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RISK ASSESSMENT FOR OCCUPATIONAL EXPOSURE TO CHEMICALS. A REVIEW OF CURRENT METHODOLOGY

(IUPAC Technical Report)

Prepared for publication by
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Abstract: This paper reviews the methodology available for risk assessment of exposure to substances in the workplace. Assessment starts with the identification and classification of hazard, which must be related to the dose–effect and dose–response information available for the hazards identified. Once the potential for exposure has been characterized, it should be quantified and compared with an established safe exposure level. The degree to which it exceeds that level is a measure of the risk. Even if the assessed risk is regarded as acceptable, there is the possibility that the situation will change with time, so it is important to monitor potentially harmful exposures. Factors relevant to effective monitoring are reviewed. Addresses of Internet sites where further information may be obtained are listed along with further reading.

CONTENTS

1. INTRODUCTION

In industry, new materials and processes are continually being introduced. Examples of new inorganic materials are carbides, nitrides, borides, and silicides in the semiconductor and optical industry. Examples of new organic materials include fibers such as para-aramid (Kevlar®, Twaron®), and carbon fibers. An example of a new process is the cutting and welding of materials with industrial lasers. Cutting with industrial lasers permits the processing of such complicated materials as aluminum sheets, glued with glass fibers and plastics. It is clear that the processing of these new materials may involve exposure to new substances in unknown amounts.

Often, substances previously thought to be inert or harmless to humans have been found to be carcinogenic (e.g., asbestos and vinyl chloride monomer) or toxic to the reproductive process (e.g., methylmercury and thalidomide). An increasing number of substances have been shown to be mutagenic or carcinogenic in animal studies.

In the face of our limited knowledge of the hazards to humans associated with potential exposure to the substances in use, most governments in the developed countries of the world have introduced legislation aimed at protecting both the working population and the general population. This has usually required the management of enterprises to eliminate, or at least to minimize, risks to workers and to the general population associated with work. Management is now required to carry out risk assessment for all industrial activities. This report reviews the approaches to risk assessment appropriate to the workplace environment in the context of currently accepted risk assessment models. Section 11 contains a glossary of the terminology used.

2. HAZARD

Hazard is the potential of any substance or situation to cause harm. This section reviews approaches to the assessment of hazard. This is the first stage of risk assessment.

2.1 Identification of hazard

The first step is the identification of the substances or processes in the workplace that might have an adverse effect on those who may be exposed to them. Any process involving potential exposure to hazardous substances may cause harm as a result of intake of the substances into the body, by inhalation through the respiratory tract, by ingestion, or through the skin. Intake by injection and swallowing may occur accidentally.

Normally, when carrying out a risk assessment of an enterprise one would divide its total work into its individual activities and assess each work activity separately. Consideration would also have to be given to activities such as maintenance, the removal of hazardous wastes, and to staff who may only occasionally be in the working area.

With established commercial substances there may be an extensive database of both their physicochemical and their toxicological properties, the latter arising from studies on animals and case reports on humans, and often from epidemiological studies. This information is used to classify substances and preparations according to possible effect and potency. Such classification is an important source of information and is found on product labels and data sheets.

Identification of hazards starts with a list of substances, processes, and circumstances that may be dangerous to the health of workers. With new or unusual substances, or processes, hazard information may not be readily available. Potential danger may have to be assessed by a variety of methods, including surveys of the scientific literature, observation, experiment, and deduction based on physicochemical properties and structure–activity relationships.

2.2 Nature of hazards to health

Health effects following exposure to chemicals can be conveniently divided into the following groups:

- acute or chronic effects
- local or systemic effects
- reversible or irreversible effects

Acute or chronic effects

An acute effect is one that occurs after a single exposure (or after a very few repeated exposures); an example is the effect on the lungs caused by short exposure to high concentrations of cadmium fumes during processing. In contrast, a chronic effect will only be observed following repeated exposure to a substance over a long period of time. Examples are hard metal disease, following exposure to carbides of tungsten and metallic cobalt dust over a period of months or years, and nickel allergy. A complicating factor might be *latency*, the time period which must elapse after exposure before an effect appears. This time period may be very long; for example, more than 15 years may pass before a bronchial cancer appears following exposure to asbestos.

Local or systemic effects

A local effect occurs at the point of contact between the substance and the body. An example might be the effect of a corrosive substance, such as strong mineral acid splashed on the skin. In systemic effects, the action of the substance takes place at a point remote from where it entered the body. An example is the damage to the kidney by cadmium compounds following their ingestion.

Reversible or irreversible effects

In reversible effects, the affected tissue recovers and returns to normal when the exposure ceases. Examples are carbon monoxide inhibition of oxygen uptake, or the inhibitory effect of low doses of lead on haem synthesis. Where the effect of exposure to a chemical is irreversible, as in cancer, recovery does not take place once exposure ceases. Both acute and chronic effects may be local or systemic and may be reversible or irreversible. For example, skin irritation caused by contact exposure is usually an acute, local, reversible effect (an exception is chloracne associated with exposure to polychloro- or polybromobiphenyls and dioxins), whereas liver cancer is chronic, systemic, and irreversible. With some toxic effects, it can be difficult to decide which of these categories apply; for example, where there is a preliminary sensitization following chronic exposure, which results in a later acute effect.

Much of the evidence for the harmful effects of substances is based on animal studies in which rats and mice have been exposed to high doses, mainly given by the oral route or by intravenous

injection. By contrast, occupational exposure to substances is much more likely to be by the respiratory tract and by secondary ingestion, with considerably lower doses than in the animal studies. There are, therefore, a number of imponderables in extrapolating data based on studies of the ingestion by rodents of high doses, which may show a dose-dependent metabolism, to the human situation, where the doses are often much lower and absorbed by a different route. This is of particular relevance to potential carcinogens, the nature of their metabolites and their proportions being entirely dependent on the magnitude of the dose. Consequently, such studies may give rise to results that are difficult to interpret.

2.3 Hazard classification of chemicals

In many countries, manufacturers, suppliers and importers of substances are responsible for classifying and labeling the substances they supply and for providing further information about them in the form of Chemical Safety Data Sheets. This is to ensure that the toxicological and physicochemical properties that make a substance dangerous have been identified and publicized to the user.

In the European Union system of classification [1], the package labeling carries hazard information comprising "indications of danger" (given below) and symbols along with "risk" numbers, to identify the particular hazards associated with the substance, and "safety" numbers, giving advice on their handling. The information describing adverse biological effects of a particular substance allows it to be allocated to one of the following categories:

- very toxic (by ingestion, inhalation, or skin contact)
- toxic (by ingestion, inhalation, or skin contact)
- harmful (by ingestion, inhalation, or skin contact)
- corrosive (to skin)
- irritant (to respiratory tract, skin, or eyes)

The category and nature of the adverse biological effect is indicated by the hazard symbol and by the risk number(s) in respect of toxicological effects including the following: acute lethal; nonlethal irreversible effects after a single exposure; severe effects after repeated or prolonged exposure; corrosive; irritant; sensitizing; carcinogenic, mutagenic, and toxic effects for reproduction, and effects dangerous to the environment.

2.4 Sources of hazard information

It is important that hazard information used in an assessment is reliable and current. For commercially available substances, the principal sources are:

- product labels
- Chemical Safety Data Sheets supplied by the manufacturer or supplier
- information from governmental and trade associations
- Internet sites (examples of Internet sites are shown in Section 13)
- specialty handbooks (see reference list)

Normally, when dealing with well-known substances, the Safety Data Sheets produced by manufacturers should permit assessment of the hazard. Unfortunately, information on these data sheets is not always reliable [2]. For recently introduced commercial substances, similar information will be available as a result of the requirement in many countries for notification of a "base set" dossier of toxicological and other data. However, it should be noted that for most substances not recently introduced, the toxicological data are inadequate and intelligent deduction is the only substitute. Also, when dealing with processes, it will sometimes be completely unclear which substances are formed during the

process. In this case, only measurements will give an insight into the hazards (see Section 5 "Measurement of Exposure").

3. DOSE–EFFECT AND DOSE–RESPONSE RELATIONSHIPS

3.1 Introduction

Effects may appear on a number of organs and systems of the human body. Once a substance has entered the body, its distribution depends on its chemical and physical properties. Bioavailability does not necessary imply toxicity. However, toxicity does not occur without bioavailability. It should be noted, however, that physiological responses such as dermal irritation or surface membrane modifications can occur without actual assimilation [3]. It should also be noted that the physicochemical properties of a substance not only influence its bioavailability but also its effect.

In general, protection from toxic effects depends upon maintaining exposures below some established "safe" level. The vast majority of occupational limits are in terms of external exposures, i.e., the amount or concentration of the substance available at the exchange boundaries (lungs, skin) during a specified time period. Internal exposure is rarely used because this can be measured only by invasive methods requiring, for example, obtaining blood samples.

3.2 Threshold and nonthreshold effects—general considerations

The adverse effects of a chemical on an organism can be divided into two types. Firstly, there are adverse effects that occur only after a threshold dose has been reached. Exposures associated with doses below the threshold are, therefore, harmless. Substances having a threshold dose for a given effect are metabolized and/or excreted before any harm is done. However, in any individual, increasing doses above the threshold level will result in increasingly severe effects (Fig. 1). Secondly, there are adverse effects which it is thought may occur at any dose; for such effects there is no harmless dose and no threshold dose. For this second group, increasing dose increases the probability of the effect occurring. Hence, such effects are referred to as stochastic effects. An example of such an effect is benz[*a*]pyrene-induced cancer.

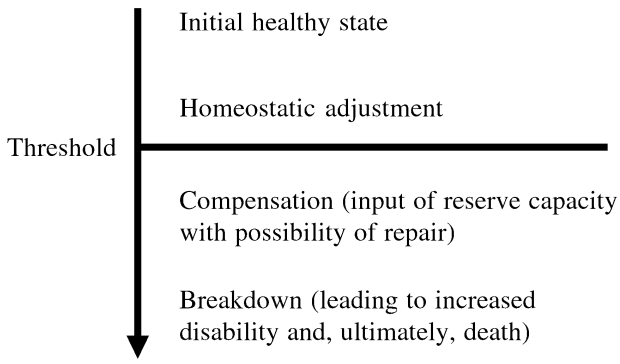


Fig. 1 Progressive changes occurring when an organism is challenged with increasing doses of a potentially toxic substance.

