Fact sheet

Swiss occupational exposure limits

Dr. med. Dr. sc. nat. Michael Koller, Dr. med. Claudia Pletscher, Dr. med. Marcel Jost

1. Introduction

The purpose of occupational exposure limits (OEL) is to protect employees from excessive exposure to hazardous substances and from possible harm to their health. Calculating OELs involves the determination of exposure limits. If these are adhered to, it can be assumed that employees are either exposed to no risk or to minimum risk. However, what does “minimum risk" mean? An OEL that is set too high costs human lives - an OEL that is set too low costs jobs. Job losses not only have negative consequences for the economy, but also - in turn - have a negative effect on the health [1].

In Switzerland, the Swiss Confederation assigned the issue of guidelines on OEL according to Article 50, §3 VUV (Regulation on the prevention of accidents and occupational diseases) to Suva (Swiss National Accident Insurance Fund). Suva first published a list with OELs in 1968. This list is published annually under the name “Grenzwerte am Arbeitsplatz” (German) or “Valeurs limites d'exposition aux postes de travail” (French) and is available at www.suva.ch/waswo/1903.d and www.suva.ch/waswo/1903.f, respectively [2].

2. Derivation of occupational exposure limits

2.1. General aspects

Determining OELs is a complex undertaking. For example, around 30 scientists are involved with this topic in the gremium responsible at the German Research Foundation (DFG). Internationally, the basic principle is generally similar (Fig. 1) although there are individual differences dependent on the country and the directive [3-11].
In the initial step of determining the OEL, both the technical literature available and the results of the latest studies on a substance to be assessed are inspected and the quality of the work is evaluated. It not only takes human data into account but also includes findings from animal studies, cell biological studies and physical-chemical considerations. The data sources include human case reports, studies on volunteers, cross-sectional studies, cohort studies and case-control studies. The probative value of these studies varies. For example, longitudinal studies generally permit better statements than cross-sectional studies.

In a second step, of the undesirable effects of a substance the one to which the OEL refers is determined. The expressions used are critical effect or end point, which is generally the adverse (undesirable) effect that occurs at the lowest concentration of a substance tested. With the continuous development of testing methods, increasingly sensitive adverse effects can be defined as the endpoint, such as laboratory changes - even in the absence of a morphologically tangible pathology - or discrete, abnormal reactions only tangible in differentiated neurological tests. With these partly low-grade changes, it is not always obvious which phenomena are to be generally regarded as adverse, such as mild irritation of the conjunctiva and of the upper airways which, depending on the individual, are perceived as having very different impairing effects.

The next steps in determining an OEL depend on,

- whether in the case of the substance in question there is what is called a threshold concentration, that is to say, whether an adverse effect is only observed above a certain concentration, and no adverse effect is present below the threshold (Fig. 2, left),

- or whether the dose-risk curve passes through zero and there is no threshold concentration (Fig. 2, right).

Toxic substances usually have a threshold concentration. When deriving the threshold value, the measuring points can be used directly and a health-based OEL as it is called can be set. In contrast, carcinogenic substances usually show no threshold value and the OEL derived from them is based on risk-based models (risk-based threshold value).
2.2. Health-based OELs for toxic substances

a) NOAEL method

In the case of the toxic-acting substances, it is assumed that the critical effect usually only occurs above a certain threshold concentration and is not observed below this dose (Fig. 2, left; Fig. 3). This threshold concentration is therefore called NAEL (No Adverse Effect Level). An attempt is made to experimentally determine the NAEL as precisely as possible. The lowest experimentally determined concentration at which no adverse effect was observed in the trials is designated NOAEL (No Observed Adverse Effect Level) in contrast to the real threshold concentration NAEL. The lowest concentration at which the critical effect is observed is the LOAEL (Low Observed Adverse Effect Level). The degree to which the NOAEL matches the NAEL depends, among other things, on the dose step chosen, the size of the collective investigated, the steepness of the dose-response relationship and the sensitivity of the critical effect.

If one does not observe the extent of a critical effect, but the incidence or risk of occurrence of the critical effect, then the NOAEL is the tested concentration at which no biologically or statistically significant change in the critical effect of the employees exposed can be seen in comparison to the control group. Sometimes it is not experimentally possible to determine a NOAEL, but only an LOAEL.
The NOAEL (or LOAEL) is used as a starting point or “point of departure” (POD), starting from which one converts to the human workplace conditions. The following situations are conceivable [12-16]:

- Ideally, high-quality epidemiological studies in humans are available. In their absence, conversions must be made from animal studies to the human situation (interspecies extrapolation).

- If we wish to calculate the risk over an entire working life and if only studies with relatively short exposure times are available, however, an extrapolation must be carried out. According to SCOEL, 8 hours per day, 5 days a week, 240 days per year and 45 years per working life can be assumed as a lifelong workload.

- If it is impossible to determine a clear dose-response relationship at very low concentrations or if high doses that do not occur in practice were chosen in animal experiments, mathematical models come into play with which extrapolations can be made from the measured high dose to the relevant low dose range (benchmark procedure, T25-method, etc.). This is called low-dose extrapolation [17].

- Since the threshold values are usually determined based on the inhalation of a chemical substance, a route-to-route extrapolation must be carried out for studies with oral administration (dose by mouth) or intertracheal instillation (delivery into the trachea).

- Within any population, there are sensitive and less sensitive individuals. Susceptibility to the development of an adverse effect may therefore be different between individuals. This fact is taken into consideration in the “interspecies extrapolation”.

