Occupational Exposure Limits to Prevent Chemical Risks

issa

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Section on Prevention in the Chemical Industry

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The ISSA Chemistry Section is an independent international organisation. Since it was founded on 17 June 1970, it has been committed to the global prevention of occupational accidents and diseases in the chemical and related industries. Our brochures, publications and international lecture programmes provide companies and their employees with guidance and assistance on safety at work. The ISSA Chemistry Section is of particular relevance to the following branches of industry:

- Plastics
- Rubber
- Pharmaceuticals
- Lacquer
- Paints
- Explosives and petroleum

Occupational Exposure Limits to Prevent Chemical Risks

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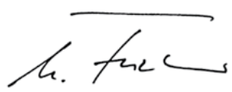
Preface

In enterprises that carry out operations involving dangerous substances or in which dangerous substances can develop or be released, all the hazards to the health and safety of the employees must be evaluated by the employer, or by persons appointed by the employer, such as safety experts or the company physician. Occupational exposure limits (OELs) are important evaluation criteria for determining possible exposure and the appropriate technical, organisational, and, in certain cases, personal protective measures. It must be ensured that employee exposure does not exceed the OELs. Furthermore, there must be regular checks to ensure that OELs are being complied with through measurements at the workplace or other suitable methods of exposure determination.

Depending on the hazard potential of substances or on the possible exposure route, different states and communities have developed different procedures for determining limit values and additional notations. A distinction is made between air limit values and biological limit values.

The objective of this brochure is to give an overview of the different aspects of and approaches to deriving OELs for protecting workers in the context of chemical risk management. This booklet has been written by a group of experts belonging to different organisations and companies from Austria, France, Germany, Italy and Switzerland. The various chapters of the brochure are conceived as independent articles dealing with separate specialised topics. The ISSA Chemistry Section would hereby like to make a contribution to the understanding of how limit values are derived and of how important it is to apply them. The brochure is supplemented by a web application, which is available at www.limitvalues.net.

Thomas Köhler
President



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1. HISTORY OF OCCUPATIONAL EXPOSURE LIMITS

Raymond Vincent

HISTORY

1.1 Dealing with chemical risks from ancient times to the 18th century

Effects of chemicals on human health were observed more than 20 centuries ago. During the Roman period, the architect Marcus Vitruvius Pollio, also known as Vitruvius, (90-20 BC), reported cases of illness for workers exposed to lead in foundries. Based on his observations, Vitruvius concluded that lead should not be used to manufacture water pipes (see "De Architectura, Book VII").

Gaius Plinius Secundus, also known as Pliny the Elder, (23-79 AD), described how workers used sheep bladders as masks to protect themselves from lead and dust when using raw materials containing lead carbonate or mercuric sulphide (cinnabar) for manufacturing dishes and plates.

Hazardous exposure of workers involved in mining and smelting of metals was well known in the European mining industries that were emerging in the 11th and 12th centuries. That situation led to guilds being set up to help workers who became ill. One of the first in Europe was founded among the silver miners of Goslar in the Harz Mountains of Germany in 1188.

At the end of the Middle Ages, the publication entitled "De re metallica" by Georg Bauer, whose Latinised pen name was Georgius Agricola, reported occupational hazards associated with mining or smelting of iron, silver, lead, gold, mercury and other metals and warned about "black lungs" in miners [1.1].

In 1700, Bernardino Ramazzini (1633-1714), considered as the "father" of occupational medicine, wrote the first important book on occupational diseases and industrial hygiene: "De morbis artificum diatriba" (Diseases of Workers) [1.2]. That book outlined the health hazards of irritating chemicals, dust, metals, and other abrasive agents encountered by workers in 52 occupations and reflected increasing concern about miners in some parts of Europe.

1.2 Setting exposure limits in Europe and America

Carbon monoxide was a hazardous gas that led to limits being determined. After studying the health effects of carbon monoxide, Peter Koffer (Germany) recommended an exposure standard of 50 ppm in 1849 [1.3].

In 1874, English Army Surgeon F. de Chamount conducted the first indoor air quality survey correlating five levels of symptoms to indoor carbon dioxide concentrations. He proposed an Internal Air Quality (IAQ) standard for carbon dioxide of 200 ppm above outdoor levels, i.e. of approximately 500 ppm [1.3].

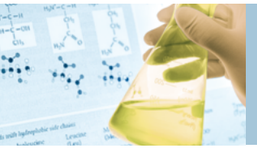
In Europe in the late 1880s, hazards associated with chemical exposure started to be taken into account.

One of the first Occupational Exposure Limits (OELs) was established for carbon monoxide, based on the work by Max Gruber at the Hygienic Institute in Munich, which was published in 1883. Gruber determined the OEL of carbon monoxide at 200 ppm after exposing hens and rabbits to known concentrations for up to 47 hours over three days [1.3]. To validate this assumption, Gruber himself inhaled carbon monoxide at concentrations of 210 ppm for three hours on two consecutive days [1.4].

In 1886, Karl Bernhard Lehmann established and published OELs for some organic solvents and irritant gases, such as sulphur dioxide, halogens and acid fumes [1.4].

In 1912, Rudolph Kobert published a list of acute exposure limits for 20 chemicals in the "Compendium of Practical Toxicology" [1.5]. These values proposed by Kobert correspond to concentrations Immediately Dangerous to Life or Health (IDLH).

Later, in 1916, South Africa set a permissible exposure limit of 8.5 million particles per cubic foot (mppcf) of air for dust containing 80-90 % of quartz. That limit was based on correlation of air dust concentration measured



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with a "konimeter" and of periodic chest X-ray examinations of gold mine workers. In 1917, the U.S. Bureau of Mines published an OEL of 10 mppcf for quartz.

In the 1920s, one of the most comprehensive lists of OELs was published in the "International Critical Tables for Numerical Data" for 27 chemicals. During the same period, the US Bureau of Mines recommended OELs for 33 substances. In 1930, the USSR's Ministry of Labour published a list of workplace maximum allowable concentrations for twelve chemicals.

In the 1940s, in the United States, a list of "Maximum Allowable Concentrations" (MAC values) was based on a consensus opinion of the American Standards Association (ASA) and of a number of industrial hygienists who had formed the American Conference of Governmental Industrial Hygienists (ACGIH) in 1938. The Thresholds Committee of the ACGIH published the first table of 63 exposure limits (MAC values) - later to be known as Threshold Limit Values (TLV). In 1946 during the 8th annual meeting of the ACGIH, the subcommittee on TLVs presented a report with the values for 131 gases, vapours, dusts, fumes, and mists, and 13 mineral dusts [1.6]. In December 1970, the United States Congress promulgated the Occupational Safety and Health Act which was the first federal law including ACGIH and American National Standards Institute (ANSI) OELs.

Many countries in the world have used the TLVs of the ACGIH as a basis to establish their own occupational standards. They are still in common use in Europe, and in some other countries especially in Latin America [1.7].

1.3 A European Directive as a legal basis for Occupational Exposure Limits

It was not until the 1980s, with the European Directive 80/1107/EEC, that a legal basis was established for OELs [1.8]. The first list of Indicative OELs (IOELs) was created in 1991 for 27 substances. Member states had two years to implement national limits. Various directives in 2000, 2003 and 2009 added to that initial list. In 1995, the European Commission created the SCOEL (Scientific Committee on Occupational Exposure Limits), composed of a maximum of 21 members proposed by the EU member states. The SCOEL members are independent experts in the fields of chemistry, toxicology, epidemiology, occupational hygiene and industrial hygiene, and are capable of conducting a scientific approach in order to recommend OELs to the European Commission. Since 1995, SCOEL has adopted 177 OEL recommendations. Each member state is obliged to transpose into its national regulations the OELs recommended by the EU Commission as binding limits (BOELs: Binding OELs) or indicative limits (IOELs: Indicative OELs). Whenever a European OEL exists, the member states have to implement the values in their national legislations.

Each EU member state has its own procedure for transposing or defining OELs. Those procedures are mostly based on tripartite models, in two stages: independent scientific assessment, informing and consulting social partners, for example within the Comité d'orientation sur les conditions de travail, COCT (Guidance working conditions committee in France) or the Ausschuss für Gefahrstoffe, AGS (Committee on Hazardous Substances in Germany). After consulting social partners, the competent authorities decide on the exposure limit value to be set.

In countries in which OELs are set, there are also broad similarities in the procedures involved. Mostly there is a two stage process in which the scientific/health-based issues are dealt with, usually by experts (sometimes representing economic interests, sometimes not, and sometimes a mixture of both) followed by a second process in which economic/technical issues of feasibility are considered. Here, economic interests and the social partners are represented.

In the context of the EU Regulation "Registration, Evaluation, Authorisation and Restriction of Chemicals" (REACH) for improving protection of humans and the environment, manufacturers or importers of chemical substances have to assess health and environment risks for registration [1.9]. Registrants must propose Derived No Effect Levels (DNELs) and are asked to determine Derived Minimum Exposure Limits (DMELs) for non-threshold compounds. DNELs and DMELs may not be considered as OELs, and the REACH Regulation indicates that if an EU OEL exists, the registrant may use the OEL in place of developing a DNEL. Nowadays, the OELs that are recommended in the world are mainly provided by two different consortiums: in North America, ACGIH plays a predominant role, and in Europe, SCOEL has a similar role.

There is a considerable difference between the number of chemicals used and the number of existing OELs.

This short chronology shows that occupational chemical hazards have been known for almost 2,000 years, but it is only over the last 150 years that these hazards have become no longer acceptable. One of the main barriers to developing OELs was the lack of chemical sampling, and the fact that analytical methods did not enable much progress to be made regarding how to evaluate the workplace environment quantitatively.

1.4 Literature

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2. PRINCIPLES OF ESTABLISHING OCCUPATIONAL EXPOSURE LIMITS

Herbert Bender

2.1 General Approach

The general approach to deriving an Occupational Exposure Limit (OEL) is based on toxicological data from animal experiments that has to be converted into limit values usable for protecting workers from adverse health effects. This approach is synthesized in *Figure 2.1*.

To establish an OEL, a minimum set of data is required. The basic toxic properties should be known, i.e.:

- Acute lethal dose,
- Irritation / corrosiveness,
- Local versus systemic effects,
- Basic information on mutagenicity / genotoxicity,
- Skin penetration.

These properties, often known as the base set, describe the acute potential of substances. In order to describe the toxicological properties of a substance more appropriately, additional knowledge of further properties is necessary.

Reproductive toxicity has to be known for a comprehensive assessment of the toxicological profile. Impact on fertility is in most cases not the most sensitive property. Developmental toxicity is important in order to eliminate harm to the unborn child. Different test methods are available to detect reproductive toxicity, including fertility and developmental hazard.

Investigations to detect a mutagenic property by in-vitro screening tests are part of the basic test set. Whenever significant positive results are found, additional in-vivo tests are required to exclude or confirm the mutagenic potential. In particular, if there is clear evidence of a mutagenic potential, long-term animal testing is needed to assess a potential carcinogenic property.

In order to establish a health-based OEL, studies of repeated exposure are required. The minimum duration of animal testing on rodents is a sub-acute study, in which rodents are typically exposed over a time period of 28 days. The substances can be administered either orally or inhalatively, and occasionally dermally. More sensitive investigations in order to recognize long-term as well as cumulative health effects require sub-chronic (90-day study) or chronic studies (normally lasting two years).

In the former case, the substance can be administered in drinking water or feed. In the case of gases or liquids, the inhalation chamber is filled with a gaseous or vapor atmosphere; solids and liquids with high boiling points are administered as aerosols.

All toxicological studies must follow the agreed international quality standards of Good Laboratory Practice (GLP). Particularly for legal requirements, such as the REACH Regulation, all studies have to be conducted in accordance with the appropriate Guidelines of the Organization for Economic Co-operation and Development (OECD). A short selection of often-used guidelines is, for example:

- OECD 401: Acute oral toxicity,
- OECD 402: Acute dermal toxicity,
- OECD 403: Acute inhalative toxicity,
- OECD 407: Repeated dose 28-day oral toxicity study in rodents,
- OECD 408: Repeated dose 90-day oral toxicity study in rodents,
- OECD 411: Sub-chronic inhalation study: 90-day,
- OECD 412: Sub acute inhalation toxicity: 28-day study,
- OECD 413: Sub-chronic inhalation toxicity: 90-day study,
- OECD 452: Chronic toxicity study.

In order to transfer the data to the situation in the workplace, knowledge of the human metabolism in comparison to that of the animals is helpful. In order to obtain the whole picture of the behavior of a chemical, all available information has to be assessed.

On an individual basis, the data for establishing an OEL can be taken from another compound with comparable

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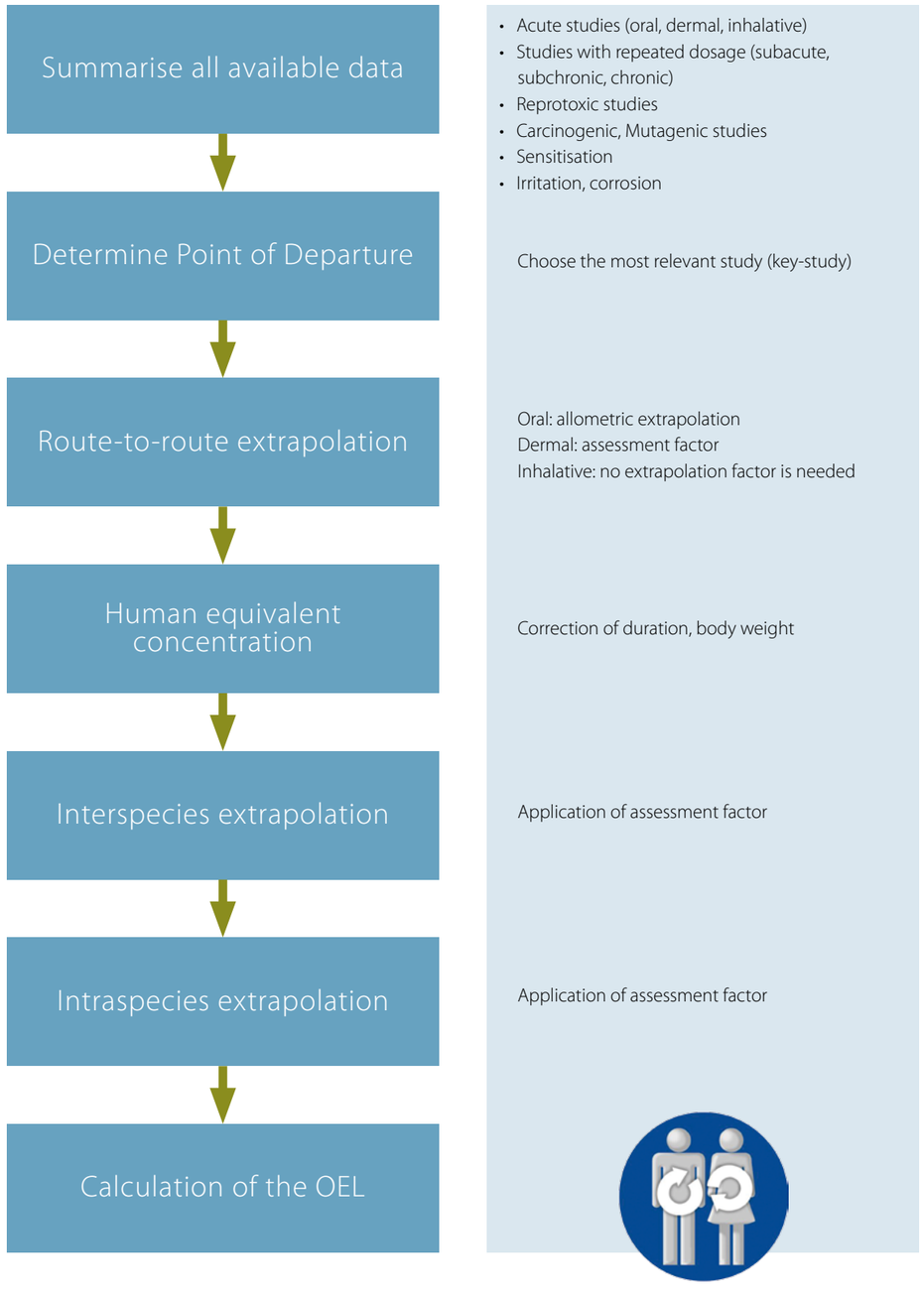

Figure 2.1: Steps for deriving an OEL

properties. Following this read-across approach, the similarity of both substances has to be shown firstly by a sound dose-response relationship and secondly by key selected toxicological investigations.

To develop an OEL, the appropriate route of exposure must be chosen. Studies that best reflect the exposure situations of employees are preferred, since many chemicals are not equally toxic by oral, dermal or inhalative uptake. In order to assess the health effects of a chemical, the relationship between the level of exposure and the corresponding health effects such as the dose-dependence relationship should be known.

To develop an OEL, first of all, the existing animal studies must be assessed and the key studies, which reflect most appropriately the behavior of the chemicals in humans, must be identified.

Based on animal studies with repeated exposure, the most appropriate dose descriptors must be identified as the starting point for further development.

Typically, a distinction should be made between the following two quite different modes of actions for the different toxicological properties:

- Mode of action with a threshold: below which no adverse health effect occurs, as is the case for most toxic properties.
- Mode of action without a threshold: typically assumed for genotoxic carcinogens or mutagens.

This mode of action determines the relevant dose descriptors.

2.2 Health-based OELs

Typically for deriving a health-based OEL, the No-Observed Adverse Effect Level (NOAEL) derived from oral or dermal studies, or the No-Adverse Effect Concentration (NOAEC) derived from inhalative studies in sub-acute, sub-chronic or chronic repeated exposure studies, are required. The NOAEL is the highest dose or concentration of a substance at which no statistically significant adverse effects were observed.

In special cases, OELs can also be derived by Quantitative Structure Activity Relationships (QSARs) as well as by comparison with well investigated substances with the same toxicological profile, which has to be shown by sound scientific data.

A further starting point in developing OELs could be a Low Observed Adverse Effect Level (LOAEL), or a Low Observed Adverse Effect Concentration (LOAEC) for inhalative studies.

For non-threshold properties, the Benchmark Dose (BMD) or the concentration or dose that induced tumours in, for example, 25 % of exposed animals (T25) derived from chronic studies over a two year time period, is typically used (*see Figure 2.2*).

In order to develop a health-based OEL, in general, animal studies with repeated administration are necessary. If different studies are available, the most appropriate studies have to be chosen. The following criteria should be considered for the decision:

- Inhalative studies are preferred to dermal or oral studies.
- Chronic studies are preferred to sub-chronic or sub-acute ones.
- Exposure durations in inhalative studies of six or eight hours per day are preferred to a 24 hour duration or short-term exposure.

