospheric concentration which results in an excess cancer risk (of benign and malignant tumours together) of 10%. This value, also referred to as the ED_{10}, was used by *Felter* and *Dollarhide* as a basis for further risk estimates. By means of linear extrapolation steps, they obtained a unit-risk value (risk to humans at lifelong exposure to 1 µg/m^3) of 8.2×10^{-6}.

This unit risk value was applied by the AK CM as a basis for its deductions. Conversion from lifetime (75 years × 7 days per week × 52 weeks = 27,300 days) to working life (40 years × 5 days per week × 48 weeks = 9,600 days) exposure in days results

in a factor of 2.8; consideration of exposure per day (for lifetime: 20 m^3/day; for working life: 10 m^3/day) results in an additional factor of 2. The overall factor is therefore 5.6 for conversion from lifetime to working life.

If the unit risk of 8.2×10^{-6} is divided by this overall factor of 5.6, the result is a value of 1.4×10^{-6}. Human working-life exposure to 1 µg/m^3 would thus correspond to a cancer risk of 1.4×10^{-6}. The specified tolerable and acceptable risks of 4:1,000 and 4:100,000 would therefore be reached at average working life exposures to 2,800 µg/m^3 (1.2 ppm) and 28 µg/m^3 (0.012 ppm) respectively, if a linear progression of the dose-effect relationship in this range is assumed.

In summary, the AK CM set out in its criteria document submitted to the AGS that this deduction of risk values for acrylonitrile is based upon a comparatively sound body of data from animal tests, even though the relevance of astrocytomas for human beings still requires clarification.

3.3 Vinyl acetate

For vinyl acetate, the AK CM adopted a different approach, owing to the presumed mechanism of action. Vinyl acetate is another important synthetic building-block; polyvinyl acetate is used in many coatings, paints and adhesives. Vinyl acetate in the drinking water of rodents causes tumours of the upper digestive tract. Although inhalation of vinyl acetate also causes nasal tumours in rats, it has not yet been classified as a carcinogen at EU level. In Germany, vinyl acetate is listed as a suspected carcinogen both in the list of MAK (maximum workplace concentration) and BAT (biological tolerance) values of the MAK-Commission [12] and in the index of carcinogenic, mutagenic and reprotoxic substances [13] of the TRGS technical rules on hazardous substances.

An occupational exposure limit of 10 ppm for vinyl acetate must be observed at workplaces in Austria and Switzerland; this corresponds to the former German technical guidance concentration.

An analysis of the dose-effect relationships and of the metabolism suggests that a threshold exists for the carcinogenic action of vinyl acetate [14]. The AK CM takes the view that the local tumours are not primarily induced by genotoxic processes, but at lower doses are the result of irritation and cell damage. Acetic acid and acetaldehyde, two products of vinyl acetate hydrolysis, are considered responsible for this. It

can be assumed that concentrations below the irritation threshold protect against tumorigenic transformation of the tissue.

The highest concentration of vinyl acetate for which no irritation effects could be detected histopathologically in rats and mice in a two-year inhalation test (NOAEL) is 50 ppm. Workplace exposure of employees over many years to between 5 and 10 ppm of vinyl acetate had no irritative effects. The AK CM therefore proposed an occupational exposure limit of 5 ppm. This is in line with a recommendation by the EU's Scientific Committee on Occupational Exposure Limits [15].

Since this limit value is based upon a threshold concept, it satisfies the criteria for a health-based occupational exposure limit in the sense of the German Hazardous Substances Ordinance (see Section 2 of this article). The proposal by the AK CM was therefore included in the German Technical Rules for Hazardous Substances (TRGS 900) [16] at the end of 2007 following adoption by the AGS.

3.4 1,4-Dichlorobenzene

For 1,4-dichlorobenzene, which is a by-product of chlorobenzene synthesis and is not easily degraded biologically, an occupational exposure limit has been stated once again since 27 December 2007 in the official German body of regulations. The AK CM has not yet been able to address 1,4-dichlorobenzene in detail. The substance has been classified by the MAK Commission as a proven animal carcinogen owing to its ability to cause tumours in various organs of rat and mouse [17], but is listed in the EU Dangerous Substances Directive only as a suspected carcinogen.

The European Commission had formulated an Indicative Occupational Exposure Limit Value (IOELV) for 1,4-dichlorobenzene without documenting the criteria upon which it was based; as a result, the responsible national authorities of the Member States were obliged to lay down occupational exposure limits of their own, the levels of which were however permitted to deviate from the Commission's proposal. In order to avoid an infringement case, the German Federal Ministry of Labour and Social Affairs provisionally adopted the IOELV of 20 ppm, but at the recommendation of the AGS, added a footnote to this value in the Technical Rule TRGS 900 to the effect that no reasoning was available for the deduction of a health-based OEL.

The scientific aspects of this OEL will be reviewed in the near future by the AK CM. For this purpose, the working group is drawing not only upon the position paper of

the former toxicology advisory group in the AGS, which was of essential importance for the EU classification of 1,4-dichlorobenzene [18], but also upon new experimental studies [19] and the evaluations of the cancer risk which consider the mechanism of action [20].

4 Discussion and future prospects

The substances used as examples above provide just a few highlights of the decision-making processes in the AK CM and AGS. The AK CM considers it standard procedure to provide detailed arguments for its proposals in the form of position papers. It would be advantageous for the AGS secretariat to make these documents available to interested parties – for example on the Internet – as soon as the proposals are adopted. This would enhance transparency, and critical feedback could assist in improving the instrument of the working group.

Close networking between three working groups – the "Risk acceptance" and "Risk deduction" working groups and the AK CM – which is evident not least from some experts being members of multiple groups, enabled the AGS within a very short time to submit recommendations suitable for implementation. It remains to be hoped that the Ministry in charge will pave the way equally quickly for risk-based OELs in the German body of regulations by a possible amendment to the Hazardous Substances Ordinance. Users in the field also require clear targets for carcinogenic substances; and as the examples presented here clearly show, the substances in question are not obscure, but working agents in widespread use for which substitutes are not readily available.

Initial experience also shows that the occupational exposure limit concentrations based upon "tolerable" and "acceptable" cancer risks may lie well below the former technical exposure concentration values (TRK) which have been abolished in Germany: in other words, observance of the new limit values may not be achievable in the short term by technical measures. In this context, urgent consideration should be given to improved protection concepts, and if appropriate also to transitional and special arrangements.

A lot has been achieved, but much still remains to be done. Careful deduction of dose-risk relationships from literature data requires specialist knowledge and considerable experience in the evaluation of mechanisms of action. The task now facing the AK CM, that of working through a large proportion of the carcinogens deleted in 2004

from the German indices of occupational exposure limits – the number of which probably runs into three figures – is one which it has no prospect of completing within a period of just a few months or a year. All members of the AK CM conduct their work for it on a voluntary basis, and have a considerable workload. Subcommittee III of the AGS, responsible for the assessment of hazardous substances, has appealed to industry to lend its support to the technical work in order to accelerate the process in the interests of improved occupational safety and health. Urgent consideration should however also be given to identifying possible sources of finance by which a part of the ambitious programme could be outsourced to competent institutes.

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Prof. Dr. rer. nat. Gisela H. Degen,
Chair of the working group responsible for limit values and classifications of CM substances, Leibniz Research Centre for Working Envirionment and Human Factors (IfADo), Dortmund.

Dr. rer. nat. Eberhard Nies,
Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA), Sankt Augustin.