3.3 Threshold effects in occupational exposure

In assessing an acceptable level of a particular substance in the workplace, the procedure usually starts from an experimental database of animal or (preferably) human data (e.g., from epidemiological studies) giving a no-observed-adverse-effect level (NOAEL) or a lowest-observed-adverse-effect level (LOAEL) to derive an occupational exposure limit (OEL) at a lower exposure value which compensates for the uncertainties in the data. Comparison of this exposure limit with a measured or estimated exposure level is then used to judge whether the situation is satisfactory or whether risk management measures are required. In practice, in workplace situations a subjective safety factor in the range 10–100 of the NOAEL or LOAEL to the limit is used for most substances where the database is from animal studies, and of about 10 when the data are from human studies. It is mostly difficult to establish LOAELs in occupational epidemiology because of the many variables in exposure levels in time, exposure entries, toxicokinetics, and toxicodynamics.

An alternative to the NOAEL/LOAEL approach is the benchmark dose method [4,5], originally applied to developmental toxicity. In this procedure, the dose–response curve is fitted to the experimental data in the range of experimental observation by appropriate curve-fitting modeling. Using the upper 95% confidence limit on the estimated curve, the dose corresponding to a risk at a prespecified risk level, say x%, the lower effective dose (LED_x), with x lying between 1 and 10%, is determined. This has been referred to as the "benchmark dose" (BMD). Typically, a 10% risk level might be used. The benchmark dose would then be the lower 95% confidence limit on the effective dose associated with an excess risk of 10% (LED_{10}). This value can be used as an alternative to the NOAEL for calculation of the reference dose (RfD) or acceptable daily intake (ADI) by dividing by a safety factor >1, e.g., $RfD = LED_{10}/F$.

This safety factor is intended to account for such uncertainties as the potentially higher sensitivity of humans to the toxicant as compared with animals, variation in sensitivity among individuals, and different exposure conditions. If a linear relation is assumed between the origin and the point corresponding to LED_{10} on the upper confidence limit of the estimated curve, at a dose of LED_{10}/F, the unknown risk in the low dose region is expected to be less than 0.1/F, since the true dose–response curve is more likely to be concave than linear [5].

The benchmark dose method has some obvious advantages over the NOAEL approach. Rather than focusing on a single test dose, as with the NOAEL, it uses data from all dose levels employed. It is also less sensitive to the choice of dose levels than the NOAEL and includes some measure of variability in the confidence limits used. However, its adoption generally is still a subject of discussion, and it has not been used to date in the derivation of occupational exposure limits.

Occupational exposure limits in air

One of the earliest moves toward an assessment of quantitative criteria with which to judge the acceptability of measured exposure levels was the development of threshold limit values (TLV®) in the 1940s by the American Conference of Governmental Industrial Hygienists (ACGIH), a nongovernmental organization [6]. TLVs are based solely on health considerations and have the status of guidelines; they are not legally binding unless adopted by a regulatory agency. The TLV concept has developed over the years and is now present in the legislation of most developed countries.

In the United States, there is the National Institute for Occupational Safety and Health (NIOSH)/Occupational Safety and Health Administration (OSHA) system of permissible exposure limits (PEL) originally based on the ACGIH TLV values. OSHA is responsible for promulgating and enforcing these limits. In Germany, there are maximale arbeitsplatzkonzentrationen (MAK, maximum concentration values in the workplace) and technische richtkonzentrationen (TRK, technical exposure limits). In the Netherlands, there is a Nationale MAC-lijst (maximaal aanvaarde concentratie). The United Kingdom has a system based on the occupational exposure standard (OES) and the maximum exposure limit (MEL). The European Union is developing a system based on the occupational exposure limit (OEL), which will apply to the whole Union. It should be kept in mind that although all standards,

TLVs, acceptable levels, etc. are based on scientific studies, the decision as to whether a certain level is acceptable is not scientific and is taken by national governments or international bodies after considering the views of management, unions, and the general public.

Biological limit values

Ideally, a biological limit value, the maximum concentration of a chemical, and/or its compounds, which can be accepted as harmless in a biological sample from an exposed person, should be determined from knowledge of the relationship between dose and effect for these substances. WHO has worked out biological limit values for lead, cadmium, and mercury on this basis. Unfortunately, there are very few biological limiting values based on dose–effect relationships, because of the great amount of work required to establish them.

Table 1 Biological limit values [6,7].

Biological monitoring	Sampling time	ACGIH BEI	DFG BAT	DFG EKA
Acetone				
Acetone in urine	ES	100 mg/L	80 mg/L	
Aluminum				
Aluminum in urine	ES		200 µg/L	
Arsenic				
Inorganic arsenic metabolites in urine	ES, EW	50 µg/g creat.		130 µg/L
Benzene				
Phenyl mercapturic acid in urine	ES	25 µg/g creat.		45 µg/g creat.
Muconic acid in urine	ES			2 mg/L
Benzene in blood	DS			5 µg/L
Lead				
Lead in blood	NC	300 µg/L	700 µg/L	
Lead in blood[1]	NC		300 µg/L	
δ-aminolevulinic acid in urine	NC		15 mg/L	
Fluoride				
Fluoride in urine	PS	3 mg/g creat.	4 mg/g creat.	
Fluoride in urine	ES	10 mg/g creat.	7 mg/g creat.	
Cadmium				
Cadmium in urine	NC	5 µg/g creat.	15 µg/L	
Cadmium in blood	NC	5 µg/L	15 µg/L	
Cobalt				
Cobalt in urine	ES,EW	15 µg/L		60 µg/L
Cobalt in blood	EW	1 µg/L		5 µg/L
Chromium (VI) soluble				
Chromium in urine	IDS	10 µg/g creat.		
Chromium in urine, total	ES,EW	30 µg/g creat.		20 µg/g creat.
Carbon monoxide				
Carbon monoxide-Hb in blood	ES	3.5%	5%	

[1]women <45 years old
creat. = creatinine
DS = during shift
ES = end of shift
EW = end of workweek
IDS = increase during shift
NC = not critical
PS = preshift

In contrast, there are many statistically determined limiting values for substances in biological samples, often set by correlating established exposure limit values in the atmosphere with concentrations in, for example, urine (Table 1). In the United States, biological exposure indices (BEI®), which are prepared by the ACGIH, are often used [6]. The BEI value is the concentration in blood, urine, or exhaled air, which can be expected in a worker who has worked at a moderate rate for 8 h while exposed to the relevant maximum limit for the substance in air. It should be stressed that BEI values indicate an exposure where no account is taken of health risks [6]. In Germany, biologische arbeitsstoff toleranz werte (BAT), prepared by the Kommission zur Prufung Gesundheitsschadlicher Arbeitsstoffe, are used [7]. These values set limit values based on long-term studies of workers exposed for 8 h a day, 5 days a week, not showing harmful effects to health over the period of the study. It is more complicated to derive biological limit values for chemicals absorbed through the skin from limit values in the air. In these cases, limit values set by measuring concentrations of metabolites in biological samples from workers have been related to good working practices. In Denmark, a limit for lead in blood of 200 μg/L has been set. Limiting values for other toxic substances will follow in an EU Directive, which contains requirements for biological monitoring and sets biological limit values for some substances, mostly metals. Technical and economic consequences have an influence on the level at which national biological limit values are set. BEI, BAT, and EU biological limit values, which are applied in several countries, are therefore higher than the limit values proposed by WHO.

4. EXPOSURE AT THE WORKPLACE

4.1 Physical processes

Mechanical machine processing such as stirring, drilling, sawing. milling, but especially grating and cutting, produce particles which may include a significant fraction of dust that is respirable. This occurs, for example, in the mining and the metal construction industry. Every mechanical process where dust is formed must be considered to form a hazard. Stirring increases the surface area of a liquid, and thus a greater vaporization rate occurs. Spraying increases the surface area of a liquid more than stirring, and also, vaporization is greater. Vaporization also increases when a liquid film is formed and the surface area increases.

Processes at high temperatures lead to exposure because substances are released into the air as vapors or fumes, e.g., from boiling metals (mercury vapor is released even at room temperature). Examples of such processes are the production of metals from ores by melting, roasting, and distilling, and the production of strings of plastic from bulk by pulling them out at high temperatures.

4.2 Chemical processes

Some chemical processes associated with exposure to potentially toxic substances are described below. Because of the enormous number of substances and processes used in industry, it is impossible to give examples from all branches.

During metal refining, high temperatures are necessary for the chemical reactions changing original inorganic compounds such as oxides and sulfides into the desired metal. Various metallic compounds of varying toxicity may be formed. An example is the production of nickel from the ores pentlandite or pyrrhotite. During the process, the highly toxic gaseous compound nickel carbonyl, $Ni(CO)_4$, is formed, removing nickel from the ore and enabling it to be transferred to nickel pellets or plated onto other materials.

Interaction of electromagnetic radiation with metals is another process leading to the release of changed metal compounds. An example of such a process is welding with arc and spark, plasma welding and cutting, and laser drilling, cutting, and welding. Stainless steel welding is a process where, from

the original compounds, metallic chromium and nickel, more toxic and possibly carcinogenic chemical species containing Cr(VI) and Ni(II) are formed following reactions with oxygen in the air.

In oils used to cool turners' lathes during drilling, carcinogenic nitrosamines are formed after reacting with nitrogen in the air.

Isocyanates enter the air during the production of polyurethane polymers, elastomers, coating materials, lacquers, and glues. Isocyanates are associated with respiratory sensitization in exposed workers.

4.3 The workplace

External factors may increase the risk of exposure to potential toxicants. A number of different factors can be distinguished:

- poor apparatus and/or poorly designed and managed processes
- unsafe combination of apparatus and/or processes
- incorrect function of apparatus or processes
- maintenance problems (technical maintenance and cleaning personnel are at greater risk than other workers)
- excessive use of protective devices leading to poor occupational hygiene
- no separate room for cleaning
- no separate room for eating and drinking
- pressure of work and undue stress
- behavior of colleagues

4.4 Workers' behavior

Workers may increase their own risk, for example by the following actions:

- not complying with safety rules or specified work practices
- not wearing personal protection equipment (p.p.e.) and clothing when this is requested
- wearing inappropriate p.p.e.
- eating, drinking, and smoking at the workplace
- not washing hands
- putting hands into mouth
- not changing clothes

4.5 Exposure assessment

In principle, the exposure of a human population can be assessed by representative monitoring data and/or by model calculations based on available information on substances with analogous uses and exposure patterns or properties [8]. Where existing substances are used in processes with a high production volume, exposure data may be available. However, it is important to decide:

- what to assess
- when to assess
- the representativeness of the measurements
- the reliability of the measurements

The reliability of the data will be determined by the adequacy of the techniques used, and the strategies and quality standards used for sampling, analysis, and protocol. Good quality data (i.e., exposure data obtained by employing good occupational hygiene practice) are essential. With regard to the representativeness of the measurements, do they give a good picture of the exposures in the different

locations? This requires consideration of the type of sampling, the location, the duration, and the frequency.