Extrapolation factors as they are called are used for these conversions. In addition, other assessment factors are estimated for uncertainties in the assumptions. For example, if a 90-day animal study is available with the oral administration of a substance for the calculation of a OEL, extrapolation factors must be calculated for the conversion of an animal experiment to human conditions, for the conversion of oral administration to exposure to the substance in

the air and for the conversion of the 90-day experiment to a working life and possibly an intraspecies extrapolation.

There are various guidelines and suggestions for default values for the determination of extrapolation factors or safety factors. These guidelines must not be understood as a “cookbook” - every substance must be assessed individually. In point of fact, the quality of the studies, the number of measurement points and their distance from each other (or the distance of the NOAEL to LOAEL), the severity and characterisability of the side effect and toxicokinetics (absorption, distribution, metabolism and excretion of a substance) and dynamics (mechanism of the harmful effect) enter into the calculations. The POD is multiplied by the extrapolation or assessment factors to obtain the health-based OEL as it is called. So as not to arrive at an unrealistically conservative value due to the multiplication of many uncertainty factors, statistical methods such as the Monte-Carlo simulation can be used in the probabilistic calculation or the setting of a maximum limit for the total factor.

**b) Benchmark procedure**

A more complex method that avoids certain drawbacks of the NOAEL approach, however, is the benchmark procedure with which a POD can also be calculated (Fig. 4) [18, 20]. In this method, which is not based on the N(L)OAEL as the POD, a mathematical function is used for which it is assumed that it reflects the dose-response relationship well because of mechanistic considerations or from which it is assumed based on mathematical and statistical experience that a good fit can be achieved using a regression procedure. After calculating the regression curve, statements can also be made about the expected effects for doses for which there are no data points. This can, for example, be the case at very low concentrations where no measurements can be taken due to technical limitations, or if - in the case of animal experiments - only high doses that are not relevant in practice were used and the aim is to extrapolate into the low-dose range. The uncertainty of the function calculated is given by the confidence intervals as they are called.

The frequency of effect, that is to say the frequency of occurrence of an adverse effect, is called “benchmark response” (BMR) - this is shown on the y-axis. When calculating an OEL, we are interested in small BMRs in the low-dose range such as 1, 5 or 10% in the low-dose range. The substance concentration belonging to a BMR is called a benchmark dose (BMD). It can be read on the x-axis. Figure 4 is an example showing the BMD_{10} belonging to a BMR of 10%. However, to determine the OEL, we do not need the BMD itself, i.e. not the dosage belonging to the regression curve itself, but we take the value of the lower end of the 95% confidence interval, the so called BMDL (benchmark dose lower bond). While the BMDs reflect the concentrations that lead with the greatest probability to a defined BMR, the BMDLs only correspond to the dose at which the BMRs may just still occur with a far smaller probability corresponding to the lower end of the confidence interval. Figure 4 shows the BMDL_{10}, the concentration of the 95% confidence interval belonging to the BMD_{10}. BMDL_{10} is used as POD - like a NOAEL - starting from which the applicable OEL for the employee is estimated taking into consideration the uncertainty factors mentioned.
The benefits of the benchmarking process over the NOAEL method are mainly the presence of confidence intervals and the possibility of including the dose-response curve if necessary.

Fig. 5 summarises the calculation of an OEL for substances with a threshold value, starting from the experimentally determined measurement points:

**Fig. 4** Benchmark procedure

**Fig. 5** Calculation procedure for an OEL, starting from the experimental measurement points
2.3. Risk-based OELs in the case of carcinogenic and genotoxic substances [20-29]

a) General aspects

2.4. The absence of a threshold concentration in the case of directly-genotoxic carcinogenic substances is under discussion. It is possible that a definitely ineffective concentration cannot be given. In this case therefore, no threshold concentration would exist and the dose-risk curve would pass through the zero point of the diagram (Fig. 2 right). The dose-risk relationship would ideally be linear. However, there are indications that a cell can repair DNA changes up to a certain degree and thus a threshold concentration must also be present in directly genotoxic substances (No Observed Genotoxic Effect Level, NOGEL) and the waveform is not linear. Since this threshold is likely to be in very low doses, however, a barrier-free dose-risk relationship is nonetheless often assumed when deriving a threshold value. In the case of indirectly-genotoxic substances that do not alter the DNA itself, but for example with certain enzymes (such as the topo-isomerases, which relax or raise the DNA), there are threshold values. The same applies to carcinogenic, non-genotoxic substances (for example, in the case of endocrine-mediated tumours).

In a carcinogenic substance without a threshold concentration or a threshold concentration close to zero, adherence to a MAK value does not protect from a residual risk for the occurrence of a malignant neoplasia. Threshold values must be determined here based on risk. The level of acceptable risk on the ordinate of Fig. 2 (on the right) determines on the basis of the known dose-risk relationship, what concentration or cumulative dose of a carcinogenic substance can be used to determine a risk-based threshold value. It has been determined for some time in the Suva (Swiss National Accident Insurance Fund) publication on Swiss OELs ("Grenzwerte am Arbeitsplatz" (German) or "Valeurs limites d’exposition aux postes de travail" (French)) that the risk when adhering to an MAK value for carcinogenic agents could be in the same range as that caused by other environmental factors such as general air pollution. Based on this definition, a risk-based threshold value was established for asbestos for the first time in 2003, which assumes an additional risk for the occurrence of a malignant tumour in an employee of about $4 \times 10^{-4}$ throughout a working lifetime or of $10^{-5}$ per year. The minimization demanded for carcinogenic agents was considered to have been attained when the value measured does not exceed 10% of the MAK value; this corresponded to an additional risk for the occurrence of a malignant neoplasia of $4 \times 10^{-5}$ over the lifetime or of $10^{-6}$ ($1:1,000,000$) per year of employment. Today, the threshold value list notes that MAK values for carcinogens are established based on risk, the goal being that the additional risk of developing malignant tumours is no more than $1:100,000$ per year. It is clearly pointed out that carcinogenic agents should be replaced by harmless or less harmful ones (bid substitution) when possible and in each case, exposure to carcinogenic agents should be as low as possible (minimization).