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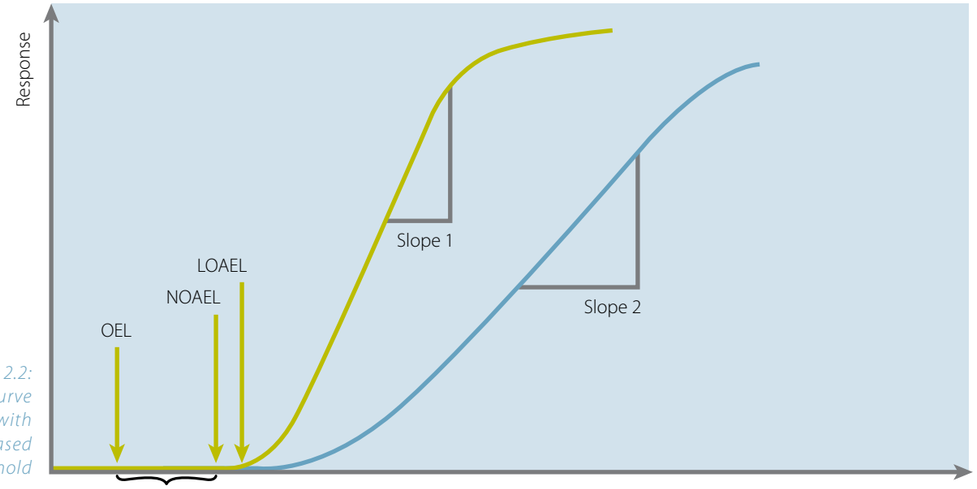

Figure 2.2: Dose-response curve for substances with a health-based threshold

OEL: Occupational Exposure Limit
NOAEL: No Observed Adverse Effect Level
LOAEL: Low Observed Adverse Effect Level

In addition, the toxicokinetics and toxicodynamics of the animal studies should be as similar as possible to human behaviour. Likewise, the target organ in animal studies should be the same as that in humans. If studies in different animals are available, the most appropriate studies that are closest to humans should be chosen.

For developing an OEL, all existing toxicological studies must be assessed. If the chemical or its active metabolite reaches the threshold concentration in the relevant organ, the adverse health effects can be determined. This depends on:

- Level of exposure,
- Route of exposure,
- Level of elimination from and degradation in the target organ.

The threshold doses vary considerably for different exposure routes and different species as a consequence of differences in toxicokinetics and modes of action.

The next stage is to identify all existing dose descriptors. Dose descriptors are:

- The acute lethal toxicity values, LD50 and LC50,
- LOAEL (or LOAEC),
- NOAEL (or NOAEC),
- T25 or BMD.

If different dose descriptors are available, the starting point for the further assessment has to be chosen in order to determine the Point of Departure (POD).

Assessment factors (AFs) are typically used to modify the POD to develop the OEL. A distinction needs to be made between two different types of AFs:

- Adjustment factor: for adjusting the dose to ensure normalisation for species or duration.
- Uncertainty factor: used, when data is lacking or of poor quality.

If the mode of action is primarily local and can be described by a concentration-dependent dose response, investigation of acute irritation or corrosion can be used to develop the OEL.

For predominantly important systemic effects, the acute dose descriptors cannot be used for developing the OEL, and animal studies with repeated exposure are then necessary. If different studies are available, the starting point must be chosen.

In order to determine the best starting point, the following arguments have to be considered:

- Bioavailability, with comparison between the test animals and humans.
- Exposure duration.

If no data for bioavailability is available, no difference between the test animals and humans is assumed as a default setting.

In order to establish an OEL for workplaces, long-term investigations into systemic effects are preferred. As the duration at workplaces is typically eight hours, studies that are significantly shorter (one hour) or longer (e.g. 24 hours for environmental exposure situations for the general public) should not be used. After considering all of the above-mentioned factors, the starting point for the following calculations needs to be set as the POD.

2.2.1 Correction of the duration

In repeated exposure inhalation experiments performed following the guidelines of the Organization for Economic Co-operation and Development (OECD) in order to develop OELs, substances are typically administered six hours per day, five days per week over 28 days for a sub-acute study, 90 days for a sub-chronic study and typically two years for chronic studies.

Workplace exposure is assumed to take place eight hours per day, five days per week and 220 days per year. Therefore, the above-mentioned experimental concentrations must be adjusted to an eight-hour exposure duration by using the following equation:

- Adjusted POD = NOAEC · 8 / 6

If a POD is selected from an inhalation scenario from an environmental study, a different approach is appropriate for developing a DNEL for the general public. In the case of a study involving 24 hours of exposure per day for seven days per week, the following equation must be used:

- Adjusted POD = NOAEC · 8 / 24 · 5 / 7

An additional assessment factor of 220/365 is necessary, if the long-term study is conducted for 365 days per year.

The utility of long-term inhalation studies concerning workplace situations is limited for the general public. Many substances are metabolised to a large extent in a relevant amount during the time without exposure at the workplace. These limitations are less relevant in the case of more cumulative behaviour and if the excretion time is significantly longer than one day.

2. PRINCIPLES OF ESTABLISHING OCCUPATIONAL EXPOSURE LIMITS

Animal	Body weight [g]	Respiratory volume [l/min]	Respiratory volume [l/min/kg bw]
Rat	250	0.2	0.8
Human	70,000	14	0.2

Figure 2.3: Respiratory volume for rats and humans

2.2.2 Route-to-route extrapolation

Route-to-route extrapolation does not have to be done if the mode of action is dominated by local effects, such as irritation or corrosiveness. Substances which cause strong irritation in the respiratory tract such as irritant gases e.g. hydrogen chloride, or acid vapours, show systemic adverse effects in significantly higher concentrations in comparison with the irritation concentrations.

Typically the route of exposure determines the:

- rate of absorption,
- distribution in the body,
- kind of metabolisation,
- excretion.

In the case of inhalation, no route-to-route extrapolation needs to be done. The extrapolation from oral results to inhalation exposure is typically done by allometric assessment. Long-term dermal studies are not usually determined and special assessment factors are not developed.

To adjust the NOAEL of oral studies, the following allometric assessment factors have to be used based on the difference in respiratory volume per kg body weight (bw) when going from the various animals to humans. *Figure 2.3* summarises the known values.

The different respiratory volumes depending on duration are expressed in *Figure 2.4*. *Figure 2.5* shows the proposed assessment factors.

2.2.3 Intraspecies extrapolation

The individual differences in the animal populations used are significantly lower in comparison with those in human beings. One major reason for this is the use of special animal selections; exclusively inbred animals are used. As a result, these animals have a narrower distribution of individual properties. Although, typically, inbred animals are more sensitive in comparison with natural ones, additional assessment factors are used in order to consider the following parameters:

- Genetic polymorphism
- Age (experimental animals are typically of younger age)
- Gender differentiation (if only one gender was tested)
- Health status (test animals may not be suffering from any illnesses)
- Nutrition status

Species/Physiological parameters	Rat	Human
Body weight	250 g	70 kg
Respiratory volume	0.2 l/min/rat **allometric scaling** 0.8 /l/min/kg bw	0.2 l/min/kg bw
For relevant duration 6 h exposure 8 h exposure 24 h exposure	 0.29 m^3/kg bw 0.38 m^3/kg bw 1.15 m^3/kg bw	 5 m^3/person 6.7 m^3/person 20 m^3/person
Respiratory volume light activity for worker 8h exposure		10 m^3/person

Figure 2.4: Allometric scaling

Species	Body weight [kg]	Allometric scaling factor
Rat	0.25	4
Mouse	0.03	7
Hamster	0.11	5
Guinea pig	0.8	3
Rabbit	2	2.4
Monkey	4	2
Dog	18	1.4

Figure 2.5: Allometric scaling factor for different species as compared to human

2. PRINCIPLES OF ESTABLISHING OCCUPATIONAL EXPOSURE LIMITS

The following assessment factors are recommended in the Technical Guidance Document (TGD) No. 8 [2.2]:

- AF (intraspecies) = 5 for worker
- AF (intraspecies) = 10 for general population

Deviations from the above mentioned AFs are justified if the parameters mentioned are not relevant for the most sensitive adverse health effects. In addition, intra-species differences are typically lower when effects are local, and, consequently, assessment factors of two or one can be justified.

2.2.4 Interspecies differences

The interspecies safety factor is applied when an animal study is used to define the OEL. It is meant to take account of the toxicokinetic and toxicodynamic differences between the species tested and humans. In order to transfer animal studies to humans, the default assumption is that humans are more sensitive than animals. On the basis of oral animal studies the allometric factor already comprises the route-to-route extrapolation. An additional assessment factor is generally not necessary for extrapolation from inhalative animal studies to workers. In the case of specific sensitivity, an additional assessment factor can be used. Given that in the general population, young people and unhealthy people can be exposed, an additional assessment factor has to be used when extrapolating to the general population. It is internationally agreed that a factor of ten is sufficient to address uncertainties. A selection of these components was published in a WHO report [2.1].

If there is sufficient knowledge, a dosimetric adjustment based on physico-chemical and biological parameters (e.g. blood flow, distribution coefficient) can be made for the respiratory route, which also enables maximum reduction of the toxicokinetic portion of the safety factor. This can be done, for example, with a Physiologically Based Pharmacokinetic (PBPK) model. In practice, the US Environmental Protection Agency (EPA) suggests a safety factor of three for the general population when dosimetric adjustment or allometric scaling is performed.

In the case of oral studies, a calculation for a human-related dose is needed. If the dose of an oral animal study with repeated exposure for the NOAEL is 10 mg/kg body weight per day, the calculation for a human equivalent concentration would be:

- Assumed body weight: 60 kg (or 70 kg, differing from committee to committee)
- Respiratory volume over eight hours: 10 m^3

A concentration of 6 (or 7) mg/m^3 inhaled over eight hours produces the same results.

If inhalation studies have been used as the POD with an NOAEC of 6 (or 7) mg/m^3, no further calculations are necessary to determine the human-related starting concentration. If the bioavailability is known for humans and is different from animals, these results have to be used to modify the above-calculated starting concentration.

2.2.5 OEL_{acute}

For special scenarios, OELs for acute exposure are requested, e.g. in the case of campaign production of only one or two weeks per year, or for assessing a one-time exposure situation. Unlike when developing a long-term OEL, test studies with a shorter exposure duration are preferred for selecting the POD. Additional existing short-duration animal studies, such as one- or two- week range-finder studies, can be selected as a POD. As a matter of course, duration assessment factors are not necessary; likewise, the intraspecies assessment factors can be reduced in comparison to the long-term OEL.

2.2.6 OEL from Lowest Observed Adverse Effect Level

In animal studies with repeated exposure, even in the lowest tested dose group, health effects or changes of some physiological parameters can be detected. In such situations the decision has to be made as to whether or not the deviation of a physiological parameter should be assessed as an adverse effect with health relevance. As a consequence of advanced analytical methods, an increasing number of such decisions arise to challenge the assessor.

In the case of minor health effects in the lowest dose group, a calculation of an OEL can be made. If the slope of the dose-response curve fits the normal situation, an additional assessment factor has to be applied. Following the TGD, an assessment factor of three seems to be appropriate. Limitations of such an approach can arise from a very flat dose-response curve or if the observed health effects are difficult to interpret.

2.2.7 Calculation of a health-based OEL

The NOAEL of an oral study is typically expressed in mg of substance per kg body weight of the animal. This has to be converted to an inhalation concentration, in accordance with the following ac cepted rules:

- Body weight (bw) of employees: 60 kg;
- Inhalation volume (eight-hour working day under light work conditions): 10 m^3.

Based on this assumption, the following correlation factors result:

[a] 1 [mg/kg bw/d] ~ 6 [mg/m^3]
(NOAEL (oral) of 1 mg/kg bw per day corresponds to an inhalative concentration of 6 mg/m^3)

Typically the resorption rate of chemicals in the case of oral ingestion is different from inhalative uptake. If no further information is available, both exposure routes are assessed to be equal. If the resorption rate for inhalative exposure is known, the real resorption rates can be used. Apart from certain exceptions, the inhalative resorption rate is typically lower than the oral one. If the oral resorption rate is assessed to be 100 %, the starting point concentration of [a] can be multiplied by the quotient of the inhalative to the oral resorption rate f_{res}.

[b] 1 [mg/kg bw/d] ~ 6 · f_{res} [mg/m^3]

Uncertainties in the extrapolation of experimental animal test data to real human exposures are addressed by applying assessment factors. The main assessment factors are used to make the following extrapolations:

- Route to route: oral to inhalative, dermal to inhalative or oral to dermal.
- Duration: sub-acute to chronic, sub-chronic to chronic.
- Interspecies: rodents to humans.
- Intraspecies: to consider individual differences.

Following the technical guidance documents of the REACH Regulation, assessment factors in *Figure 2.6* are recommended for establishing a Derived No Effect Level (DNEL).

The slope of the dose-response curve indicates the severity of health effects in the case of uptake of a dose above the NOAEL. The DNEL is the concentration of a substance for a given exposure duration without any health risk to workers or to consumers.

For workplaces with repeated exposure, this typically reflects an exposure of eight hours per day (shift duration), five days per week, 220 days per year over the whole working lifetime. The intraspecies differentiations for workers are typically significantly lower than those of the normal population, e.g. there are no ill or elderly people in workplaces. Consequently the intra-species AF in

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Reason	Description	AF for systemic effects	AF for local effects
Interspecies	Correction of differences in metabolic rate (allometric factor)	4: rat - human	1
		7: mouse - human	1
	Remaining differences	2.5	2.5
Intraspecies	Worker	5	5
	General population	10	10
Time extrapolation	Sub-acute to sub-chronic	3	3
	Sub-chronic to chronic	2	2
	Sub-acute to chronic	6	6
Route to route extrapolation	Oral to inhalation	2	
	Inhalation to oral	1	
	Dermal to oral	1	
	Oral to dermal	1	
	Dermal to inhalation	Case by case	
	Inhalation to dermal	Case by case	
Dose response/ Severity of effect	Reliability of the dose-response, LOAEL/NAEL extrapolation and severity of effect	≥ 1	≥ 1
Quality of whole data	Completeness and consistency of the available data	≥ 1	≥ 1
	Reliability of alternative data	≥ 1	≥ 1

Figure 2.6: Default Assessment Factors (AFs) in accordance with the technical guidance document R8 [2.2]

Figure 2.6 for consumers is double the assessment factor for workers. The AF given in *Figure 2.6* can be changed, if additional information about the behaviour of the human metabolism is known.

In general, the mode of action for carcinogens can follow two different principles:

- carcinogens with a health-based threshold: non-genotoxic
- non-threshold carcinogens: genotoxic

For the former, the approach to developing an OEL is no different than for substances without a carcinogenic property. For genotoxic carcinogens, a different approach is needed in order to develop OELs for keeping the risks at the workplace at an acceptable level.

Various national committees for developing OELs follow these principles. In Germany, the MAK-Commission added further categories four and five years ago.

Genotoxic carcinogens and mutagens typically follow a non-threshold mode of action. It is therefore not possible to derive a DNEL. In the technical guidance document, deriving a risk-based Derived Minimum Exposure Limit (DMEL) is described. In the REACH Regulation there is no requirement for developing a DMEL. Consequently, developing a DMEL is not obligatory. Additionally, no direct correlation to a health risk is described. In contrast, the exposure risk relationships developed in Germany are correlated to well-defined risks of inducing a tumour.

The flowchart in *Figure 2.1* shows a simplified procedure for establishing health-based OELs.

2.2.8 Example

In order to illustrate the procedure of developing health-based OELs, the following example was created.

Experimental result: sub-acute oral study
(drinking water), rat:

NOAEL: not determined
LOAEL: 1,000 mg/kg/d
(slight hepatotoxic effects, reversible within one week)

LOAEL to NOAEL: AF = 3
Calculated NOAEL: 333 mg/kg/d
Human oral NOAEL: 333 mg/kg/d · 60 kg = ~ 20 g/d

(Default) assumption: Resorption in the lung: 100 %
With AF oral to inhalative (allometric rat to human: 4) → 5 g/d

Human Equivalent Concentration (HEC) (10 m^3 respiratory volume under light working conditions for 8 h for workers): 5 g/d/ 10 m^3/d = 500 mg/m^3

Intraspecies factor (rat to human) =
5 → HIC = 100 mg/m^3

Time-extrapolation sub-acute to chronic:
AF = 6 → HIC= ~ 15 mg/m^3

If the experimental data is good: OEL = 15 mg/m^3

Following the ECHA-TGD [2.2], an additional assessment factor of 2.5 has to be used:

OEL = 6 mg/m^3

These default assessment factors can be changed depending on the quality of the available experimental data.

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Species/Physiological parameters	Rat	Human
Body weight	250 g	70 kg
Respiratory volume	0.2 l/min/rat **allometric scaling** 0.8 /l/min/kg bw	0.2 l/min/kg bw
For relevant duration 6 h exposure 8 h exposure 24 h exposure	0.29 m^3/kg bw 0.38 m^3/kg bw 1.15 m^3/kg bw	5 m^3/person 6.7 m^3/person 20 m^3/person
Respiratory volume light activity for worker 8h exposure		10 m^3/person

Figure 2.7: Allometric scaling

Test animal	Sex	Body weight [kg]	Food consumption per day* [g]	Water consumption per day* [ml]
Mouse	Male	0.03	3.6 (120)	5 (167)
	Female	0.025	3.25 (130)	5 (200)
Rat	Male	0.5	20 (40)	25 (50)
	Female	0.35	17.5 (50)	20 (57)
Hamster	Male	0.125	11.5 (92)	15 (120)
	Female	0.11	11.5 (105)	15 (136)

Figure 2.8: Default values for body weights, food and water intake for the calculation of doses in lifetime studies

* The daily food or water consumption is given in brackets in g or ml per kg body weight per day, as appropriate.

2.3 Risk-based OELs

For genotoxic carcinogens and for mutagens, it is typically postulated that no dose or concentration without health effects exists. In order to assess the health risks that are associated with a given workplace exposure, risk-based OELs can be developed.

A prerequisite for developing risk-based OELs is the existence of valid long-term animal studies or epidemiological studies with clear evidence of excess tumours in the exposed worker group. In this short booklet, the epidemiological approach is not discussed any further due to the limited number of existing studies.

If tumour data is available for several of the customarily used animal species, preference is to be given to the data on the species that reacts most sensitively. The extent to which quantitative transferability to humans can be assumed must be considered when selecting the animal species and the types and locations of tumours observed in it.

The starting point for the further derivation is the choice of the most relevant study as Point of Departure (POD). For the POD, the risk in terms of cancer incidence as a percentage is compared with the relevant concentration (mg/m^3). It is necessary to standardise the conversion to lifetime (occupational) exposure, route-to-route extrapolation to the route of inhalation and consideration of the background incidence of tumours.

If sufficient valid studies are available, the Benchmark Dose (BMD) is preferred as POD, typically in the range from 5 to 10% tumour likelihood, expressed as BMD10. The benchmark dose approach can be used in general, if data for at least the control group and three dose groups are available. The benchmark approach is an instrument for determining a point of departure for quantitative risk assessments. The dose that leads to an effect with certain likelihood can be estimated for a defined effect frequency or a defined effect measure, i.e. the Benchmark Response (BMR). This dose is referred to as BMD. A BMD10 indicates the dose at which there is a 10% risk that the effect concerned would be likely to occur.

In the next step, an extrapolation of tumour incidences to lower risks has to be done, typically in a range of one to a thousand and one to a million. Different models can be used for curve fitting, which must be consistent with the mechanistic considerations about carcinogenicity. Therefore, the multistage model, which corresponds to the multistage model of carcinogenicity, is often used. The gamma function also corresponds to a mechanistic understanding of the multihit model of chemical carcinogenicity. Multistage or gamma functions are thus the preferred models for modelling with the benchmark approach in the experimental range.