In assessing exposure, representative and reliable data and the detailed information to use in modeling calculations may not be available in sufficient detail. As a general rule, in risk assessment the best and most reliable data should be given extra weighting. However, particularly where data is of an unsatisfactory quality, it is often useful to conduct an assessment using "worst case" assumptions. If this indicates a risk that is of "no concern", no further action is needed. If this is not the case, the assessment will have to be refined further.

The predictions of the exposure levels should describe a worst case situation, covering normal use patterns and allowing for consumers or workers using several products containing the same substance if this is at all possible; upper estimates of extreme use and even reasonably foreseeable misuse should be taken into account. However, prediction cannot adequately cover exposures as resulting from accidents or abuse. In making an assessment, it must be emphasized that the best and most realistic data available should always be given preference. Where the outcome of the assessment is that the exposure is of "no concern", care should be taken to be able to justify this assessment. This is particularly the case when dealing with the use of high-volume materials in the workplace. When carrying out an assessment, account should be taken of risk reduction/control measures, which are in place. Generally, the exposure assessed will be an external exposure, i.e., the concentration in the atmosphere.

Exposure-route models

Exposure-route models are a particular subgroup of exposure models intended to answer the question: What is the actual uptake by an individual of a substance in the environment (external exposure)? They can use data obtained either directly by measurement or indirectly from modeling. Absorption and bioavailability, which will affect the uptake, are taken into account at the risk estimation stage.

Models generally calculate intake by multiplying the pollutant concentration in the medium by an estimated intake rate for that medium multiplied further by the duration or time an individual is exposed to that medium.

If a pollutant is present in multiple media, or if multiple exposure routes exist, each must be modeled separately. For example, if a substance is present in water, consideration has to be given to several routes to obtain the total external exposure dose. These include direct ingestion through drinking; skin absorption from water during washing or bathing; inhalation during showering or bathing, etc.; ingestion of plants and animals exposed to the water; and skin absorption from contact with soil exposed to the water. In some cases, it may be appropriate to sum all the doses, although toxic effects often depend on the route of exposure and the resultant distribution of dose in different organs and tissues. Certain chromates, asbestos fibers, and beryllium are carcinogenic if inhaled over a long period, but not when ingested.

Physiological routes of exposure

Physiological routes of exposure, also called routes of entry, can be divided into three categories:

- inhalation exposure
- ingestion exposure
- dermal exposure

Considering the different possible physical states—gases, liquids, liquid aerosols, and solid aerosols (dusts)—a number of combinations are possible. Table 2 shows the conditions to be considered for dusts.

An important parameter of a substance is its solubility in water. An example is the water-soluble (ionic) cobalt–zinc–silicate used in pottery plate painting, which showed 30 times higher cobalt in urine levels for painters using this compound as compared to the urine levels of painters using the water-insoluble cobalt aluminate [9].

Table 2 Conditions to be considered in the analysis of absorption of chemicals from dust in the air.

1.	**Inhalation and absorption via the lungs**
	Concentrations in the air, variations over time
	Volume of contaminated air inhaled
	Amount of inhaled risk-chemical which is absorbed
	Body weight
2.	**Inhalation and absorption through the digestive system**
	Amount of risk-chemical swallowed after inhalation
	Amount of risk-chemical in the digestive system which is absorbed
	Average body weight
3.	**Oral intake and absorption via the digestive system**
	Concentration of dust and particles on exposed skin
	Amount of dust and particles on exposed skin consumed through the mouth and swallowed
	Amount of risk-chemical in the digestive system which is absorbed
	Body weight
4.	**Absorption through the skin**
	Area of exposed skin
	Concentration of dust and particles on exposed skin
	Amount of risk-chemical absorbed through the skin
	Body weight

Inhalation exposure

Gases, fumes, and vapors can be absorbed from the respiratory tract. The extent of absorption will depend on the atmospheric concentration of the substance and on its ability to cross cell barriers.

The behavior of solid particulates will depend on their particle size. Dust and fibers of aerodynamic diameter <0.1 μm behave in the same way as vapors. Particles of aerodynamic diameter >10 μm become trapped in the upper respiratory tract and may be swallowed. Particles of intermediate size <10 μm (known as PM10 dusts) may penetrate deep into the lungs and reach the alveoli. Workload and hence lung ventilation may vary, and it is characteristic for many chemicals that the amount absorbed correlates with the air intake. Small particles may stay in the alveoli for periods as long as several years, since alveolar membranes have no cilia to move the particles out of the lungs toward the pharynx.

Ingestion exposure

A part of any inhaled dust may be swallowed. This process of swallowing is called primary ingestion, and is of particular importance when the dust originates from very toxic substances. In the 1980s it became clear that the behavior of the worker could be an important parameter in intake of cadmium and nickel dust [10]. Factors such as frequency of hand–mouth contact and smoking with contaminated hands may explain up to 74% concentration variance in blood lead (an uptake measure) in cases of lead exposure, and up to 48% of the variance in urine chromium concentration (an uptake measure) in cases of chromium exposure [11,12].

Ingestion following unhygienic behavior is called secondary ingestion and may be responsible for a major share in the intake (uptake) of dust. Workload and time pressure also affect intake (uptake) [13,14]. The reason for the importance of ingestion exposure for metal dusts is these dusts show a fast fall-out rate from air. Thus, concentrations of metal dusts in air may be low, while large amounts have been deposited as a dust layer on all available surfaces. Dust layers may be touched by unprotected hands and reach the mouth by hand–mouth contact.

Dermal exposure

Table 3 summarizes what we know about uptake of various types of substance following dermal exposure. Dermal exposure is of limited importance for inorganic substances as long as the skin is undamaged. Only a relatively small number of inorganic substances can cross the skin barrier because their ionic character and the resultant water solubility prevent it from happening. Metals and other insoluble substances cannot easily cross the skin barrier either. In the case of damaged skin, however (e.g., following exposure to corrosive agents such as chromates and permanganates), uptake of many substances may occur quite easily.

Covalent inorganic compounds that are fat-soluble, such as the metallo-organics, hydrogen sulfide, and carbon disulfide can penetrate the skin easily.

Organic compounds that are fat-soluble can also penetrate the skin easily. There are numerous organic substances like this, for example, alkanes (hexane), aromatics (benzene), aromatics with functional groups (nitrotoluene, hexachlorobenzene, aniline), ketones (acetone), and many others. Experiments with *cis*-l,3-dichloropropene vapor [15] showed that the dermal uptake was 2–5% of the inhaled uptake. In the case of 2-methoxyethanol (ME) vapor, the dermal uptake is as much as 55% of the total uptake, and in the case of 2-ethoxyethanol (EE), it is 45% [16]. Dermal uptake resulting from skin contact of both hands and forearms with ME and EE for 60 min would exceed inhalation uptake relative to the 8-h European occupational exposure limit by 100 times at 16 mg/m^3 of ME and 20 times at 19 mg/m^3 of EE [16].

With liquids that are dermal hazards, the less volatile the liquid, the greater its exposure potential. Under normal conditions, a highly volatile liquid is likely to have evaporated from the skin before significant amounts have been absorbed through the skin. Exposure will, of course, be greatly reduced, or even eliminated, if the liquid is separated from the skin by a protective barrier, such as that provided by

Table 3 Uptake following dermal exposure.

Substance	Dermal exposure	
	Intact skin	Damaged skin
Inorganic insoluble (e.g., cadmium sulfide, cobalt aluminate)	No	No
Inorganic soluble (ionic) (e.g., sodium chloride, potassium permanganate)	No	Yes
Inorganic covalent (e.g., methyl bromide, carbon disulfide)	Yes	Yes
Metals (e.g., lead, mercury)	No	Some
Organic soluble (ionic) (e.g., acetic acid)	No	Yes
Organic covalent (nearly all organic compounds, e.g., alkanes, ethers, aromates)	Yes	Yes

adequate protective clothing. However, exposure may be increased if the liquid is trapped inside the protective clothing.

As a route of entry, dermal exposure appears to be of particular significance in workers using solvents (painters, cleaners of metals, printers, dry cleaners), and in agricultural workers involved in pesticide application. Drenched clothes, inadequate protective equipment, and, in agriculture, unsafe spraying methods have resulted in a number of intoxications, mainly due to skin absorption.

5. MEASUREMENT OF EXPOSURE

5.1 Introduction

In most situations, it is unlikely that continuous monitoring of a potential hazard can be carried out. It is therefore necessary to resort to sampling measurements, usually intermittent, in order to obtain a picture of the exposure in different areas and for different people. Decisions have to be made about what is going to be measured, where it is going to be measured and for how long and how often. Sampling objectives can be of two types:

- to aid the engineering control of in-plant emissions
- to assess the likelihood of risk to workers' health

Sampling for the first purpose is concentrated on the sources of contaminant emissions, and for the second in the area where personnel work.

5.2 In-plant emissions

In-plant emission control can be used both for engineering purposes, and to identify the presence of hazards. In an ideal situation, it may be assumed that the workroom is homogeneously filled with the substance of concern. In this situation, if the concentration of the substance in the workroom is constant, one sample would be enough to get an exact figure for the risk assessment.

In common practice the ideal situation is never approached. The concentration of a substance may fluctuate under the influence of a number of parameters. Some of the more important parameters are discussed below.

5.3 Input concentrations

A given process generates an input of a substance of concern. The input may be constant, but generally will be fluctuating, perhaps as a result of batch processing. Several physical changes may occur in the input mode. The input may be dependent on the nature of the process, the temperature, and fugitive emissions of material. Also, chemical changes may occur in the input mode. Such changes may result from changes in the process, in the temperature, or in availability of oxygen or of other gases. The changes may cause the appearance of new substances in the workroom. Once a substance appears in the workroom, it will be dispersed throughout the workroom. The distribution of the substance will depend on the physical state of the substance and on the workroom conditions.

