Expert appraisal on recommending occupational exposure limits for chemical agents

Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs)

OEL permanent mission
Request n°2009-SA-0339

Collective expert appraisal
REPORT

Expert Committee 'Expert appraisal for recommending occupational exposure limits for chemical agents in the workplace' (OEL Committee)

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[1] see Annex 1

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Presentation of participants

Foreword: Outside experts, Expert Committee and WG members, or designated rapporteurs are all appointed in their personal capacity, *intuitu personae*, and do not represent their parent organisation.

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CONTENT

Abbreviations

ACGIH: American Conference of Governmental Industrial Hygienists
AF: Adjustment factor
AIHA: American Industrial Hygiene Association
ATSDR: Agency for Toxic Substances and Disease Registry
BLV: Biological Limit Value
BMD: Benchmark dose
BME: Biomarker of exposure
BRV: Biological Reference Value
BW: body weight
CES: Expert Committee
CLP: refers to Regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixtures (European Parliament, 2008)
COCT: Steering Committee on Working Conditions
DAF: Dosimetric Adjustment Factor
DECOS: Dutch Expert Committee on Occupational Safety
DNA: deoxyribonucleic acid
EC: European Commission
ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals
EU: European Union
FDA: Food and Drug Administration (USA)
GC: Gas Chromatography
GC/FID: Gas Chromatography with Flame Ionisation Detection
GESTIS: GEfahrStoffInformationsSystem (German database on hazardous substances)
HPLC: High Performance Liquid Chromatography
HSE: Health and Safety Executive
IARC: International Agency for Research on Cancer
INRS: National Research and Safety Institute (France)
IRSST: Occupational Health and Safety Research Institute Robert-Sauvé
ISO: International Organization for Standardization
LC_{50}: Lethal concentration 50
LD_{50}: Lethal dose 50
LOAEL: Lowest Observed Adverse Effect Level
LOD: Limit of Detection
LOQ: Limit of Quantification
MDHS: Methods for the Determination of Hazardous Substances (methods defined by the HSE)
MW: Molecular Weight
NIOSH: National Institute for Occupational Safety and Health (USA)
NMAM: NIOSH Manual of Analytical Methods
NOAEL: No Observed Adverse Effect Level
OECD: Organisation for Economic Cooperation and Development
OEL: Occupational Exposure Limit
OEHHA: Office of Environmental Health Hazard Assessment WHO: World Health Organization
OSHA: Occupational Safety and Health Administration
Pa: Pascal (unit)
PEL: Permissible Exposure Limits (values defined by OSHA)
POD : point of departure
ppm: parts per million
PST: Occupational Health Plan
REACh: Registration, Evaluation, Authorisation and Restriction of Chemicals
REL: Recommended Exposure Limits (values defined by NIOSH)
SCOEL: Scientific Committee on Occupational Exposure Limits
STEL: Short Term Exposure Limit

TGD: Technical Guidance Document
TWA: Time Weighted Average
US-EPA: United States Environmental Protection Agency
UV: ultraviolet

Glossary

Allometric scaling
It corresponds to the adjustment of exposure levels found in animals to determine an equivalent human concentration. Allometric scaling is based on the ratio between the body areas of the species tested and humans, with the body area of a species considered proportional to its average weight raised to the 2/3 power.

CAS (or Chemical Abstract Service) number of a chemical substance
This is the registration number of the substance in the database of the Chemical Abstract Service, which is a division of the American Chemical Society. A single and specific number is assigned to each substance that has been described in scientific literature.

Case-control study
The principle is to compare the frequency of prior exposure in subjects with a disease (cases) and subjects without the disease used as controls. Subjects are enrolled in the study at the time of onset of the disease.

Cohort study
It involves comparing individuals who have been exposed to a particular agent with individuals who have not (or groups of people who have had different levels of exposure), monitoring the occurrence of disease for each group over time.

Epidemiological indicators
The most used indicators in epidemiology are:

- Relative Risk (RR), ratio between the probability of contracting a disease for exposed individuals and the probability of contracting it for those who are non-exposed;
- Odds Ratio (OR), equivalent of relative risk in the case of rare diseases. It is used to estimate relative risk when the aforementioned probabilities cannot be estimated, particularly in case-control studies;
- Standardised Mortality Ratio (SMR) or Standardised Incidence Ratio (SIR) expresses the number of observed deaths (or new cases for SIR) relative to the number of expected deaths if the mortality of the studied population was the same as that of the benchmark population.

For these three indicators, the value 1 corresponds to an equal risk between compared populations, with higher (or lower) values corresponding to higher (or lower) risk in the exposed population.

Incidence
This is a value corresponding to the number of new cases of a given disease occurring during a specified period.

LOAEL (Lowest Observed Adverse Effect Level)
It corresponds to the lowest level leading to a biological or health effect considered to be harmful and statistically significant in comparison with the control.

Meta-analysis
It is a statistical procedure that pools the estimates from several studies into one, with greater weight given to estimates from large studies.

NOAEL (No Observed Adverse Effect Level)
It corresponds to the maximum dose not leading to statistically significant adverse biological or health effects in comparison with the control, from the identification of the LOAEL. In other words, it is the tested dose that directly precedes the LOAEL.

PBPK model
Physiologically based pharmacokinetic models are used to describe the biodistribution of a substance (i.e. its absorption, distribution, metabolism and excretion) within an organism. The body is modelled as a set of compartments that are grouped physiologically. The interconnections between these various compartments represent the exchange of blood between different organs. The flux of substances can be modelled by a system of differential equations primarily linking the quantity or concentration of the substance in the different organs, blood flow, organ volume, distribution coefficients and ventilation rate.

Prevalence
This is a value including all of the cases of a disease counted within a specified period, independently of moment of onset.

Prospective cohort
People exposed or not to a risk factor are monitored for a long period of time. At the start of the period, the studied population must not present the judgement criterion that will be examined, so that incidences of the criterion can be calculated for the exposed group and the non-exposed group.

QSAR (quantitative structure-activity relationship)
It is a process by which a chemical structure is correlated with a specified effect such as biological activity or chemical reactivity.

Retrospective cohort or historic cohort
It is a study that begins post-exposure and is traced back. These studies are carried out when it is possible to locate the majority of the population targeted by the study and when there is sufficient information to recompose the exposure levels.

Risk assessment
It is a quantitative estimate of the probability that adverse effects can result from exposure to pollutants. The assessment has to take scientific proof into consideration, but also social, political, economic and technical factors by assessing all the possible alternatives. It is a four-step process:

- Identification of the hazard;
- Assessment of the response (according to the dose);
- Assessment of the exposure;
- Characterisation of the risk.

Systematic review
It is a compilation, assessment and summary of the findings of initial investigations raising a problem or specific subject and using a strict, structured protocol.

Preamble

The French system for establishing OELVs has three clearly distinct phases:

- Independent scientific expertise (the only phase entrusted to ANSES);
- Proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- Stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

The organisation of the scientific expertise phase required for the establishment of Occupational Exposure Limits (OELVs) was entrusted to AFSSET in the framework of the 2005-2009 Occupational Health Plan (PST) and then to ANSES after AFSSET and AFSSA merged in 2010.

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical and animal toxicology studies. Identifying concentrations that are safe for human health generally requires correction factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- 8-hour occupational exposure limit (8h-OEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over the course of an 8-hour work shift. In the current state of scientific knowledge (toxicology, medicine and epidemiology), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working life from the medium- and long-term health effects of the chemical in question;
- Short-term exposure limit (STEL): this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure;
- Ceiling value: this is the limit of the concentration of a chemical in the worker's breathing zone that should not be exceeded at any time during the working period. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a very short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air, and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;
- or in $mg.m^{-3}$ only for liquid and solid aerosols;

- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- - the weighted average of values over the entire working day is not exceeded;
- the value of the short term limit value (STLV), when one exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a “skin” notation, when significant penetration through the skin is possible. This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee assesses the need to assign an “ototoxic” notation indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical)[2].

The OEL Committee also assesses the applicable reference methods for the measurement of exposure levels in the workplace. The quality of these methods and their applicability to the measurement of exposure levels for comparison with an OEL are assessed, particularly with regards to their compliance with the performance requirements in the NF-EN 482 Standard and their level of validation. Once they have been assessed, these methods can be classified into one of the following categories:

- Category 1A: the method can be used to measure a binding OELV; the method has been recognised and validated (all of the performance criteria in the NF-EN 482 Standard are met);
- Category 1B: the method can be used to measure a binding OELV provided that some aspects of the method are clarified (the vast majority of the performance criteria in the NF-EN 482 Standard are met);
- Category 2: the method can be used to measure an indicative OELV; data are missing for validation of the method;
- Category 3: the method is not recommended and should not be used for comparison with OELVs.