If a sufficiently qualified benchmark concentration cannot be specified, the T25 is to be used as the POD for the calculation. The T25 is the tumourigenic dose at which 25% additional incidence in the animal studies was observed. T25 is originally specified as a dose (mg/kg/d).

If the T25 model is used as POD, further modelling to lower concentrations is not necessary or even possible.

2. PRINCIPLES OF ESTABLISHING OCCUPATIONAL EXPOSURE LIMITS

Animal	Allometric scaling factor
Dog and monkey	2
Rat	4
Mouse	7

Figure 2.9: Allometric scaling factors (rounded)

For lower concentrations, the linear interpolation to the zero-point (no tumours only in case of zero exposure) is used.

In deriving risk figures, it is generally assumed that test animals and humans have the same sensitivity for carcinogenic effects after inhalation exposure. Oral or dermal studies can be used only if a route-to-route extrapolation is allowed.

2.3.1 Procedure based on inhalation studies

For substances with systemically occurring tumours, the airborne concentration (six-hour exposure/day; resting conditions) used in animal studies must be adjusted to the workplace scenario (eight-hour exposure/day; light activity) as the human equivalent exposure level by means of a correction factor of two. Furthermore, the blood/air partition coefficient should be less than ten or, if it is not known, the water solubility should be > 1 g/l. The various assessment factors are summarised in *Figure 2.7*.

2.3.2 Procedure based on oral studies

If there is no study-specific data on the dose related to body weight, and only concentrations in the diet or water have been reported, the default values in *Figure 2.8* can be used for conversion.

A dose administered in an animal study (unit: mg/kg body weight/day) is transformed into a human equivalent dose by applying an allometric scaling factor. As a default, conversion is carried out via allometric scaling based on the basal metabolic rate (body weight human/body weight animal 0.25). The rounded factors are obtained in *Figure 2.9*.

In the next step, the human equivalent dose is to be transformed into an airborne concentration unless specific reasons militate against route-to-route extrapolation, in particular:

- Pronounced first-pass effect.
- Local tumours in the respiratory tract are expected (especially relevant for locally-acting substances, but also for persistent substances such as metal compounds).
- Local tumours after oral administration are relevant for the assessment (e.g. forestomach tumours in rodents).
- Organ concentrations deviating considerably in the critical target organ are expected after inhalation and relevant to assessment (e.g. often decisive in studies with administration by gavages).

Differing route-specific absorption rates must be corrected in a route-to-route extrapolation. If no route-to-route extrapolation can be made based on a study with oral administration and if no inhalation studies or findings from inhalation of the carcinogen by humans are available, risk quantification is generally not possible.

Exposure parameters for workers	Standard assumption
Exposure period during working lifetime (years)	40
Duration of exposure (workday hours)	8
Working days per week	5
Working weeks per year	48
Body weight (kg)	60
Inhaled volume (m^3/workday)	10

Figure 2.10: Standard assumptions for exposure parameters for workers

The standard assumptions in *Figure 2.10* apply to occupational exposure.

Deviating exposure patterns are generally converted linearly to the standard assumptions referred to here. If information from the general population is available, the exposure parameters in *Figure 2.11* are assumed.

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Exposure parameters for general population	Standard assumption
Exposure period during lifetime (years)	75
Duration of exposure (hours/day)	24
Body weight (kg)	60
Food intake (kg/day)	1.4
Water intake (kg/day)	2.0
Inhaled volume (m^3/day)	20

Figure 2.11: Standard assumptions for exposure parameters for general population

2.3.3 Extrapolation to lower risk levels

For genotoxic carcinogens, the linear extrapolation is carried out as a default and is to be used exclusively for a T25 approach. If the extrapolation starts with the T25 approach, linear extrapolation is required as a consequence of limited data.

If the benchmark approach is appropriate, it is assumed that non-linearity can also be reproduced in a risk range ≥ 1:1,000 using benchmark modelling even if the experimental range only covers risks, for example, 1% or 5%. Nevertheless, the linear extrapolation is carried out between the BMD0.1 (1:1,000) and the origin or background.

For some carcinogens, sub-linearity or non-linearity behaviour is scientifically proven. In such cases, different and more complicated calculations are justified to express the real behaviour of the substance. However, such complicated relationships cannot reasonably be described in this booklet.

2.4 Literature

[2.1] http://www.who.int/ipcs/methods/harmonization/areas/uncertainty/en/

[2.2] Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health.

ECHA-2010-G-19-EN.
European Chemicals Agency, 2012.
http://echa.europa.eu/

3. OCCUPATIONAL EXPOSURE LIMITS IN DIFFERENT REGIONS AND COUNTRIES

Norbert Neuwirth

In contrast to the worldwide harmonised classification of chemicals by the Globally Harmonised System (GHS), Occupational Exposure Limits (OELs) at the workplace are a national affair.

In different countries, OELs may either be (legally) binding or else be merely recommendations. Determination of OELs can be health-based, technical-based or risk-based.

Taking into account the reference period, the following types of OEL usually exist:

- 8-hour-OEL
  The 8-hour-OEL indicates the limit of the time-weighted concentration of a chemical in the breathing zone of a worker during a working day of eight hours. It aims to protect workers from adverse effects in the medium and long terms, and to protect workers regularly exposed during a lifetime of work with the chemical concerned.
- 15-min-OEL or Short-Term-OEL (STEL)
  The Short-term-OEL aims to protect workers against adverse effects (immediate or short-term toxic effects, such as irritation phenomena) on health due to peak exposures. The reference period is usually 15 minutes, unless otherwise indicated.
- Ceiling OEL or Momentary OEL
  The Ceiling OEL is an atmospheric concentration in the workplace that must not be exceeded at any time of the day. It mainly concerns substances recognised as corrosive or irritant that can cause potentially serious and irreversible effects in the very near term. Specific analytical measures are implemented to measure this value.

The national approaches to setting an OEL are described below for different regions and countries.

3.1 European Union

The Chemical Agents Directive (CAD) requires that the European Commission evaluate the relationship between the health effects of hazardous chemicals and the level of occupational exposure by means of an independent scientific assessment of the latest available scientific data [3.1].

The Scientific Committee on Occupational Exposure Limits (SCOEL) gives advice to the European Commission concerning the Occupational Exposure Limit (OEL) at European level [3.2]. SCOEL findings also include the results of consultation of stakeholders for expanding the possible set of health-based data concerning hazardous substances, and for securing higher acceptance of the recommended limit values.

The CAD distinguishes two different types of limit values:

- Binding OEL
  BOELVs are binding limit values for occupational exposure to non-carcinogenic substances (health-based) as well as to carcinogenic substances (typically technical-based). BOELVs have been determined for non-carcinogenic substances, e.g. for lead and its inorganic compounds, as well as for carcinogenic substances, such as benzene, vinyl chloride monomer and hardwood dust. For many other substances BOELVs are under discussion.

BOELVs are published under the Carcinogen Directive 2004/37/EC, except for lead, which is mentioned in the CAD. Member States have to establish a corresponding OEL that must not exceed the European BOELV. In addition to the factors that are used when determining IOELVs, certain socio-economic factors may also be taken into account, provided that, at all times, worker health protection is ensured.

- Indicative OEL
  IOELVs are health-based, recommended values. They are exposure limits for any substance concentration, below which, in general, no adverse health effects are expected after short-term or daily exposure over a working lifetime.

Additional notations are allocated to some of the occupational exposure limit values in the respective lists. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects.

IOELVs are derived on the basis of the latest scientific data, and of the currently available measurement techniques. If there is an IOELV established at Community level, Member States are required to establish a national OEL, taking into account the Community limit.

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3.2 Austria

The Austrian OELs are regulated in the Regulation on Occupational Exposure Limit Values ("Grenzwerteverordnung") [3.3].

The MAK ("Maximale Arbeitsplatzkonzentration") is a health-based value. There are long-time values (eight-hour average and peak value) and short-time values (average and peak value over 15 minutes, mostly three times per shift). If necessary, notations provide further information concerning sensitising and other effects.

The TRK ("Technische Richtkonzentration") values are established for carcinogenic substances. The values are based on technical feasibility. They are derived by the Austrian MAK Committee. That committee consists of various stakeholders and mostly decides on the scientific basis of other foreign committees on occupational exposure levels.

3.3 Finland

In Finland the OELs (Haitallisiksi tunnetut pitoisuudet, HTP-värden) are published by the Ministry of Social Affairs and Health. The recommendations are established by the Finnish Advisory Committee for Occupational Health and Safety on Chemicals.

The OELs are defined for long-time exposure (eight hours) and short-time exposure (15 minutes). For some substances there are also ceiling values. The notation "iho" (the Finnish for skin) marks substances in the list of OELs that are resorbed through skin [3.4].

In Finland, a committee appointed by the Ministry develops a document on the health effects of a specific substance. In addition, the Committee on OELs ("HTP-jaos") recommends a certain maximum level of exposure. That committee is put together by all of the relevant stakeholder groups (the Ministry, the chemicals industry, employers' organisations, and the trade unions).

3.4 France

In France, the OELs (Valeurs limites d'exposition professionnelle, VLEP) are set by the Ministry of Employment and Solidarity.

There are currently two categories of regulatory OELs set by decree:

- Compulsory VLEPs set by decree from the Council of State (Conseil d'Etat). They are determined for the most hazardous chemicals for which exposure can be measured with validated methods.
- Recommended VLEPs set by decree in relation to the French Labour Code. Sometimes, recommended VLEPs correspond to very hazardous chemicals for which exposure can be measured only with partially validated methods.

Reference periods are as follows:

- Short-term average exposure limit values (valeurs limites d'exposition à court terme, VLEP-CT) are measured over a duration of 15 minutes. For some specific chemicals (for example isocyanates), the sampling duration could be reduced to five minutes).
- Long-term average exposure limit values (valeurs limites d'exposition - 8 heures, VLEP-8h) are measured over a duration of eight hours.

The potential for cutaneous absorption is taken into account through the addition of the notation "peau" (French for skin) to the VLEP.

After endorsement, the VLEPs are published in the French Official Journal and in the publications of the Institut National de Recherche et de Sécurité (INRS). INRS publishes some of the VLEPs on the internet (***www.inrs.fr***).

The French system for regulatory OELs is based on risk assessment being separate from risk management, and consists of three different steps:

- The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) proposes VLEPs to the Ministry of Employment and Solidarity. Those VLEPs result from the work of the ANSES-VLEP committee (CES VLEP).
- The Ministry decides whether or not to take the VLEPs recommended by ANSES into account, and, where applicable, prepares a draft decree.
- That draft is then submitted for advisory notice to the French steering committee for working conditions (COCT). This step enables the social partners (employers and employees) to propose delayed application of the regulatory VLEPs in view of technical or economic feasibility problems.

The ANSES-VLEP committee is made up of independent scientific experts appointed for three years by the ANSES scientific committee, after a public call to recruit. The experts of the VLEP committee are specialised in toxicology, biology, medicine, chemistry, industrial hygiene, etc. They must propose OELs and Biological Exposure Indices (BEIs) based on published scientific studies in order to prevent occurrence of health effects for workers. They are also in charge of proposing sampling and analytical methods for exposure measurements with regard to the recommended levels of the OELs and of assigning the "skin" notation (French: "Peau").

These tasks are conducted by the VLEP committee using a methodology developed by the experts and published by ANSES (***www.anses.fr***). Checking worker exposure to chemicals having compulsory OELs is required at least once per year. That obligation is unavoidable for carcinogenic, mutagenic and reprotoxic (CMR) chemicals with compul-

3. OCCUPATIONAL EXPOSURE LIMITS IN DIFFERENT REGIONS AND COUNTRIES

sory OELs. For non-CMR chemicals, the exposure measurements are not necessary when risks are low. Exposure measurements must be conducted by an independent accredited laboratory. Since December 2009, it has been a requirement for the laboratory in charge of exposure measurements to establish a sampling strategy based on nine measurements, collected during three surveys in a year and for each Similar Exposure Group (SEG) of workers. Compliance with OELs is determined by using a statistical test which calculates the probability of exceeding OELs in reference to a log normal distribution.

All the results collected by accredited laboratories must be stored in the SCOLA database administrated by INRS. That structured data enables information to be retrieved with a view to defining prevention actions at national level.

3.5 Germany

In Germany, the Regulation on Hazardous Substances ("Gefahrstoffverordnung") defines the health-based legally binding OEL (Arbeitsplatzgrenzwert, AGW) as the limit of the time-weighted average over a time period of eight hours. Peaks of exposure have to be assessed by short-time exposure values.

Additional notations are allocated to some occupational exposure limit values. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects. In the Technical Rules for Hazardous Substances, TRGS 900, the abbreviations "Sa", "Sh", "Sah" or "H" are also allocated to respiratory tract sensitising, skin sensitising and percutaneous absorption properties. For all such substances, further measures in addition to compliance with the AGW are necessary. Developmental toxic effects are not assessed when establishing the occupational exposure limit. Notation "Y" (no risk of developmental toxic effects in the event of compliance with the air limit values and the biological limit values) or "Z" (that risk cannot be excluded in the event of non-compliance with the air limit values and the biological limit values) is allocated to substances and their AGW values in TRGS 900.

The corresponding biological values are called BGW (Biologischer Grenzwert) and are published in TRGS 903.

The Committee on Hazardous Substances ("Ausschuss für Gefahrstoffe", AGS) develops and assesses the AGWs. Accepted AGWs are published in TRGS 900 [3.5]. The most important sources for AGWs are:

- MAK-values of the Deutsche Forschungsgemeinschaft (DFG),
- OELs of the European Community,
- Other international limit values.

For carcinogenic substances, the exposure risk relationship (Exposition Risiko Beziehung, ERB) describes the statistical probability of cancer after inhalative exposure to a certain concentration of the substance. ERB values are published in TRGS 910.

The ERB is equivalent to a dose-response relationship, or concentration-response relationship. From this relationship, substance-specific concentration figures can be derived for carcinogenic substances in the air at the workplace. The figures correspond to the Acceptable Risk and the Tolerable Risk. A work-life long occupational exposure (40 years; eight hours per day) is the basis for the derivation of the exposure-risk relationship. The workplace exposure should not exceed the tolerable risk.

The AGS discusses and determines exposure-risk relationships on the basis of occupational medicine data, and of epidemiological and toxicological data.

The MAK value ("Maximale Arbeitsplatz-Konzentration") is a health-based limit value for occupational exposure. There are no known adverse health effects for the employees and no unreasonable annoyances (e. g. by a nauseous odour) are caused even when the person is repeatedly exposed during long periods, usually for eight hours daily but assuming on average a 40-hour working week. Exposure peaks during a working shift are assessed through short-term values.

Additional notations are allocated to some of the MAK values in the respective lists. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects.

MAKs are based on scientific criteria for health protection, and not on technical and economic possibilities for practical implementation. When using data for deriving MAKs, knowledge gained from humans has the highest priority (NOAEL-oriented). If there is no data or not enough data from humans, the derivation is based on animal experiments. Respiratory tract sensitising, skin sensitising and danger of percutaneous absorption properties are separately allocated with respective labels "Sa", "Sh", "Sah", "SP" or "H".

MAK values are developed by the "Senatskommission zur Prüfung gesundheitsschädlicher Stoffe" in the "Deutsche Forschungsgemeinschaft" (DFG) with respect to their toxicological, occupational health or occupational hygiene effects. The decisive aspects for deriving a MAK value are scientifically based criteria for the protection of worker health and not the technical or socio-economic reasons. The various substances are also evaluated for their carcinogenic potential, their harmfulness during pregnancy, their germ cell mutagenic effect and their contribution to systemic toxicity after percutaneous absorption. MAK values and their derivations are also published with open access. More than 800 substances have been evaluated since the early 1970s [3.6].

The biological values corresponding to the MAK values are called BAT (Biologischer Arbeitsplatztoleranzwert) values.

3.6 Italy

In Italy, OELs are called "Valori limite di esposizione professionale" (VLEPs). They are set by decree [3.7], approved jointly between the Ministro del Lavoro e delle Politiche Sociali (Ministry of Labour and Social Affairs) and the Ministro della Salute (Ministry of Health).

VLEPs are set with the support of the advisory committee for the development and updating of occupational exposure limit values and biological limit values for chemical agents, and in agreement with the permanent conference for relations between the State, the regions and the autonomous provinces of Trento and Bolzano. The advisory committee was set up by decree in the year 2011 (Decreto Ministeriale 3 Dicembre 2008) and, among its tasks, it has to provide an advisory service to the Ministry of Labour and to the Ministry of Health on the implementation at national level of exposure limit values proposed in European Union directives. The committee is composed of nine national experts specialised in toxicology and health topics.

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In the VLEP endorsement process, the Ministries hear the opinion of the Ministry of Economic Development and also the opinion of the social partners. In the overall decision-making process to prepare the decree, the Ministries may or may not take into account the opinions of the various parties.

There are two categories of regulatory VLEPs set by decree:

- Binding VLEPs.
- Recommended VLEPs.

Reference periods are as follows:

- Short-term average exposure limit values (valore limite di esposizione a breve termine) are measured over the duration of 15 minutes.
- Long-term average exposure limit values (valore limite di esposizione - 8 ore) are measured and calculated over the duration of 8 hours.

The potential for cutaneous absorption is taken into consideration through the addition of the notation "pelle" (skin) to the VLEP.

Exposure measurements to assess compliance with VLEPs must be conducted for representative exposure periods as a function of space and time. The general reference standard for the sampling strategy and for compliance with OELs is the EN 689 standard. Sampling devices must comply with the requirements of EN 482/94 and in wider terms with specific ENs on sampling devices for workplace atmospheres.

In 2012, Italy implemented the Directive 2009/161/EU, containing the third list of OELs to have been published, with several changes, in the Official Gazette of the Italian Republic (Ministerial Decree of 6 August 2012, G.U. n. 218, 18 September 2012).

3.7 Poland

The Polish OEL values are published quarterly in "Principles and Methods of Assessing the Working Environment" [3.8].

Depending on the reference periods, they are called:

- NDS (najwyższe dopuszczalne stężenie), a time-weighted average concentration for an eight-hour workday.
- NDSCh (najwyższe dopuszczalne stężenie chwilowe), an average concentration over 15 minutes that may be reached only twice a day.
- NDSP (Najwyższe dopuszczalne stężenie pułapowe), the maximum admissible ceiling concentration.
- NDN (najwyższe dopuszczalne natężenie), the maximum admissible intensity.

The Polish Minister of Labour and Social Policy introduces new limit levels after considering the recommendation of the Interdepartmental Commission. That Commission represents health and labour administration, industry, unions and research. Expert groups of the Interdepartmental Commission prepare scientific dossiers on OELs. Those dossiers are then evaluated within the tripartite Interdepartmental Commission and, if they are accepted, are recommended to the Minister. After approval, they are published.

3.8 Sweden

In Sweden, OELs are established in a multi-stage process. The Swedish Work Environment Authority (SWEA) sends a list of proposals to the Criteria Group of the National Institute of Working Life ("Kriterigruppen for hygieniska gränsvärde"), which prepares a scientific-based report. That report is published and the National Board of Occupational Safety and Health proposes an OEL according to the consensus report for the Labour Market Parties.