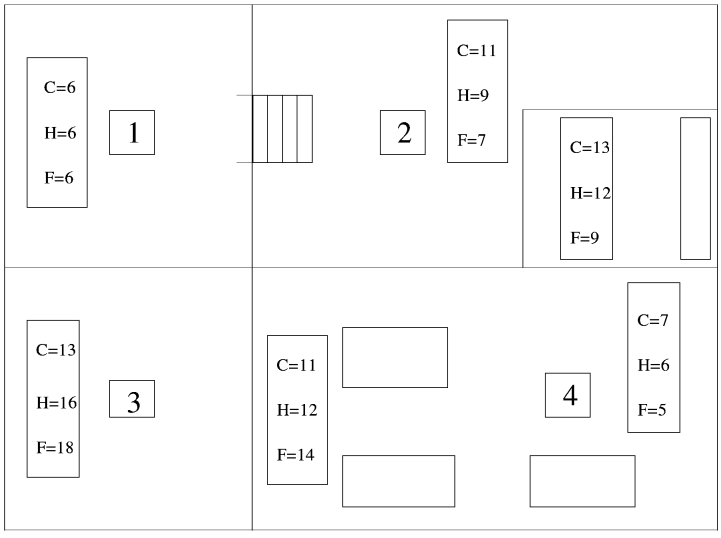
Gases

Gases at room temperature with a low relative molecular mass (M_r) will fill all the available volume in a short time. Examples are He (helium M_r 4), N_2 (nitrogen M_r 28), and CO (carbon monoxide M_r 28). Gases with a high density will tend to cover the lowest surface with a layer. Examples are $C1_2$ (chlorine M_r 71), and CO_2 (carbon dioxide M_r 76). The thickness of the layer depends on the amount of gas. Important parameters affecting mixing are the temperature and the air circulation. It must be pointed out that, on parts-per-million concentrations of a contaminant gas, the dominant effect is that of air, and thus the effect of the properties of the trace gas is negligible.

Heavy vapors

Most substances have a relative molecular mass (M_r) that is higher than that of air. This makes them "heavy vapors". However, in the workplace the transport of vapors is influenced only on a small scale by the M_r. The main transport mechanism is due to turbulence mixing of the air caused by temperature gradients. People and machinery are heat sources, and walls and windows are often colder than the workplace air. Inflow of colder air from outdoors via open doors and windows is often the dominant mixing mechanism at the workplace.

Figure 2 shows measurements of the concentrations of vapors (on an arbitrary scale) in a serigraphic printing shop made by one of the authors, Erik Olsen. These measurements illustrate the points made in the preceding paragraph. The empty boxes are machines, closets, etc. In room no. 3, lower concentrations are found at the ceiling than at the floor. The concentration at the breathing zone is in between the values at the floor and the ceiling. Room no. 3 is a storeroom without any heat sources. The same picture is found just outside the storeroom. This pattern is probably caused by the nearby printing machine, which during operation "waves" air-containing vapor from the printing table in the direction of the floor. The air in room no. 1 is homogeneously polluted. This homogeneous pollution is probably caused by the person working on a computer in room no. 1. In all other parts of the facility, the concentration is higher at the ceiling, and the concentration in the breathing zone is higher than the concentration at the floor, even though the solvents used were 1.5 to 3.5 times heavier than the workroom air.



C=ceiling; H=headlevel (breathing zone); F=floor. Concentrations in arbitrary units

Fig. 2 Variation in concentration of a pollutant in a printing shop.

Liquids

Nonpolar liquid volatile substances with a low M_r (e.g., the vapors CH_4, methane, acetylene, C_2H_2, liquids as hexane) have a high volatility at room temperature and will easily be distributed as vapor in the workroom. Nonpolar liquid volatile substances or metals with a high M_r, such as bromine, polycyclic aromatics, or elemental mercury, will not vaporize so easily. Owing to their higher mass, these substances will remain on the lowest possible surface, generally the workbench or work floor. A gradient of the substance in the air just above the surface will be formed. The thickness of the layer is dependent on the amount of substance, the volume, the temperature, and the circulation rate.

Polar liquid substances have a low volatility at room temperature (e.g., water, ethanol, formic acid, acetic acid). A number of slightly polar nonfat-soluble compounds with low M_r will vaporize easily (e.g., acetone, formaldehyde, ethyl acetate, and ether). Longer aliphatic or aromatic chains will diminish the vaporization (e.g., decanol, stearic acid, caproaldehyde, benzaldehyde, and benzophenone). Others may still vaporize enough to be detected by their smell (e.g., anisole, aniline, tetrahydrofuran, and aromatic alcohols).

Liquids with low volatility and those that are nonvolatile, such as many insecticides, are not easily distributed in the air. They will remain where they are released, with a concentration gradient around the liquid dependent on the volatility.

Figure 3 shows the relation between boiling point and vapor pressure for alkanes and aromatics. The relationships between the two groups of compounds are nearly the same. Such a simple relationship between boiling point and vapor pressure exists only for covalent compounds, where addition of methyl groups (in a homologous series) results in a proportional enhancement of the boiling point and thus of the vapor pressure. For organic compounds with functional groups (e.g., alcohols, amines, acids, metals, and ionic compounds), the situation is more complex, although for homologous series of such organic compounds again a relatively simple relationship between increasing molecular size and vapor pressure can be found.

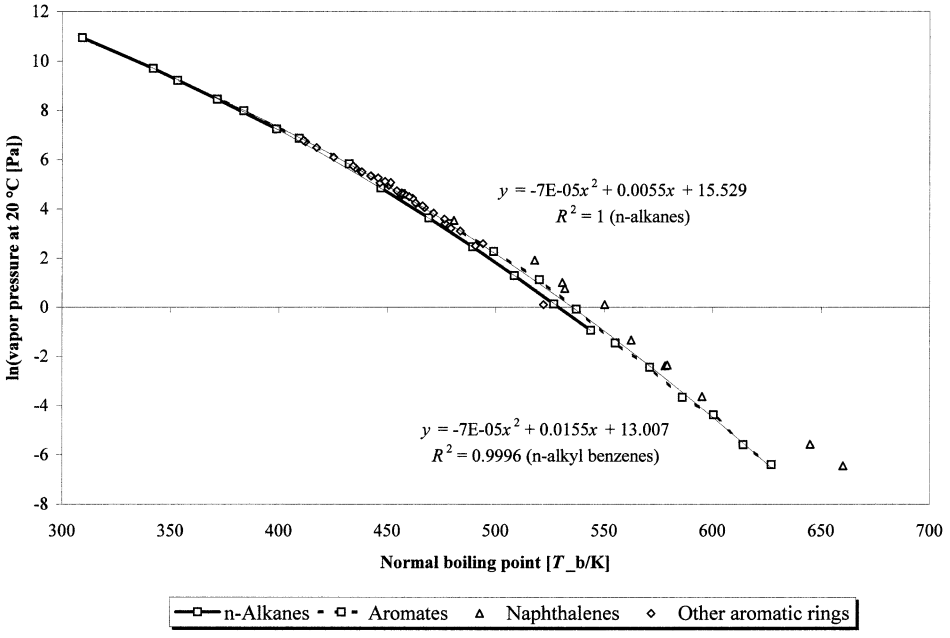


Fig. 3 Vapor pressure as a function of boiling point.

Mixtures: mutual interaction between mixture of components—The UNIFAC Method for Calculation of Activity Coefficients

It has been found that more than 95% of the liquid products used in industry are mixtures [17]. For exposure assessment of mixtures in the workplace, knowledge of the presence of a particular substance, therefore, is necessary, but is not sufficient. When substances are mixed, they interact. Possible interaction must be taken into consideration in the exposure assessment.

The activity coefficient is a factor correcting for mutual interaction between components of a mixture. The activity coefficient can be calculated using the UNIFAC method. UNIFAC stands for UNIQUAC Functional Group Activity Coefficient [18], where UNIQUAC stands for UNIversal QUasi Activity Coefficient [19].

UNIFAC considers molecules as consisting of functional groups. Mixtures are considered, not as mixtures of molecules, but as mixtures of these fragments of molecules. Thousands of molecules of interest can be modeled from a limited number of functional groups.

A mixture of ethanol, butanol, and normal hexane, for instance, is not considered as a mixture of the molecules:

CH_3–CH_2–OH
CH_3–CH_2–CH_2–OH
CH_3–CH_2–CH_2–CH_2–CH_2–CH_3

but as a mixture of the three functional groups:

–CH_3 –CH_2– –OH

In principle, the activity coefficients of all alkane-alkanol mixtures can be predicted from hexane-ethanol-butanol data, only. Table 4 shows that the interaction between molecules can reduce, as well as increase, the evaporation rates [20,21]. Toluene evaporates 3700 times faster than ideal calculation shows. The calculation does not take into consideration the mutual interaction between toluene and water. The last example was found in a printing shop where a water-based glue was introduced to improve the working environment, but the exposure was actually increased.

The calculation of these activity coefficients is not very complicated. With a computer, such calculations can be performed within seconds. The SUBTEC software package [20,21], developed for personal computers, calculates evaporation rates and vapor pressures, taking deviation from ideality into account. The calculations named "real" in Table 4 are calculations where the mutual interaction of the molecules in the mixtures is taken into consideration. It can be seen that the results of "real' calculations are closer to experimental values than those from "ideal" calculations.

Liquid aerosols

If a liquid is nebulized (e.g., in spray painting), the mist will fill the available volume dependent on the amount of substance, and the temperature. The density of the mist is also dependent on the amount.

Mists in aerosol form, solid or liquid particles dispersed in air, have quite different transport properties from air pollutants that are gases or vapors. That can easily be understood by considering that the weight of a spherical droplet of toluidine with a diameter of 4 μm, which is a typical droplet diameter for aerosols met at the workplace, is approximately 2×10^{11} times the weight of a single toluidine molecule. The transport properties of a particle also depend on its shape and size. This is all summarized in the concept of the aerodynamic diameter. A particle's aerodynamic diameter is defined as the diameter of a spherical particle, with a density of 1 g cm^{-3}, which has the same fall velocity as the particle considered. Table 5 shows the influence of droplet size on evaporation rates for aerosols.

When breathing through the nose, most particles with aerodynamic diameters above approximately 10 μm will be deposited in the upper airways, following impaction and sedimentation. Particles with aerodynamic diameters below approximately 10 μm can reach the alveoli when inspired. For example, toluidine has a liquid density of 0.998 g cm^{-3} (23 °C), i.e., very close to a density of 1 g cm^{-3}. A droplet

Table 4 Measured and predicted evaporation rates at 23 °C [20,21].

Moderately nonideal mixtures

			R_{iA} (mmol m^{-2} s^{-1})		
	x_{iA}	γ_{iA}	Exp.	Real	Ideal
Trichloroethene +	0.1	0.69	0.37	0.47	0.68
n-butyl acetate	0.9	1.00	0.70	0.78	0.78
2-Butanone +	0.1	1.23	0.93	1.10	0.90
toluene	0.9	1.00	2.20	2.30	2.30
Ethanol +	0.1	3.95	3.00	2.40	0.61
trichloroethene	0.9	1.05	6.00	6.10	5.70

Strongly nonideal mixtures

			R_{iA} (mmol m^{-2} s^{-1})		
	$x_{iA(initial)}$	γ_{iA}	Exp.	Real	Ideal
n-Butylacetate +	$6.8 \cdot 10^{-4}$	970	0.21	0.33	0.0005
water	1.0	1			
Trichloroethene +	$1.5 \cdot 10^{-4}$	4900	1.80	1.80	0.0009
water	1.0	1			
Toluene +	$8.5 \cdot 10^{-5}$	10000	1.10	0.93	0.0003
water	1.0	1			

R_{iA}: evaporation rate of substance i from the mixture A
x_{iA}: mol fraction of I
γ_{iA}: activity coefficient; Exp.: experimental values
Real: real calculations, which take into consideration mutual interactions of the components
Ideal: ideal calculations, which do not take into consideration mutual interactions between the components

of liquid toluidine, with a diameter of 4 μm, can therefore penetrate into the alveoli. It should be remembered, however, that some of the particles with small aerodynamic diameters may be expired again.

