

# General Aspects



## Significance, use and derivation of MAK values

### Definition

The MAK value (“maximale Arbeitsplatz-Konzentration”: maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (e.g. by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. As a rule, the MAK value is given as an average concentration for a period of up to one working day or shift. MAK values are established on the basis of the effects of chemical substances; when possible, practical aspects of the industrial processes and the resulting exposure patterns are also taken into account. Scientific criteria for the prevention of adverse effects on health are decisive, not technical and economic feasibility.

For the establishment of a MAK value,

**the carcinogenicity** (see Section III)

**the sensitizing effects** (see Section IV)

**the contribution to systemic toxicity after percutaneous absorption** (see Section VII)

**the risks during pregnancy** (see Section VIII)

**the germ cell mutagenicity** (see Section IX)

of a substance are evaluated and the substance classified or designated accordingly. Descriptions of the procedures used by the Commission in the evaluation of these end points may be found in the appropriate sections of the *List of MAK and BAT Values*, in the “Toxikologisch-arbeitsmedizinischen Begründungen von MAK-Werten” (available in English translation in the series *Occupational Toxicants*)<sup>1</sup> and in scientific journals.<sup>2,3,4,5,6</sup>

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<sup>1</sup> obtainable from the publisher: WILEY-VCH, D-69451 Weinheim

<sup>2</sup> Adler ID, Andrae U, Kreis P, Neumann HG, Thier R, Wild D (1999) Vorschläge zur Einstufung von Keimzellmutagenen. *Arbeitsmed Sozialmed Umweltmed* 34: 400–403.

<sup>3</sup> Drexler H (1998) Assignment of skin notation for MAK values and its legal consequences in Germany. *Int Arch Occup Environ Health* 71: 503–505.

<sup>4</sup> Hofmann A (1995) Fundamentals and possibilities of classification of occupational substances as developmental toxicants. *Int Arch Occup Environ Health* 67: 139–145.

<sup>5</sup> Neumann HG, Thielmann HW, Filser JG, Gelbke HP, Greim H, Kappus H, Norpoth KH, Reuter U, Vamvakas S, Wardenbach P, Wichmann HE (1998) Changes in the classification of carcinogenic chemicals in the work area. (Section III of the German List of MAK and BAT Values). *J Cancer Res Clin Oncol* 124: 661–669.

<sup>6</sup> Neumann HG, Vamvakas S, Thielmann HW, Gelbke HP, Filser JG, Reuter U, Greim H, Kappus H, Norpoth KH, Wardenbach P, Wichmann HE (1998) Changes in the classification of carcinogenic chemicals in the work area. Section III of the German List of MAK and BAT Values. *Int Arch Occup Environ Health* 71: 566–574.

#### 4      *Significance, use and derivation*

In line with the so-called “preferred value approach” also used e.g. in the European Union, MAK values are to be established preferentially as the numerical values 1, 2 or 5 ml/m<sup>3</sup> or, for non-volatile substances, 1, 2 or 5 mg/m<sup>3</sup>, multiplied by powers of ten.

In the use of MAK values, the analytical procedures used for sampling and analysis and the sampling strategy are of great importance.

#### **Purpose**

MAK values promote the protection of health at the workplace. They provide a basis for judgement of the toxic potential or safety of the concentrations of substances in the workplace air. However, they do not provide constants from which the presence or absence of a health hazard after longer or shorter periods of exposure can be determined; nor can proven or suspected damage to health be deduced, in an isolated case, from MAK values or from the classification of a substance as carcinogenic. Such deductions can be made only on the basis of medical findings, taking into consideration all the circumstances of the particular case. Therefore, on principle, statements in the *List of MAK and BAT Values* are not to be seen as *a priori* judgements for individual cases. On principle, observation of MAK values does not eliminate the necessity for regular medical examination of the exposed individuals.

MAK values are not suitable for providing constant conversion factors for deduction of health risks associated with long-term exposure to contaminants in the non-occupational atmosphere, e.g., in the vicinity of industrial plants.