Binding values for the health-based OEL refer to the following reference periods:

- eight hours (level limit value, "nivågränsvärde"),
- momentary (ceiling, "takgränsvärde").

Indicative values for the health-based OEL refer to the 15-minute reference period (short-time exposure limits, "kortidsvärde").

For carcinogens without a health-based threshold, OELs are set with consideration for socio-economic factors.

In the OEL lists „K" ("Cancerframkallande, Grupp C") annotates carcinogenic substances, „S" ("Sensibiliserande, Grupp D") annotates sensitizers, and „R" ("Reproduktionsstörande, Grupp E") indicates toxic to reproduction. The notation "H" is used for substances which can be absorbed through the skin.

The OELs are published in the "hygienic limit values and measures for air pollutants" and are available on SWEA's website.

3.9 Switzerland

The Swiss "MAK-Wert" is a health-based limit value for occupational exposures, usually for eight hours daily and assuming on average a 42-hour working week.

Exposure peaks during a work shift are assessed through short-term values. Additional notations are allocated to some of the MAK values in the respective lists. Those notations provide specific information on certain substance properties.

Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects. Further protection measures are necessary. Respiratory-tract-sensitising, skin sensitising and danger of percutaneous absorption properties are separately allocated with respective labels "S" or "H".

The "Schweizerische Unfallversicherungsanstalt" (Suva) issues guidelines on the maximum workplace concentrations of harmful substances as well as on threshold values for physical impact. The legal basis is the Swiss ordinance regulating accident prevention and occupational diseases.

The threshold values under discussion are assessed by Suva specialists with due consideration for the most recent research findings. In addition, measuring and technical implementation factors are discussed, with the health aspects being decisive in determining the

3. OCCUPATIONAL EXPOSURE LIMITS IN DIFFERENT REGIONS AND COUNTRIES

threshold values. For carcinogens, either technical or health-based values are set and published in the official OEL list (Suva publication „Grenzwerte am Arbeitsplatz").

Suva's OEL proposals are submitted to the OEL Committee of Suissepro (Swiss Association for Occupational Health, Hygiene and Safety) for their opinion. This Committee consists of university professors, the State Secretariat for Economic Affairs, industrial and private occupational physicians and safety specialists as well as Suva. The Committee decides on any mandatory inclusion in the annually published list of Swiss OELs.

3.10 United Kingdom

In the UK, the Control of Substances Hazardous to Health (COSHH) Regulations define the health-based Occupational Exposure Standard (OES) and the technically based Maximum Exposure Limit (MEL) for carcinogens, mutagens, and inhalable sensitisers.

The reference periods are as follows: average airborne concentrations over a long-term period of eight hours and additionally over 15 minutes.

OEL development in the UK is a tripartite process. The Health and Safety Executive (HSE) gathers data on a certain chemical. The Working Group on Assessment of Toxic Chemicals (WATCH) proposes limit values for OESs or that an MEL should be developed for a substance. In this step, the Advisory Committee on Toxic Substances (ACTS) is also involved. WATCH is an exclusively scientific committee. A public consultation follows and the data can be downloaded (***www.hse.gov.uk\condocs***). The Health and Safety Commission (HSC) endorses the limit value [3.9].

3.11 USA

In the USA, Permissible Exposure Limits (PELs) are regulatory limits on the amount or concentration of a hazardous substance in the air in order to protect workers against adverse health effects. They may also contain a skin designation. PELs are based on an eight-hour time weighted average (TWA) exposure. PELs are addressed in specific standards for the general industry, shipyard employment, and the construction industry. PELs are published by the Occupational Safety and Health Administration (OSHA).

The National Institute for Occupational Safety and Health (NIOSH) also establishes limits for exposure: the Recommended Exposure Levels (RELs). They are published through OSHA but are not legally binding.

Since 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) has been establishing Threshold Limit Values (TLVs), which are not legally binding. They represent a limit "to which it is believed nearly all workers can be exposed day after day for a working lifetime without ill effect". The three categories of TLVs are:

- Time-Weighted Average (TWA): Concentration for a conventional eight-hour workday and a 40-hour workweek.
- Short-Term Exposure Limit (STEL): a 15-minute TWA exposure that should not be exceeded at any time during a workday.
- Ceiling (C): Concentration that should not be exceeded during any part of the working exposure.

The TLV committee derives new OELs based on the available, relevant, scientific data. TLVs may have notations for skin and carcinogenicity.

The biological values corresponding to the TLVs are called BEIs for Biological Exposure Indices.

3.12 Japan

In Japan, legally binding and recommended OELs exist. The binding OELs (Administrative Control (AC) Levels) are published by the Ministry of Health, Labour and Welfare. The committee for deriving the AC Levels is the National Expert Meeting and it considers the levels recommended by the Japan Society for Occupational Health (JSOH).

JSOH-recommended values have to be compared with the results of personal sampling techniques.

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[3.3] http://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20001418

[3.4] http://www.stm.fi/c/document_library/get_file?folderId=28707&name=DLFE-3519.pdf&title=HTP_arvot_2007__Haitallisiksi_tunnetut_pitoisuudet_fi.pdf

[3.5] http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-900.pdf?__blob=publicationFile&v=15

[3.6] http://onlinelibrary.wiley.com/book/10.1002/9783527675128

[3.7] Decree 626/1994 and subsequent modifications and supplements (actually with legislative decree 81/08, art. 232)

[3.8] http://www.ciop.pl/8524.html

[3.9] http://www.hse.gov.uk/pubns/books/eh40.htm

4. AIR MONITORING OF OCCUPATIONAL EXPOSURE TO CHEMICALS

Raymond Vincent

AIR MONITORING

4.1 Variability of chemical air concentrations and exposures

Occupational exposure to chemicals may occur at many different workplaces and in many different tasks. Exposure corresponds to inhalation by workers of chemicals in the form of gas, vapour, dust or fibre. Exposure is generally defined as a function of the concentration of chemical in the breathing zone atmosphere and is normally presented as an average concentration over a reference period. To avoid long-term health effects, the reference period is set at eight hours, and for acute effects this reference period corresponds to 15 minutes or less depending on the toxicity of the chemical. For example, the reference period for isocyanates is five minutes.

To check for compliance with long-term or short-term OELs, personal air samples must be taken with a sampling time close to the reference period of the OEL. At this point, it should be emphasised that area samples (static or background) do not reflect worker exposure and may not be used to assume compliance with OELs: generally, results of area air sampling are lower than personal samples, probably due to the distance between the sampler and the emission source. *Figure 4.1* illustrates this situation for exposure to toluene in the printing industry.

The day-to-day or task-to-task variability of worker exposure is very considerable depending on different workplace factors such as:

- type of task;
- processes used (e. g. temperature, closed vs. open system);
- type of emission sources;
- duration and routes of exposure;
- control procedures;
- presence of local exhaust ventilation;
- production rate (low vs. high);
- seasons (winter vs. summer).

Personal air monitoring to assess the effectiveness of the ventilation system

Simultaneous combination of these factors contributes to a large variability of air concentrations at workplaces. The resulting exposure will also vary from task to task, from day to day and between workers having a similar job in the same workshop.

Figure 4.2 illustrates the variability of exposure to toluene, measured with a portable photoionisation detector (PID) analyser (HNU®) within a working day for an operator in a printing shop while the operator is doing different tasks.

As a result of this variability, and in terms of statistics, the exposure of a group of workers is well described by the log-normal distribution with a large tail on the right due to high exposures. In other words, the results of exposure measurement after transformation into logarithms will follow a normal distribution. Based on this assumption, the variability of exposure in a group of workers exposed in a similar way (similar exposure group, SEG)

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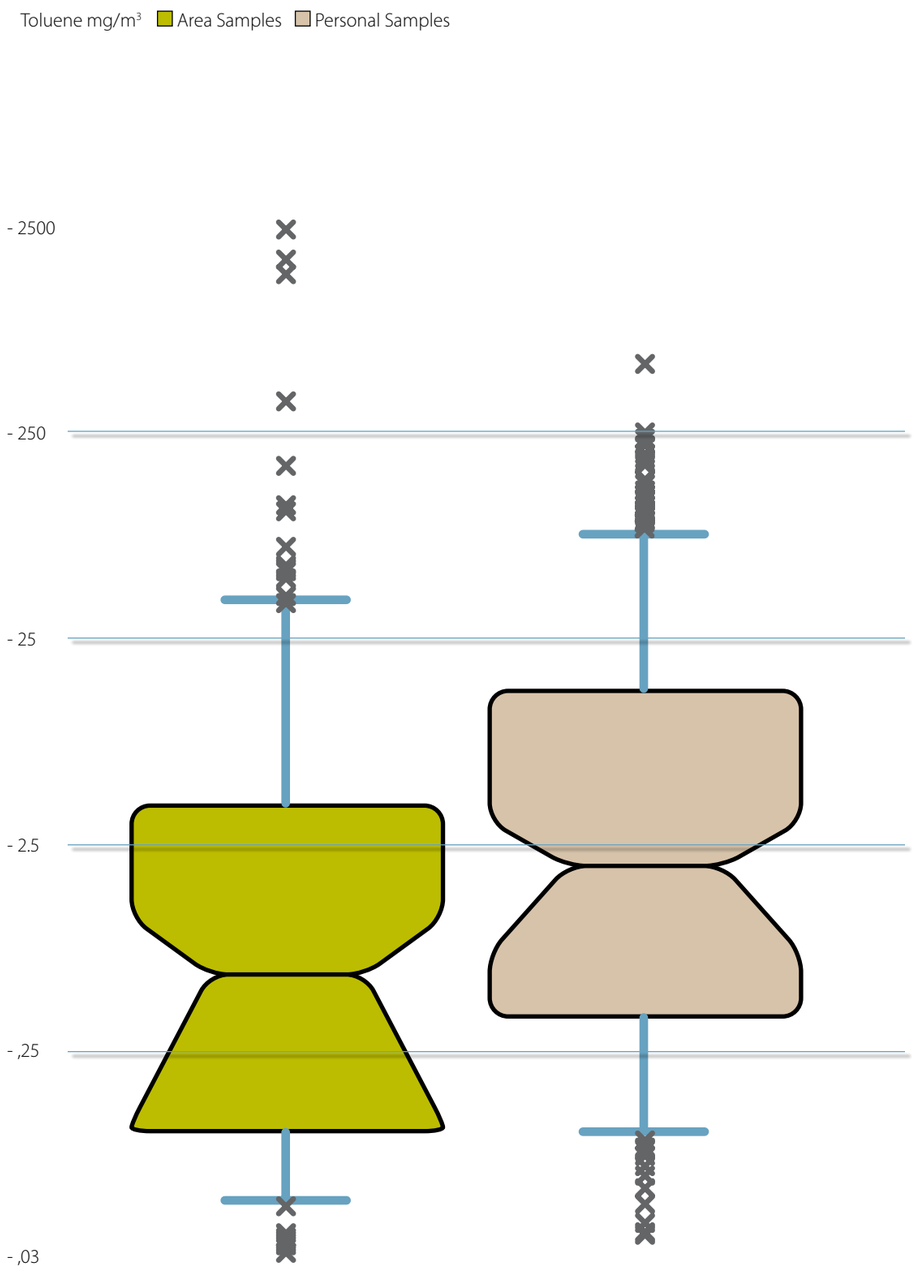

Figure 4.1: Results of toluene exposure measurements in the printing industry by long-term area and personal sampling (Source: INRS/ COLCHIC database [4.1]).

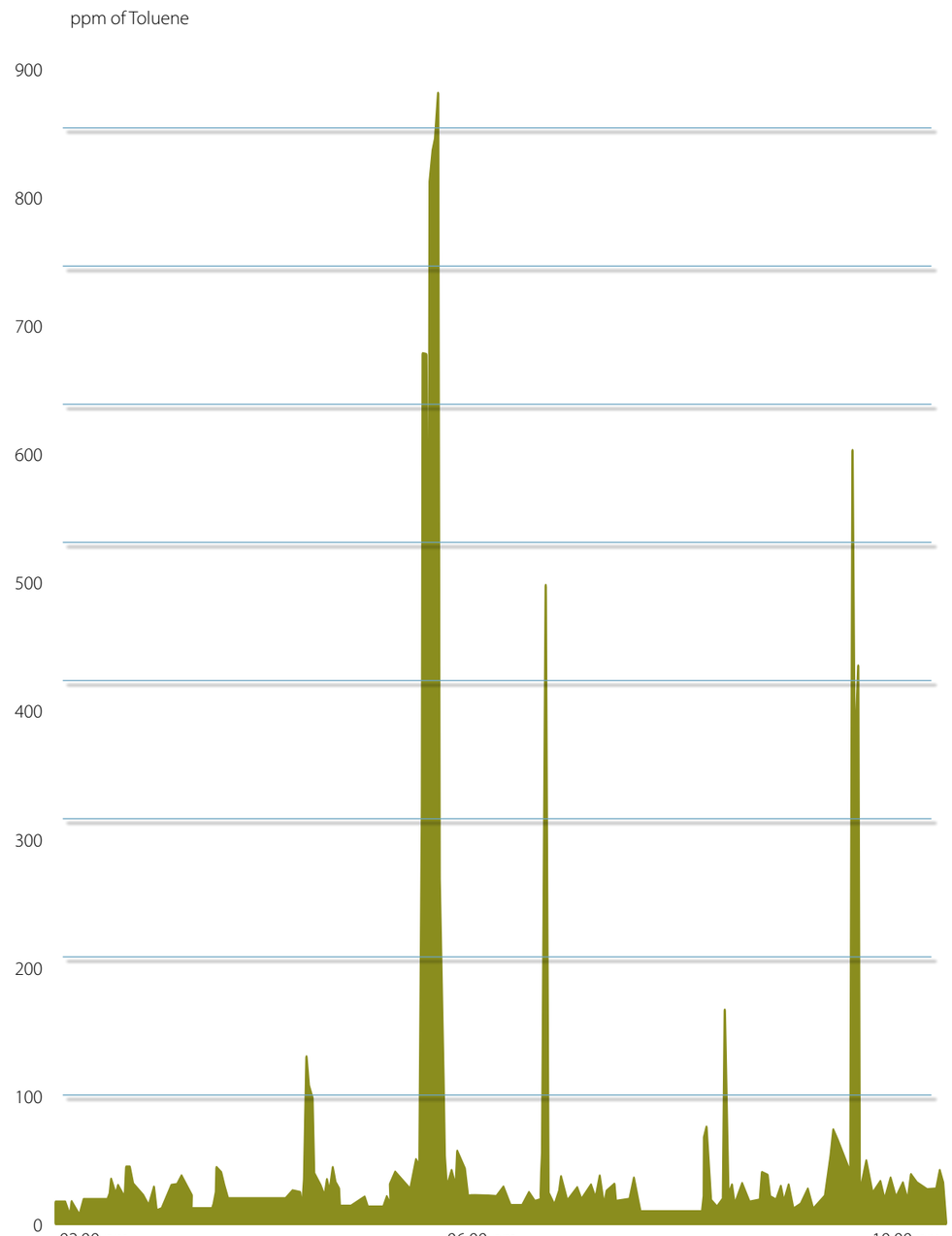

Figure 4.2: Variability of toluene exposure for an operator in a printing shop. In this graph, the exposure peaks correspond to specific tasks such as cleaning printing machines by hand using toluene and rags

4. AIR MONITORING OF OCCUPATIONAL EXPOSURE TO CHEMICALS

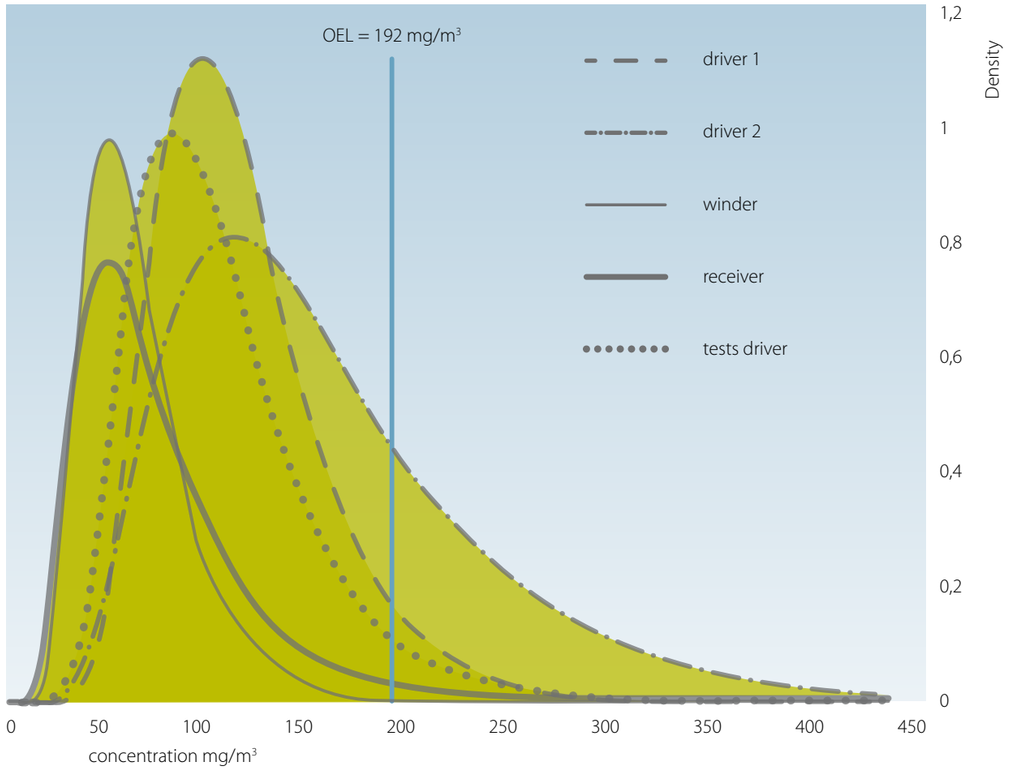

Figure 4.3: Log normal distributions issued from eight-hour measurements for different SEGs of workers in a printing shop

Footnote: *An SEG is a group of workers having the same general exposure profile because of the similarity and frequency of the tasks they perform, the similarity of the materials and processes with which they work, and the similarity in the way they perform the tasks [4.2].*

can be characterized by the geometric standard deviation (GSD). The value for the GSD can vary from one to three. A GSD value close to one corresponds to a very low variability, while a GSD value close to three corresponds to high exposure variability.

Figure 4.3 illustrates this situation for different jobs involving exposure to toluene in the printing industry. The highest exposures and variability were measured for the SEG "Driver 2" (GSD = 1.64 and arithmetic mean = 115.1 mg/m³) compared to the exposure of the SEG "Winder" (GSD = 1.5 and arithmetic mean = 48.1 mg/m³).

Considering the variability of exposures and the requirement for having a set of representative measurements in order to compare the results to OELs, a sampling strategy is needed.

4.2 Sampling strategy

The first document about sampling strategy, for testing compliance of occupational chemical exposure with OELs, was published by the American National Institute for Occupational Safety and Health (NIOSH) in 1977 [4.3]. In 1993, the British Occupational Hygiene Society (BOHS) published the technical guide 11: Sampling Strategies for Airborne Contaminants in the Workplace. Two years later, the European Committee for Standardisation (CEN) provided the European standard EN 689: Workplace atmospheres - Guidance for the assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy.