Aerosol-forming processes may contribute significantly to the concentration of vapors in the workroom. Evaporation from an aerosol is fast, because it has a large surface compared to its mass or volume. Table 5 shows some examples. It is shown that the surface area is drastically increased when a

Table 5 Evaporation surfaces of aerosols.

Diameter [μm]	Number of droplets which can be created, per cm^3 of liquid	Area of aerosol per cm^3 of liquid	Relative evaporation surface
12 408	1	4.8	1
1 241	1 000	48.8	10
124	1 000 000	483.6	100
12	1 000 000 000	4836.4	1000
4	30 000 000 000	15 003.6	3102

liquid is dispersed as an aerosol. Risk assessment of aerosol-forming processes, therefore, should take into consideration exposure to both liquid aerosol and vapors.

Vapors

Creation of vapors from liquids

The amount of vapor created from a liquid is the product of the specific evaporation rate in mg per second per m^2 multiplied by the evaporation area.

The specific evaporation rate of a substance depends on its vapor pressure and diffusion coefficient and on its interactions with other components, if present in a mixture. The specific evaporation rate is not only a property of the substance or of the mixture of substances, it depends also on "outer" parameters such as air velocity over the evaporation surface and the intensity of any air turbulence. In Table 6, the evaporation rates for some substances are listed [20]. It is of note that acetone evaporates 118 000 times faster than hexadecane and 1.4 million times faster than 1,2,3-propanetriol. Hence, to make a proper exposure assessment, exact knowledge of the physical properties of the substances used at the workplace is essential.

Table 6 Evaporation rates and vapor pressures for some pure substances at 20 °C [20].

	R_{ii} [g m^{-2} min^{-1}]	$R_{n\text{–}BuAc}$	P_{ii} [Pa]
Hydrogen cyanide	769.1	242.0	91584.215
Trichlorosilane	771.6	579.6	80819.796
Acetone	57.6	17.1	28077.613
1,1-Dichloroethane	89.1	26.5	27829.634
1,2-Dichloroethane	24.9	7.4	9581.852
n-Butyl acetate	3.178	1	1362.151
o-Toluidine	0.064	0.02	29.066
1,3-Propanediol	0.00907	0.0027	4.936
Hexadecane	0.00049	0.000147	0.153
1,2,3-Propanetriol	0.00004	0.000018	0.017

R_{ii}: evaporation rate
Laminar airflow, air velocity: 0.1 m s^{-1}
$R_{n\text{–}BuAc}$: evaporation rate relative to the evaporation rate of n-butyl acetate
P_{ii}: pure substance vapor pressure

Solids

Some solids (e.g., iodine, phenol, camphor) will sublime—vaporize directly without forming a liquid. The distribution in the workroom of vapor from these substances can be compared with the distribution of vapor from volatile liquids. Other solids may melt at room temperatures and should then be treated as liquids. Solids that do not sublimate or vaporize at ambient temperatures will remain where they are if they are large or heavy enough. If a solid consists of particles, an aerosol may be formed (e.g., in welding, cutting, or sawing). The density of the aerosol will be dependent on the amount of substance and the mechanical process by which the aerosol is formed. Table 7 [22] provides a simple basis for qualitative classification of solids in relation to their potential to release aerosolic dusts.

Table 7 Solids: how dusty [22]?

LOW Pellet-like solids that don't break up. Little dust seen during use (e.g., lead stearate pellets, waxed flakes, pills).
MEDIUM Crystalline, granular solids. When used, dust is seen, but settles out quickly. Dust is left on surfaces after use (e.g., cadmium sulphide powder, most dust from mechanical cutting of metals).
HIGH Fine, light powders. When used, dust clouds can be seen to form and remain airborne for several minutes (e.g., cement, carbon black, chalk dust, welding).

5.4 Output concentrations

A prime objective of occupational hygiene is to prevent exposure of workers to any potentially toxic substance. An effective exhaust ventilation system will lower or completely eliminate the output of a toxicant gas or vapor to the workplace. An example of the theoretical situation is given in Fig. 4. It should be emphasized that the time axis may be anything between seconds and hours, depending on the slope of the input and output parts of the figure. The distribution of a gas or vapor as a function of time is rarely stable.

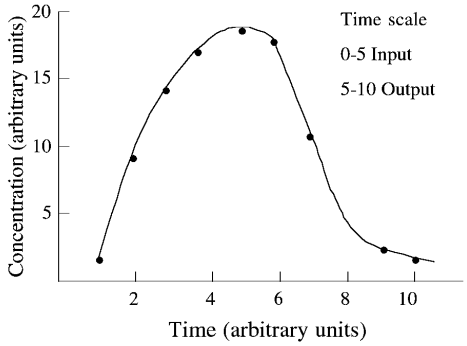


Fig. 4 Concentration of gas in a workroom as a function of time.

6. MONITORING OF EXPOSURE FOR OCCUPATIONAL HYGIENE

Monitoring of exposure is essential in order to regulate exposures and to identify any change which may threaten to increase exposures beyond acceptable levels.

6.1 Monitoring by continuous sampling

Continuous sampling can be performed by any instrument that can follow the concentration of a relevant substance on a real-time basis (e.g., an infrared absorption spectrometer). Such an instrument can

measure absorption of gases and vapors in the infrared spectrum and thus can detect carbon dioxide, alkenes (e.g., ethene), alkynes (e.g., acetylene), and aryl compounds (e.g., benzene). Methane, nitrogen, helium, and vapors and gases which do not show infrared absorption cannot be monitored.

6.2 Monitoring by discrete sampling

A simple measure of exposure might be an indicator tube, which changes color when a vapor or gas interacts with its contents. The measuring time for such tubes is only a few minutes, and thus the results are only indicative of relevant exposure (OEL limits are set for at least 15-min samples). Sampling a flow of ambient air stream and measuring its light absorbance, or collecting a sample on a filter with subsequent determination of the substance of interest, may be used to give a substantive quantitative measurement. If the time axis is very short (seconds), it is clear that discrete sampling may be hard to perform. Thus, this method can be used only if the time axis (in fact, the residence time) is long enough.

6.3 Monitoring by diffuse sampling

An adsorbing material in a suitable container is placed in the workroom for a certain time period. During this period the substance of concern is adsorbed onto the medium (carbon, silica gel, zeolite). Subsequently, the compound is desorbed and determined by gas chromatography or by another suitable method. This method gives the total amount that has been sampled. The method is valuable for measuring time-weighted average concentrations over a workshift.

6.4 Gases with a low vapor pressure, evaporating liquids, subliming and melting solids

With regard to these substances, there always exists a concentration gradient from floor to ceiling. Instead of real-time measurements, monitoring as a function of the distance from floor to ceiling is more important. Thus, in addition to continuous sampling and diffuse sampling, discrete targeted sampling methods may be needed. Air turbulence is common in workrooms and must be taken into account.

6.5 Mists

The nature of a mist is dependent on the droplet diameter, the temperature, and the ventilation rate. If the droplets are very small, and the other parameters are appropriate, the mist may remain stable (like a natural "water and air" mist, or an "oil and air" mist). Monitoring can be done in this situation by continuous or discrete methods. Only a few samples are needed in such a stable situation. A fall in temperature may cause condensation of mist droplets, and a liquid may be formed. This liquid may be volatile, and then the appropriate sampling methods must be adopted.

6.6 Aerosols, particles, and/or dusts

Aerosols generally behave in the same way as fogs. If the particle size is small enough, the aerosol concentration will remain constant in time (e.g., smoke in a cafe). Monitoring of smoke can be performed both by continuous and discrete sampling. Generally, however, the particles will be heavy, and the aerosol will disappear completely and form dust. If the dust sublimes, or vaporizes, we have situations already described above. If not, monitoring will require sampling the dust. A complicating factor is that mechanical disturbance of dusts may produce an aerosol again. Sampling of dust can only be performed by collection of dust from the surfaces where it is deposited. Recently, a geltape method for the optical measurements of the total amount of dusts on surfaces has been developed [23]. If a correlation exists between the total amount of dust and the concentration of the substance in the dust, the geltape method

may be a supplement to air measurements in a routine surveillance of the work environment. If the period over which the dust is formed is known, a time-weighted average over that period can be calculated. Otherwise, dust sampling must be only qualitative.

6.7 Environmental monitoring or ambient monitoring

Inhalation exposure

Appropriate measurement of inhalation exposure requires the use of a sampling device in the worker's personal breathing zone as he or she moves around. Such a device can be in the form of a pumping system where, during a prolonged period, workplace air is sucked through a filter (solid or liquid aerosols) or a tube filled with adsorbing material (charcoal, silica, zeolite, or polymers for collecting vapors). The amount of contaminant found on the filter, or on the adsorbing materials, can be compared with any relevant limit value after division by the volume of air passed through. Appropriate action should then be taken if the readings indicate excessive exposure. When sampling from the air breathed by a worker is performed, attention must be paid to variations in space and time (as mentioned before), as well as the performance of the worker and his or her work pattern [24]. A real situation can be seen in Fig. 5, where the exposure during one work day, including one lunch break and two coffee breaks, is given (after [25]).

Commonly, for technical reasons, pollutants in the working environment cannot be collected in a full shift, but must be sampled in a series of consecutive sampling periods. The combined result of such consecutive measurements is reported as the time-weighted average concentration (TWA) [6]. The results of those measurements can be compared with appropriate standards such as TLV or MAC values which may be for a measurement period of 15 min or for a working week. In the case of TLV or MAC values for a working week, measurements should be taken over an 8-h period each day throughout a 5-day working week. In practice, a series of consecutive sampling periods is used (cf EN 689 [26]).