Based on the level of protection that is assumed when determining the risk-based threshold values for carcinogenic agents, the Federal Coordination Commission for Occupational Safety FCOS also demanded a similar level of protection for the prevention of fatal and very serious occupational accidents.
For example, the concept of risk-based threshold values is also applied in Germany, Austria and The Netherlands.

b) Calculation of risk-based OELs using benchmark and T25 procedures

In the case of risk-based limits, we are almost always in a very low dose range in which no experimental measurements have been acquired (Fig. 6). The lowest value measured as a POD (Point of Departure) is therefore assumed and extrapolated into the "low-dose range." For carcinogenic substances, a linear extrapolation through the zero point is used in a standard case. If the operating principle cannot be explained solely by direct-genotoxic events, however, a sub-linear curve is possible depending on the mechanism, or a threshold must be assumed. If the waveform in the low-dose range is unclear, a function is calculated based on well-founded assumptions. Here, the benchmark method can be used. If this is not possible, a risk quantification with the T25 process as it is known can be conducted [30, 31]. Here, the lowest dose at which a significantly increased tumour incidence was observed is taken as a starting point. After including its background incidence and other assessment factors, the dose at which the tumour occurs with an incidence of 25% for lifetime exposure is calculated. The T25 value is used as the POD to move into the low-dose range by means of linear extrapolation and to read off the dose for the risk that is of interest. In the T25 method, the actual dose-risk relationship and the confidence intervals of the measurement points are not taken into account.

![Fig. 6 Risk extrapolation in the low dose area for substances without threshold concentration](image-url)
2.5. Substances without a clear dose-response relationship

Sensitizing substances for which no single dose-response relationship and no NOAEL can be derived as a rule represent a special case. While the risk of occurrence of sensitization is greater at high concentration, personal factors such as atopy (tendency to certain hypersensitivity reactions) are also decisive. If a person is sensitized, even the smallest amounts of substances can lead to a reaction. In the case of certain allergenic substances, a reference value can be given based on epidemiological studies. One good example is flour dust, such as wheat or rye flour dust, which can cause asthma; for these exposures, not only TWA values are recommended, but it is laid down that short-term peak exposures in particular should be avoided.

3. Threshold value definitions

3.1. Overview

Threshold values can be determined for different negative effects and for different areas (workplace, environment, foodstuffs, pharmaceuticals, etc.). The list of Swiss OELs ("Grenzwerte am Arbeitsplatz" or "Valeurs limites d’exposition au poste de travail") for the following exposures:

- Chemical and biochemical substances and mixtures
- Physical impact (ionising radiation, laser, UV-light, electromagnetic fields, sound and vibrations, excess pressure, heat resp. infrared radiation)
- Physical loads (weights)
- Microorganisms

This publication describes synthetic and biochemical substances. For these, there are different kinds of threshold values, dependent on the criteria on which their derivation is based:

- The route taken by the substance into the body (inhalation, percutaneous, by mouth)
- Place of measurement of the substance (air and biological material)
- Type of determination (direct measurement, indirect calculation)
- Effect size (no effect, minimum effect)
- Endpoint
- Length of exposure
- Applicability (guidelines, recommended threshold values, mandatory threshold values)

Table 1 is a listing of the different threshold value definitions, their abbreviations as well as the country in which these threshold values are in use. The two most important limits for industrial hygiene and occupational health issues in Switzerland - the MAK and BAT values - are then discussed in the following chapters.
### Table 1: Listing of the various threshold value definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGW</td>
<td>Arbeitsplatzgrenzwert</td>
<td>Germany (AGS)</td>
</tr>
<tr>
<td>BAT</td>
<td>Biologischer Arbeitsstoff-Toleranzwert</td>
<td>Switzerland (DFG)</td>
</tr>
<tr>
<td>BOELV</td>
<td>Binding Occupational Exposure Limits</td>
<td>EU (SCOEL)</td>
</tr>
<tr>
<td>BEI</td>
<td>Biological Exposure Index</td>
<td>USA (ACGIH, NIOSH, OSHA)</td>
</tr>
<tr>
<td>BLV</td>
<td>Biological Limit Value</td>
<td>EU (SCOEL)</td>
</tr>
<tr>
<td>BGW</td>
<td>Biologischer Grenzwert</td>
<td>Germany</td>
</tr>
<tr>
<td>DMEL</td>
<td>Derived Minimal Effect Level</td>
<td>EU (REACH)</td>
</tr>
<tr>
<td>DNEL</td>
<td>Derived No Effect Level</td>
<td>EU (REACH)</td>
</tr>
<tr>
<td>IDLH</td>
<td>Immediately Dangerous To Life or Health Concentration</td>
<td>USA (NIOSH)</td>
</tr>
<tr>
<td>IBE</td>
<td>Indicateurs Biologiques d’Exposition</td>
<td>France</td>
</tr>
<tr>
<td>IOELV</td>
<td>Indicative Occupational Exposure Limits</td>
<td>EU (SCOEL)</td>
</tr>
<tr>
<td>MAK</td>
<td>Maximale Arbeitsstoffkonzentration</td>
<td>Switzerland (DFG), Austria</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Low Observed Adverse Effect Level</td>
<td>International</td>
</tr>
<tr>
<td>NAEL</td>
<td>No Adverse Effect Level</td>
<td>International</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No Observed Adverse Effect Level</td>
<td>International</td>
</tr>
<tr>
<td>OEL</td>
<td>Occupational Exposure Limit</td>
<td>International</td>
</tr>
<tr>
<td>PEL</td>
<td>Permissible Exposure Limit</td>
<td>OSHA (EU, USA)</td>
</tr>
<tr>
<td>RBG</td>
<td>Risikobasierter Grenzwert</td>
<td>Switzerland (DFG), Austria</td>
</tr>
<tr>
<td>REL</td>
<td>Recommended Exposure Limit</td>
<td>USA (NIOSH)</td>
</tr>
<tr>
<td>TLV</td>
<td>Threshold Limit Value</td>
<td>USA (ACGIH)</td>
</tr>
<tr>
<td>TWA</td>
<td>Time Weighted Average</td>
<td>EU (SCOEL), USA (ACGIH)</td>
</tr>
</tbody>
</table>