[2] ANSES. (2013). Collective expert appraisal : summary and conclusions regarding the expert appraisal on recommending occupational exposure limits for chemical agents. Reference document on preventing the effects of occupational co-exposure to noise and chemicals. Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail, Maisons-Alfort. 69 p.

Background and procedure for handling the request

AFSSET, which became ANSES in July 2010, received a solicited request on 12 June 2007 from the French Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limit values (OELVs).

The agency decided to conduct the assessments for setting the limit values of the substances in its work programme while also implementing a clear and reliable working methodology that can be applied from one substance to another.

The aim of this report is thus to propose a way of collecting and organising data, and of considering the selection criteria necessary for choosing hypotheses into consideration before defining occupational exposure limit values and biological limit values or recommending suitable measurement methods in an occupational environment.

ANSES entrusted the examination of this request to the Expert Committee (CES) for recommending exposure limit values for chemical agents in the workplace (OEL CES). The Agency also mandated the Working Group on Health effects, the Working Group on Metrology and the Working Group on biomarkers for this expert appraisal.

The methodological and scientific aspects of this group's work were regularly submitted to the OEL Committee. The report produced by the Working Group takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities – General Requirements of Competence for Expert Appraisals (May 2003)" to ensure compliance with the following points: competence, independence, transparency and traceability.

Section A – Drafting the assessment report on the health effects of the substance

1 General information

The chemical substances handled by the OEL Committee can be either organic or inorganic, in the form of a gas, vapour or aerosol consisting of either solid or liquid particles. The first section of the report explains the conditions and physico-chemical properties of the substance and lists the limit values proposed by other expert appraisal or regulatory bodies.

This generic section serves to identify each substance by its CAS number.

When the objective is to set OELs for a substance and its derivatives (in the case of metals, for example) all of the CAS numbers concerned must be mentioned.

The chemical name of the substance according to international nomenclature, as well as any commonly used synonyms, are given.

The substance has to be described as accurately as possible, particularly if there are impurities commonly associated with it.

The physico-chemical properties should mention a certain number of properties, particularly melting point, boiling point, density, vapour pressure and the conversion ratio between ppm and $mg.m^{-3}$.

The European regulatory classification[3] is given together with hazard statements as defined in Annex I of Regulation (EC) no. 689/2008.

Moreover, IARC classification is used for the carcinogenic effect.

The OEL Committee position

The substance will be named throughout the report by its official title as defined by the IUPAC-International Union of Pure and Applied Chemistry (IUPAC, 2009). Specific names that have become accepted through usage but are not compliant with the established nomenclature are sometimes tolerated.

The conversion ratio between ppm and $mg.m^{-3}$ is to be given at 20°C under 101.3 kPa of pressure.

Provisions relating to the classification, packaging and labelling of hazardous preparations and substances that have been significantly amended by the European regulations (CLP Regulation) on hazardous products are indicated (European Parliament, 2008). The OEL Committee takes into account the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). These hazard statements can be found in the European chemical Substances Information System (ESIS) database of the Institute for Health and Consumer Protection (IHCP).

1.1 Existing OELVs

The OELVs cited can be either regulatory or from exert appraisal bodies. European and American OELVs are sought.

[3] Regulatory classification of substances: harmonised classification (CLP), Annex VI of Regulation 1272/2008/EC and its adaptations. List of hazard statements: Annex III of Regulation 1272/2008/EC (equivalent to the former R-phrases from Annex III of Directive 67/548/EEC).

The OEL Committee **position**

The report must provide a clear indication of both the type of value cited (regulatory or from an expert appraisal body) and the date the value was adopted.

1.2 Tables of occupational diseases

In accordance with the French law of 25 October 1919, a disease can be recognized as occupational if it is listed in one of the tables annexed to the French Social Security Code. These tables are created and amended by decree in keeping with technological developments and advancements in medical knowledge (INRS, 2013).

2 Summary of the SCOEL report

SCOEL (Scientific Committee on Occupational Exposure Limits) was created in 1995 by decision of the European Commission.

Its main task is to study relevant scientific documentation on the toxicological properties of chemicals, and to recommend specific occupational exposure limit values to the Commission for the substance studied.

For each substance, SCOEL thus draws up a summary report outlining the scientific criteria it has chosen for recommending occupational exposure limit values.

Each new scientific report produced by SCOEL is sent to the OEL Committee of ANSES, the French scientific correspondent for the committee. The OEL Committee does a critical reading of the consultation documents and sends its comments back to the committee. It clearly conveys its position on the values recommended by SCOEL.

When the OEL Committee agrees with the values chosen by SCOEL, the substance in question is not registered in its work programme. This decision is forwarded to the French Ministry of Labour, which then has the option of regulating the substance's OEL by proposing to accept the value adopted by SCOEL.

When a substance is registered in the OEL Committee work programme and its occupational exposure limit values have been recommended by SCOEL, the OEL Committee studies the document and dedicates a section to it in the assessment report on health effects.

The OEL Committee position

The SCOEL reports studied can have either a 'validated' status or be a 'draft', i.e. submitted for public consultation to receive opinions and/or additional information. In this case, the document's status is not permanent and is subject to change. That is why, in this section, the OEL CES always indicates the status of the SCOEL document being summarised and explains, when necessary, that the comment relates to an interim report.

In this section, the OEL Committee does not perform a critical reading of the SCOEL report. It considers that it does not have to judge the reliability or relevance of the SCOEL committee's choices.

The OEL Committee only reports on the studies selected, the global effects noted, the critical effect chosen, the key study from which the dose-response relationship was selected and the final recommendations.

3 Overview of the toxicological profile

A toxicological profile consists in collecting and assessing currently available scientific data that are useful for defining guideline values, which include OELs (WHO, 1994).

This assessment is used to form a judgement to define the toxic effects tied to different types of exposure to the substance (acute, chronic, by inhalation, skin contact, etc.).

The document produced allows for a classification (non-exhaustive) of the different effects, based on:

- Duration: acute, chronic, etc. ;
- Type of action: local, systemic, etc.;
- Mechanism of action: stimulant, inhibitor, etc.;
- Route of entry: respiratory, cutaneous, digestive, etc.;
- Affected tissue or organ: blood, liver, kidney, nervous system, etc.;
- Nature of the effect: irritant, sensitising, asphyxiant, carcinogenic, etc.

Generally, the nature, number, seriousness, incidence and prevalence of the specific toxicological effects increase according to the exposure, which can be determined by dose, duration and frequency. A dose-response relationship is always sought for each effect identified.

In addition to the dose, other factors can influence toxicological effects, such as the exposure pathway to the substance, the species tested (and in the case of animals, the breed or strain), genetic susceptibility, physiological state, sex and age of the exposed population, etc.

With this aim, a frame of reference was developed for *in vivo* toxicological studies to aid in choosing the most relevant studies (cf. Annex A1).

4 Choice of Data

Based on the available information, it is necessary to determine whether the human and/or animal data can reasonably be used to predict long- or short-term effects in occupational exposure conditions.

The OEL CES has to make the best use of all the information available and explicitly take account of uncertainties in data. It is difficult to specify in advance the minimum data standards for defining an OEL. Databases listing publications on hazards, the dose-response relationship and exposure vary greatly depending on the substance, as much with regard to their volume as to their scope or their quality. In some cases, the data can be very limited; in other cases, they are plentiful and require careful selection work.

The OEL Committee position

The aim of the assessment report on health effects is not to summarise all the studies published. Those deemed insufficient or irrelevant to the assessment are generally dismissed.

The OEL Committee bases its data collection on an in-depth and documented analysis of relevant scientific data from suitable databases, and particularly from scientific literature that has already undergone peer review.

When the summary reports and research studies have already been published by internationally recognised bodies (IARC, ATSDR, DECOS, etc.), the OEL Committee can use them as a basis from which to develop the toxicological profile, provided the bibliography is updated. Investigators refer back to source articles whenever it is deemed necessary.

When they are accessible or when they are provided, other sources of unpublished studies (e.g. from stakeholders: unions, industries, etc.) can be examined if they are relevant and the source of information is clearly indicated.

5 Toxicokinetics – Metabolism

This section summarises all of the data on toxicokinetics and the metabolism identified in animals and in humans.

Toxicokinetics involves the study of the disposition of substances in the organism through four phases: absorption, distribution in the organism, metabolism and excretion (Vialla and Botta, 2005; Greim and Snyder, 2008).

Absorption is the process by which a substance passes through the organism from the route of entry to the organs or tissues. Its importance varies depending on the substance, its chemical form and the exposure pathway.

Distribution is the process by which a substance reaches various compartments and organs of the organism according to its mobility, solubility in water and in lipids and, globally, its affinity for certain tissues.

Metabolism is the process, generally enzymatic, by which a chemical substance is transformed into another substance (metabolite, for example, in the case of organic substances) within the organism. In the case of metals, it can also involve changes in the state of oxidation.