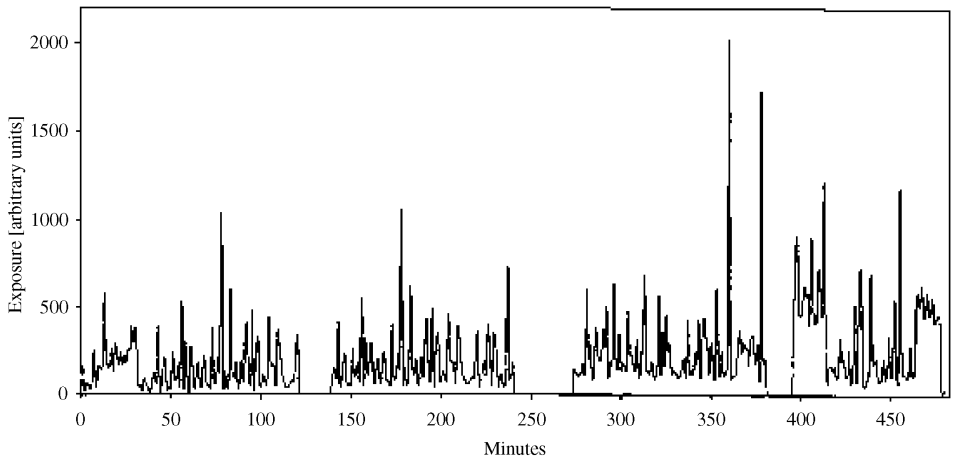


Fig. 5 Exposure during a working day, inclusive of coffee and lunch breaks.

Skin exposure

Several methods, none completely satisfactory, have been used to estimate exposure of the skin to chemicals [27]. One technique is the use of wipe samples from a known area of the skin surface, followed by their analysis for the substance of interest. However, uncertainties arise both from how quickly the substance is absorbed through the skin and also the extent of its recovery from the skin by this technique. Methods of this type have been useful for chemicals that are only slowly absorbed through the skin, such as polychlorinated biphenyls, polyaromatic hydrocarbons, and certain pesticides.

6.8 Dose (internal exposure)—biomarkers

To determine the dose of a human to a chemical substance, analysis of tissues and body fluids can be carried out [28]. In determining the dose, analysis is aimed at measuring amounts of the substance itself and/or of its metabolites. It must be kept in mind that the dose is defined as the total amount of a substance absorbed. Thus, the measurement of the substance of concern should be repeated over the period of exposure, and the measurement results should be integrated over time.

The initial changes in enzymes and other biological substances or responses affected by the substance are called early effects. The term "biomarker" is used in a very broad sense to include a whole range of biological effects reflecting an interaction between a toxicant and human biology. The term may be applied to a functional, biochemical, or physiological change, or it may be applied to a specific molecular interaction (Fig. 6). Biomarkers provide direct evidence for the exposure of individuals in a population to a particular substance, for example, lead in bone, cadmium in the kidney (both *in vivo* determinations), mercury in urine, or trichloroethylene in exhaled air. Quantitative measurements may permit the determination of a dose–effect relationship, particularly if the toxicokinetics of the substance are well established. Contrary to sampling for clinical purposes, in occupational health only limited numbers of samples are available. Mostly, samples of blood, urine, and exhaled air are used. There is a preference for noninvasive methods. Where available, such measurements may be used for screening and, if repeated at timed intervals, for monitoring either an individual or a group.

Figure 6 indicates what methods should be used for monitoring. For some substances, especially those in the form of dusts, where worker behavior strongly influences the intake, biomarkers are the

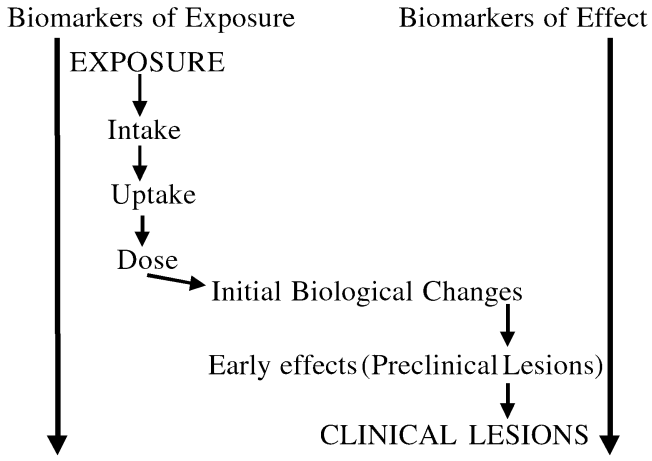


Fig. 6 The relationship betweeen biomarkers of exposure and biomarkers of effect.

methods of choice. This is also true for solvents where skin exposure occurs. An advantage of biomarkers of exposure is that they are an integrative measure, that is, they provide information about exposure through all routes including those of nonoccupational exposure. An example where this is important is the combination of occupational exposure to lead with exposure to lead through hobbies (such as in soldering, shooting, glazing with glazes containing lead) and environmental exposure to leaded gasoline. Another example is occupational exposure to solvents combined with exposure at home during painting or hobbies involving paint and glue. Biological data must be collected to take account of differences in lifestyles, including gender, age, height and weight, smoking, alcohol, intake of medicine, food consumption, and personal habits and characteristics.

Biomarkers of exposure or effect may be used to evaluate compliance with recommended methods for minimizing exposures or to indicate the need for remedial measures (e.g., the reduction of lead exposure). Biomarkers can conveniently be classified into three groups:

- biomarkers of exposure (biological monitoring)
- biomarkers of effect (biological effect monitoring)
- biomarkers of susceptibility

Biomarkers of exposure (biological monitoring)

Measurements of body burden rather than of exposure need to be established, and these should be related to measures of effect. Measurements of body burden will need biological monitoring [3].

To assess body burden, the amounts of exogenous substances or their metabolites and/or derivatives in cells, tissues, body fluids, or excreta are measured. Alternatively, the biomarker of exposure may take the form of cytogenetic change or reversible physiological change in exposed individuals. It must be understood that, generally, biomarkers of exposure give an indication of the substance circulating in the body and/or the amount excreted. Thus, we have measures of intake (e.g., cadmium in faeces) or uptake (e.g., lead in blood). If lead effects on haem synthesis appear, lead in blood may be used in addition as a dose measure (if integrated in time) for this particular effect. In the case of cadmium in blood, there is no effect on the blood, and thus cadmium in blood has to be used exclusively as an uptake measure. An early effect of cadmium is an effect on the kidney, the leakage of proteins in urine. A good dose measure to relate to effect in this case is the concentration of cadmium in urine (integrated in time), and this measure also gives an indication of the body burden.

Lifestyle (smoking, drinking and eating habits, exercise and leisure pursuits, etc.) can influence the effective dose of a chemical. Alcohol increases the absorption of certain chemicals and interacts with cobalt in the production of harmful effects. Many organic substances, including DDT and PCB, and drugs, including prescribed medicines, change the body's ability to metabolize toxic chemicals.

Assessment of data

When the properties of biological samples are measured in order to assess risk, it is important that there is adequate documentation of the sampling techniques applied and the associated uncertainty.

Data for substances that disappear rapidly from the blood are only useful in risk assessment if there is a standard time at which samples are taken. For substances with a short half-life, the sample should be taken no later than 30 min after work has stopped at the end of a work period, and the sampling time should be documented. Data for chemicals in urine will usually be acceptable for risk assessment if they reflect both current and long-term exposures. However, a standard time for sampling is important if the half-life of the toxicant in the body is less than 20 h. Furthermore, several samples (2–5) taken over a longer period than 20 h should be analyzed. If the half-life is relatively short, measurements where the time of sampling has not been recorded are not acceptable. Other factors that contribute to inadequate data are contamination of samples from the surroundings or from the sample container, evaporation, and chemical changes and bacterial growth in urine samples standing at room temperature. Contamination is the worst source of errors when analyzing many chemicals, especially metals such as nickel, chromium, and cadmium. Contamination can come from the air, the skin and sweat,

sample containers, and anticoagulants (for blood samples). The risk of contamination from skin, clothes, and hair, as well as from the air at the workplace, is particularly great when collecting urine samples. Precipitation and adsorption are big problems when collecting and storing urine samples. Certain chemicals, for example, aluminum and volatile organic compounds, are adsorbed on glass and plastic. It is important to check that the correct sample containers recommended for any given analysis are used.

Sample materials

The most common sample materials are blood (whole blood, serum, or plasma) urine, and exhaled air. Saliva, sweat, hair, and nails may also be used in biological monitoring. In workplace surveys, urine samples are frequently used as urine is easy to collect in large amounts. Variations in liquid intake and liquid loss, for example, in a warm working environment where a lot of liquid is lost through sweat, result in large variations in concentrations of substances in urine. This variation is often corrected using the creatinine concentration of the urine or by measuring the urinary 24-h volume output.

Multiple exposure

There are several examples where the toxicity of a metal is influenced by the presence of a second substance. For example, with carcinogens, there are at least three stages in the development of a cancer—initiation, promotion, and progression. Toxic substances can act at any of these stages. Clearly, simultaneous exposure to agents that function as initiators, promoters, and progressors, will increase the risk of cancer compared with the risk when exposed to just one agent. There are many natural and synthetic initiators, promoters, and progressors in the "external environment", food, the atmosphere, and water. However, it is very difficult to classify a cancer-inducing chemical as exclusively an initiator, promoter, or progressor. From a legislative point of view, the extent to which a certain dose of agent induces cancer in humans and animals is the matter of concern. With regard to setting limit values within the working environment, it is generally assumed, in the absence of better knowledge, that the impact of the various agents in a simultaneous mixed exposure is additive. However, in particular cases, this may not be so, and we must always be alert for this possibility.

Biomarkers of effect (biological effect monitoring)

Biomarkers of effect are measurable biochemical, physiological, or other alterations within an organism that can be recognized as associated with an established or potential health impairment or disease. Biomarkers of effect are often not specific for a certain substance. They may be used for so-called "umbrella" measurements. If many compounds are used in a factory, some biomarkers of effect can be applied to find out if a risk exists by looking for effects that may be a result of the mixed exposure. If one or more markers is positive, additional biomarkers of exposure or environmental monitoring can be used to determine the substance responsible for the effect.

Examples of biomarkers of effect:

- The inhibition of certain enzymes of the haem synthesis pathway is caused by lead (or by dioxins), resulting in elevated concentrations of the precursors protoporphyrin and δ-aminolaevulinic acid dehydratase in blood and δ-aminolaevulinic acid and coproporphyrin in urine.
- The leakage into urine of certain proteins, such as β_2-microglobulin, δ-microglobulin, retinol-binding protein, and albumin, is caused by a number of metals and solvents; in addition, there is inhibition of the activity of certain enzymes in the urine (e.g., *N*-acetyl-D-glycosaminidase).
- The occurrence of negative changes in higher cognitive function (e.g., learning and memory) may occur in workers exposed to metals or solvents.
- The inhibition of the enzyme acetylcholinesterase occurs following exposure to a number of organophosphate and carbamate insecticides (e.g., parathion).
- An increase in haemoglobin adducts follows exposure to aromatic amines, ethylene oxide, propylene oxide, butadiene, and alkylating or arylating agents of all kinds.