### 3.2. MAK value

The **maximum workplace exposure limit (MAK value)** is the maximum permissible average concentration of a gas, vapour, or dust-like substance in the air, which, according to current knowledge, is generally not a health risk when effective for a working period of 8 hours daily and up to 42 hours per week, even over longer periods for the great majority of healthy employees at their workplaces.

Maximum workplace concentration values are therefore 8-hour averages. In practice, concentrations vary continuously, however. Depending on the substance and level of concentration significant health hazards can also arise in the case of short-term exposure. As a result, a limit must also be introduced here in terms of amount, duration and frequency. These “short-term OELs” are also included in the OEL list. For local irritants, the short-term exposure limit for a 15-minute sampling is usually the time-weighted average, which means that the MAK-value of these substances must not be exceeded even when measured over a period of 15 minutes. In the case of these substances, the short-term OEL corresponding to the time-weighted average is given in the short-term OEL column complemented with the reference “15 minutes” in the column for the time limit. For substances with a short-term OEL higher than the MAK value, the short-term OELs are expressed as averages over 15 minutes. The gap between the four permissible exposure peaks per layer should be at least one hour. The 8-hour average must be adhered to without exception.
The maximum workplace concentration value does not represent a safe threshold between hazardous and non-hazardous ranges. On the one hand, material concentrations below a maximum workplace concentration value do not guarantee the health of all those exposed. Particularly sensitive people or people with health issues may be at risk due to lower concentrations. On the other hand, short-term exposure above the maximum workplace concentration value does not necessarily mean that those exposed will suffer from health problems. Particularly sensitive people include those whose skin or respiratory tract is sensitive to certain materials. Among these people, allergic reactions (hypersensitivity reactions) can be caused by many substances even in very small concentrations. Here, compliance with MAK-values only provides limited security.

No MAK values are published for many substances used industrially. However, that does not mean that these substances are harmless and the use of these substances in no way differs from those with existing MAK values. Here, the safety data sheet enclosed with each substance proves to be an important source of information. In addition, international companies must comply with the REACH regulation, which requires a toxicological profile for all substances traded in the EU region.

By definition, MAK values are for exposure to single substances. MAK values are only of limited use for the evaluation of gaseous mixtures with the possible interactions of individual components, of polymerizing substances such as isocyanates or of complex materials whose composition is not exactly known such as coolants or mineral oils. In operational practice, models are used to be able to assess air quality in the workplace nevertheless. Details can be found in the Swiss threshold value list.

Together with the BAT value mentioned in section 3.64, the MAK value forms a basis for assessing the possible hazard posed by or the acceptance of concentrations of hazardous substances occurring in the workplace. Measures for occupational disease prevention must be taken depending on the outcome of the investigations. Occupational hygiene is dedicated to the improvement of external effects (workplace environment) in accordance with the STOP principle (substitution, technical measures, organizational measures, person-related measures). Occupational health care involves employees’ internal exposure levels, which are evaluated by clinical examination and the determination of appropriate laboratory parameters, for example, as part of biological monitoring (see Section 3.64).

MAK values are determined according to the latest scientific information. However, the MAK value concept also has its limitations. Measurements of substance in ambient air provide information on external, but not on internal levels to which employees are exposed; in certain situations, the assessment of exposure to agents must therefore be complemented by biological monitoring (see section 3.64). The definition of the MAK value is designed not to compromise the predominant number of healthy employees. The particular sensitivity of certain employees to substances must be noted such as, for example, employees with asthma or other respiratory diseases if they are exposed to dust or respiratory irritants.
3.3. **Assessment of MAK values for mixtures of substances**

In practice, employees are not usually exposed to single substances, but to mixtures of substances. By definition, however, MAK values apply to exposure to single substances. They are only partially suitable for the assessment of mixtures of substances and technical products containing accompanying substances or impurities with greater toxicity. The reason for this limitation is the circumstance that the toxicological assessment of mixtures whose components can both strengthen or weaken each other in terms of their action has not been adequately verified on the basis of scientific findings. Nevertheless, it must be possible to use uniform criteria to assess the quality of the air in workplaces where pollutant mixtures occur.

If no interactions occur, an independent effect of the substances can be assumed for a different target organ. An additive effect takes place for the same target organ. This corresponds to the toxic effect of the total concentration of the individual agents and/or the sum total of the individual concentrations of the substances involved. The additive effect is not caused by an “effect addition” but by a “dose addition”.