#### **Prerequisites**

In principle, the substances are dealt with according to their importance for practical occupational hygiene and the expertise of the members of the Commission. The prerequisite for the establishment of a MAK value is the availability of sufficient data for the substance from the fields of toxicology, occupational medicine or industrial hygiene. Adequate documentation is not always available. The List is revised annually and suggestions for substances to be added and new information on listed substances are welcome.<sup>7</sup>

#### **Derivation of MAK values**

MAK values are derived by the “DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area” exclusively on the basis of scientific arguments and are published in the *List of MAK and BAT Values* which is issued annually. For the derivation of MAK values, certain rules of procedure have been developed by the Commission on the basis of established toxicological and occupational medical concepts; answers to at least the more common questions are repeatedly sought in the same way. Therefore the usual procedures and the general principles for the derivation of MAK values are described below. Essentially, these principles correspond with those

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<sup>7</sup> Please contact the Geschäftsstelle der Deutschen Forschungsgemeinschaft, Kennedyallee 40, D-53175 Bonn; or the Sekretariat der Kommission: Technische Universität München, Institut für Toxikologie, Hohenbachernstraße 15–17, D-85350 Freising-Weihenstephan.

published by the European “Scientific Committee on Occupational Exposure Limits, SCOEL”.<sup>8</sup>

First the most sensitive parameters described in the available data are to be identified, i. e., those effects which appear first during exposure to increasing concentrations of the substance. To be taken into account in this process are both local effects, that is, the results of effects on surfaces of the organism which are in contact with the environment (e. g. mucous membranes of the respiratory tract and the eyes, skin) and also systemic effects, that is, the results of uptake of the substance into the organism. Generally the concentration-effect relationships for these two kinds of effects are different. The derivation of the MAK value is based on the “no observed adverse effect level” (NOAEL) for the most sensitive effect with relevance for health. It must be decided whether or not such effects may be considered to be adverse effects. At present there is no generally accepted definition for an “adverse” effect, at least in part because of the lack of clarity about the still changing definition for the state of being “healthy”;<sup>9,10</sup> therefore this decision must be made anew in every case.

Fundamentally, known effects of a substance in man are given highest priority in the derivation of the MAK value.

In the evaluation of a substance, known effects of structural analogues may also be taken into account.

If no NOAEL may be derived from the available data, a scientifically founded MAK value cannot be established and the substance is listed in Section II b of the *List of MAK and BAT Values*.

#### **a. Selection of substances and collection of data**

For the substances being studied, the epidemiological data published in scientific journals, occupational medical reports, toxicological properties and any other potentially useful information is first assembled by carrying out researches in appropriate data-banks. The references found in the literature search are checked for their relevance for the assessment of the substance in question and the original publications of the selected literature are examined. When necessary, unpublished internal company data in the form of complete study reports are also included. These are then identified as such in the reference list at the end of the documentation. The validity of the available information and studies is checked. Whether or not a study is relevant for the current assessment is decided on a case to case basis. Whenever possible, evaluation of the studies is based on the guidelines of the OECD or similar bodies.

The unabridged reports are made available to the Commission and are filed at the Commission’s scientific central office. Information required by a third party about the company reports cited in the Commission’s documentation is supplied in writing by the chairman of the Commission at his discretion. Access to company reports is not made available to third parties. Copies, even of parts of reports, are not provided.

<sup>8</sup> European Commission (Ed.) (1999) Methodology for the derivation of occupational exposure limits: Key documentation Cat. No. CE-NA-19253-EN-C, ISBN 92-828-8106-7, EUR 7, Office for Official Publications of the European Communities, L-2985 Luxembourg.

<sup>9</sup> DFG (Deutsche Forschungsgemeinschaft) (Ed.) (1997) Verhaltenstoxikologie und MAK-Grenzwertfestlegungen. Wissenschaftliche Arbeitspapiere. Wiley-VCH, Weinheim.

<sup>10</sup> Henschler D (1992) Evaluation of adverse effects in the standard-setting process. Toxicology Letters 64/65: 53–57.

**b. Values based on effects in man**

For many substances encountered at the workplace, irritation or central nervous depression is the critical effect. Valuable information – at least for these acute effects of single exposures – may be obtained from studies of volunteers exposed under controlled conditions which yield data for concentration-effect relationships and also for concentrations without effects (NOAEC). A detailed review of the methods required of such studies and of the usefulness of various parameters for the establishment of threshold concentrations has been published.<sup>9</sup> Such studies often demonstrate differences in sensitivity between persons who have never been exposed to the test substance and those who have been repeatedly exposed, e. g., at work.

Occupational medical and epidemiological studies provide further information from which the health risks associated with handling particular substances may be evaluated. However, not only the parameters determined in the exposed persons, but also any differences in study design, in the analytical methods and sampling strategies must be considered in evaluating such studies. Various confounders, exposure to mixtures, previous disorders or inadequate exposure records can alter or falsify any detected concentration-effect relationships.

Cross-sectional studies with only single determinations of exposure levels and only single examinations of the exposed persons do not generally permit the association of any observed symptoms with the current exposure situation. This requires information as to past exposure levels.