Effect parameters may show a short half-life, and therefore, correct sampling methodology is crucial to the production of useful data. The methodology is not the same for all parameters and must be appropriate to the parameters to be measured. Moreover, time lags often appear between exposure and effect or between the monitored parameters and effect. This must be known for an adequate sampling strategy. Multisampling within a working week may be necessary.

Biomarkers of susceptibility

Biomarkers of susceptibility are parameters that may indicate an increase or decrease in the risk of an individual developing an adverse effect following exposure to a toxicant. Often, susceptibility results from differing rates of enzyme activity controlling activation or detoxification of toxicants. Often there is a genetic component to susceptibility. The following are some examples of biomarkers of susceptibility:

- People with glucose-6-phosphate dehydrogenase deficiency have more fragile red cells than those with average human levels. They are thus more likely than the average person to develop anemia upon exposure to certain industrial chemicals such as aromatic amines. Low glucose-6-phosphate dehydrogenase activity in blood is therefore a biomarker of susceptibility to these substances.
- People with decreased concentrations of α-1-antitrypsin are more at risk than others of developing emphysema. This protease inhibitor protects the connective tissue of the lung from damage by the proteases that increase in activity when the lung becomes inflamed after exposure to toxicants such as dusts or cigarette smoke. Thus, low α-1-antitrypsin in blood is a biomarker of susceptibility to substances that may damage the lungs.
- About half the population acetylates aromatic amines rather slowly. Such slow acetylators are at greater risk of developing aromatic amine-induced bladder cancer, and low acetylase enzyme activity is a biomarker for this susceptibility.
- There is a wide variation in the rate at which different people can detoxify para-oxon, a more toxic compound produced in the body from the insecticide parathion. Monitoring the corresponding enzyme activity provides a measurement that may be used as a biomarker of susceptibility.

7. RISK ASSESSMENT—GENERAL PRINCIPLES

In risk assessment for human health, the normal procedure is to compare the total exposure to which a population is exposed or likely to be exposed with the exposure at which no toxic effects are expected to occur. This is usually done by comparing the calculated exposure with a NOAEL, adjusted by appropriate "uncertainty", "modifying" and/or "safety" factors to obtain a conservative assessment of a likely "safe dose". Where it has not been possible to obtain a NOAEL, a LOAEL may be substituted. The N(L)OAEL values are derived from results obtained from testing with animals or from available human data, usually expressed as mg/kg/day. Where a N(L)OAEL is not available, a qualitative evaluation is made of the likelihood of an adverse effect occurring. N(L)OAEL values are not usually available for substances not considered to have a threshold for adverse effects. These include genotoxic substances and substances which are noncorrosive skin or eye irritants and/or skin or lung sensitizers. For assessment of human exposure in the workplace, factors such as pulmonary ventilation rate and absorption fraction in the case of inhalation exposure are needed. For other routes of entry, comparable parameters are needed for assessment of exposure.

For assessments of both exposure and of effects, data on the physicochemical properties (e.g., vapor pressure, pKa, and lipophilicity) and chemical reactivity may be required. Knowledge of the physicochemical properties is needed to estimate potential human exposure, to assess the design of toxicity tests from which data have been obtained, and for analysis of the likely extent of absorption of a substance by different routes of exposure. The chemical reactivity may be important in estimating human exposure to the substance and will affect its toxicokinetics and metabolism.

Prediction of the effects of the exposure must be carried out:

- for each exposed human population (e.g., workers, general public)
- for each effect

The risk assessment will lead to one or more of the following results for each population exposed and for each effect:

- there is a need for more information or testing
- there is sufficient information available, and the present risk reduction measures are satisfactory
- there is a need for action to introduce further risk reduction measures, followed by re-analysis

7.1 Analytical quality in relation to risk assessment

Risk assessment may be followed by decisions with wide-ranging and significant consequences for workers' health and for the engineering of industrial processes. It is therefore essential that the underlying analytical data are trustworthy. Thus, there are fundamental criteria to be applied to determine the acceptability of the analytical methods and of the results obtained. Firstly, the analytical method must be described in sufficient detail to allow others to repeat determinations. Secondly, the performance of the method must be documented (i.e., the method should be validated in order to document analytical characteristics). Thirdly, a value from a determination should be traceable, and the uncertainty known. The International Standard Organization (ISO) defines traceability as "the property of a result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of components all having stated uncertainties". However, in many fields such unbroken chains do not exist.

Uncertainty may be expressed as a standard deviation, or as the half-width of a confidence interval or as a range. Uncertainty is basically a measure of the "goodness" of the determination result [29].

Determinations will always be subject to a degree of uncertainty which must be assessed. Measurement uncertainty of biomonitoring results is partly due to natural variation in the measurement process and partly due to interfering substances which occur naturally in high concentrations in the sample (e.g., salt and proteins in a blood sample).

Data should be used only from laboratories that can document continuous use of quality control results and approved reference material as well as traceability and uncertainties in measurements. Documentation of the analytical quality can be obtained through accredited laboratories, which are subject to external quality tests and interlaboratory comparisons with reference material.

7.2 Semiquantitative characterization of risk from chemicals

Where a process is in operation and adequate measures of both external and, where possible, internal exposure have been made, it is possible for a risk assessment to be made to assess whether the measures taken to control the risk are adequate. In practice, in many circumstances, an assessment has to be made prior to the setting up of a process, where there is a lack of hard reliable information. This could particularly apply in research and/or development. In this situation some form of modeling has to be applied based on consideration of the hazards associated with the substances involved and estimates of likely exposures. One relatively simple procedure has been formulated [22,30,31] as being suitable for the assessment and control of chemical risks in small- and medium-size enterprises, and also appropriate for many assessments in research and development. Sections from this guidance are:

- Getting started
- What is a health hazard?
- How dusty or volatile?
- How much is being used?
- Find the control approach and general advice

- Find the task—specific control guidance sheet(s)
- Implement and review

In this guidance, both risk assessment and risk management are described at a basic level. This guidance is not suited for lead and asbestos, for which in the United Kingdom other procedures must be followed. Also excluded are substances formed in industrial processes and external factors influencing the risk and behavior of workers. A particularly useful part of the scheme is the table on assessment of dustiness (Table 7).

Risk assessment can be used to guide health surveillance by occupational physicians [32]. Biological monitoring and fitness for work may be used in health surveillance for primary prevention. For secondary prevention, biological effect monitoring and routine surveillance for adverse effects due to occupational risks may be used.

8. OCCUPATIONAL DISEASES

When risk management has failed, occupational diseases may appear. A common division of occupational diseases is based on the cause of the disease:

- chemicals
- physical processes, such as radiation, noise, heat, and pressure
- mechanical stress, such as heavy load and dynamic burden
- psychological burdens, such as stress

As there are about 120 000 chemicals with a Chemical Abstracts Service (CAS) Registry Number used in industry, one may expect that occupational diseases are described for a fraction of these chemicals only. A possible way to simplify prediction of chemically induced diseases is to base it on classes of substance (e.g., polyaromatic hydrocarbons or solvents), which produce characteristic effects such as, for these examples, cancer and neurological disturbances respectively. A second possibility is to look at homologous series (e.g., formic acid is corrosive to eyes, lungs, and skin). For the related homologous series, acetic acid, propionic acid to palmitic acid, it is observed that corrosive effects start to disappear with propionic acid, owing to the domination of the long alkyl chain over the acid functional group. A third possibility is to look at the properties of functional groups such as alcohols, organic acids, and esters.

A quite different approach is to look first at the disease (e.g., occupational asthma, cancer, effects on the reproduction system, and dermatology). There are a number of chemicals that may cause these pathological conditions, and these may be grouped according to the symptoms which they produce [33].

Once a disease is diagnosed, its cause has to be established from the case history of the patient, including workplace description, and, if possible, biological monitoring or environmental monitoring data. After establishment of a possible occupational cause, an assessment has to be made to find out if the exposure levels were high enough to cause the disease. Moreover, a minimum exposure time must exist. Between exposure and disease, there will be a time lag with a maximum latency time (the maximum time that the disease can take to appear). The time lag and maximum latent period criteria must be satisfied. Subsequently, a differential diagnosis must be performed to exclude nonoccupational causes.

9. CONCLUSIONS

The importance of risk assessment can hardly be overestimated. In every situation dealing with storage, transport, or handling of chemicals, risk assessment is necessary to protect the environment, the general population, and the workers.

Nearly all countries have at least some regulations on safe handling of flammable or poisonous chemicals. Generally, these regulations depend on the production by chemical manufacturers or suppli-

ers of informative labels and material safety data sheets or chemical safety cards. In addition, the International Labor Organization and the World Health Organization along with the European Community have produced International Chemical Safety Cards since 1993 [34]. An example of the current state of the development of safety regulations is the Risk Inventory and Evaluation (RIE) Directive of the European Community (Framework Directive 89/391) for all workplaces (including offices) [35]. Under this directive, on the basis of the available written information (chemical safety cards, quantity of chemicals, hazardous situation, and other relevant information), a hazard identification must take place to be followed by risk assessment. Finally, control measures (risk management) must be taken, to reduce the risk to an acceptable level. Control measures must be followed by regular evaluation (auditing) to ensure their effectiveness. In principle, this approach should be effective.

10. ACKNOWLEDGMENTS

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11. GLOSSARY OF TERMS USED IN THIS REVIEW

Acceptable daily intake (ADI)
Estimate of the amount of a substance in food or drinking water, expressed on a body mass basis (usually mg/kg body weight), which can be ingested daily over a lifetime by humans without appreciable health risk. For calculation of the daily intake per person, a standard body mass of 60 kg is used. ADI is normally used for food additives (tolerable daily intake (TDI) is used for contaminants) [36].

Adverse effect
Change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences [37].

Benchmark dose (BMD) and lower effective dose (LED)
The statistical lower bound on a dose corresponding to a specified level of risk [38].

Bioavailability
Extent to which a substance to which the body is exposed (by ingestion, inhalation, injection, or skin contact) reaches the systemic circulation and the rate at which this occurs [39].

Biological effect monitoring
Continuous or repeated measurement of early biological effects of exposure to a substance to evaluate ambient exposure and health risk by comparison with appropriate reference values based on knowledge of the probable relationship between ambient exposure and biological effects [40].

Biological exposure index (BEI)
Reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene. BEIs represent the levels of determinants that are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the TLV [6].