However, interactions frequently occur in the case of multiple exposures to agents. In this case, the concentration of toxic substances or metabolites (conversion products) are influenced at the target organ and the parameters of biological monitoring change. In general, interactions in the area of absorption, distribution, biotransformation (activation of agents to active metabolites or detoxification to inactive metabolites) and excretion can occur. In this case, we speak of toxicokinetic interactions. Interactions can also occur at the target organ in the area of receptors for agents. These are toxicodynamic interactions.

If a working substance inhibits the metabolism of another agent, then the detoxification of the active substance slows down to an (in)active metabolite. Mutual inhibition of the metabolism is also known. In this situation given the simultaneous effect of these substances, increased concentrations of toxic substances in the blood occur with a supra- or hyper-additive overall effect. The excretion of inactive metabolites in the urine is delayed and has a smaller peak. This can lead to misinterpretation since an excessively low internal load on the part of the employees with these substances is assumed.

The effect of an agent can also be weakened by another substance (infra-additive effect or antagonism), for example by an acceleration of the metabolism.

In day-to-day operations, the following assumption is used as a basis for assessment for mixtures that act on the same target organs and whose components strengthen each other in their effect independently of each other in the sense of the above “dose addition”, for example, in solvent mixtures:

\[
\frac{C_1}{\text{MAK}_1} + \frac{C_2}{\text{MAK}_2} + \frac{C_3}{\text{MAK}_3} + \ldots + \frac{C_i}{\text{MAK}_i} \leq 1
\]

If the sum of the MAK value shares of the individual components exceeds the value 1, their total concentration must be reduced by appropriate measures to the extent that the total index is reliably below 1.
However, if there are any mixtures of substances present that act on different target organs and/or whose components are not mutually strengthened in terms of their overall effect, e.g. vehicle exhaust fumes, each quotient on its own must be <1.

In the case of a risk analysis and alongside multiple effects in the workplace, consideration must also be given to non-occupational factors such as alcohol, drugs or smoking, which can also interact with occupational effects. Attention must also be paid to the different toxicokinetics or half-life of the metabolites of the agents involved. The interaction between noise and ototoxic agents must also be included as part of the risk assessment.

### 3.4. Risk assessment for substances without MAK values (control banding)

Adequate toxicological and/or work experience when handling a substance are preconditions for establishing a MAK value. For many substances in commercial use, there is no MAK value. However, this does not mean that these substances are harmless. Handling these substances differs in no way from handling ones with an existing MAK value. Even when handling these substances, an assessment of the health risk must be carried out. This assessment requires a knowledge of the operational requirements and includes a

- risk analysis
- determination and an assessment of the exposure
- definition of the measures
- reassessment after a certain time or when new data is available.

Safety data sheets are an important source of information for assessing the health risk. Among other things, they contain the most important properties known, protective measures and first aid measures. Safety data sheets are supplied with every product or can be ordered from the distributor.

If there is no MAK value for a substance, it may be difficult to make an exposure assessment and to derive any appropriate measures. In practice and among other things, the procedures described below for this problem have proved their worth. These procedures presuppose, however, an in-depth knowledge of occupational health, toxicology and occupational hygiene.

If sufficient in-house toxicological data is available and/or the pharmacological effect is sufficiently well known, it may be possible to determine a value in compliance with which no observed adverse effect levels are to be expected (NOAEL). Own guidelines for such substances can be determined given a knowledge of the NOAEL and with consideration for additional safety factors. This approach is used, for example, in the pharmaceutical industry to derive values for substances they manufacture themselves. In this case, the measures are defined in a manner that enables the values to be adhered to.

If sufficient information is not available for the determination of own values, it is sometimes still possible to categorize substances based on an existing knowledge of their physical and chemical properties and, based on these, to derive the measures. For example, “control banding” can be used as an approach. In this method, groups or “bands” are defined to which substances with similar health risks can be assigned according to their material properties. For each band a package of measures is defined at the same time that is matched to the risk level of the band concerned.

3.5. Further designations in the MAK list

In addition to the MAK value, the list also contains other designations, these being the importance of skin absorption, the incidence of allergies, the impact on fertility and foetal development as well as a possible carcinogenic or mutagenic effect.

- **H** (poisoning by skin absorption is possible).

In the case of substances that can penetrate the skin easily, the inner exposure level can be much higher due to additional absorption through the skin than is the case with sole absorption through the respiratory system. If the air concentration is measured, the actual internal exposure level of the organism caused by this material can be underestimated. Thus, for example, aniline, nitrobenzene, nitroglycol, phenols and certain pesticides can also result in dangerous poisoning solely on their way through the skin. In these cases, the goal must also be biological monitoring for the assessment of a workplace.

- **S** (sensitisers)

The substances marked with S lead to hypersensitivity reactions (allergies) of the airways and/or skin with particular frequency. Adherence to the MAK value offers no security against the occurrence of such reactions (see section 2.4.). Particular attention must be paid to the risk of sensitization to acrylates, flour dusts (rye, wheat), α-amylase, rosin, and rubber. The aim of this information is to encourage special attention when handling these materials.

- **C** (Carcinogenic substances)

Depending on evidence, a difference is made between three categories. C1 includes those substances known to be carcinogenic for humans while C2 includes those, which should be considered carcinogenic on the basis of animal experiments. C3 includes those, which should give cause for concern because of potential, but insufficiently documented carcinogenic effects in humans.

- **M** (Mutagenic substances)

Substances identified with an M are those that have a mutagenic effect or of which there is evidence of a mutagenic effect. As is the case with carcinogenic substances, a distinction is made between three categories of M1 to M3.