While most metabolic transformations of organic substances give rise to compounds that are more polar, more easily excretable in urine and bile, and generally less toxic (detoxication), it is possible for a product of biotransformation to be more reactive and capable of binding to target molecules, and thus more toxic (bioactivation). Within this context, metabolites can thus play a major role in the toxicity of the mother molecule. There are inter- and intra-species differences in the mechanisms of biotransformation (in part tied to biological and genetic diversity).

Metabolism enzymes are widely distributed throughout the body, although the liver is the most important transformation organ due to its high concentration of enzymes; the kidneys and lungs represent 10 to 30% of hepatic capacity. Other organs such as skin, intestines, testis and placenta have a low capacity to metabolise xenobiotics.

The mode of elimination of a compound outside of the organism plays a central role in its toxicity. Indeed, the accumulation of a toxic substance in an organism is generally an aggravating factor in terms of toxicity. There are several means of excretion, the main routes being via urine, faeces and exhaled air. The urinary or faecal excretion of a substance is strongly affected by its physical properties (molecular weight), any plasma protein binding and its polarity. The lungs are a major route of excretion for substances, or their metabolites, if they are volatile and their distribution coefficient between the blood and the air allow for elimination via this route.

The OEL Committee **position**

Toxicokinetics play an important role in defining OELs. In conjunction with toxicodynamics, they provide insight into the toxic material's mechanism of action and help determine a portion of the safety factors. This section could therefore be used to discuss and justify all the elements that could be useful for the derivation of the OEL: allometric scaling, availability of PBPK models, species specificities, etc.

Data on absorption through the respiratory tract and the skin are to be addressed first due to the primary purpose of OELs. Inhalation is often the main exposure pathway in an occupational environment. The absorption of an inhaled substance must be analysed on the basis of parameters such as respiration rate, substance solubility, rheological differences between species based on conformation of the respiratory tract, particle size in the case of aerosols, etc. It is important to indicate any absorption via the skin for assigning skin notation (see chosen methodology later in

the report).

Absorption via the gastro-intestinal tract is only taken into account in certain cases, particularly when there is insufficient data on inhalation. In such cases it may be needed to define OELs by extrapolation from one route to another.

The distribution phase is important for highlighting inter- and/or intra-species differences. It provides information for inter-species extrapolation, on the toxic material's sites of action and its availability in the organism. Placental transfer is another point to be documented.

The elimination phase is especially crucial for the section on choosing exposure biomarkers, where it will be detailed. Since the processes of biotransformation and elimination are variable, it is necessary to indicate differences with regard to species, age, sex, genetic variation, etc., in order to characterise variability in the studied population.

6 General toxicity

Toxicological information is a decisive factor when defining OELs and must provide an overview of all of the substance's known effects on health.

The OEL Committee position

Sometimes, scientific literature can provide a comprehensive toxicological profile of the substance for both humans and animals (which is the case for documents from the EU, US EPA, WHO, OSHA, ATSDR, NIOSH, etc.). The OEL Committee can use these documents and only includes in its summary information that is useful for defining OELs.

6.1 Toxicity in humans/epidemiological studies

6.1.1 Types of studies on humans

In addition to the epidemiological studies described below, experimental studies on healthy volunteers for example can also prove to be of interest. Since the exposure is controlled, the dose-response relationship is easier to describe. However these studies are only carried out on a limited number of people, which can restrict its use for extrapolation to less homogenous populations than the ones chosen.

Several types of epidemiological study contribute to the assessment of the toxicity of a substance in humans, such as cohort studies, case-control studies, cross-sectional studies, and so on. Clinical trials and case-reports may also be examined (IARC, 2006).

Meta-analyses, which consist in compiling data from comparable studies and re-analysing them using the appropriate statistical tools, are very useful for finding critical and quantitative answers to specific questions and thus drawing firmer conclusions than isolated studies would permit. They also improve the strength of the findings obtained.

Cohort studies and case-control studies associate the different levels of exposure with the occurrence of an effect in subjects and are used to calculate a relative risk (RR) or an odds ratio (OR) (for case-control studies).

Relative risk is the ratio between the occurrence of the event in the exposed group and the occurrence in the non-exposed group, i.e. the ratio between the probability of contracting a disease for exposed individuals and the probability of contracting it for those who are non-exposed. RR and OR measure the strength of association between the occurrence of the event and exposure to the risk factor.

In correlational studies, a causal relation is more difficult to prove since the individual exposure is not known.

Uncertainties surrounding the interpretation of case-reports and correlation studies make them unsuitable, barring exceptions, for forming the sole basis for conclusion of a causal relation. However, when these findings are taken together with case-control studies and cohort studies, they can substantiate the judgement that there is indeed a causal relation. There are different criteria for substantiating causation, the best-known being the Hill criteria (Hill, 1965).

The OEL Committee position

The Committee takes into account the relevance of epidemiological studies (mainly cohort and case-control studies) to establish OELs.

For the derivation of OELs, preference is given to the studies where calculating relative risk (or odds ratio) by exposure unit is possible.

6.1.2 Taking bias into account

The potential role of bias, confounding factors and chance needs to be taken into account when interpreting epidemiological studies (IARC, 2006).

'Bias' is used to refer to the contributing factors in the protocol of a study or its procedure that would lead to erroneously overestimating or underestimating the association between the disease and an agent, a mixture or an exposure circumstance (example: misclassification).

'Confounding factor' is used to refer to a situation in which the relationship with the disease appears stronger or weaker than it actually is due to an association between the visible causal factor and another factor associated with an increase or decrease in the incidence of the disease.

The OEL Committee position

The elements to be analysed when defining an OEL are taken from the IARC document on methodology (IARC, 2006). The OEL Committee also drafted a frame of reference for judging epidemiological studies (cf. Annex A2). The main criteria chosen are as follows:

- The population studied; the disease and the exposure need to have been well defined by the authors. Cases of disease in the studied population need to have been identified independently of the exposure in question, and the exposure needs to have been established independently of the disease condition;
- Authors need to take into account other variables that can influence the risk of disease and may be related to the exposure in question. In cohort studies, comparisons with local disease rates may be more appropriate than with national rates when choosing the benchmark population. The study should also include internal comparisons of disease incidence between individuals with differing levels of exposure;
- Authors must have indicated the basic data on which the conclusions were based, even if sophisticated statistical analyses were used: number of cases and exposed and non-exposed controls in a case-control study and number of cases observed and expected in a cohort study;
- Finally, authors must have clearly stated the statistical methods used to obtain estimates of relative risk, rates of diseases, confidence intervals and tests of significance, as well as the method used for taking into account of any confounding factors.

6.2 Toxicity in animals

This assessment is used to define the toxic effects related to different types of exposure to the substance (acute, chronic, by inhalation, skin contact, etc.).

The three usual forms of toxicity are sought: acute toxicity, short-term toxicity (sub-acute and sub-chronic) and long-term toxicity (chronic).

The CES position

Most of the toxicological data used to assess risks are derived from studies on animals. The OEL Committee recommends taking account of studies conducted according to guidelines (OECD, EPA, etc.) whenever possible. Study quality can be determined using the Klimisch scoring scheme (Klimisch, 1997) (cf. Annex A3).

6.2.1 Acute toxicity

Acute toxicity concerns the adverse effects resulting from a single exposure or exposures in less than 24 hours. The total observation period of effects can reach up to two weeks, checking for toxic damages that can be clinical or biological signs, abnormal changes in organs and tissues, which can in some cases, lead to death.

6.2.2 Sub-chronic toxicity

Sub-chronic toxicity is the effect of repeated or continued exposure of a substance over a period of less than three months.

The study must report on:

- Potential toxic effects after repeated exposure during a specified period;
- Affected organs;
- Reversible and irreversible effects;
- Possible cumulative and delayed effects.

6.2.3 Chronic toxicity

Data from long-term (chronic) studies are of crucial importance since theses studies search for serious toxicological manifestations or effects, particularly cancer and effects on reproductive organs. Studies on mammals have to cover much of the lifetime of the animals.

Chronic toxicity concerns effects due to the repeated administration of a substance over a period of time determined according to the species studied. The study informs on physiological, biochemical and haematological effects, as well as anatomical changes. It allows for an assessment of the following in particular:

- Latency in occurrence of effects;
- Nature of effects (functions and organs affected);
- Carcinogenic or tumour-inducing effects;
- Reprotoxic effects;
- Reversibility of effects.

6.3 Genotoxicity and mutagenicity

The genotoxicity of a product is an intrinsic chemical characteristic derived from the electrophilic potential of the substance, i.e. its ability to bind to nucleophile sites like those in DNA.