Biological monitoring
Sometimes also called "biomonitoring". Continuous or repeated measurement of potentially toxic substances or their metabolites in tissues, secreta, excreta, expired air, or any combination of these to evaluate occupational or environmental exposure and health risk by comparison with appropriate reference

values based on knowledge of the probable relationship between ambient exposure and resultant health effects [41].

Biological tolerance values for working materials (biologische arbeitsstoff toleranz werte) (BAT)
BAT is defined as the maximum permissible quantity of a chemical compound or its metabolites, or any deviation from the norm of biological parameters induced by those substances in exposed humans [42].

Biomarker
A biomarker can be defined as a parameter that can be used to identify a toxic effect in an individual organism and can be used in extrapolation between species, or as an indicator signalling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility [39]. The term "biomarker" is generally used in scientific publications. In occupational hygiene and health, "biological monitoring" and "biological effect monitoring" are used with the meaning "monitoring biomarkers".

Body burden
Total amount of substance of a chemical present in an organism at a given time [39].

Dose
Total amount of a substance administered to, taken, or absorbed by an organism [39]. Sometimes also called "effective dose".

Dose–response and dose–effect relationships
The dose–response curve can be defined as the graph of the relation between dose and the proportion of individuals responding with an all-or-none effect, and is essentially the graph of the probability of an occurrence (or the proportion of a population exhibiting an effect) against dose [39]. Typical examples of such all-or-none effects are mortality or the incidence of cancer.

The dose–effect curve is the graph of the relation between dose and the magnitude of the biological change produced measured in appropriate units [39]. It applies to measurable changes giving a graded response to increasing doses of a drug or xenobiotic. It represents the effect on an individual animal or person, when biological variation is taken into account. An example is the increased effect of lead on the haem synthesis, e.g., on activity of the enzyme 6-amino laevulinic acid dehydratase in blood serum or coproporphyrin levels in urine.

Environmental (or ambient) monitoring
Continuous or repeated measurement of agents in the (working) environment to evaluate environmental exposure and possible damage by comparison with appropriate reference values based on knowledge of the probable relationship between ambient exposure and resultant health effects [39].

Exposure
In this context it is defined as: the concentration, amount, or intensity of a particular physical or chemical agent or environmental agent that reaches the target population, organism, organ, tissue, or cell, usually expressed in numerical terms of substance concentration, duration, and frequency (for chemical agents and micro-organisms) or intensity (for physical agents such as radiation). The term can also be applied to the process by which a substance becomes available for absorption by the target population, organism, organ, tissue, or cell by any route [39].

Half-life (half-time, $t_{1/2}$)
Time in which the concentration of a substance will be reduced by half, assuming a first-order elimination process [39].

Hazard
Set of inherent properties of a substance, mixture of substances or a process involving substances that, under production, usage, or disposal conditions, make it capable of causing adverse effects to organ-

isms or the environment, depending on the degree of exposure; in other words, it is a source of danger [39].

Health surveillance
Generic term used for the procedure for effects of work on the health of employees [43].

Intake
Amount of a substance that is taken into the body regardless of whether or not it is absorbed; the total daily intake is the sum of the daily intake by an individual from food and drinking water, and inhaled air [39].

LOAEL
Lowest-observed-adverse-effect level. Lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure [39].

Maximum latent period
The length of time after which no causal relationship can reasonably be established. This length of time is the period from the last exposure to the point of time at which an exposed person has demonstrated the initial signs or symptoms [44].

NOAEL
No-observed-adverse-effect level. Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions [39].

Reference dose (RfD)
Term used for an estimate (with uncertainty spanning perhaps an order of magnitude) of daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime [45].

Risk
Risk expresses the likelihood that the harm from a particular hazard is realized and is a function of hazard and exposure. More formally, it can be defined as: the possibility that a harmful event (death, injury, or loss) arising from exposure to a chemical or physical agent may occur under specific conditions. Alternatively, the expected frequency of occurrence of a harmful event (death, injury, or loss) arising from exposure to a chemical or physical agent may occur under specific conditions [39].

Risk assessment
The identification and quantification of the risk resulting from a specific use or occurrence of a chemical or physical agent, taking into account possible harmful effects on the individual people or society from using the chemical or physical agent in the amount and manner proposed and all the possible routes of exposure. Quantification ideally requires the establishment of dose–effect and dose–response relationships and most likely targets individuals and populations [39].

Risk estimation
Assessment with or without mathematical modeling, of the probability and nature of effects of exposure to a substance based on quantification of dose–effect and dose–response relationships for that substance and the population(s) and environmental components likely to be exposed and on assessment of the levels of potential exposure of people, organisms, and environment at risk [39].

Stochastic effect
Consequence for which the probability of occurrence depends on the absorbed dose; hereditary effects and cancer induced by radiation are considered to be stochastic effects. The term "stochastic" indicates

that the occurrence of effects so named would be random. This means that, even for an individual, there is no threshold of dose below which there is absolutely no probability of an effect occurring, and the chance of experiencing the effect increases with increasing dose [46].

Threshold limit value (TLV)

The TLV is defined as the concentration in air to which it is believed that most workers can be exposed daily without an adverse effect (i.e., effectively, the threshold between safe and dangerous concentrations). The values were established (and are revised annually) by the ACGIH and are time-weighted concentrations (TWA) for a 7- or 8-h workday and a 40-h workweek, and thus are related to chronic effects. A short-term exposure limit (STEL) is defined as a 15-min TWA exposure, which should not be exceeded at any time during a workday even if the 8-h TWA is within the TLV-TWA [6].

Uptake

Entry of a substance into the body, an organ, a tissue, a cell, or the body fluids by passage through a membrane or by other means [39]. Sometimes, the uptake is also called absorbed dose or internal exposure.

12. ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Government Industrial Hygienists
ADI	acceptable daily intake
BAT	biologische arbeitsstoff toleranz werte
BEI	biological exposure index
BMD	benchmark dose
CAS	Chemical Abstracts Service
CEN	European Committee for Standardization, Brussels
DDT	dichlorodiphenyltrichloroethane
EE	ethoxyethanol
ICME	International Council on Metals in the Environment
LOAEL	lowest-observed-adverse-effect level
LED	lower effective dose
MAC	maximaal aanvaarde concentratie
MAK	maximale arbeitsplatzkonzentrationen
ME	methoxyethanol
MEL	maximum exposure limit
NOAEL	no-observed-adverse-effect level
OEL	occupational exposure limit
OES	occupational exposure standard
OSHA	Occupational Safety and Health Agency
PCBs	polychlorinated biphenyls
PEL	permissible exposure level
PM10	particles of aerodynamic diameter less than 10 μm
RfD	reference dose
RIE	risk inventory and evaluation
SUBTEC	substitution technology
TLV	threshold limit value
TRK	technische richtkonzentrationen
TWA	time-weighted average
UNIFAC	UNIQUAC functional group activity coefficient
UNIQUAC	universal quasi activity coefficient

13. INTERNET SITES RELATED TO OCCUPATIONAL HYGIENE AND HEALTH

International organizations

Environmental Chemicals Data and Information Network (ECDIN, European Union)
Web site: http://ecdin.etomep.net/

The European Agency for Safety and Health at Work
Web site: http://europe.osha.eu.int/

International Program on Chemical Safety (IPCS), a program from WHO, ILO, and UNEP
Web site: http://www.who.ch/programmes/pcs/index

International Chemical Safety Cards
Web site: http://www.cdc.gov/niosh/ipcs/icstart.html

International Labor Organization (ILO)
Web site: http://turva.me.tut.fi/cis/home.html

United Nations Environmental Program (UNEP)
Web site: http://irptc.unep.ch

World Health Organization (WHO)
Web site: http://www.who.int/home-page/

National organizations

Agency for Toxic Substances and Disease Registry (ATSDR)
Country: USA
Web site: http://www.atsdr.cdc.gov/

Cancer Information Service, National Cancer Institute
Country: USA
Web site: http://cis.nci.nih.gov

Cancer Research Campaign
Country: UK
Web site: http://www.crc.org.uk

Health and Executive
Country: UK
Web site: http://www.open.gov.uk/hse/

National Institute of Environmental Health Sciences (NIEHS)
Country: USA
Web site: http://www.niehs.nih.gov/

Occupational Safety and Health Administration (OSHA), U.S. Department of Labor
Country: USA
Web site: http://www.osha.gov

Nongovernmental organizations

American Conference of Governmental Industrial Hygienists, Inc. Some free sites of the founders of the ACGIH threshold limit values (TLVs). The information about the TLVs is not free of charge.
Country: USA
Web site: http://www.acgih.org

British Occupational Hygiene Society
Country: UK
Web site: http://www.bohs.org

Chemical Abstracts Service (CAS)
Web site: http://info.cas.org

Universities and institutes

Canadian Centre for Occupational Health and Safety
Country: Canada
Web site: http://www.ccohs.com/

Cornell University, Material Safety Data Sheets
Country: USA
Web site: http://msds.pdc.cornell.edu/msdssrch.asp

EdinTox. Introduction to Applied Toxicology (Self Study Course)
Country: UK
Web site: http://www.aqius.com/hew/resource/toxicol.htm

Finnish Institute of Occupational Health
Country: Finland
Web site: http://www.occuphealth.fi/e/

Institute of Occupational Safety and Health (IOSH)
Country: UK
Web site: http://www.iosh.co.uk/home.html

International Agency for Research on Cancer (IARC)
Country: France
Web site: http://www.iarc.fr

IARC Monographs
Web site: http://193.51.164.11/default.html

Karolinska Institute Library, Occupational Diseases
Country: Sweden
Web site: http://www.kib.ki.se/index_en.html

University of Lund, Occupational and Environmental Medicine
Country: Sweden
Web site: http://www.ymed.lu.se

McGill University, Occupational Health Services
Country: Canada
Web site: http://www.mcgill.ca/occh/

National Institute for Occupational Safety and Health (NIOSH)
Country: USA
Web site: http://www.cdc.gov/niosh/homepage.html

NIOSH Pocket Guide to Chemical Hazards
Web site: http://www.cdc.gov/niosh/npg/pgdstart.html

Swedish Institute for Working Life
Country: Sweden
Web site: http://www.niwl.se

Where to find MSDS on the Internet
Country: USA
Web site: http://www.ilpi.com/msds/index.html

University of Occupational and Environmental Health
Country: Japan
Web site: http://www.uoeh-u.ac.jp

University of Vermont (host). Vermont SIRI Material Safety Data Sheet Collection
Country: USA
Web site: http://hazard.com/msds2/

University of Uppsala, Department of Occupational and Environmental Medicine
Country: Sweden
Web site: http://www.occmed.uu.se/english/index.html

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