- **R** (Reproduction-toxic substances)

The term “reproductive toxicity” includes both the impairment of male and female fertility as well as the prenatal induction of non-inheritable harmful effects on progeny. The corresponding abbreviations are Rf (impairment of reproductive performance or fertility) and Re (birth defects, developmental toxicity). The classification of a substance as Re refers to the properties of the substance itself and not to its relationship with the MAK value.
Teratogenic substances are also divided into three groups, which link to the MAK value: in group A, injury of the foetus may occur even when the MAK value is adhered to; in the case of group B, it cannot be excluded and in Group C it need not be feared. For a large number of substances, no information about their teratogenic risks is possible for the time being.

- **Ol (Noise-enhancing ototoxicity)**

Noise effects can damage the cells of the inner ear, leading to a temporary permanent hearing loss in terms of masking or permanent loss of hearing with deafness. Animal experiments and epidemiological investigations have shown that certain agents are able to produce permanent hearing loss and/or to enhance the effects of noise on the hearing. Various mechanisms for this effect are discussed, such as a central inhibition of the middle ear reflex or direct toxic effects on the outer hair cells of the organ of Corti in the inner ear.

In the Swiss threshold value list, ototoxic substances that enhance the ototoxic effects of noise are marked with “OL”.

Ototoxic substances that admittedly damage the hearing but for which an interaction with noise has not been shown with sufficient evidence are not marked.

The allocation of an O⁎-notification is based on investigations by the Nordic Expert Group (NEG) for the Criteria Documentation of Health Risks from Chemicals, the European Agency for Safety and Health at Work (EU-OSHA) and other institutions such as l’Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles (INRS) or l’Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST)

The interaction between noise and the ototoxic agents marked with “OL” must be factored in as part of risk assessment. In the case of relevant exposures to these substances, technical and organizational noise reduction measures and/or the wearing of hearing protection are recommended possibly even at noise exposures below 85 dB(A). The question of whether the threshold values for the agents mentioned are protective for ototoxicity respectively for interaction with noise can, in future, only be answered with greater precision based on further investigations.

- **KT (critical toxicity)**

If a person is exposed to a substance, substance-specific undesirable effects (known as adverse effects) can occur. Their expression is dependent on the concentration of the substance in the air as well as, among other things, absorption through the skin or the gastrointestinal tract as well as the physical strain with increased respiratory minute volume.

Common adverse effects include irritation or burns of the mucous membranes of the upper and lower respiratory tract or the eyes, heart rhythm disturbances, impaired brain function, chronic toxicity with organ damage (lung, liver, kidneys, skin, bone marrow, skeleton, brain, nerves, etc.) or malignant tumours. The lower the concentration of the substance, the fewer the number of adverse effects observed. Below a certain concentration, no more adverse effects occur. Whether a threshold like this exists in the case of direct-genotoxic substances has not yet been clarified.
The one significant adverse effect which is used to calculate the MAK value is called "critical toxicity". As a rule, this is the adverse effect that occurs at the lowest concentration.

Critical toxicity is derived from epidemiological or animal-test studies. By means of extrapolation and safety factors as well as other situational considerations, the concentrations used in these studies are converted to the current conditions in the workplace and the MAK value is determined from this. Sometimes the studies are insufficiently robust to show a single adverse effect as critical toxicity. In this case, several undesirable effects that occur in the low concentration range are used to determine the threshold value. It is also not always clear which of the body’s reactions to exposure can be considered “undesirable” and which adversity is “relevant” enough to be used as the critical toxicity (e.g. subclinical laboratory changes).

Critical toxicity and/or some adverse effects that are important for determining the MAK limit are given in a separate column in the Swiss list. Either the anatomical structures (target organs) concerned which are affected by the substance in an undesirable way or the pathological changes themselves are mentioned (for example, pulmonary fibrosis, corneal edema). Critical toxicity is marked with “KT” in superscript form (for example, lung\textsuperscript{KT}). If the findings have their origins in animal experiments, this is shown by “AN” in superscript form for “animal” and in human studies, this is represented by “HU” for “human” (e.g. heart\textsuperscript{KT HU}); no notification is given if the origin cannot be established or is known both for humans as well as for animals. A designation with AN or HU does not mean that a corresponding critical toxicity only occurs in animals or humans, but it means that the threshold value was derived from experiments on animals or human beings.

In addition to critical toxicity, other adverse effects can be included in the column which occur when the threshold value is exceeded slightly and which may be of significance when calculating the MAK value. This is not critical toxicity in the narrow sense, and they do not have any KT or AN/HU designation. It should be noted that this is not a list of all the important adverse events, but only of those that are important for setting threshold values; therefore, it does not make any consultation of toxicological literature superfluous.

- **e and a (inhalable and respirable suspended particles)**

Suspended solids or particulates are classified according to their lung deposition into:

- **e = inhalable dust (formerly: total dust)**
  English and French: inhalable
  Inhalable dust is understood to mean the totality of the particles in the air breathed that can be inhaled through the mouth and nose.

- **a = alveolar dust (formerly: fine dust)**
  English: respirable/French: alvéolaire
  Respirable dust is defined as the totality of the particles in the air breathed that can reach the lung alveoli.
3.6. BAT value and biomonitoring

The BAT value (biological agent tolerance) describes the occupational medically and toxicologically derived concentration of a substance, its metabolites or a stress indicator in biological material, in which generally the health of employees is not impaired, even with repeated and long-term exposure [32]. BAT values are based on a relationship between external and internal exposure, or between internal exposure and the effect of the working substance caused. The BAT value is considered to have been exceeded if the mean concentration of the parameter is above the BAT value in several examinations of an employee.