The definition of genotoxicity, as established in the IARC consensus report, is broad and includes both direct and indirect effects on DNA (IARC, 1992):

- Mutation inductions (genetic, chromosomal, genomic, by recombination) which, at the molecular scale, are events similar to those that play a role in carcinogenesis;
- Events indirectly associated with mutagenesis (unscheduled DNA synthesis or sister chromatid exchange);
- DNA lesions (formation of adducts) that can lead to mutations.

Mutagenicity is the property of certain substances to cause permanent hereditary changes in germinal or somatic cell lines. Genetic changes in these cell lines can potentially be transmitted to offspring.

Genotoxicity thus precedes mutagenicity. It is recognised that genotoxic lesions can be repaired and are not always expressed by mutation.

A genotoxic carcinogen is a substance that can initiate a cancer process by causing an increase in the rate of mutations or chromosomal abnormalities within a cell or an organism. Toxicity assays performed *in vitro* and in animals are used to characterise carcinogens. They can reveal a mutagenic, clastogenic and/or aneugenic effect.

A non-genotoxic carcinogen is a substance that participates in the process of carcinogenesis (promotion or progression stage) without bringing about an increase in mutations. The non-genotoxic mode of action includes epigenetic changes, i.e. effects that do not involve DNA alteration, but that influence gene expression, communication between cells or other factors in the process of carcinogenesis.

Although the two types of compound appear to have distinct mechanisms of action, recent studies downplay the separation between genotoxic and non-genotoxic compounds: a number of compounds that are not genotoxic cause oxidative stress that can alter DNA and thereby cause genotoxicity. Other non-genotoxic compounds have metabolites capable of binding to DNA and initiating a process of carcinogenesis.

Genotoxic carcinogens are generally considered to have a non-threshold mode of action. Any dose of a genotoxic carcinogen is responsible for an excess risk of cancer.

Non-genotoxic carcinogens are considered to have a dose threshold below which there is no effect.

The OEL Committee position

To judge the genotoxic or mutagenic effect of a substance, the OEL Committee favours assessments by international organisations such as the IARC and the European Union, providing that current data and state of knowledge have been taken into account[4].

Otherwise, the main tests of mutagenicity and genotoxicity, classified into three categories, must be sought:

- Markers of mutagenic activity in biological environments such as the Ames test;
- Markers of cytogenic abnormalities: chromosomal aberrations, micronuclei (indicators of chromosome breakage), sister chromatid exchanges, etc.;
- Markers of DNA binding or adducts: to detect binding between genotoxic substance and macromolecules (adducts to DNA, haemoglobin, proteins, etc.).

[4] The ANSES is explicitly informed when the OEL Committee challenges a classification.

In vitro tests are carried out predominantly and can be supplemented with *in vivo* tests.

The mechanism of genotoxicity must be discussed to decide whether or not a threshold of toxicity can be said to exist.

To help make an informed decision on the most relevant studies, a frame of reference for *in vitro* genotoxicity/mutagenicity tests is included in Annex 4.

6.4 Carcinogenicity

The objective is to identify via ad hoc studies the majority of carcinogenic effects in mammal species, and the dose-effect relationships following prolonged and repeated exposure. These effects are generally revealed during chronic studies or carcinogenicity studies conducted on one or more animal species.

Typically, rats are used for a combined assessment of chronic/carcinogenetic toxicity. The OECD has issued guidelines for testing for chronic toxicity and carcinogenicity in chemicals (OECD, 1993).

The OEL Committee position

To judge the carcinogenic effect of a substance, the OEL Committee favours assessments by international bodies such as the IARC or the European Union, providing that current data and state of knowledge have been taken into account.

Carcinogenesis is a complex process and, for the assessment of carcinogenic potential, no predetermined approach is suitable for all chemical substances used in an occupational environment.

Exposure frequency and conditions in animal experimentation must be chosen in accordance with occupational exposure.

Some items of information are decisive for adopting the strategy to assess the carcinogenic potential of a chemical substance: its genotoxic properties, the administration route (bearing in mind that inhalation studies are to be researched as a priority), the pharmacodynamic properties in animals and in humans (selectivity, dose-response relationship) and the results of repeated-dose toxicological studies.

In rodents, the carcinogenic activity of non-genotoxic chemicals is characterised by high specificity with regard to species, breed and target organs, as well as the thresholds that mark the dose-response relationship. Research on mechanisms of action helps distinguish between effects specific to rodents and those that are also likely to be seen in humans (Boobis, 2008, 2006; Guyton, 2008).

6.5 Reprotoxicity

Generally, reprotoxic effects are structured as follows:

- Abnormal development of foetuses and infants. This includes spontaneous abortions, stillbirths, failure to thrive at birth, malformations and physical and mental developmental disabilities, up to and including abnormal pubertal development;
- Impaired fertility. This includes effects on libido, spermatogenesis, oogenesis, the oestrous cycle, and fertilisation itself, up to and including implantation.

The OEL Committee position

To assess the reprotoxic effect of a substance, the OEL Committee favours the European Union assessment, providing that current data and state of knowledge have been taken into account.

If a reprotoxic effect becomes apparent during the review of toxicology literature, the OEL Committee has to take account of the exposure period.

With regard to embryo-foetal development, the window of exposure (period of gestation in which exposure to a substance can cause adverse effects for the embryo or the foetus) must be taken into consideration in order to validate the extrapolation from data obtained in animals to potential exposure situations among female workers. High exposures occurring in critical periods of organogenesis can prove, for example, to be more relevant than average doses of exposure over days or weeks.

Effects on fertility must be sought in adults and offspring (alterations in reproductive organs, long-term effects).

6.6 Human-animal consistency and determining the mode of action

This stage is necessary for transposing the effects observed in animals to humans and ensuring the consistency of toxicokinetic and toxicodynamic data in animals and in humans.

The OEL Committee position

Whenever possible, the OEL Committee uses experimental studies in which the sensitivity of the species and breed is as close as possible to that of humans. Since this assertion is not always verifiable, the plausibility of extrapolating the effects of one species to another can be strengthened by the use of different species. In any event, the default hypothesis is that the effect shown in animals can also arise in humans, unless the analysis of the mode of action proves otherwise (US EPA, 1994a).

The differences in kinetics and metabolism of a substance in several species are sometimes corrected by applying an adjustment factor that takes into account, for respiratory exposure, the rate of inhalation (physiological parameter) and distribution coefficients between air and blood (physico-chemical parameters tied to the substance) or physiologically based toxicokinetics models.

In vitro studies and models such as QSAR are also used to confirm a toxic effect or tie the physico-chemical properties of the chemical substance to the biological activity (toxicity, binding affinity, etc.), but also to other properties such as stability, solubility and bioavailability.

Furthermore, when toxicodynamic experimental data are not available, the default hypothesis is to consider humans to be more sensitive than animals, within the allometric variations outlined above.

7 Defining OELs

The toxicological profile must allow for characterising hazards and establishing the relationships between the administered dose of the substance and the qualitative/quantitative responses produced.

A response threshold, i.e. the level of concentration below which there is no response, is sought. It is likely to have such a threshold for each response caused by the substance (acute or chronic toxicity, neurotoxicity, irritation, reprotoxicity, etc.).

There are, however, effects for which there is considered to be no response threshold (e.g. genotoxicity, carcinogenicity) and for which the risk increases according to exposure. They are subject to different risk assessment methods than threshold effects.

7.1 Critical effect

Only harmful or adverse health effects are taken into consideration during the literature review. These are all the changes in morphology, physiology, growth and development resulting from deterioration of functional capacity or the capacity to offset additional stress or an increase in sensitivity. These effects contribute to the danger of a substance. Some effects considered to be physiological or adaptive are excluded for the choice of the critical effect. However, before dismissing these effects during the toxicity assessment, it is important to ensure they are not a manifestation of toxicity (Lu, 1988; WHO, 1994).

This generic definition is very broad and it is sometimes difficult to distinguish adverse effects from other effects that would not correspond to a direct manifestation of toxicity.

The OEL Committee position

Some substances with an effect threshold have undesirable effects on several organs. When defining an OEL, a critical effect is chosen from the adverse effects deemed relevant. As a general rule, it is the first adverse effect that occurs in the exposed population when the dose is increased. It has to be judged plausible in workers for establishing OELs. *A priori*, this is a protective choice with regard to the other effects observed on the condition that, when the key study is on animals, the nature of the dose-effect relationships is the same for both animals and humans.

Effects on reproduction and embryo-foetal development are a special case[5]. Even if they do not necessarily correspond to a critical effect, the OEL Committee considers their specific quantification. They are considered to be severe when they affect offspring. The main reason is that the period of embryogenesis is critical for foetal development and that a single exposure, no matter how brief, is likely to have irreversible consequences (cf. section on reprotoxicity).

[5] Unless the window of exposure coincides with exposure of female workers or the toxic material can be accumulated in the organism and show elimination kinetics that are compatible with effects in the foetus.