Since those pioneering documents, many attempts have been made by organisations from different countries:

- American Industrial Hygiene Association (AIHA, USA) [4.4]
- Institut National de Recherche et de Sécurité (INRS, France) [4.5]
- Institut de recherche Robert-Sauvé en santé et sécurité au travail (IRSST, Canada) [4.6]
- Health and Safety Executive (HSE, United Kingdom) [4.7]
- Federal Institute for Occupational Safety and Health (BAuA, Germany) [4.8]
- British Occupational Hygiene Society (BOHS, United Kingdom) [4.9]

The examples are not exhaustive and many others could be found by using web searches. For example, in Germany, according to the German Hazardous Substance Ordinance, the employer is responsible for implementing and complying with the requirements of the ordinance. The employer also has to make sure that exposure in the air at the workplace is determined if necessary. This can be done with company-internal capacities as well as by order from accredited measuring bodies. The order in which the common OELs should be used is defined in the technical rule TRGS 402 [4.8]:

Stationary dust monitoring during filling process

- (National) Occupational Exposure Limit ("Arbeitsplatzgrenzwerte", AGW),
- (European) Binding Occupational Exposure Limit Value (BOELV),
- (National) Maximum Workplace Concentration ("Maximale Arbeitsplatzkonzentration", MAK)
- (European) Indicative Occupational Exposure Limit Value (IOELV),
- Health-based limit of other countries,
- Derived No Effect Level (DNEL) noted in REACH,
- Company-internal limit,
- Other procedures like the control banding concept.

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The strategy for determination of exposure and the frequency of measurements is given in TRGS 402 and DIN EN 689 as recommendations. The frequency of measurements depends on the degree of compliance with the OEL.

Those technical guidelines generally propose a strategy prior to conducting exposure measurements and in some cases a statistical methodology for comparing results to OELs and for checking compliance. The strategy consists of different stages:

- Conducting a survey to assess worker exposure and to determine why and when exposures occur in relation, for example, to processes, to tasks, and to time period.
- Constituting SEGs of workers in order to optimise the number of representative measurements.
- Determining the sampling plan: which chemicals, which OELs and which type (long or short term), number of workers to monitor with personal sampling, for what period.
- Conducting exposure measurements and collecting all information concerning tasks, and incidents.

Since it is not possible to measure the exposure of each worker, exposure measurements are conducted on a sample of workers belonging to a group performing the same tasks and for which working conditions and exposure are similar (SEG). It is assumed that the worker exposure of the SEG is that measured on the sample of workers.

During this preliminary step, it is recommended to gather information from previous measurements, the literature, and public databases in order to finalise the sampling strategy. The collected information can provide indications concerning levels of exposure, sampling time, and tasks to monitor. Use of direct reading instruments may help to detect exposure peaks related to certain tasks.

Before starting an exposure assessment survey, it is recommended to ensure that all prevention actions have been taken and checked in accordance with the regulations: substitution of hazardous substances, process modification, and collective protection such as general or local exhaust ventilation.

Due to the different sources of exposure variability and in order to verify compliance with OELs, EN 689 recommends collecting at least six exposure measurements for each SEG.

The most important recommendation when testing compliance with OELs concerns the representativity of results in relation with sampling duration, activity when sampling, and incidents.

It is highly recommended that technicians in charge of the survey supervise the sampling procedure continuously in order to note information concerning the events occurring. That information will be very useful to confirm, a posteriori, the representativity of each measurement or to eliminate those considered as unrepresentative.

4.3 Performance of sampling and analytical methods

The general performance requirements for procedures for determining the concentration of chemical agents in workplace atmospheres are specified by the Chemical Agents Directive 98/24/EC [4.10]. Those requirements apply to all measuring procedures, irrespective of the physical form of the chemical agent (gas, vapour, and airborne particles), of the sampling method and of the analytical method used. The European standard EN 482 specifies the general requirements for the performance of procedures for the measurement of chemical agents.

Whatever the objectives of the exposure measurements, the performance of the sampling and analytical method must be verified in the context of the survey, e. g. substances to be sampled, type of OEL, expected air concentrations, duration of exposure.

Prior to the survey, the following parameters must be checked:

- The selectivity of the method.
- Ability to conduct personal exposure measurements.
- Type of collected fraction (respirable, thoracic, inhalable).
- The measuring range, breakthrough volume for active sampling.
- Influence of possible interferences, relative humidity and temperature.
- Limit of detection.
- Conditions for storing and transporting the collected samples.
- Storage time before analysis.

Specific European standards relate to different types of measuring procedures and measuring devices. These include European standards for:

- Dust samplers (EN 13205),
- Diffusive samplers (EN 838),
- Pumped samplers (EN 1076),
- Metals and metalloids (EN 13890),
- Mixtures of airborne particles and vapour (EN 13936).

European Standard EN 482 specifies the general requirements for the performance of procedures for the measurement of chemical agents.

European Standards EN 1232 and EN 12919 specify the performance requirements and test methods for pumps used to determine the concentration of chemical agents and mainly to sample aerosols in the workplace.

Additionally, some international (ISO) or European standards concern sampling and analytical methods for specific substances, e.g. ISO 8762 for determination of vinyl chloride or ISO 16740 for hexavalent chromium.

For other chemicals which have no standardised methods, some national organisations or institutes have developed their own.

In Germany, the database "GESTIS" [4.11] includes all of the sampling and analytical methods developed in France by INRS (Metropol), in the United Kingdom by HSE, in Spain by Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT) and in Germany by Institut für Arbeitsschutz (IFA). GESTIS also includes some methods developed in the United States by NIOSH [4.12] and by the Occupational Safety and Health Administration (OSHA) [4.13]. In Canada, IRSST proposes a sampling guide for air contaminants [4.14].

Generally, the performance of the methods developed by those bodies refers to national or international guidelines for method development and evaluation (NIOSH and OSHA guidelines).

4.4 Interpretation of exposure measurement results in reference to OELs

Before conducting any interpretation of results from exposure measurements, some basic checks must be conducted:

- Assessment of the representativity of each measurement in relation to process or sampling incidents, and sampling time.
- Elimination of erroneous results.
- Validation of the SEG constituted prior to the survey.

After this step, the results can be analysed in order to assess compliance with OELs.

For an SEG, non-compliance can be clearly demonstrated when one or more results exceed the OEL of the measured chemical. With due consideration being given to variability and log normal distribution of exposures, and based on a small set of representative measurements, this situation corresponds clearly to frequent overexposure in comparison to the OEL.

4. AIR MONITORING OF OCCUPATIONAL EXPOSURE TO CHEMICALS

On the other hand, compliance can be accepted when all the results of a data set corresponding to an SEG are below an OEL fraction. In Europe, several approaches are recommended in this way. Standard EN 689, French regulation [4.15] and the BOHS guide recommend referring to the fraction of 0.1 OEL in order to set up the diagnosis of compliance. Some other reference values are proposed by different organisations, e. g. 0.25 or 0.3. In fact, the best reference value must take into account the variability of exposure to establish the diagnosis of compliance based on a few measurements. *Figure 4.4* from an INRS study [4.16] indicates the reference value to consider in relation to the number of exposure measurements and the variability (geometric standard deviation, GSD) of the SEG.

When the two situations mentioned above are not encountered, which means that all the results of exposure measurements range from > 0.1 OEL to < OEL, other approaches must be applied. Such approaches are based on statistical calculations considering a log-normal distribution of the SEG results (majority of the cases) in order to estimate the probability of exceeding the OEL. This type of approach needs to have at least six results of representative exposure measurements for an SEG. The probability of 0.05 (5%) has been proposed by many scientists and industrial hygienists for establishing a diagnosis of non-compliance with the OEL. In other words, this method may correspond to an exposure situation for which overexposure could occur for five working days out of one hundred.

The probability calculation is done with the geometric mean (GM) and the geometric standard deviation (GSD) and the OEL value. GM corresponds to the arithmetic mean of the logarithm of the results, GSD is the standard deviation calculated with logarithms of the results. With reference to the normal distribution law, the parameter U calculated as indicated below makes it possible to estimate the probability of overexposure with reference to P = 0.05.

$$U = \frac{GM - Ln\ OEL}{SG}$$

Some software can be used to attempt these calculations (e.g. Altrex-INRS (www.inrs.fr), IHDHA-LE exposure assessment solutions U.S. (www.oesh.com)).

Compliance or non-compliance with OELs can also be assessed by comparison of the upper confidence limit of the 95th percentile of the distribution [4.17].

4.5 Combined exposures to chemicals

Nowadays, occupational exposure to a single chemical is very rare. Usually workers can be simultaneously exposed to several chemicals during their shift, e.g. metal dusts, solvent vapours, and fibres. When monitoring exposure, several chemicals belonging to the same family can be sampled and analysed. In such a case, exposure must be considered not only for a single chemical but also for the resulting combined exposure, taking into account the antagonistic or synergistic effects on health. For workers exposed to several chemicals with similar effects on the same target organ, the effect of the mixture of these chemicals should be considered rather than considering each chemical with an isolated effect.

In this case, an exposure index for the mixture that corresponds to the sum of the concentrations of each pollutant divided by its OEL is calculated. If the index value of the mixture is less than 1, compliance with the mixture OEL is assumed.

Predicting risk from exposure to chemical mixtures is complex, as chemicals in mixtures can interact both in terms of toxicokinetics and of toxicodynamics. The "Mixie" software [4.18], developed by the Montreal University in cooperation with IRSST, makes it possible to identify the similar health effects of different chemicals in order to assess exposure and compliance with OELs.

Number of measurements	Geometric standard deviation					
	1.1	1.5	2	2.5	3	4
1	0.85	0.51	0.32	0.22	0.16	0.10
2	0.90	0.63	0.45	0.35	0.29	0.21
3	0.92	0.70	0.54	0.45	0.38	0.30
4	0.93	0.75	0.61	0.52	0.46	0.37
5	0.95	0.79	0.67	0.59	0.53	0.45
6	0.95	0.82	0.71	0.64	0.59	0.51
7	0.96	0.85	0.76	0.69	0.65	0.57
8	0.97	0.87	0.79	0.74	0.69	0.63
9	0.97	0.89	0.84	0.78	0.74	0.68
10	0.98	0.91	0.86	0.81	0.78	0.73

Figure 4.4: OEL fraction with respect to geometric standard deviation and number of measurements, which the series maximum must not exceed, corresponding to a probability of exceeding the OEL less than or equal to 0.05

4. AIR MONITORING OF OCCUPATIONAL EXPOSURE TO CHEMICALS

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5. BIOLOGICAL MONITORING

Claudia Pletscher, Michael Koller

BIOLOGICAL MONITORING

5.1 Biological agent tolerance values

Biological limit values are set for the assessment of internal exposure levels. The biological agent tolerance (BAT) value is determined as a mean value in most countries. It describes, as derived through occupational medicine and toxicology, the concentration of a substance, of its metabolites, or of a stress indicator in biological material at which generally the health of employees is not impaired, even with repeated and long-term exposure. BAT values are based on a relationship between external and internal exposure or between internal exposure and the effect caused by the substance. A 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.

Analytical equipment for biological monitoring

In order to assess employee exposure to chemicals and the corresponding hazard, biomonitoring can be used to supplement substance measurements in ambient air. Assessment of the external exposure level refers to the concentration of the substance in the ambient air and the duration of exposure. Biomonitoring can assess the internal exposure level. Sampling, which is usually easy to perform, makes it possible to obtain measurements that are independent of the half-life of a substance, as well as documentation of the internal exposure level over a longer period of time. This is not achievable with ambient air measurements, which can generally only be carried out selectively due to the effort involved.

5. BIOLOGICAL MONITORING

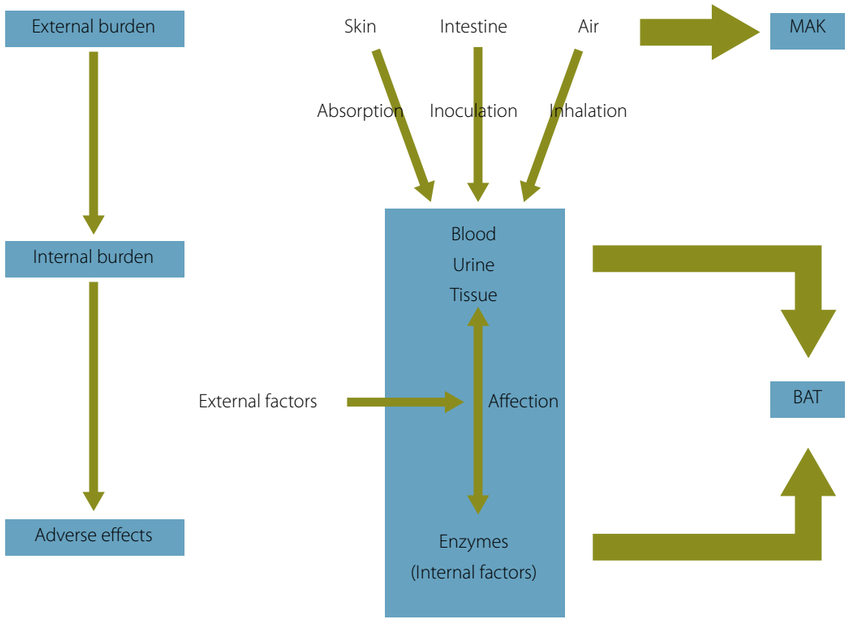

Figure 5.1: Determination of a BAT value

Biomonitoring is understood to mean an assessment of employee exposure to chemical substances by measuring the substance in biological material such as blood, urine or exhaled breath, by measuring metabolites, i.e. metabolic substances of the material, or by measuring an endogenous parameter that is influenced by the substance [*Figure 5.1*]. Using biomonitoring, the internal level of exposure caused by a substance can thus be assessed as a reaction of the human organism to the substance. In this process, all influencing factors are noted as well as the exposure levels.

5.2 Absorption routes

Substances can be absorbed via the respiratory tract, the gastro-intestinal tract and the skin. In such processes, absorption is influenced by additional factors. For example, the extent of the physical exposure level, bio-availability, particle size and wearing of respiratory protection, play roles in absorption via the respiratory tract. Percutaneous absorption of substances is of special significance. In the case of low-vapour-pressure substances that penetrate the skin easily and involve relatively low substance absorption via the respiratory tract, the hazard represented by percutaneous absorption is far greater than the hazard represented by breathing in the substances. Typical substances for which skin absorption is particularly significant for a toxic event are aromatic amines, nitro compounds, organophosphates, e.g. in pesticides, or glycol ethers.

5.3 Toxicokinetics

Toxicokinetics encompasses the metabolic processes of a substance in the body following its absorption, such as distribution, biotransformation, absorption and excretion. Knowledge of a substance's toxicokinetics is essential for the assessment of its effect on health. Among other things, distribution and storage in different organ systems are dependent on the properties of a substance. For example, lipophilic substances accumulate in fatty tissues to a greater degree than in tissues low in fat. Alongside substance-specific toxicokinetic properties, there are also differences from person to person, as is the case with polymorphisms. Between the concentration of a substance in ambient air and the effect on the target organ, several variables such as body size, weight, metabolism, excretion as well as interactions with other substances, alcohol and medicine can influence the dose-effect relationship.

5.4 Interactions

Interactions can occur in the area of activating substances to an active metabolite or detoxification to a hydrophilic inactive metabolite. Both inhibition and also acceleration of the metabolic steps are possible. These interactions can lead to increased serum concentrations by inhibition of the detoxification of substances. This delayed breakdown can moreover lead to lower concentrations in the urine. This must be taken into account when making an assessment. In general, the effect of a substance can be weakened by other substances (antagonism) or reinforced in the sense of an additive or potentiating effect (synergism). For example, this is known for substances containing toluene and hexane.

Factors outside the workplace can also influence the relationship between external exposure levels and the effects on the target organ and thus the biomonitoring parameters. For example, the metabolism of certain substances can be inhibited under the acute effect of alcohol, whereby the concentrations of the substances increase in the blood and the concentrations of the metabolites decrease in the urine. In the case of smokers, there is an additional exposure level, for example, with regard to carbon monoxide, cadmium, nickel and polycyclic aromatic hydrocarbons; smokers thus show higher concentrations of these substances in the blood and in the urine than non-smokers do. However, increased internal exposure levels among smokers can also result from the contamination of the cigarettes, for example, when people smoke at workplaces with exposure to lead.

5.5 Exposure and effect indicators

Exposure limits in the workplace (maximum workplace exposure limit, MAK value) are set for assessing external exposure levels, and exposure limits in biological material are set for assessing internal exposure levels. As described at the beginning, a distinction is made between reference values for the general population and BAT values. BAT values are preferably derived with the help of examinations among exposed employees based on the correlation between biological measurements and health impairments among the employees exposed.

For example, this was possible for deriving BAT values for lead, mercury and cadmium. In the case of substances for which there are no studies, BAT values are derived indirectly from knowledge of the correlation between

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external and internal exposure levels in such a way that there is a relationship between BAT and MAK values. In addition, the absorption, distribution, metabolism and excretion of the substance as well as influences arising from other parameters are taken into consideration. When setting exposure limits, it is assumed that there is a clear dose-effect relationship between the concentration of the substance in ambient air and the effects on health.

5.6 Measuring the internal exposure level

The substance, metabolites or exposure level indicators are measured in the biological material. Preference is given to bodily fluids that can be obtained without any invasive interventions as is the case, for example, with urine. Urine is suitable for a large number of substances that are mainly excreted by the kidneys. Blood is used as a test material for substances that are either not predominantly excreted via the kidneys or whose exposure level indicators in urine do not reflect the internal exposure level to a meaningful, adequate degree.

Depending on the toxicokinetics of the substance, an acute or chronic internal exposure level can be better assessed in the different bodily fluids. For example, when biomonitoring employees exposed to mercury, the mercury concentration can be measured in the urine and in the whole blood. Comparisons of mercury measurements in ambient air and on a group basis in blood and urine indicated that the mercury content in the urine reflects the long-term exposure level and mercury in the blood reflects acute exposure. For some time now, substances such as metals have also been experimentally determined in an exhaled breath condensate. The methods of doing this have not yet been adequately validated for them to be used routinely. However, this method promises some interesting possibilities for the future.

Biomonitoring has several advantages over ambient air measurement. By measuring the substance or metabolites in biological material, the internal exposure level is assessed. Basically, for substances that have an effect on people's internal organs, it is always the internal exposure level, i.e. the amount of substance absorbed that is significant for the assessment of the hazard. It covers all the absorption routes for the substance, which also includes absorption via the skin and via the gastro-intestinal tract.

5.7 Taking samples

When determining the sampling strategy, care must be taken to ensure that - depending on metabolism and on the speed of decomposition - the right moment in time is chosen, such as before a shift or at the end of a shift. This is usually determined together with the determination of the exposure limits in the biological material. Information on this is given in the different national exposure limit lists.