Therefore longitudinal studies with repeated determination of the workplace and systemic exposure levels and repeated examination of the exposed persons play a decisive role in the establishment of thresholds. Valid epidemiological studies of persons exposed for long periods to concentrations which do not produce adverse effects provide a reliable basis for the establishment of threshold levels for the workplace, especially when the study design permits statements as to both local and systemic effects.

The diverse sensitivities of individual employees (as determined by age, constitution, nutrition, climate, etc.) are taken into consideration in the establishment of MAK values. It is currently not possible to take sex-specific differences in toxicokinetics and toxicodynamics into account when establishing MAK and BAT values because of the lack of appropriate scientific data.

When the NOAEL has been determined from effects of the substance in man, the MAK value is generally established at the level of this NOAEL.

**c. Values based on effects on animals**

Because the effects in man are not known for many substances, MAK values are often derived from results obtained with experimental animals. This is carried out in the clear understanding of the problems associated with extrapolation between species and of the much smaller group sizes than is usual in epidemiological studies. On the other hand, animal studies carried out according to modern principles also offer advantages including precise characterization of exposure levels, the wide range of parameters that can be studied, and the possibility of determining dose-response relationships and NOAELs. The minimum database for the derivation of a MAK value is generally considered to be a NOAEL from a valid 90-day inhalation study with experimental animals. Of the re-

<sup>9</sup> DFG (Deutsche Forschungsgemeinschaft) (Ed.) (1997) *Verhaltenstoxikologie und MAK-Grenzwertfestlegungen*. Wissenschaftliche Arbeitspapiere. Wiley-VCH, Weinheim.

sults of studies in which substances were administered to experimental animals by the oral or dermal route, mostly only the systemic effects may be considered to be relevant for persons exposed at the workplace. Therefore, in the documentation of a MAK value such results must be accompanied by information about the local effects of the substance, especially the effects on the respiratory tract.

When the NOAEL has been determined from effects of the substance in animals, the MAK value is generally established at the level of half of this NOAEL. However, in some cases species differences in sensitivity to the substance must be taken into account and here the toxicokinetic data are particularly important.

#### **d. Exceptional workplaces**

During exposure to gaseous substances which are metabolized rapidly and for which the blood/air distribution coefficient is larger than 10, it must be taken into account that the concentrations of the substances in blood and tissues are positively correlated with the level of physical activity.

Likewise, the concentrations of inhaled gaseous substances in blood and tissues of persons working under hyperbaric pressure have been shown to correlate positively with the pressure.

This dependence of the body burden on the workplace conditions must be taken into account in the establishment of MAK and BAT values.

#### **e. Odour, irritation and annoyance**

Exposure of persons to substances at the workplace can cause smells (*nervi olfactorii*) or sensory irritation (*nervus trigeminus*). Such effects must be differentiated according to their relevance for health. This differentiation can cause difficulties because the parameters of interest can still not be determined with sufficient objectivity. Smells are mostly detected at lower concentrations than is sensory irritation. In general, if the smell and irritation are unpleasant and powerful enough, both can cause annoyance. When assessing these effects on the well-being of exposed persons, the physiological process of habituation (adaptation) must also be taken into account. In particular the sense of smell is affected markedly by habituation processes so that during constant exposure even to high concentrations the smell of a substance may no longer be noticed after a while. Excessive annoyance of workers by sensory irritation or persistent intensive or nauseous smells is taken into account when establishing thresholds.

#### **f. Habituation**

Even at constant exposure concentrations, persons can become accustomed to sensory irritation, effects on the sense of well-being or smells so that these no longer function adequately as warning signals. At present, however, not enough is known about the mechanisms and dose-response relationships involved. With many substances, on the other hand, habituation is the result of toxic effects such as inactivation of enzymes or inhibition of receptor molecules. Especially in such cases, and when the warning signals produced by sensory irritation are reduced or cancelled out by disorders of well-being or the sense of smell, it is necessary to take habituation into account when establishing thresholds.

## Documentation

A detailed scientific documentation of each decision is published in the series *Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten*, also available in English translation in the series *Occupational Toxicants*.<sup>1</sup> Annual supplements are planned. These documents present, clearly and in detail, the scientific data and the reasons for the establishment of a MAK value. Because of this system, it is sufficient to establish only general principles for the derivation of MAK values. The assessment of individual substances on the basis of all the available toxicological and occupational medical data yields a more differentiated and specific evaluation than would the observance of stringently formulated rules.