7.2 Choosing the best study according to the chosen critical effect

The best study or studies are selected according to the chosen critical effect. The objective is not to classify all of the studies according to a quantified grading system, but rather to give a structured and systematic presentation of the criteria for making a final, scientifically based decision. While the additional information is not used directly to define OELs, it provides arguments for the choices made.

7.2.1 Human data

Good quality data on humans are largely preferable to data on animals but such data are often not available or methodologically suitable for defining OELs.

When there is positive epidemiological data, it is important to take account of variations in sensitivity in humans, genetic predisposition, sensitivity based on age and sex, as well as the presence of certain confounding factors. Furthermore, negative epidemiological data can be difficult to interpret, since they can be due to the limited statistical strength of the studied sample; this is especially true when the risk to be shown is low.

In studies on humans, with the exception of exposure on volunteers, exposure is not characterised as specifically as in experimental studies and it is rarely possible to demonstrate a clear dose-effect relationship. The importance given to studies on humans for defining an OEL will thus depend on the nature of the undesirable effect and the quality of the studies (particularly information on the dose-effect relationship).

7.2.2 Animal data

Most of the toxicological data used for risk assessment are derived from studies on animals.

For a threshold effect (cf. definition of the concept below), the selected toxicology studies on animals must be designed to establish a no observed adverse effect level (NOAEL), a lowest observed adverse effect level (LOAEL)[6] or a benchmark dose (BMD). The doses chosen must be high enough to reduce as much as possible the likelihood of false negative results in areas such as metabolic saturation, cell proliferation induced by cytogenetic and mitogenetic factors, etc. Intermediary doses must be chosen to provide information on the shape of the dose-response curve. Insofar as possible, studies on animals must provide information on the mechanism of action, the relationship between the administered dose and the dose actually delivered, as well as on the relevant pharmacokinetics and pharmacodynamics.

7.2.3 Benchmark-dose (BMD)

Certain cases could allow for a BMD approach to describe the dose-response relationship. The main advantage of this approach is that it uses all of the information provided by the dose-response curves. It is important to note that the BMD method is only appropriate when the data are conducive to modelling (i.e. observable data available in the appropriate range of concentrations). A BMD is thus used as a substitute for an NOAEL or a LOAEL.

6 Sometimes studies make it possible to rule on a concentration as opposed to a dose. In this case, the terms No Observed Adverse Effect Concentration (NOAEC) and Lowest Observed Adverse Effect Concentration (LOAEC) are used.

Moreover, a BMD can be estimated from the same experimental findings as the NOAEL/LOAEL. The objective of this approach is to estimate the dose corresponding to a given response level or a given additional response percentage with respect to the control. This level or percentage is called the BMR for BenchMark Response level; it can be set in advance at 10, 5 or 1% according to the effect in question or the power of the study (BMD_{10}, BMD_5, etc.). The BMD is often associated with the lower bound of its confidence interval (interval at 90 or 95%: $BMDL_{90}$ or $BMDL_{95}$). To summarise, the results for the value corresponding to the lower bound of the 95% confidence interval of a BMD calculated for a 10% response level is expressed by: $BMD_{10}L_{95}$. The graph below illustrates the concepts defined in this section.

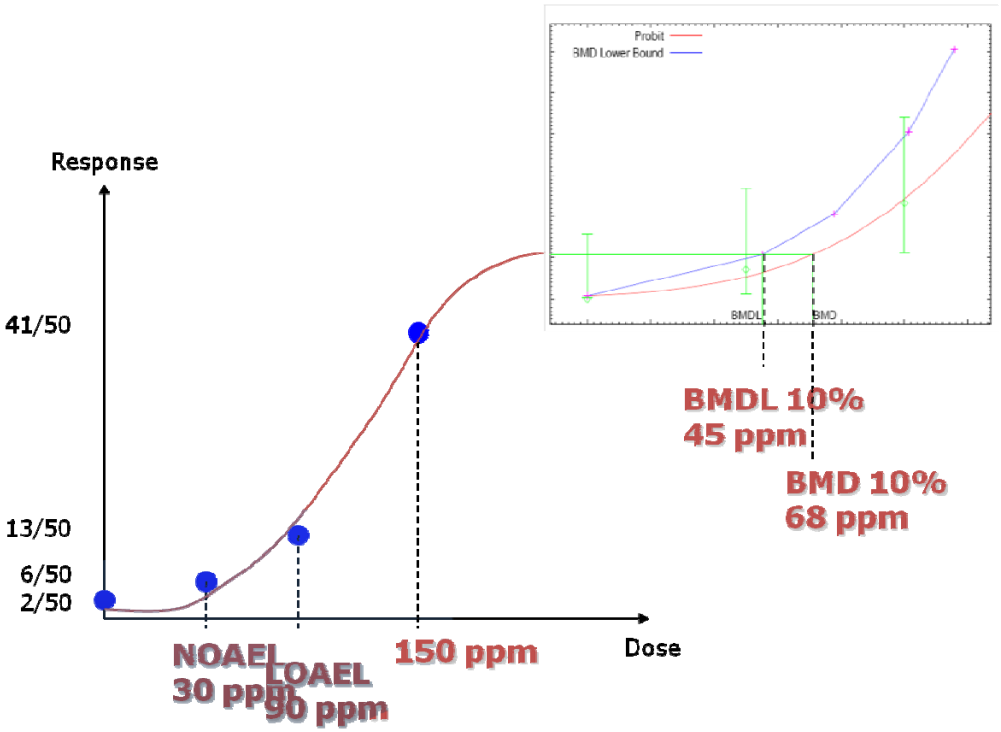


Figure 1: Advantage of choosing the benchmark dose as reference dose

The OEL Committee position

To facilitate the choice of the 'best study' with total transparency, the OEL Committee has adopted the following reasoning:

- Give preference to epidemiological studies that are of high quality with well-characterised exposures;
- In second line, use experimental studies judged to be of good quality.

7.3 Effects with a concentration threshold

7.3.1 Choosing a reference dose

Threshold effects are those that only occur above a certain level of exposure. A toxicological threshold can be defined as a dose below which no adverse effect is expected based on the literature available at the time of the expert appraisal.

The main hypothesis here is the supposition of the existence of a toxicity threshold for the substance below which almost all workers will show no adverse effects on health. This threshold is generally not observable, however, and can only be estimated.

For a threshold effect, it is assumed that small doses of a hazardous substance can be tolerated due to the presence of metabolic detoxification, physiological homeostasis and cell adaptation and repair systems. Below a certain minimum dose, these compensatory mechanisms can mitigate the adverse effects of a substance, even during chronic exposure. Higher doses, however, exceed the organism's capacity to compensate or adapt, which leads to impairment of organ function or a change toward a morbid state. It can also occur following repeated, frequent or continuous exposure at low concentrations of a substance that can accumulate in the organism (Bonvallot and Dor, 2002).

To assess the substance for which the toxic reaction presents a threshold, the dose-response relationship needs to be determined with the aim of identifying the highest dose of the substance showing no adverse effect. This dose is defined as the no observed adverse effect level (NOAEL). This term contains two specific qualifiers: 'observed', which indicates that there may be other, undetected effects (e.g. subtle biochemical effects or specific hormonal effects), and 'adverse', which indicates that not all of the effects observed are adverse.

If experimental data does not allow for identification of a NOAEL, then a LOAEL should be identified, as the lowest dose causing the undesirable effect selected as critical effect.

It is generally considered that the toxic effects of a substance in laboratory animals are presumed to occur in humans as well under appropriate conditions. As a consequence and due to the lack of relevant epidemiological studies, animal studies are the primary source of toxicological data. During these experiments, high doses are administered in order to observe clear signs of toxicity, ensuring better evaluation of the target organ and a specific effect.

The variety and severity of toxic effects observed in the sample populations generally increases with the level of exposure: this is the dose-effect relationship. It is necessary to distinguish between this and the dose-response relationship, defined as the relationship between how frequently a disease occurs in a population and the level of exposure to a toxic material (Holsapple and Wallace, 2008).

The OEL Committee position

The OEL Committee has chosen to retain, by order of preference:

- Use of the BMD approach for situations in which the data are conducive to this type of modelling: the reference dose used is thus the BMDL (the lower bound of the BMD confidence interval) with a BMR generally set at 10%;
- Studies that provide the most information, particularly on the NOAEL/LOAEL pair for the selected critical effect;
- Lastly, when studies only allow for one reference dose (LOAEL or NOAEL), it is important to favour studies that give the NOAEL rather than a LOAEL.