Readings above the BAT value should be evaluated both occupational medically and toxicologically. In general, a health impairment cannot be concluded from a single exceedance of a BAT value. For individual substances, a BAT value is, however, considered to be the maximum value in each individual case due to the toxicological situation; this applies, for example, to cholinesterase inhibitors or carbon monoxide.

BAT values are preferably derived with the help of studies among exposed employees due to the correlation between biological measured values and health hazards of the employee exposed. For example, this is possible for the derivation of the BAT-values of lead, mercury and cadmium. For agents for which there are no such studies, BAT values are derived indirectly from a knowledge of the correlation between external and internal load levels so that the value of BAT and MAK value are related to each other. In addition, the absorption, distribution, metabolism and excretion of the substance as well as any influences are taken into account by other parameters.

As a result of biomonitoring, the internal level caused by a substance or a load as a reaction of the organism to the substance is assessed. In the case of systemically operating toxic substances, the inner level, that is to say, the amount of substance absorbed is of primary significance for assessing the risk. In this way, all absorption routes of the substance are recorded, that is to say, as well as absorption through the skin and the gastrointestinal tract. An increase in intake of a substance during physical exercise with increased respiratory minute volume and exposure when doing hobby work or through the environment is also taken into consideration. Increased substance intake may also occur as a result of inadequate personal hygiene and this is also recorded in the assessment of internal load levels. The effect of protective measures such as respiratory and skin protection can also be assessed with biomonitoring. Further advantages of biomonitoring are the continuity of the monitoring and - if a biological parameter has a long half-life - the assessment of workplace exposure over a certain period.

The interpretation of the results of biological monitoring for employees must take into account the background levels of the non-occupationally exposed population. A distinction must thus be made between the reference values for the non-occupationally exposed population and the biological substance tolerance values for those exposed occupationally. Reference values are typically reported as 95%-percentile values and they thus correspond to a statistically derived value that roughly corresponds to the upper limit of the fluctuation range of the contaminant concentrations in the biological material of the general population. If this reference value is exceeded for employees, this means that the employee concerned shows a higher internal exposure than is the case with the general population.

The reference values (BAR values) determined by the German Research Foundation DFG must be differentiated from the reference values for the general population. The BAR values describe existing background levels at a certain time in a reference population of persons of working age not occupationally exposed to the substance with substances present in the environment. The difference between the BAR value and the reference value of the occupationally not affected population thus represents the basic population; BAR values are derived from people of employable age, reference values of the population from the total population.

In Switzerland, BAT values are also published for carcinogenic substances with the classification C1 (substances known to have a carcinogenic effect on people) and C2 (substances which should be regarded as carcinogenic to humans). Biological monitoring is useful in many situations including exposure to carcinogenic agents. Regarding the interpretation of BAT values for carcinogenic substances, the same restrictions as for the interpretation of MAK values also apply to carcinogenic substances; given the current state of knowledge, no ineffective concentrations with any degree of certainty can be stated. Section 2.3 should be consulted with regard to the question of limits for carcinogenic substances. The BAT values for carcinogenic substances are thus subject to the same restrictions as the MAK-values for the carcinogenic substances. The American Conference of Governmental Industrial Hygienists ACGIH also publishes Biological Exposure Indices (BEI) for carcinogenic substances. For carcinogenic substances, the German Research Foundation DFG issues exposure equivalents for carcinogenic substances (EKA). These describe the relationships between material concentration in the air at the workplace and the material or metabolite concentration in the biological material. The EKA can be used to establish which internal harm would result from exclusively inhaled absorption.
4. Determining OELs in Switzerland

4.1. Publication of Swiss OELs

In Switzerland, Suva (Swiss National Accident Insurance Fund) issues guidelines according to Article 50, §3 VUV (ordinance regulating accident prevention and occupational diseases) on the maximum workplace concentrations of harmful substances as well as on threshold values for physical impact. The threshold values under discussions are assessed by Suva specialists with due consideration for the most recent research findings according to the methods described in section 2. In addition, measuring and technical implementation factors are discussed whereby the health aspects are decisive for determination.

Suva’s OELs proposals are submitted to the OEL Committee of Suissepro (Swiss Association of Occupational Health, Hygiene and Safety) for their opinion. This committee consists of university researchers, the State Secretariat for Economic Affairs seco, occupational physicians and other occupational safety specialists (ASA) and Suva. It decides on any mandatory inclusion in the annually published list of Swiss OELs (“Grenzwerte am Arbeitsplatz” (German) or “Valeurs limites d’exposition aux postes de travail” (French)). In the event of any uncertainties, if the basis of the study is not considered sound enough, or if the threshold value concentration cannot be measured with current equipment, the substance is put on a pending items list for further clarification or marked in the list with a “P” (provisional).

The Swiss list of OELs can be ordered from Suva (order no. 1903.d (German) or 1903.f (French)) or downloaded from www.suva.ch/waswo/1903.d or www.suva.ch/waswo/1903.f. It currently contains more than 600 MAK values and nearly 50 BAT values. The limits are also available in the international database GESTIS (http://www.dguv.de/bgia/de/gestis/limit_values/index.jsp) [41].