Contamination of the sample material by the substance itself can result in false conclusions if the substance in the urine is selected as a parameter, and if inadequate consideration is given to personal hygiene. Attention must be paid to percutaneous absorption when determining substances in the blood since peripheral-venously measured values do not always correspond to the mixed venous value with venipunctures in the arm. Attention should also be paid to any contamination of the sample material caused by dirty hands. For this reason, participants should receive training in personal hygiene and in taking samples correctly at the start of biomonitoring.

The right kind of sample vessels, the method of transport and storage must also be agreed on with the analysis laboratory. This is the only way to ensure that the result corresponds to the internal exposure level and is not distorted by incorrect sampling, contamination, incorrect storage or by transport. The laboratory analysis should be performed in accordance with recognised quality criteria and regularly validated by the laboratories using ring trials. This is the only way to ensure that results are comparable beyond a single laboratory.

5.8 Discussion

If the BAT value has been exceeded, the results must be evaluated by an expert in terms of occupational medicine and toxicology. Based on the expert's assessment, further technical, organisational and people-related measures are taken.

When interpreting the results, attention must be paid to the length of exposure time that the biological parameter provides information about, i.e. whether the current exposure or the body burden is reflected based on the half-life of the parameter. This can differ according to the substance (cf. the determination of mercury in blood and urine). In addition, influential factors as well as the background exposure level must be taken into account.

For example, smoking influences various workplace substances since many of these substances are found in cigarette smoke. The direct contamination of the cigarette by the workplace substance itself with the subsequent percutaneous absorption can also lead to an increase in internal exposure level.

Eating habits have a heavy influence on certain metabolites such as tt-muconic acid, which is used as one of the parameters for the assessment of exposure to benzene. The consumption of large quantities of ascorbic acid (vitamin C) leads to a significant increase in tt-muconic acid. This must be clarified and inquired about when discussing the results of biomonitoring. When discussing the measurements, the difference between reference values for the general population and the BAT values must be taken into account.

Non-compliance with the reference value for the general population may indicate exposure of occupational origin and must be investigated. Similarly, when the BAT value is exceeded, the possibility of the appearance of adverse effects must be explored, particularly if it is repeatedly exceeded.

A marked concentration or dilution of the urine can also lead to problems in interpretation. When determining exposure limits, the question is clarified as to whether a correction is to be made by the creatinine reference for the determination of levels of metabolites or workplace substances in the urine. When making the assessment, attention must therefore be paid to the creatinine value.

The data acquired is subject to data protection. The country-specific demands of data protection must not be ignored. Archiving is also subject to country-specific regulation either individually or collectively. Results are discussed by the company doctor with the employees and the measures implemented with those in charge.

5.9 Use of BAT values

BAT values are determined for the assessment of internal exposure levels. In Germany and Switzerland, the BAT value has so far been described as the maximum permissible quantity of a workplace substance or workplace substance metabolites in human beings, which, according to the current status, does not affect the health of employees in general even if it is regularly attained as a result of occupational exposure. In recent years, many BAT values have been reduced since sub-clinical effects were assessed as adverse effects to an increasingly frequent degree.

Investigations into the relationship between external and internal exposure levels usually show a substantial scattering of the biological parameters given certain external exposure levels. This is due to measurement technology problems, inter- and intra-individual diffe-

5. BIOLOGICAL MONITORING

rences among employees, different working conditions as well as relatively small sample groups in many cases. Given that the tolerance value has usually been derived as a mean value from the studies and that a clear distinction between hazardous and non-hazardous exposures cannot be derived, the tolerance values in the USA (biological exposure indices, BEI) as well as in the EU (biological limit values, BLV) have not been defined as a maximum value for an individual worker's long-term exposure.

Reference values for the general population correspond to the background exposure level and cannot be used for the assessment of workplace-related exposure levels.

5.10 Biomonitoring applications in health protection

Biomonitoring can be used in preventive occupational medicine, to clarify occupational diseases, assess workplaces for supplementing ambient air measurements, and to document longer-term exposure levels.

For clarification of any job-related intoxication in the sense of an occupational disease and alongside measurements of the workplace substances in ambient air, biological measurements are always advisable whenever they can be evaluated on the basis of published BAT values or literature.

For the assessment of workplace conditions, biological measurements should be taken to supplement ambient air measurements particularly if there is a possibility of skin absorption or an additional gastro-intestinal absorption of a substance, if an increase in substance absorption when doing physically hard work needs to be taken into account, if personal hygiene factors can play a substantial role for an internal exposure level or if the effect of personal protective equipment such as breathing masks or protective gloves needs to be assessed.

When ambient air measurements and biological measurements are carried out, there are basically four possibilities when the results are evaluated:

- MAK and BAT values are adhered to.
- The MAK value is exceeded, but the BAT value is adhered to.
- The MAK value is adhered to, but the BAT value is exceeded.
- Both exposure limits are exceeded.

While there are no difficulties in interpretation with either method where adherence to or exceeding exposure limits are concerned, the issue with the discrepancy of an assessment based on the MAK value and the BAT value lies with its evaluation. If the BAT value is exceeded, but the MAK value is adhered to, additional skin absorption of the substance, absorption via the gastro-intestinal tract, a lack of personal hygiene, an increase in absorption via the respiratory tract in the case of physical work, an additional exposure level resulting from hobby activities or environmental factors must be considered as possible causes.

Thought must also be given to an inadmissible exposure level arising from past exposure to the substance if the biological parameter shows the body burden based on the long half-life. Interactions with workplace substances or alcohol can similarly result in this constellation. If the MAK value is exceeded, but the BAT value is adhered to, the wearing of personal protective equipment can result in the internal exposure level remaining low despite an unacceptably high level of exposure in ambient air. A high external exposure level might be measured intermittently and not be recorded by a biological parameter which might reflect exposure over a long period of time.

Problem-solving approaches must be selected in accordance with the interpretation. In the case of only the BAT value being exceeded, personal protective equipment and personal hygiene must be examined in particular, and additional exposure levels or interactions outside the workplace must be found and excluded. Even if only the MAK value is exceeded, technical and organisational measures must also be taken; if the BAT value is adhered to, personal protective equipment comes last among the measures to be taken according to the STOP principle (Substitution - Technical measures - Organisational measures - Personal protective equipment).

5.11 Literature

[5.1] Jost, M. and Pletscher, C.: Biologisches Monitoring und biologische Arbeitsstofftoleranzwerte. Suva Medical (2009)

[5.2] Lauwerys, R. R. and Hoet, P.: Industrial Chemical Exposure: Guidelines for Biological Monitoring; 3rd Edition. CRC Press (2001)

6. DEDUCING RISK MANAGEMENT MEASURES IF NO OEL[S] ARE AVAILABLE

DEDUCING RISK MANAGEMENT

Andreas Königer

For a number of hazardous substances, indicative or binding health-based, risk-based or technical-based OELs have been set at international or national levels. Such OELs may or must be used to evaluate the health hazard of a worker at the workplace and to deduce suitable risk management measures.

Despite all efforts, the number of substances for which OELs are not yet available is much higher. Therefore, for such substances, there is a lack of comprehensible criteria for evaluating inhalative exposure as a basis for deducing risk management measures.

In this chapter, two approaches to risk assessment and to evaluation of risk management measures in the absence of OELs will be described.

6.1 Control banding concept

The control banding concept is a strategy for reproducible risk assessment and hazard management at the workplace, without OELs and on the basis of substance properties and the working process. The concept also serves to provide a simple and easy-to-use tool with readily available information for deducing risk management measures to persons in charge of assessing risks for their workers, and who probably do not have much experience in hazardous substance evaluation.

The concept does not replace regulatory requirements for deducing health-based limit values according to, for example, the REACH Directive. It also does not replace experimental determination of the inhalative exposure of workers at the workplace as part of an effectiveness check.

The control banding concept was developed and is used in different countries in a similar way using different names [6.1]:

- France: Hierarchisation des risques potentiels [6.2]
- Germany: Einfaches Maßnahmenkonzept Gefahrstoffe [6.3]
- Netherlands: Stoffenmanager [6.4]
- Norway: KjemiRisk [6.5]
- United Kingdom: Control of Substances Hazardous to Health (COSHH) Essentials [6.6]

6.1.1 Starting information

The evaluation starts with information which generally can be taken from the material safety data sheet. In addition, information is required about the working procedure, process data and information about risk management and protective measures applied. Each substance and each working procedure has to be examined separately.

Information about physico-chemical properties, e.g.:

- Physical condition during process (solid, liquid, gaseous),
- Boiling point, vapour pressure,
- Grain size, dust potential (wax/paste, pellets, granulate, coarse-/fine-grained).

Information about the toxicity and hazard potential:

- Classification (Hazard class and category),
- Limit values (if available).

Information about the planned working process:

- Amount of substance used in one process step,
- Process parameters such as reaction temperature and pressure,
- Activities at the workplace and design of the process (technical protective measures, e.g. open, temporarily open, closed, strictly contained; exhaust,
- Protective measures applied (organisational, e.g. barriers, exclusion zones; personal, e.g. working clothes, special personal protective equipment, chemical safety gloves, respiratory protection).

6. DEDUCING RISK MANAGEMENT MEASURES IF NO OEL^S ARE AVAILABLE

6.1.2 Evaluation

The risk assessment according to the control banding concept is performed in four steps.

- **Tier 1: Hazard band:**
  In the first tier, classification information (H-classes) is used to allocate the substance to a hazard band. The more critical a classification and/or the lower a limit value (if available), the higher the hazard band.

- **Tier 2: Potential of release:**
  Within the second tier, the potential of release has to be predicted using the physico-chemical properties of the substance in combination with the reaction parameters. For example, the lower the boiling point, the lower the vapour pressure, the higher the dust potential and the higher the reaction temperature, the higher the potential of release of the substance.

- **Tier 3: Substance amount:**
  Within the third tier, the substance amount handled in the process step has to be determined and allocated to a quantity band. The bigger the amount, the higher the hazard risk is assumed to be.

6.1.3 Risk assessment and risk management measures

In the last tier, the results of the preceding steps are combined and working procedures and risk management measures are deduced. The higher the hazard band (tier 1) the higher the potential of release (tier 2), and the bigger the amount handled (tier 3), the more challenging the requirements are concerning working procedure and protective measures. These can vary from simple standard risk management measures to strictly controlled containment. Technical protective actions must be preferred before applying organisational or personal risk management measures. In cases of very high risks, a special risk assessment beyond the control banding concept has to be performed.

6.1.4 Implementation

The risk management measures deduced by applying the control banding concept must be compared with the working procedure and the protective measures originally planned. If necessary, corrective actions must be taken.

Figure 6.1: Process Indices

Process Index	
0.25	The plant or process component is strictly contained. A (supposed) OEL will most definitely and sustainably be complied with.
0.5	The plant or process component is contained. A (supposed) OEL will undoubtedly be complied with.
1.0	The plant or process component is mainly closed. A (supposed) OEL will not always be complied with certainly.
2.0 and 4.0	The plant or process component is (partly) open. A (supposed) OEL will probably not be complied with certainly.

6.2 Process indices

If there are no limit values and no classification available for a substance, the risk for human beings or the environment must be considered as high. In this case, not only the substance itself should be evaluated but the protective potential (e.g. leak-tightness) of the technical equipment has to be determined and assessed. In the German technical rule TRGS 500 [6.7], a procedure for such a risk assessment has been described.

Each component of the process has to be assessed and a process index defined. This process index represents a degree of leak tightness and corresponds to the remaining exposure potential or, in other words, how reliably an occupational exposure limit will be complied with (*Figure 6.1*). The entire plant or process can be considered "strictly contained", if the process indices of all components of the process are assessed at 0.25.

If there are single components or process steps assessed as having a lower process index, additional risk management measures for improving the technical measures or for determining further organisational or personal protective actions are necessary. In some cases, it is possible to improve an initially defined process index of 0.5 or 1 to 0.25 or 0.5 by applying further organisational measures such as preventive maintenance.

6.3 Literature

All web sites consulted on 05 June, 2014

[6.1] Qualitative Risk Characterization and Management of Occupational Hazards: Control Banding (CB). NIOH Publication 2009-152 (2009)

[6.2] www.inrs.fr/accueil/produits/mediatheque/doc/publications.html?refINRS=ND%202121

[6.3] www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/EMKG/EMKG.html

[6.4] https://www.stoffenmanager.nl/Default.aspx?lang=nl

[6.5] www.ohs.no/ChemiRisk/english/about.htm

[6.6] www.hse.gov.uk/coshh/

[6.7] TRGS 500 "Schutzmaßnahmen": www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-500.html

7. LIMIT VALUES FOR NANOMATERIALS

LIMIT VALUES FOR NANOMATERIALS

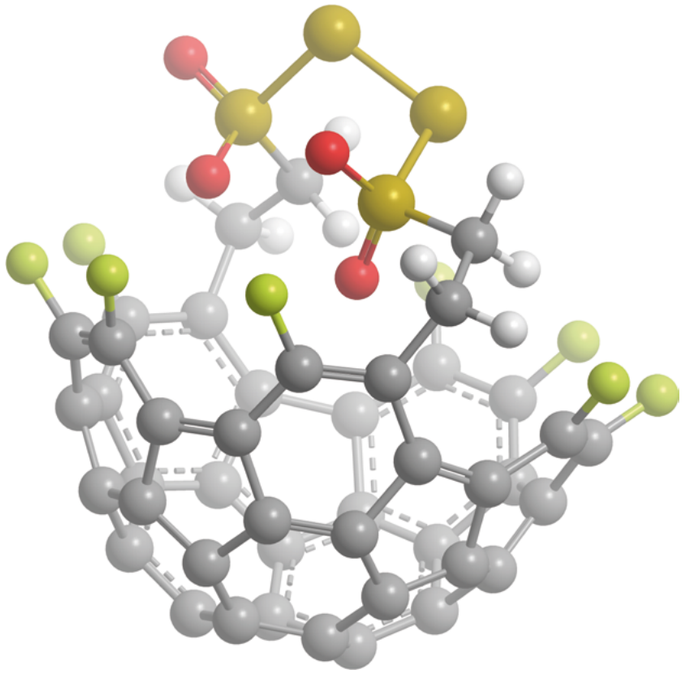
Thomas Brock

7.1 About nanomaterials

Nanomaterials are pure substances, mixtures or other complex structures that are manufactured, processed or treated using nanotechnological procedures. In this context, they are distinguished from unintentionally produced ultrafine dusts. The EU also classifies products that possess a minute proportion of nanoscale particles with regard to weight as nanomaterials, because this covers some macroscopic materials containing small amounts of finer particles.

The dimensions of the individual particles or of nanoscale structures range from around one nanometre up to approximately 100 nanometres. For observations regarding occupational health and safety, it has proven useful to set the upper limit at several hundred nanometres. These technologies are thus in the same range as individual large molecules or clusters of comparatively few atoms or molecules.

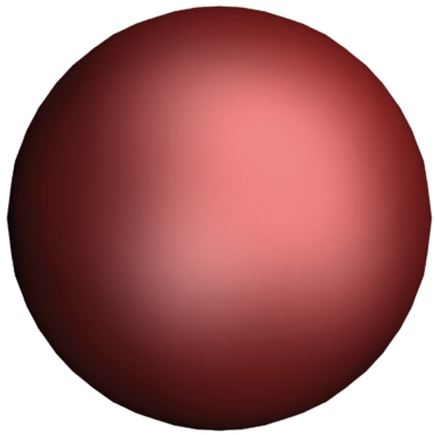
In 2011, the EU Commission adopted the recommendation on the definition of a nanomaterial: a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm to 100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1% and 50%. By derogation from the above, fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials. The definition in that Recommendation should also include particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm to 100 nm. In addition, a material should be considered as lying within the definition when the specific surface area by volume of the material is greater than 60 m^2/cm^3 [7.8].



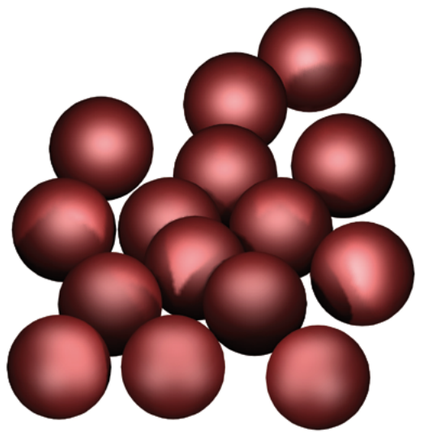
7.2 Nano-objects vs. nanostructured materials

The term nanotechnology - and the less common but more appropriate plural "nanotechnologies" - describes a multitude of procedures dealing with the preparation or manipulation of minute structures. Nanotechnology is regarded as a crossover technology between various disciplines. Alongside the classic disciplines concerned with conducting such manipulations, e.g. Chemistry and Physics, other disciplines such as Biology, Medicine, Engineering and Materials Science, are also affected, and with regard to the consequences for humankind and the environment, also Humanities.
No standard nomenclature yet exists for these materials, although classification as per international standards has proven useful. That classification draws a distinction between nano-objects and nanostructured materials within the scope of nanomaterials.

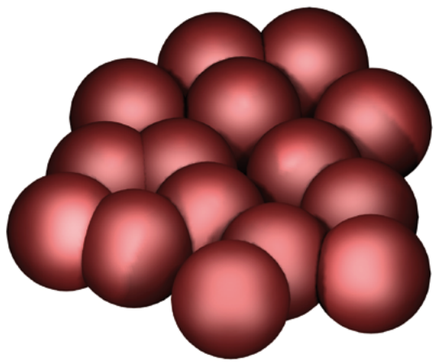
7. LIMIT VALUES FOR NANOMATERIALS



Primary particle



Agglomerate of primary particles



Aggregate of primary particles

According to those standards, nano-objects are not components of larger structures, but are differentiated and free, and can, for example, exist suspended in a liquid. Furthermore, they tend to form bonds of varying strengths with one another or with other surfaces, thereby forming agglomerates or aggregates, which are not nano-objects due to their size. Under certain conditions, nano-objects can - occasionally or intentionally - be set free again from these larger units.

There are three types of nano-objects: nanofilms and nanoplates, which have a thickness ranging from approx. 1 nm to approx. 100 nm but are unlimited in length and width. One example of this is the innovative carbon modification of graphene with unusual mechanical and electrical properties, the discoverers of which were awarded the Nobel Prize in Physics in 2010. Nanotubes, nanorods, nanowires and nanofibres have a diameter in the same range, but are not limited in their length. Carbon nanotubes are the best-known members of this category and also possess a number of unusual properties. Nanoparticles are more or less spherical objects with nanoscale dimensions in all three spatial dimensions. Therefore, in contrast to the other two types, they cannot assume macroscopic dimensions.

Although only a very limited number of nanomaterials have currently found their way into practical application, the variety of theoretically possible nanomaterials is vast. Alongside variations in their chemical nature, nanomaterials may, in particular, show different effects due only to variations in their structures, morphologies, physical and physicochemical properties for a given chemical composition and structure. This leads to a plethora of possible different nanomaterials that may have different properties. For this reason, general statements along the lines of "Nanomaterials do this or that" cannot be made, since, even with regard to carbon nanotubes, this observation would represent an undue generalisation for tens of thousands of different nanotubes. However, thanks to the improving understanding of active mechanisms, ever more accurate categorisations can be made, e. g. by aspect ratio or by biopersistance.