7.3.2 Adjustment factors

Adjustment factors (also called safety factors, uncertainty factors, depending on organisms) are applied to toxicity data to allow a protective margin between the reference dose and the dose that should not cause an effect in workers, including the most susceptible. The purpose of this margin is to provide reasonable certainty that no damage to human health will result from exposure to the product. Absolute certainty of safety is impossible to attain, since the results generally obtained from toxicity studies conducted on a homogenous population of laboratory animals have to be

extrapolated to a heterogeneous population of workers (Dourson and Stara, 1983; Lewis et al., 1990; OEHHA, 2000).

Despite efforts to use the best scientific data available, safety factors are necessary to take account of the uncertain nature of data and ensure that the value of the OEL chosen guarantees with reasonable certainty an absence of danger for human health.

The different adjustment factors (safety or uncertainty) proposed in scientific literature for defining reference values can be found in the following documents: Who, 1994; ECETOC, 1995; Mohamed, 1995; US-EPA, 1996; WHO, 2001.

There are typically five adjustment factors, as shown in the table below. They are not specific to OELs.

Table 1: adjustment factors proposed in the literature for establishing reference values

Acronym	Interpretation of AF
AF_A	**Kinetic/dynamic inter-species variability**
AF_H	**Kinetic/dynamic inter-individual variability**
AF_L	**Use of an LOAEL rather than an NOAEL**
AF_S	**Transposition from sub-chronic to chronic exposure**
AF_D	**Insufficient data (quality and quantity)**
	Severity of the effect

Since the number of adjustment factors and their numerical value can vary from one expert group to another, the results of one toxicological study can lead to different reference values (Kalberlah, 1998).

The OELs for chemical substances with threshold effects are established using the “Reference Dose/Adjustment Factor (uncertainty or safety)” method (US EPA, 1989; WHO, 1987). The reference dose identified in the source study is divided by the product of several adjustment factors:

- Inter-species variability (animal-human transposition of experimental data);
- Intra-species or inter-individual variability (specific sensitivity of certain individuals);
- Inadequacy of study length (if the observation period is insufficient);
- Use of a LOAEL rather than a NOAEL;
- Inadequacy of exposure pathway (e.g. transposition to respiratory route of data observed by oral route);
- And any other methodological inadequacies of the study.

Scientific literature often mentions (especially for environmental risk assessments) that when no information is available for establishing reference values, a default upper value of 10 is used for each adjustment factor (AF). Application of a lower value must be supported by relevant scientific facts (Stevenson, 1995).

There is no universally accepted method for applying AFs when deriving OELs and expert judgment is used whenever necessary to complement or supplement objective data.

It is important to take into account the homogeneity of the population of interest when establishing limit values and applying AFs. For example, certain factors related to variability in the population of interest may be lower than those proposed for the establishment of reference values applicable to the general population which includes especially sensitive populations.

For the establishment of short-term exposure limits (generally based on an effect such as local irritation or corrosion), the document of the National Research Council (1993) recommended applying two factors to take into account inter- and intra-species variability. These factors should take into account inter-species differences in sensitivity, individual sensitivity, variability in the population, toxicological mechanisms of action, internal availability when applicable and the evaluation of database quality.

Adjustment factor tired to inter-species variability (AF_A)

The inter-species adjustment factor is applied when an animal study is used to define the OEL. It is meant to take account of the toxicokinetic and toxicodynamic differences between the species tested and humans. The default maximum value used internationally is 10, on the assumption that humans are more sensitive than animals.

This value of 10 corresponds to the application of two components respectively for toxicokinetic and toxicodynamic differences. The selection of these components was published in a WHO report (WHO, 2001).

Dosimetric or allometric adjustment based on physico-chemical and biological parameters (blood flow, distribution coefficient, etc.) can be made, which also allows for maximum reduction of the toxicokinetic portion of the adjustment factor (US-EPA, 1994a). In practice, the US-EPA suggests an AF_A of 3 when an adjustment is performed.

Like when allometric or dosimetric adjustments are applied, PBPK models take into account toxicokinetic differences between animals and humans. Thus, it may be appropriate to only take into account the toxicodynamic component of the adjustment factor and not use the default value of ten but reduce this value.

Adjustment factor tied to inter-individual variability (AF_H)

The inter-species variability adjustment factor takes account of the potential variability of response in the human population. This variability can be the result of differences in effect criteria such as genetic make-up, age, sex, lifestyle and health condition. As a consequence, this factor takes account of the differences in response between the average person and a sensitive person in the population of workers. For defining OELs, a maximum value of 5 was chosen for this factor on the basis that a population of workers is more homogenous than the general population (factor of 10 commonly chosen).

Adjustment factor tied to use of a LOAEL (AF_L)

This adjustment factor is applied when the OEL is defined from a LOAEL. Some authors or bodies may also use this factor when the reference dose is a BMDL, considering the fact that at a BMDL (unlike a NOAEL), an effect is expected. The discussion must, in this case, centre on the level of response chosen for defining the BMDL.

In the past, this factor has been taken from the study of LOAEL/NOAEL ratios determined for different substances on different animal models. The ECETOC recommended using a factor of 3 in the majority of cases, a value that corresponds to an approximate average of existing data (ECETOC, 1995). This value cannot be considered protective, however, since in approximately 50% of cases, a higher LOAEL/NOAEL ratio can be observed. The OEL Committee considers that other values can be assigned to this adjustment factor in certain cases.

Adjustment factor tied to sub-chronic to chronic transposition (AF_S)

This adjustment factor is applied when it is necessary to extrapolate short-term studies to a long-term exposure scenario due to lack of relevant data. Chronic toxicity studies could point to health effects undetected in short-term studies. What is more, the critical effects observed in short-term studies can increase with chronic exposure, which would have the effect of lowering the NOAEL.

Other adjustment factors (AF_D)

Other adjustment factors can be tied to insufficient data, severity of the critical effect or transposition from one route to another.

Insufficient data

In the first case, various sources of uncertainty due to gaps in the database can justify the use of this adjustment factor. The cases of extrapolating from an LOAEL to an NOAEL and from sub-chronic to chronic exposure described above can be likened to gaps in the database, but the OEL CES has chosen to treat them separately.

Route-to-route transposition

For certain chemical substances, scientific literature does not provide a dose-response relationship that can be used for defining an OEL. To avoid overlooking the risk tied to exposure via inhalation, the OEL CES may employ the route-to-route transposition process for deriving the dose-effect relationships found.

The OEL Committee position

The terms “safety factor”, “assessment factor”, “extrapolation factor”, “protection factor” and “adjustment factor” are also used in similar contexts. The reasons for using different terms are not always clear. The OEL CES has chosen to use the term “adjustment factor” since it feels this is the term that best describes the situation.

The rules for applying adjustment factors are not set in stone; they are subject to change on a case-by-case basis. It is thus important to have recourse to a qualitative expert judgement based on the type of effect studied, the mechanism of the substance and the type of exposure. Moreover, these considerations are used in an approach based on the weight of the evidence to make a scientific judgement on the level of concern. This integrated method maximises the use of all available information rather than being based on isolated findings.

Acronym	AF Interpretation	AF Values
AF_A	Pharmacokinetic/pharmacodynamic inter-species differences	1 to 10
AF_H	Kinetic/dynamic inter-individual variability	1 to 5
AF_L	LOAEL to NOAEL	1 to 10
AF_S	Differences in length of exposure	1 to 10
AF_D	Database quality Difference in exposure pathways	1 to 10
	Severity of the effect	1 to 10

AF_A - Inter-species differences:

- this factor is generally set at 10 to take account of differences in sensitivity between species and extrapolate laboratory results to occupational exposure conditions and when it is not possible or relevant to do dosimetric or allometric adjustment;
- since this factor takes into account toxicokinetic and toxicodynamic components, it is generally set at three when an allometric or dosimetric adjustment has been applied (if relevant) to the critical dose;
- **for substances with irritating or corrosive effects,** two values are adopted based on expert judgement: three or one.

AF_H - Inter-individual differences:

- These are differences in toxicokinetic (e.g. genetic polymorphisms in the enzymes of the metabolism) or toxicodynamic (different sensitivities with regard to the target, hereditary disease leading to DNA repair deficiency) responses that can be examined;
- The OEL CES takes into consideration the information available on groups of particularly vulnerable people. However, the variability of responses among individuals at the same level of exposure and the existence of special risk groups may mean that the OEL recommended does not provide protection for all;
- The application of adjustment factors to values from human studies depends largely on the reliability of the study. If the critical effect was based on a sound and high-quality study, the OEL CES might not apply any adjustment factors;
- **for substances with an irritating or corrosive effect,** the OEL Committee applies an intra-species AF of one. However, an AF of three or even five may be used if credible information or data are available to justify it.

AF_L - Transition from LOAEL to NOAEL:

- There is no specific rule on choosing a numeric value for this factor;
- The use of a BMDL does not preclude the application of a adjustment factor since this approach can serve to estimate the dose corresponding to a determined response level. It is thus not a no-effect dose. The OEL CES will apply a adjustment factor of 1 to 3 and justify it when using a BMDL.