The published data for the toxicity and effects of a substance in man and animals and all other relevant information are organized according to the kind of effect and presented in the form of a review. This review of the toxicological and epidemiological data for a substance serves initially as a basis for the discussion within the Commission for the derivation of a MAK value and for detailed evaluation of the physicochemical properties, percutaneous absorption, sensitizing effects, carcinogenic effects, prenatal toxicity and germ cell mutagenicity of the substance. When new data become available, the MAK value, classification and designation of the substance are reassessed and, when necessary, altered.

## Publication

Prospective changes and new entries are announced each year in the *List of MAK and BAT Values*<sup>11</sup> and in the periodical *Zentralblatt für Arbeitsmedizin* and in the *Bundesarbeitsblatt*. The periodical *Arbeitsmedizin, Sozialmedizin, Umweltmedizin* also publishes a detailed discussion of the list with notes of changes and new entries. Following ratification of the annual List, the organizations listed below are officially informed of the planned changes: “Länderausschuß für Arbeitsschutz und Sicherheitstechnik (LASI)” (Federal Committee for Occupational Safety and Technical Security), the “Bundesverband der Deutschen Industrie” (Federation of German Industries), the “Hauptverband der gewerblichen Berufsgenossenschaften” (Central Association of Industrial Injuries Insurance Institutes) and the “Deutsche Gewerkschaftsbund” (the German Trade Union Federation). The purpose of this measure is to give these organizations enough time to send to the Commission any available scientific documentation relevant to the planned changes and additions to the *List of MAK and BAT Values*.

## Mixtures of substances

In general, the MAK value is only valid for exposure to a single, pure substance. It cannot be applied unconditionally to one component of a mixture in the workplace air or to a technical product which might contain more toxic impurities. Simultaneous or successive exposure to several substances may be much more or, in isolated cases, even less dangerous than the exposure to one of the substances on its own. A MAK value for a mixture of substances cannot be satisfactorily determined by simple calcula-

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<sup>1</sup> obtainable from the publisher: WILEY-VCH, D-69451 Weinheim

<sup>11</sup> see yellow pages



tion because the components of the mixture generally have very different kinds of effect; MAK values can presently be established for such mixtures only after specific toxicological examination or studies of the particular mixture of substances. Given the inadequacy of the currently available data, the Commission decidedly refrains from calculating MAK values for mixtures, particularly for liquid solvent mixtures. However, it is willing, on the basis of its own investigations, to provide values for defined vapour mixtures of practical relevance.

### Analytical controls

The observance of the MAK, BAT and EKA values (that is, keeping the exposure levels below these values) is intended to protect the health of persons exposed to dangerous substances at work. This objective is only to be attained by regular monitoring of the concentration of the dangerous substances in the workplace air or of the concentration of the substances, their metabolites or other parameters of intermediary metabolism in the body fluids of exposed persons. For this purpose it is necessary to use analytical methods which have been tested for reliability and practicability. The Commission's analytical chemistry group has developed such methods and published them in the series *Luftanalysen* and *Analysen in biologischem Material*.<sup>12</sup> New issues of these publications appear regularly in both German and English. The methods are conceived as so-called standard operating procedures (SOP) which are intended to ensure comparability of the analytical results from laboratory to laboratory and with the above-mentioned thresholds. Thus they contribute to the quality control of the results. They also provide a good basis for the health protection which is the objective of the threshold values.

In the development and selection of these analytical methods, the accuracy and reliability of the results they yield is the most important factor. The methods reflect the current state of technology. They are repeatedly modified in the light of recent developments.

The methods for analyses in biological material are, whenever possible, designed so that their analytical range includes the concentration range relevant in environmental studies. This makes it also possible to differentiate the occupational from the environmental concentration range and to evaluate any differences.

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<sup>12</sup> *Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe*, available from the publisher: WILEY-VCH, D-69451 Weinheim

Volume 1: *Luftanalysen (Analyses of Hazardous Substances in Air)*

Volume 2: *Analysen in biologischem Material (Analyses of Hazardous Substances in Biological Materials)*

Supplementary reports at yearly intervals are anticipated. The Commission welcomes suggestions for inclusion of new chemical compounds as well as analytical methods. Contact the group "Analytische Chemie" at the Deutsche Forschungsgemeinschaft, D-53170 Bonn. Analytical methods for carcinogenic workplace substances are published in cooperation with the analytical chemistry group from the association of German industrial chemists, 'Arbeitsgruppe Analytik des Fachausschusses Chemie der BG Chemie' *Von den Berufsgenossenschaften anerkannte Analysenverfahren zur Feststellung der Konzentration krebserzeugender Arbeitsstoffe in der Luft in Arbeitsbereichen*, Carl Heymanns Verl. KG, D-50939 Köln.