7.3 Properties and use of nanomaterials

Nanomaterials have special properties arising from the minute size of the objects or structures and the limited number of atoms or molecules assembled therein. The first noticeable aspect is the enormous size of the surface in comparison with the amount of material. This means that, in contrast to macroscopic objects in which "nearly all" of the atoms or molecules are "hidden" inside the object, a large proportion or even the majority are located on the surface and can interact with their chemical and biological environment.

This is apparent in the dust explosion properties of some nanomaterials, for which the minimum ignition energy may be significantly lower in comparison with the macroscopic material. Some of these materials are therefore also highly catalytically active, ranging from a self-cleaning surface for paints upon reaction with (sun) light and oxygen, right through to more efficiency in chemical synthesis compared to conventional catalysts.

In addition, surfaces can be modified by chemical reactions, leading to a change in their properties. Molecules from the surrounding environment can be adsorbed by and carried on the surface. In the same vein, some nanomaterials can also incorporate atoms and molecules and act as vehicles "simulating" quite different properties to the surrounding environment, for example through biological structures in order to release active components within cells. Aerodynamic properties of smaller nano-objects bear a closer resemblance to those of gases than to those of dusts.

These properties are leading to innovative product developments or already marketable products, e.g. materials with significantly improved properties such as strength. Furthermore, nanomedicine is offering new treatments for serious illnesses such as cancer, and new ways of energy storage or conversion will, in the future, allow us to use the planet's resources in a more sustainable way. Whereas, to date, most products have still relied on adding nano-objects like carbon nanotubes or metal oxide particles in order to improve properties, developments are in progress that intend to use a much more "intelligent" approach, right through to self-organising systems or even - although this is as yet only a possibility - self-reproducing systems that could then completely cross the boundary to synthetic biology.

7.4 Estimating biological effects

Nevertheless, a conclusive assessment of the risks is not possible based on present knowledge. There are still gaps in our understanding of the properties and effects on people and the environment, and those gaps will require considerable work if they are to be closed. Both in-vitro and in-vivo experiments provide evidence that at least some nanomaterials can have negative effects. For instance, certain nanotubes show an alarming effect on the lung in animal testing, nanomaterials can release

7. LIMIT VALUES FOR NANOMATERIALS

metal ions, oxidative stress can occur and a protein corona with currently poorly-known properties can form around nano-objects in the body.

It has been demonstrated that some nano-objects (particles and fibrous structures) undergo a translocation, i.e. they can penetrate biological barriers such as cell membranes, so that they are transferred from the lung to the blood stream. Alongside the dosage, important factors here are the dimensions and stability of nanomaterials in the body. Nanomaterials that disintegrate quickly in the body do not cause effects through their specific nanostructure, but rather - if at all - through released and dissolving chemical compounds and metal ions. The experimental findings by no means apply for all nanomaterials, but rather only for certain individual materials or groups of materials. Neither are these findings regularly connected with a negative effect. However, they do at least show that a higher level of vigilance is a necessity.

7.5 Occupational health and safety

Within the scope of occupational health and safety, it is however, highly advantageous that, according to all sober evaluation, the risk of negative effects be based not solely on the material and its properties, but also on the probability of the effects, and in particular on the dosage, which in turn can be monitored and controlled very well. All examinations and test results performed on site show that exposure to nanomaterials can be controlled using the classical methods of minimising exposure, thereby indicating that the risk can be minimised this way.

However, such measures require a certain level of expertise in order to be effective. According to all test results thus far, nanomaterials can be handled very well in laboratory fume cupboards with virtually no exposure, although this does not work in fume cupboards with limited function (which is to be expected, as this also applies for other substances). However, an excessive air current can result in light materials such as fullerene being carried along in the current and instead contaminating the interior of the fume cupboard. Nonetheless, although it is easy to gain a good command of the technical aspects of the protective measures, their handling sometimes needs to be improved because of lack of care or knowledge of the users. Additional training is certainly required here.

The metrological assessment remains challenging. From the expensive testing equipment right through to assessment, for which limit values are not available and cannot be expected in the near future, this field is not yet at an advanced stage of development compared to other measurements of hazardous substances. Despite this, measurement systems are at least available that, once the user is familiarised with them, allow orientation values on exposure to be obtained, which can then be substantiated with more complex measurements (e.g. by DGUV). The question of the relevant measurement unit or units has not yet been conclusively answered. While the mass of particles per unit volume of air gives very low values, the number of particles in the same unit of volume is very high, which means an identification of the available surface area per volume would be needed (in addition) for describing exposure.

Footnote: *A suggestion for alternative values can be found at the Institute for Occupational Safety and Health (IFA) of the German Social Accident Insurance (DGUV) at* ***www.dguv.de/ifa/de/fac/nanopartikel/beurteilungsmassstaebe/index.jsp****.*

An initial problem is that it is hardly possible to define a dedicated limit value for each nanomaterial. Considering the lack of data from the non-existent epidemiology and the unbearable workload of animal testing, it seems difficult to apply the classical way of setting limit values. Sensible and justifiable grouping according to effects, insofar as these can be assessed, is a first approach. In the USA, the National Institute for Occupational Safety and Health (NIOSH) has defined an assessment value for nanoscale titanium dioxide of 0.3 mg/m³ and for carbon nanotubes of 0.007 mg/m³ (each for ten hours per day, 40 hours per week), and a British standard recommends deriving concentrations for nanoscale material with a standardised factor from the value for the same non-nanoscale material.

Manufacturers of nanomaterials have also recommended individual values (0.05 mg/m³ for multi-walled carbon nanotubes).
DGUV proposes a limit value of 20,000 particles per cm³ for biopersistent granular nanomaterial with a density higher than 6 g/cm³ and 40,000 particles per cm³ for the same type of material with a lower density, both in the size range of 1 nm to 100 nm. Both values are not health-based but are rather based on measurement considerations. All limit values shall be used only as a component of an expert judgment.

Personal protection for working with special nanomaterials.

The Committee on Hazardous Substances of the German Ministry of Labour proposes a procedure for a risk assessment for nanomaterials.

As a minimum assessment, consideration should be given to the effects based on the chemical composition of the nanomaterial (e.g. toxicity of arsenic compounds for a nanoscale arsenic-(III)-oxide) and to the effect based on the compound's characterisation as a biopersistent nano-object irrespective of its chemical composition (e.g. dust of a practically insoluble compound, where a solubility of less than 100 mg in one litre of water is considered as "insoluble" in this context, which defines calcium sulfate as soluble – 0.255 g/l at 20°C – but calcium carbonate in the modification of calcite as "insoluble" with 6·10–4 g/l at 20°C). This criterion can be used as a yardstick and is applied in coherence with the European Pharmacopoeia, but significant differences between the solubility in water and the solubility in serum or lung surfactant are possible.

Therefore four classes of nanomaterials are defined:

- soluble nanomaterials (class I),
- biopersistent nanomaterials with specific toxicological properties (class II),
- biopersistent nanomaterials without specific toxicological properties (granular biopersistent particles) (class III),
- biopersistent fibrous nanomaterials (class IV).

For class I materials, a risk assessment following the general guideline of TRGS 400 is sufficient.

For class II materials, it must be taken into account that the material may show harmful properties or that the

7. LIMIT VALUES FOR NANOMATERIALS

microscale form has toxic properties provided that no data to the contrary is available. Limit values for such materials are typically less than 0.1 mg/m³.

No substance-specific toxicity is shown by materials of class III so they are sometimes designated by the outdated term of "inert substances", because in fact they may not really be inert to biological systems. If no limit values from qualified sources are available (e.g. international limit values or proposed limit values, preliminary corporate internal observation or action levels, DNELs), an assessment criterion of half of the occupational limit value in relation to the binding occupational limit value for alveolar dust may be used. It should not be higher than 0.5 mg/m³ for a material with a density of 2.5 g/cm³.

The risk assessment for fibrous materials of class IV is more challenging. In addition to the difficult measurement methods, the limit values for these materials should be oriented towards the limits for asbestos since some of them may show similar effects. This is not necessary if it is proven that a specific product does not show these effects or evidence is provided that the fibres do not fulfill the WHO fibre criteria.

However, even these approaches are only an attempt at dealing with uncertainty. Nevertheless, the lack of limit values cannot be used to justify inaction; rather, the principle of precaution applies. A minimisation to zero would be equivalent to a "strong" precautionary principle, which would be tantamount to ceasing all activities and the use of all products.

This certainly cannot be the solution to the problem; from a philosophical point of view the question could even be posed as to whether it can be acceptable to declare a moratorium on a technology that in many ways can improve the living conditions of people, bring about a more respectful approach to the environment and provide practical help for individuals, for example cancer patients. If entirely satisfactory answers to all questions were demanded before allowing nanotechnology products to be chosen, we would probably never be able to make progress.

7.6 Recommendations

If no applications were allowed to be introduced onto the market, there would be no motivation to address the complex questions. For logical reasons and the necessary competence of dealing with risks, a more prudent precautionary principle is therefore applied. Not only are helpful tools available for dealing with how to reduce exposure, but initial approaches to defining concentration values that can be useful for assessing workplaces have also been made. One such approach consists of the values put forward by the German Institut für Arbeitsschutz (IFA), for which the latest technical advances and metrological possibilities were taken into account. The size and density of the nanomaterials serve as orientation values here. A detailed description can be found on the IFA website.

A tiered approach to the measurement of nanomaterials in the workplace air has been published by IFA, Berufsgenossenschaft Rohstoffe und Chemische Industrie (BG RCI), Verband der Chemischen Industrie (VCI), Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA) and Institut für Energie und Umwelttechnik (IUTA). It allows a prudent assessment strategy to be implemented in which expensive and complex equipment is used only when unavoidable. This has the benefit of making it possible to measure a much larger number of workplaces with simpler equipment and contributes to increasing the availability of exposure data from workplaces.

Recent research shows that an uncoordinated flood of additional study results could bring about more confusion than elucidation. For this reason, an intensive, specialist, yet also public dialogue between researchers and users remains a necessity. A proper understanding of risks is necessary for all participants.

The field of nanotechnology will certainly continue to be an important topic in occupational health and safety for a long time to come. Tested and effective strategies for monitoring and reducing exposure are available, although it is advisable to keep a watchful eye on the topic for further developments.

7.7 Literature

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[7.5] Committee on Hazardous Substances (AGS): Announcement on Hazardous Substances 527: Manufactured Nanomaterials, GMBl 25, 498 (2013)

[7.6] Federal Institute for Occupational Safety and Health (BAuA), Association of the German Chemical Industry (VCI): Leitfaden für Tätigkeiten mit Nanomaterialien am Arbeitsplatz.
https://www.vci.de/Presse/Pressemitteilungen/ Seiten/Aktualisierter-Leitfaden-fuer-den-Umgang-mit-Nanomaterialien.aspx#

[7.7] DGUV-I 213-855 „Handling of Nanomaterials in Laboratories"
www.dguv.de.

[7.8] COMMISSION RECOMMENDATION of 18 October 2011 on the definition of nanomaterial (2011/696/EU)

8. GLOSSARY

Antje Ermer

GLOSSARY

Acceptable Concentration and Tolerable Concentration

Acceptable concentration and tolerable concentration are substance-specific values. These figures state the substance concentration in the workplace air, to which the non-substance-specific tolerable or acceptable risk corresponds. These limits can be derived using the exposure-risk relationship for the substance in question.

An exposure to a carcinogenic substance that is only slightly higher than the acceptable concentration requires much less urgent minimisation than an exposure that is significantly higher. The workplace exposure should not exceed the tolerable risk.

Acceptable and tolerable concentrations are not limit values in the sense of AGW values. They are always to be understood as assessment criteria for risk minimisation in connection with the graduated measures concept.

Country: DE
Responsible authority: Committee on Hazardous Substances (AGS), Federal Ministry of Social and Labour Affairs (BMAS)
Status: TRGS 910, established with GefStoffV 2013 (***www.baua.de***)
Unit: e.g. ml/m³ (ppm) or mg/m³, for fibres: fibres/m³
Source: TRGS 910

Acceptable Risk and Tolerable Risk

Acceptable risk and tolerable risk state the additional risk, i.e. the risk arising from a given exposure, exceeding the natural background rate, or the probability of health damage occurring as a result of exposure to carcinogenic hazardous substances.

Both risk values refer to a working lifetime of 40 years and continuous exposure every working day. The concept includes a guide for the quantification of cancer risk figures to derive substance-specific concentration figures and exposure-risk relationships.

Acceptable Risk

limit 4: 10,000 (interim value)
limit 4: 100,000 (no later than 2018)
Below these values a risk is accepted; above these limits, the risk will be tolerated if the measures specified in the catalogue of measures are complied with.

Tolerable Risk

limit 4: 1,000
Above these values a risk is intolerable.

Country: DE
Responsible authority: Committee on Hazardous Substances (AGS), Federal Ministry of Social and Labour Affairs (BMAS)
Status: TRGS 910, established with GefStoffV 2013 (***www.baua.de***)
Unit: dimensionless
Source: TRGS 910

Adverse Effect

An undesirable, e.g. health-damaging, effect for the human organism.

AF (Assessment Factor, also Extrapolation Factor)

The AF is a numeric value, used to adjust toxicological data gained from animal experiments on dose-response relationships, since this kind of data for humans cannot be gained through experiments. Extrapolation allows an

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estimation of a human exposure concentration at which no damaging health effects are to be expected.

The various extrapolation factors can be scientifically ascertained to a varying extent. That means they are verified in different degrees and therefore include more or less uncertainties. This explains the use of terminology such as certainty factor and uncertainty factor in some publications.

The sum of all extrapolation factors results in a total extrapolation factor.

Sources: Following ECHA Guidance R 8, ECETOC Technical Report No. 110, Announcement on Hazardous Substances 901 (***www.baua.de***)

AGW (Arbeitsplatzgrenzwert)

In Germany, the AGW is a limit value for the time-weighted average concentration of a substance in the air at the workplace in relation to a specified reference period. It indicates up to what substance concentration there are no acute or chronic effects to be expected for the health of the workers in general. Therefore, the AGW is a health-based limit value for occupational exposures.

The AGW values are average values for an exposure on a daily eight-hour shift for five days a week, during the entire working life. Exposure peaks during a working shift are assessed through short-term values.

AGWs are determined for acutely or chronically health-damaging, yet non-carcinogenic effects, which generally have a threshold. Therefore, AGWs are not derived for genotoxic carcinogenic substances.

When deriving the AGW value from animal studies, it is the quotient from the lowest valid effect value and certain assessment factors.

Additional notations are allocated to some occupational exposure limit values. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects. In the TRGS 900, the abbreviations "Sa", "Sh", "Sah" or "H" are also allocated to respiratory tract sensitising, skin sensitising and percutaneous absorption properties. For all such substances, further measures in addition to compliance with the AGW are necessary. Developmental toxic effects are not assessed when establishing the occupational exposure limit. Notation "Y" or "Z" is allocated to substances and their AGW values in TRGS 900.

Country: DE
Responsible authority: Committee on Hazardous Substances (AGS), Federal Ministry of Social and Labour Affairs (BMAS)
Status: binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Sources: GefStoffV, TRGS 900, Announcement on Hazardous Substances 901 (***www.baua.de***)

BAT (Biological Agent Tolerance) Value, Germany

In Germany, the BAT value describes, as derived through occupational medicine and toxicology, the concentration of a (non-carcinogenic) substance, of its metabolites or of a stress indicator in biological material, at which, according to current scientific evidence, the health of employees is generally not impaired, even with repeated and long-term exposure. The BAT value is considered to be exceeded if the average concentration of the parameter is above the BAT value in several examinations of an employee. Measurements above the BAT must be evaluated using occupational medical and toxicological criteria.

The BAT values constitute the essential basis for Biological Limit Values. BAT values are based on a relationship between external and internal exposure, or between internal exposure and the effect caused by the working substance.

Country: DE
Responsible authority: MAK Commission
Status: State of Science
Unit: Concentration in blood, in erythrocyte fraction of whole blood, in urine or in plasma/serum
Source: List of MAK and BAT values 2012 (DFG), see also ***http://www.dfg.de/en/index.jsp***

BAT (Biological Agent Tolerance) Value, Switzerland

In Switzerland, the BAT value describes, as derived through occupational medicine and toxicology, the concentration of a substance, of its metabolites or of a stress indicator in biological material, at which generally the health of employees is not impaired, even with repeated and long-term exposure.

Country: CH
Responsible authority: Suva, (Suissepro)
Status: binding
Unit: Concentration in blood, in erythrocyte fraction of whole blood, in urine or in plasma/serum
Source: Grenzwerte am Arbeitsplatz , suvapro Sicher arbeiten

BEI (Biological Exposure Index)

The BEI provides guidance values for assessing results gained through biological monitoring, which reflect the uptake (intake, absorption) of substances. BEIs generally indicate a concentration below which nearly all workers should not experience adverse health effects.

The BEI determinant can be the chemical itself, one or more metabolites, or a characteristic, reversible biochemical change induced by the chemical. In most cases, the specimen used for biological monitoring is urine, blood, or exhaled air.

Most BEIs are based on a direct correlation with the TLVs. That means the BEIs reflect the concentration of the determinant in the biological media that can be expected when the inhalative exposure is at the TLV. ACGIH indicates that those who use the BEIs must consult the latest written "Documentation of the Threshold Limit Values and Biological Exposure Indices" to ensure that they understand the basis for these values and the information used for their development. BEI® is registered.

Country: US
Responsible authority: American Conference of Governmental Industrial Hygienists (ACGIH)
Status: non-consensus standard, recommendation
Unit: Concentration in blood, in erythrocyte fraction of whole blood, in urine or in plasma/serum
Source: ***www.acgih.org/TLV/***

BLV (Biological Limit Value) / BGW (Biologischer Grenzwert)

The BLV is a limit value derived by toxicological and occupational medical means, for the concentration of a substance, of its metabolite or of an indicator of effect in the corresponding biological material. It is normally determined by taking into consideration the characteristic level of substances in blood and/or urine in the general population. It indicates up to what concentration the health of workers is generally not impaired.

Biological Limit Values are conceived as mean values for healthy individuals. The BLVs are, just like the AGWs, based on a substance exposure of a maximum of eight hours per day, forty hours per week.

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Country: DE
Responsible authority: AGS, BMAS
Status: binding
Unit: BLVs can be defined as concentrations, as production rates, or as excretion rates (quantity / time unit)
Sources: GefStoffV, TRGS 903 (***www.baua.de***)

BOELV (Binding Occupational Exposure Limit Value)

BOELVs are binding limit values of the European Commission for occupational exposure to non-carcinogenic substances (health-based) as well as carcinogenic substances (typically technical-based). Member States determine a binding national OEL based on, but not exceeding the European Community OEL.

BOELVs have been determined for non-carcinogenic substances, e.g. for lead and its inorganic compounds, as well as for the carcinogenic substances benzene, vinyl chloride monomer and hardwood dusts. For many substances, BOELVs are under discussion.

For the establishment of these limit values, the European Commission is supported by the Scientific Committee for Occupational Exposure Limits to Chemical Agents (SCOEL). In addition to the factors that are employed when determining Indicative Occupational Exposure Limits, certain socio-economic factors may also be taken into account, if, at all times, the health protection of the workers is ensured.