AF_S - Sub-chronic to chronic transposition: the scientific evaluation to determine the value of this factor takes into account bioaccumulation potential and the nature of the response (e.g. if there is risk of aggravated or increased frequency). There is no concrete justification for applying a set value for this factor. This application is thus left to the judgement of experts.

AF_D :

- Route-to-route transposition: this type of extrapolation requires an analysis of toxicokinetic data. It is not necessary to use a safety factor when toxicokinetic data are available (absorption for the two routes considered). When they are not available, it is then necessary to use this safety factor, considering that absorption for the route of exposure in the key study is lower than for inhalation. For example, an AF of two would mean that absorption for the route of exposure in the study is two times lower than for inhalation (e.g. 50% for the oral route versus 100% for inhalation);
- Severity of the effect: a practical definition of serious effect is required. Consequently, with regard to a threshold response, a serious toxicological effect for a chemical substance is an effect that causes malformations, is a source of incapacity or a major or permanent disability, poses a threat to life or causes death to exposed animals.

The OEL Committee considers the final numerical value of an SF to be an indicator of confidence in the source study from which the OEL was defined. If the overall factor applied exceeds 1000 or if more than three adjustment factors are applied, the OEL Committee considers the study to be unsuitable for defining an OEL.

7.4 Non-threshold effects

The OEL Committee position

For non-threshold substances, the OEL Committee does not consider the method of applying a adjustment factor to a reference dose to be suitable for establishing an OEL.

When there are no established mechanisms of action with a threshold, mutagenic, carcinogenic and genotoxic effects are considered non-threshold effects.

7.4.1 Calculating an excess risk

To define an OEL based on health effect with no toxicity threshold, it is assumed that there is a relationship (often linear) between exposure and the probability of an adverse effect (generally cancer) occurring at low doses, and the slope of the curve is determined (US EPA, 1996).

The indicator of interest is excess risk per unit (ERU), which is defined by the additional probability, compared to a non-exposed individual, of an individual contracting a disease (often cancerous) if exposed for a long period of time (in workers, this often corresponds to 40 years) to a unit dose of the substance in question.

Excess risk per unit is generally established from the dose-response relationships observed in laboratory animals or, more rarely, from epidemiological studies. In most cases, the studies examine high doses of the chemical substance and extrapolations are made to low dose levels. The experimental studies are generally not robust enough to show a statistically significant effect at low exposure levels, unless a very large number of animals are involved (Williams, 2009).

The point of departure (POD) for calculating the slope of the line to the origin represents the excess risk per unit during an extrapolation with no threshold at low doses. According to the US-EPA, it corresponds to a high estimate of excess risk per unit dose, as illustrated in the graph below.

For carcinogenic effects, the assessment is quantitative. The probability of cancer occurring in exposed subjects over a lifetime, added to the baseline risk not related to this exposure, is called individual excess risk (Calabrese, 2009).

To calculate individual excess risk or IER (non-threshold effects), it is necessary to know the ERU that corresponds to the number of additional cases for a given dose and a lifetime exposure and the dose received by the individual (concentration and duration of exposure) extrapolated to lifetime. The graph below illustrates how such a construction is done when a BMDL of 10% is chosen as reference dose.

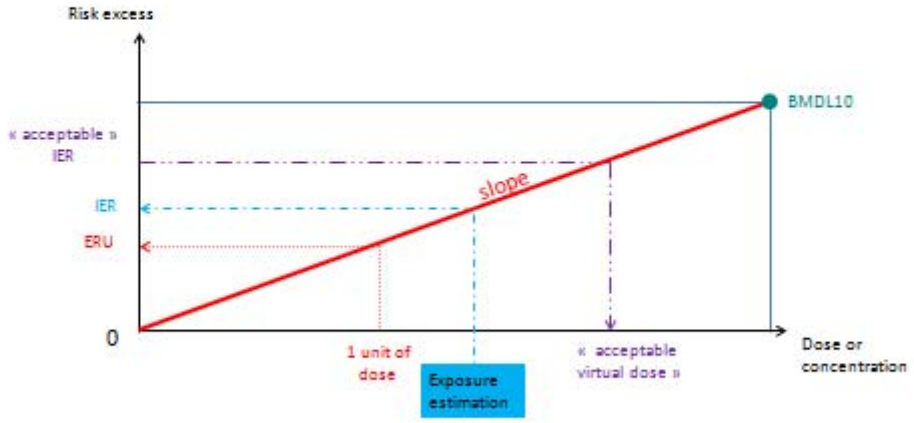


Figure 2: Determining individual excess risk using a benchmark dose at 10%

The generally accepted generic formula for risk assessment is:

IER = [exposure dose][7] x ERU x [T/Tm]

Where:

- T = duration of exposure (years)
- Tm = duration of lifetime (generally 70 years)

When using epidemiological data, calculating excess lifetime risk (ELR) can be more complicated than linear extrapolation to low doses from a point of departure, as described above.

When the risk assessment is based on epidemiological data, the excess risk can be calculated using epidemiological indicators (relative risk: RR, odds ratio: OR, etc.), and the exposure concentration (average or cumulated over the duration of exposure) related to the risk indicator. The value calculated corresponds to an excess risk per unit, i.e. excess risk (RR-1) per unit dose. Only the dose-response relationships published by the authors may be used since the entire individual database is required to calculate them.

Relative risk (RR) modelling produces 00 and rarely a linear function. Moreover, calculating excess risk based on a predetermined exposure scenario can be done in two ways to take account of the frequency of disease in the studied population or other “naturally” occurring diseases in a human population:

- Simplified, linear approach taking account of the probability P of the occurrence of a disease in a benchmark population: ELR=RR*P- P

7 In the case of inhaled toxic material, the dose is sometimes replaced by the inhaled concentration.

- Approach using the life table technique, which consists of compiling excess risks based on life tables of the benchmark population.

To ascertain the duration of exposure, the scenarios used to calculate excess risks must be clearly described. One of the scenarios often chosen for occupational exposure is the following: 40 years of exposure 8 hours a day, 5 days a week and 48 weeks a year.

Thus, the choice to use a given calculation of excess risk must be substantiated by taking account of the different stages in defining excess risk and accepting the limits inherent to these extrapolations (Goldbohm, 2006).

7.4.2 Limits of the method

In the methodology described by the US-EPA, the relationship assumes that risks are proportional to the doses received. “Proportionality” is mathematically represented by a straight line (a linear relationship) passing through the origin. The virtue of a “linear relationship” is its simplicity. If the relationship is linear, proportionality requires that a residual risk remain, even if the dose is very low.

In addition to animal-human transposition, which is often taken into account through an adjustment of body weight, there is also the issue of the high dose/low dose extrapolation of the data observed. A number of extrapolation models (regression line, mechanistic, etc.) are used to estimate the risks incurred at low and very low doses. These models correctly adjust the results recorded at high doses and, for some, mathematically integrate knowledge of the mechanisms of carcinogenesis.

It is important to understand that due to the great number of hypotheses and approximations made to establish a given OEL, the numerical values produced are merely orders of magnitude and not accurate and precise values.

No corrections are made for high-dose toxicity, intensification of cell proliferation or DNA repair, so that current linear models are considered to overestimate risk somewhat, especially since the point of departure is the upper bound of the confidence interval of the dose-response relationship. This is what is expressed when the risks determined by these models are said to be a “plausible upper bound” or calculated on a worst-case assumption.

As a high estimate of the probability of the occurrence of cancer by unit dose, this index can be applied to all the individuals of a population, whether they belong to a sensitive group or not (Nielsen and Ovrebo, 2008).

Sometimes, to reduce the overestimation of risks inherent to linear extrapolation, a non-linear model that better satisfies the statistical criteria for data adjustment quality can be suggested.

This non-threshold extrapolation model enables the calculation of concentrations associated with individual excess risks.

The OEL Committee position

For each substance considered to act through a non-threshold mechanism, the OEL Committee studies the different quantifications of risk published in scientific literature. The data can come from epidemiological studies or toxicological studies on animals. Using a BMD is strongly encouraged in the case of co-existing studies.

The different extrapolation models used are discussed and the Committee decides on the most coherent and reliable model to adopt for quantitative risk assessment.

Data permitting, and when no published risk assessment is deemed satisfactory for defining the OEL of a substance, the OEL Committee can decide to carry out its own risk assessment following

its methodology.

Based on the different data, the OEL is expressed by a scale providing three individual excess risks, respectively 10^{-4} (i.e. an excess risk of contracting an additional cancer for 10,000 exposed people), 10^{-5} and 10^{-6}, and their corresponding pollutant concentration levels. It is important to bear in mind that IER is an increase in probability of an individual contracting the health effect in question (cancer) following exposure to the risk factor.