4.2. REACH

The REACH regulation of the European Chemicals Agency ECHA [42] has been established in the EU since 2007. This regulation prescribes an accurate volume-dependent characterization of all chemicals in circulation in the EU. This includes a toxicological assessment with a determination of the concentration below which there is no harmful effect (DNEL = Derived No Effect Level). For substances for which no threshold value can be specified, an exposure concentration with mild adverse effects (DMEL = Derived Minimal Effect Level) must be given. The derivation of these threshold values is the responsibility of industry and largely corresponds to those for the official MAK values. However, DNELs are often calculated fairly roughly with default factors according to the ECHA guideline [43] as there are not always enough studies for an individual assessment - in contrast to MAK values, which are always assessed by scientists from case to case. Unlike official MAK values, DNELs are also not binding to the same degree in regulatory terms and DNELs need not only be calculated for the inhalative, but also for other absorbency routes (through the skin, etc.). Detailed information on REACH can be obtained from the BAG website on chemical law (http://www.bag.admin.ch/themen/chemikalien) or directly from the relevant ECHA website (http://echa.europa.eu/reach_en.asp).

## 5. Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>advers</td>
<td>undesirable</td>
</tr>
<tr>
<td>AGS</td>
<td>Committee for Hazardous Substances</td>
</tr>
<tr>
<td>ASA</td>
<td>Occupational doctors and other occupational safety specialists</td>
</tr>
<tr>
<td>BAT</td>
<td>Biological tolerance value</td>
</tr>
<tr>
<td>BMD</td>
<td>Benchmark dose</td>
</tr>
<tr>
<td>BMDL</td>
<td>Benchmark dose lower bond</td>
</tr>
<tr>
<td>BMR</td>
<td>Benchmark response</td>
</tr>
<tr>
<td>DFG</td>
<td>German Research Foundation</td>
</tr>
<tr>
<td>DMEL</td>
<td>Derived minimum effect level</td>
</tr>
<tr>
<td>DNEL</td>
<td>Derived no effect level</td>
</tr>
<tr>
<td>ECHA</td>
<td>European Chemicals Agency</td>
</tr>
<tr>
<td>FCOS</td>
<td>Federal Coordination Committee for Occupational Safety</td>
</tr>
<tr>
<td>EU-OSHA</td>
<td>EU Occupational Safety and Health Administration</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>Calculation that goes beyond the range verified</td>
</tr>
<tr>
<td>INRS</td>
<td>Institut national de recherché et de sécurité pour la prevention des accidents du travail et des maladies professionnelles</td>
</tr>
<tr>
<td>IRSST</td>
<td>Institut de recherche Robert-Sauvé en santé et en sécurité du travail</td>
</tr>
<tr>
<td>LOAEL</td>
<td>Low Observed Adverse Effect Level</td>
</tr>
<tr>
<td>Low-dose range</td>
<td>Low-dose range</td>
</tr>
<tr>
<td>MAK</td>
<td>Maximum workplace concentration</td>
</tr>
<tr>
<td>NAE</td>
<td>No adverse effect level</td>
</tr>
<tr>
<td>NIOSH</td>
<td>National Institute for Occupational Safety and Health</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No observed adverse effect level</td>
</tr>
<tr>
<td>NOGEL</td>
<td>No observed genotoxic effect level</td>
</tr>
<tr>
<td>OEL</td>
<td>Occupational Exposure Limit</td>
</tr>
<tr>
<td>OSHA</td>
<td>Occupational Safety and Health Administration</td>
</tr>
<tr>
<td>POD</td>
<td>Point of departure</td>
</tr>
<tr>
<td>REACH</td>
<td>Registration, evaluation and authorisation of chemicals</td>
</tr>
<tr>
<td>SCOEL</td>
<td>Scientific Committee for Occupational Exposure Limits to Chemical Agents</td>
</tr>
<tr>
<td>Suva</td>
<td>Swiss National Accident Insurance Fund</td>
</tr>
<tr>
<td>T25</td>
<td>Dosage with 25% additional frequency of occurrence of a tumour</td>
</tr>
</tbody>
</table>
6. Bibliography

1. Pesch B. et al.: Low-dose extrapolation in toxicology: an old controversy revisited; Arch Toxicol (2009); 83: 639-640
2. Suva: Grenzwerte am Arbeitsplatz, order no. 1903
7. INRS (Institut national de recherche et de sécurité): Principes de construction des valeurs limites d’exposition professionnelle françaises et comparaison avec la méthodologie adoptée au niveau européen, dossier médico-technique TC 133; Documents pour le Médecin du Travail, No 124 (4th trimester 2010): 399-412
8. SCOEL (Scientific Committee on Occupational Exposure Limits): Methodology for the Derivation of Occupational Exposure Limits; Key Documentation (version 6) (2009)
11. Jayjock M. A.;, Quantitative Level of Protection Offered to Workers by ACGIH Threshold Limit Values Occupational Exposure Limits; Am Indus Hyg Ass J (2001); 62: 4-11
15. Schenk L. und Johanson G.: Use of Uncertainty Factors by the SCOEL in their derivation of health-based Occupational Exposure Limits; Critical Reviews in Toxicology (2010); 40: 791-798
17. Rhomberg L. R.: Linear Low-Dose Extrapolation for Non-cancer Responses Are Not Generally Appropriate; Environ Health Perspectives (2009); 117: A141-A142
33. ACGIH (American Conference of Governmental Industrial Hygienists): Documentation of the Threshold Limit Values and Biological Exposure Indices
34. AGS (Ausschuss für Gefahrstoffe): Bekanntmachung 900, Arbeitsplatzgrenzwerte
36. DFG (Deutsche Forschungsgemeinschaft): MAK- und BAT-Wertliste. Verlag Wiley-VCH
42. European Community Regulation on chemicals and their safe use: REACH (Registration, Evaluation, Authorisation and Restriction of Chemical Substances), EC 1907/2006 (June 2007)