Country: EU
Responsible authority: EU Commission
Status: binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Sources: Cancer Directive 2004/37/EC, Chemical Agents Directive 98/24/EC, Bender, H. F.: Sicherer Umgang mit Gefahrstoffen, 4. Aufl. Wiley-VCH (2011)

Ceiling Value, Momentary Value

The Ceiling value is an atmospheric concentration in the workplace that must not be exceeded at any time. It mainly concerns substances recognised as strong irritants or corrosives that can cause potentially serious and irreversible effects in the very near term. Specific analytical measures are implemented to measure this value.

Critical Toxicity

The one significant adverse effect which is used to calculate the MAK value. As a rule, this is the adverse effect that occurs at the lowest concentration.

Source: Grenzwerte am Arbeitsplatz (Suva)

DMEL (Derived Minimal Effect Level)

The DMEL is a risk-based limit for non-threshold carcinogenic and mutagenic substances. DMEL-values are explicitly not stated in the REACH regulation; various ECHA guidelines merely advise registrants to state them. For non-threshold effects, the underlying assumption is that a no-effect level cannot be established and a DMEL therefore expresses an exposure level corresponding to a low, possibly theoretical risk. However, there are no legally binding reference risks defined by EU legislation at the moment. When DMEL values are derived by manufacturers or importers, the risks they use as a calculation basis are – just like the values themselves - not legally binding.

Country: EU
Responsible authority: - (company/registrant under REACH)
Status: not binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Source: ECHA Guidance R.8, ECETOC Technical Report No. 110

DNEL (Derived No Effect Level)

The DNEL value is the derived exposure level for a substance below which there is no adverse effect on human health. These limit values are health-based.

DNEL values differentiate between the most probable exposure routes: oral (ingestion), dermal (absorption), and inhalative (respiration). Furthermore, a differentiation is made between the most likely durations of exposure (long-term or short-term values). Depending on the substance, DNEL values may have to be established for systemic effects (that are normally observed distant from the site of first contact), for local effects (that are observed at the site of first contact) or for both.

DNEL values are derived for all relevant groups of persons such as employees, consumers and humans in general, who are indirectly exposed via the environment. Evaluation criteria for workplace exposure are mainly long-term inhalation values, and short-term values are used for the evaluation of exposure peaks. GESTIS-DNEL-Database provides these values which have been established for the inhalative long-term exposure by manufacturers and importers under their own responsibility and have been published by the European Chemicals Agency (ECHA). GESTIS-DNEL-Database is a service of the German Social Accident Insurance (DGUV) ***http://www.dguv.de/ifa/Gefahrstoffdatenbanken/GESTIS-DNEL-Datenbank/index-2.jsp***

DNEL values are derived like AGWs for non-carcinogenic substances with a threshold that cause acute or chronic adverse health effects. The DNEL is a quotient from the lowest effect value (NOAEL or LOAEL) and certain assessment factors. DNEL values can be more stringent than binding national limits (e. g. AGWs). This is due to a higher total extrapolation factor in the derivation of DNEL values.

DNEL values must be determined by manufacturers and importers in compliance with their specific duties and obligations according to the REACH Regulation. They can be found in the Chemical Safety Report, and in the Safety data sheet, section 8 "Exposure Controls, Personal Protection".

Country: EU
Responsible authority: - (company/registrant under REACH)
Status: not binding
Unit: e.g. ml/m³ (ppm) or mg/m³
For oral and dermal values: e.g. mg/kg bodyweight/day
Source: REACH-V

EKA (Exposure Equivalents for Carcinogenic Substances)

An EKA describes the relationships between the concentration of the carcinogen in the workplace air and the substance or its metabolites in biological material resulting from uptake exclusively by inhalation.

EKAs are derived and published by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) of the German Research Foundation (DFG). EKAs describe the relationships between the concentration of substances in carcinogen categories 1 to 3 in the workplace air and the concentration of the substance or of its metabolites in biological material resulting from uptake exclusively by inhalation. Concentrations of the substance or of its metabolites in biological material that are higher than those known to correspond to the concentration of the substance in the workplace air are indicative of additional exposure by other routes than inhalative, usually percutaneous and/or peroral.

Country: DE
Responsible authority: DFG MAK-Commission
Status: not binding
Unit: miscellaneous
Source: MAK and BAT Value List (Wiley-VCH), ***http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics (open access)***

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ERB (Exposure-risk relationship)

The ERB of a carcinogenic substance describes the statistical probability of cancer after inhalative exposure to a certain concentration of the substance.

The exposure-risk relationship is equivalent to a dose-response relationship, or concentration-response relationship. From this relationship, substance-specific concentration figures can be derived for carcinogenic substances in the air at the workplace. The figures correspond to the Acceptable Risk and the Tolerable Risk. A worklife-long occupational exposure (40 years; eight hours per day) is the basis for the derivation of the exposure-risk relationship. The Committee on Hazardous Substances (AGS) discusses and determines exposure-risk relationships on the basis of occupational medicine data, and of epidemiological and toxicological data.

Country: DE
Responsible authority: AGS, BMAS
Status: TRGS 910, established with GefStoffV 2013
Unit: dimensionless
Sources: TRGS 910 and Announcement on Hazardous Substances 911 (***www.baua.de***)
FAQ-catalogue, developed by the IFA (Institute for Occupational Safety and Health) of the DGUV (German Social Accident Insurance), only available in German
http://www.dguv.de/ifa/Fachinfos/Exposition-Risiko-Beziehung-(ERB)/Fragen-aus-der-Praxis-Antworten-der-DGUV/index.jsp

ERI (Excès de Risque Individuel)

An ERI (Excess Individual Risk) corresponds to the increased likelihood of an individual developing the health effect in question (cancer) following occupational exposure to the risk under the conditions defined and explained in the exposure scenario. By adopting this approach, the CES VLEP (French OEL Expert Committee) wanted determination of an acceptable level of risk to be left to risk managers (Ministry of Employment).

Country: FR

HTP-värden (Haitallisiksi tunnetut pitoisuudet)

The HTP-värden are the Finnish OELs and are defined for long-time exposure (eight hours) and short-time exposure (15 minutes). For some substances there are also ceiling values. The notation "iho" (the Finnish for skin) in the list of OELs marks substances that are resorbed through skin.

A committee appointed by the Ministry develops a document on the health effects of a specific substance. In addition, the Committee on OELs ("HTP-jaos") recommends a certain maximum level of exposure. That committee is put together by all of the relevant stakeholder groups (the Ministry, the chemicals industry, employers' organisations, and the trade unions).

Country: FI
Responsible authority: Ministry of Social Affairs and Health
Status: some values are binding, some are recommended
Unit: e.g. ml/m³ (ppm) or mg/m³
Sources: ***www.ketsu.net/htp/indes.htm***
Sperk, C.; Scutaru, A. M.; Scutaru C.:„Emissionsbegrenzung aus Bauprodukten - Konzeptentwicklung europäischer NIK-Werte". Institut für Arbeitsmedizin der Charité Universitätsmedizin, Berlin, im Auftrag des Umweltbundesamtes (UBA). UBA Texte 17/2012,
http://www.uba.de/uba-info-medien/4281.html

IOELV (Indicative Occupational Exposure Limit Value)

IOELVs are health-based, recommended values of the European Commission for the protection of workers from chemical risks. Like the AGW or MAK Values, they are exposure limits for any substance concentrations, below which, in general, no adverse health effects are expected after short-term or daily exposure over a working life time.

With short-term exposure limits, it is possible to assess peaks of exposure during one shift. These values are usually determined as 15-minute average values. Additional notations are allocated to some of the occupational exposure limit values in the respective lists. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects.

IOELVs are derived on the basis of the current scientific data, and of the currently available measurement techniques. The Commission is assisted by the Scientific Committee for Occupational Exposure Limits to Chemical Agents (see also SCOEL) in determining these values.

Country: EU
Responsible authority: European Commission
Status: IOELVs are determined by the European Community and must be taken into account, when national exposure limits are established
Unit: e.g. ml/m³ (ppm), or mg/m³
Sources: Directive 98/24/EC, 2000/39/EC, 2006/15/EC, 2009/161/EU
Bender, H. F.: Sicherer Umgang mit Gefahrstoffen, 4. Aufl. Wiley-VCH (2011)

LOAEL (Low Observed Adverse Effect Level)

The LOAEL is the lowest dose or concentration of a substance at which any adverse effects in animal experiments can be observed.

The LOAEL should be used to define the Occupational Exposure Limit (OEL) for substances with a threshold when it is not possible to identify the NOAEL.

Country: -
Responsible authority: Different scientific studies
Status: Scientific Data
Unit: For an oral dose mg/kg bodyweight/day
Sources: ECETOC Technical Report No. 110,
Bender, H. F.: Sicherer Umgang mit Gefahrstoffen, 4. Aufl. Wiley-VCH (2011)

MAK value, Austria

The Austrian MAK value ("Maximale Arbeitsplatzkonzentration") is a health-based value. In Austria, there are long-time values (eight-hour average and peak value) and short-time values (as well as average and peak value over 15 minutes, mostly three times per shift). There is also some additional information concerning sensitising effects and other notations.

Country: AT
Responsible authority: Federal Ministry of Labour, Social Affairs and Consumer Protection
Status: binding
Unit: e.g. ml/m³ (ppm), or mg/m³
Source: Regulation on occupational exposure limit values

8. GLOSSARY

MAK value, Germany

In Germany, the MAK value is the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air at which it generally does not have known adverse health effects on the employees or cause unreasonable annoyances (e.g. by a nauseous odour) even when the person is repeatedly exposed for long periods, usually for eight hours daily but assuming on average a 40-hour workweek.

The MAK value is a health-based limit value for occupational exposures. MAK values are the main basis for AGWs. Exposure peaks during a working shift are assessed through short-term values.

Additional notations are allocated to some of the MAK values in the respective lists. These notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects.

MAKs are based on scientific criteria for health protection, and not on technical and economic possibilities for practical implementation. When using data for deriving MAKs, knowledge gained from humans has the highest priority (NOAEL-oriented). If there is no data or not enough data from humans, the derivation is based on animal experiments. The respective labels "Sa", "Sh", "Sah", "SP" or "H" are allocated to respiratory-tract-sensitising, skin-sensitising and percutaneous absorption properties.

Country: DE
Responsible authority: MAK Commission
Status: State of Science
Unit: e.g. ml/m³ (ppm), or mg/m³
Source: List of MAK and BAT values 2012

MAK value, Switzerland

In Switzerland, the MAK value is the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air at which it generally does not have known adverse health effects on the employees even when they are repeatedly exposed for long periods, usually for eight hours daily but assuming on average a 42-hour workweek.

The MAK value is a health-based limit value for occupational exposures. Exposure peaks during a working shift are assessed through short-term values. Additional notations are allocated to some of the MAK values in the respective lists. Those notations provide specific information on certain substance properties. Such properties can result in increased total workplace exposure in addition to inhalative exposure. Therefore, compliance with the occupational exposure limit value alone does not protect workers from the adverse health effects. Further protection measures are necessary. The respective labels "S" or "H" are allocated to respiratory-tract-sensitising, skin-sensitising and percutaneous absorption properties.

Country: CH
Responsible authority: Suva (Suissepro)
Status: binding
Unit: e. g. ml/m³ (ppm), or mg/m³
Source: Limit values at the workplace, suvapro working safely

NOAEL (No Observed Adverse Effect Level)

The NOAEL is the highest dose or concentration of a substance, at which no adverse effects can be observed. NOAELs can be derived from animal experiments as well as from knowledge gained from humans. NOAELs are used to define the OEL values using assessment factors.

Country: -
Responsible authority: Different scientific studies
Status: Scientific Data
Unit: For an oral dose e. g. mg/kg bodyweight/day
Sources: Following ECETOC Technical Report No. 110, ECHA Guidance R 8

OEL (Occupational Exposure Limit)

The term OEL is often used as a collective term for all limit values connected with workplace exposure. For example, TLV, AGW, MAK, and DNEL values for the employee, as well as company internal limit values can be considered to be OELs.

In accordance with the European chemicals legislation, the Occupational Exposure Limit value means, unless otherwise specified, the limit of the time-weighted average of the concentration of a chemical agent in the air within the breathing zone of a worker in relation to a specified reference period. The European Commission defines as OELs the Binding Occupational Limits (BOEL) and the Indicative Occupational Limits (IOEL).

PEL (Permissible Exposure Limit)

PELs are regulatory limits on the amount or concentration of a hazardous substance in the air in order to protect workers against adverse health effects. They may also contain a skin designation. PELs are based on an eight-hour time-weighted average (TWA) exposure. PELs are addressed in specific standards for the general industry, shipyard employment, and the construction industry.

Country: US
Responsible authority: Occupational Safety and Health Administration (OSHA)
Status: binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Source: ***http://www.osha.gov/dsg/topics/pel/index.html#recognition***

POD (Point of Departure)

POD is the starting point, from which the OEL, for example the AGW, is derived by extrapolation.

This POD value can be a NOAEL or a LOAEL, gained from dose-response data from animal experiments. Starting with the Point of Departure, extrapolation factors are used to determine data for workplace conditions for humans. The starting point for substances without any threshold, such as genotoxic carcinogenic substances, can be derived from mathematical models such as the Benchmark procedure or the T25 procedure.

Country: -
Responsible authority: Different scientific studies
Status: Scientific Data
Unit: For an oral dose e.g. mg/kg bodyweight/day
Sources: Following Linda Schenk, ECETOC Technical Report No. 110, TRGS 910

REL (Recommended Exposure Level)

RELs describe limits of exposure. In contrast to PELs, RELs are recommended and not binding values.

Country: US
Responsible authority: National Institute for Occupational Safety and Health (NIOSH), communicated through the Occupational Safety and Health Administration (OSHA)
Status: not binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Source: ***http://www.osha.gov/dsg/topics/rel/index.html#recognition***

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SCOEL (Scientific Committee on Occupational Exposure Limit Values)

SCOEL is a multinational group of scientific experts at EU level. SCOEL makes recommendations for Occupational Exposure Limit Values (OELs), which are discussed by the Advisory Committee on Safety, Hygiene, and Health Protection at Work / Directorate-General Employment. These recommendations are forwarded to the European Commission for determining Europe-wide limit values. As opposed to IOELVs, BOELVs are discussed in the European Parliament.

STEL (Short-term-OEL)

The STEL aims to protect workers from adverse effects (immediate or short-term toxic effects, such as irritation phenomena) on health due to peak exposures. The reference period is usually 15 minutes, unless otherwise indicated.

TRK (Technical guidance concentration / Technical reference concentration)

The TRK is the concentration in the air at a workplace that can be achieved with the latest technological standards. These limits were applied in Germany for carcinogenic substances until 2005, but they are no longer valid pursuant to the German Hazardous Substances Ordinance. These values are still used in Austria.

Country: AT
Responsible authority: Federal Ministry of Labour, Social Affairs and Consumer Protection
Status: binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Source: Regulation on occupational exposure limit values, Annex I

Regulation (in German): ***http://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20001418***
Anhang I (in German): ***http://ris.bka.intra.gv.at/Dokumente/Bundesnormen/NOR40135110/ BGBl._II_429_2011_Anhang_I_2011.pdf***

Threshold

A toxicological threshold level of a dose is generally understood to mean a dose or exposure concentration below which a specific effect does not occur.

TLV (Threshold Limit Value)

TLVs are guidelines or recommendations to assist in the control of workplace health hazards, e.g. caused by chemical substances, noise or radiation. The three categories of TLVs for chemical substances are TLV-TWA, TLV-STEL and TLV-C.

TLV-Time-Weighted Average (TWA): Concentration for a conventional eight-hour workday and a 40-hour workweek.

TLV-Short-Term Exposure Limit (STEL): Means a 15-minute TWA exposure that should not be exceeded at any time during a workday.

TLV-Ceiling (C): Concentration that should not be exceeded during any part of the work exposure.

TLVs for chemical substances refer to their airborne concentrations and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day over a working lifetime, without adverse health effects. These values are health-based values.

The ACGIH indicates that those who use the TLVs must consult the latest written "Documentation of the Threshold Limit Values and Biological Exposure Indices" to ensure that they understand the basis for these values and the information used in developing them. TLV® is registered.

Country: US
Responsible authority: American Conference of Governmental Industrial Hygienists (ACGIH)
Status: Guidelines or recommendations
Unit: e.g. ml/m³ (ppm), or mg/m³ for fibres: fibres/m³
Source: ***www.acgih.org/TLV/***

TWA (Time-Weighted Average)

The TWA value is the time-weighted average of the concentration of a substance in the workplace air for a defined reference period. TWA values are usually set for an eight-hour day and for a 40 hour week. Another reference period is the "15 minute period".

Source: EU SCOEL 95/320/EG, ACGIH

VLEP (Valeurs Limites d'Exposition Professionnelle), France

VLEPs are the regulatory limits in France, recommended by ANSES (French Agency for Food, Environmental and Occupational Health & Safety) through the CES (Comité d'Experts Spécialisés) and then adopted or not adopted by the Ministry of Employment. Reference periods:

VLEP-8h: Valeur Limite d'Exposition Professionnelle – 8 hours

It indicates the limit of the time-weighted concentration of a chemical in the breathing zone of a worker during an eight-hour workday (typical workday). It aims to protect workers from adverse health effects in the medium and long terms, and to protect workers regularly exposed during a lifetime of work with the chemical concerned.

VLCT-15 min: Valeur Limite Court Terme - 15 minutes

This is the limit of the 15-min weighted average concentration of a chemical agent in the breathing zone of a worker. It corresponds to an exposure measured over a period of 15 minutes regardless of the duration of peak exposure. It aims to protect workers from immediate or short-term adverse effects due to peak exposures.

VP: Valeur Plafond. This is the atmospheric concentration in the workplace, which must not be exceeded at any time of the day.

Country: FR
Responsible authority: Ministry of Employment
Status: binding
Unit: e.g. ml/m³ (ppm) or mg/m³
Source:

VLEP (Valori limite di esposizione professionale), Italy

VLEPs are set with the support of the Advisory Committee for the development and updating of occupational exposure limit values and biological limit values for chemical agents, and in agreement with the Permanent Conference for relations between the State, the regions and the autonomous provinces of Trento and Bolzano. In the VLEP endorsement process, the Ministries hear the opinion of the Ministry of Economic Development and also the opinion of the Social Partners. In the overall decision-making process to prepare the decree, the Ministries may or may not take into account the opinions of the various parties. There are two categories of regulatory VLEPs set by decree:

- Binding VLEPs.
- Recommended VLEPs.

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Reference periods are short-term average exposure limit values, which are measured over the duration of 15 minutes and long-term average exposure limit values, which are measured and calculated over the duration of eight hours.

The potential for cutaneous absorption is taken into consideration through the addition of the notation “pelle” (skin) to the VLEP.

Exposure measurements to assess compliance with VLEP must be conducted for representative exposure periods as a function of space and time.

Country: IT
Responsible authority: approved jointly between the Ministry of Labour and Social Affairs and the Ministry of Health
Status: binding
Unit: e.g. ml/m^3 (ppm) or mg/m^3
Source:

Visit the Websites of the International Sections:

Agriculture: www.issa.int/prevention-agriculture
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