In adopting this approach, the OEL Committee intends to indicate that determining an acceptable risk level is the responsibility of risk managers. At the same time, detection limits of techniques used to measure the substance in the workplace are clearly described in the metrology document (cf. below).

Concept of a "pragmatic" OEL

For certain adverse effects (particularly genotoxicity, carcinogenicity and respiratory tract sensitisation), it can prove to be impossible, with the current state of knowledge and data available, not only to define a toxicity threshold, but also to quantify the health risk at low doses.

In such cases, the OEL Committee considers that any level of exposure, even low, can have a risk of causing the selected health effect. However, its usual practice is to recommend what is referred to as a "pragmatic" OEL, which does not aim to set a value below which there is no health risk, but rather to provide OSH experts with a risk management tool for limiting occupational exposure to these substances.

This type of OEL will be set based on a threshold critical effect and will follow the same stages as those described earlier in the section on "Threshold Effect Methods".

7.5 Extrapolation and adjustments of the critical dose

7.5.1 Taking into account respiratory volume (activity vs. rest)

The issue is taking into account the ratio of minute volume at rest versus during activity as an adjustment factor for the POD value.

Position of the OEL Committee

For the establishment of a 15min-STEL (average value over 15 minutes) or a ceiling value (for a period of less than 15 minutes), the OEL Committee considers that the difference in respiratory rate between healthy volunteers at rest and workers should be taken into account.

For an aerosol, if no specific data can be used to quantify the difference in respiratory rate at rest versus during activity, the OEL Committee applies the proportionality factor to the POD.

For an irritating gas, the OEL Committee considers that the POD is the same irrespective of the activity.

Thus, when data from volunteers at rest are used as the key study to establish a 15min-STEL or ceiling value, the OEL Committee will examine the need to recalculate the POD value (NOAEL, LOAEL), taking into account the respiratory volume of the workers.

7.5.2 Animal/human dosimetric adjustments for gases

The aim of these dosimetric adjustments is to recalculate a human POD (Point of Departure) value (NOAEL/LOAEL) from the one identified for animals.

The US-EPA (1994b) presents a method for determining a human equivalent dose based on animal exposure. In practice, this method has primarily been applied to three types of contaminants: gases with respiratory effects, gases with systemic effects and particles with respiratory effects.

The US-EPA divides gases into the following three categories:

- Category 1: gases that are highly water-soluble (> 1000 $mg.L^{-1}$) and/or rapidly irreversibly reactive in respiratory tract tissue;
- Category 2: gases that are moderately water-soluble (10 to 1000 $mg.L^{-1}$) that may be rapidly reversibly reactive or moderately to slowly irreversibly reactive;
- Category 3: gases that are relatively water-insoluble (< 10 $mg.L^{-1}$) and unreactive in the extrathoracic and tracheobronchial regions.

Gases in categories 1 and 2 have the greatest potential for respiratory tract effects because they are water-soluble and react with the respiratory tract. Gases in these categories are rapidly deposited on the surface of the upper respiratory tract (extrathoracic and tracheobronchial regions) and the fraction that reaches the pulmonary alveoli is much smaller. At low concentrations, effects are only observed in the extrathoracic region. Category 1 gases do not accumulate in the blood due to their high reactivity with the respiratory tract. Some examples of gases in this category are chlorine, hydrogen fluoride and formaldehyde (Walsh and Bouchard, 2002).

Category 2 gases are moderately soluble and react with the respiratory tract. Sulphur dioxide, ozone and propanol belong to this group. Gases in this category can accumulate in the blood and therefore cause systemic toxicity elsewhere than the route of entry.

Category 3 gases are relatively insoluble and therefore do not react in the respiratory tract; they primarily have extrarespiratory effects.

The following equations have been taken from the US-EPA report (1994b).

For a Category 1 gas, i.e. a gas with local action on the respiratory tract, the following equation can be applied:

Human equivalent concentration = animal concentration x DAF

where DAF: Dosimetric Adjustment Factor. This is an adjustment factor for the respiratory tract region.

For the extrathoracic region

$DAF = (Ve/ S_{ET})_{animal} / (Ve/ S_{ET})_{human}$

where:

- Ve: minute volume (cm^3/minute)
- S_{ET}: surface area of the extrathoracic region (cm^2)

For the tracheobronchial region

$DAF = [(Ve/S_{TB}) \times fp_{ET}]_{animal} / [(Ve/S_{TB}) \times f_{pET}]_{human}$

where:

- Ve: minute volume (cm^3/minute)

- S_{TB}: surface area of the tracheobronchial region (cm^2)
- fp_{ET}: the fraction of inhaled chemical concentration penetrating the extrathoracic region and thereby available for uptake in the tracheobronchial region, calculated as follows:

$fp_{ET} = \exp^{[-(KgET \times SET/Ve)]}$ where Kg_{ET} is the mass transport coefficient of the substance in the extrathoracic region. If its value is not known, the US-EPA proposes using a value of one.

For the pulmonary region

$DAF = [(Q_{alv}/S_{PU})_{animal} / (Q_{alv}/S_{PU})_{human}] \times [\exp^{(-STB/Ve)animal}/\exp^{(-STB/Ve)human}]^K$

where:

- Q_{alv}: alveolar ventilation rate (cm^3/minute)
- S_{PU}: surface area of the pulmonary region (cm^2)
- Ve: minute volume (cm^3/minute)
- S_{TB}: surface area of the tracheobronchial region (cm^2)
- K corresponds to $Kg_{ET} = Kg_{TB}$ (in animals and humans)

These dosimetric adjustments, irrespective of the route considered, enable a reduction in the value of the inter-species adjustment factors that will then be applied.

Since most substances only have short-term effects, they belong to Category 1 when in gas state.

Position of the OEL Committee

For Category 1 gases, when the animal data are sufficient, the OEL Committee will apply dosimetric adjustment as described in the US-EPA document (1994b) in the process for establishing occupational exposure limits.

7.6 Taking into account the time scale in the establishment of 15min-STELs

The relationship between concentration and exposure time related to mortality was examined by ten Berge et al. (1986) for around 20 irritating and systemically acting vapours and gases. The authors showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between the concentration of exposure and the exposure time for a given chemical and for a given health effect.

When n is equal to 1, the toxicity of the chemical is equally dependent on the concentration and exposure time; when n is less than 1, the exposure time determines the toxicity of the chemical much more than the concentration; and when n is greater than 1, the toxicity of the chemical is determined much more by the concentration than by the exposure time.

Ideally, the n value should be determined for all chemicals by evaluating the concentration compared to the response for several exposure times. However, this information is only available for a limited number of substances.

Position of the OEL Committee

When sufficient data are available, the OEL Committee specifically analyses the toxicity of the chemical and evaluates exposure data to identify the n value used in the equation of ten Berge before applying it to derive a 15min-STEL value.

If the data are not available, the Committee identifies the most appropriate n value by applying the rules commonly accepted by the scientific community.

The OEL Committee uses time adjustment (e.g. the equation of ten Berge) when the exposure time in the study differs from that for which the short-term exposure limit has been calculated.

However, it is important to stress that the values calculated with this equation should always be compared to field data to assess their plausibility and that expert judgement should be used to determine the validity of the derivations.

Table 1: n values taken from ten Berge et al. (1986)

	Value of n (average)
Systemic Chemicals	2.7
Hydrogen Sulfide	2.2
Methyl *t*-butyl ether	2
Methylenechlorobromide	1.6
Ethylenedibromide	1.2
Tetrachloroethylene	2
Trichloroethylene	0.8
Carbon tetrachloride	2.8
Acrylonitrile	1.1
Irritants	
Ammonia	2
Hydrogen Chloride	1
Chlorine pentafluoride	2
Nitrogen dioxide	3.5
Chlorine	3.5
Perfluoroisobutylene	1.2
Crotonaldehyde	1.2
Hydrogen Fluoride	2
Ethylene imine	1.1
Bromine	2.2
Dibutylhexamethylenediamine	1

8 Recommending OELs

The objective of the OEL Committee is to make recommendations, based solely on the most recent scientific knowledge, to determine OELs during inhalation exposure, so that repeated exposure 8 hours a day, 5 days a week throughout a working life does not cause adverse effects on the health of workers.

To establish OELs, the Committee considers both short-term and long-term adverse effects.

8.1 8h-OELs

The method used to form a recommendation for an OEL time-weighted over 8 hours follows the principles outlined in the section on General Toxicity. In particular, all the data available for each substance is analysed in order to determine:

- The critical effect that must clearly explain what the application of a given level of OEL in the workplace is supposed to protect against,
- The key study or studies describing the critical effect and the chosen reference dose (NOAEL, LOAEL or BMD).

After setting a reference dose, the OEL Committee establishes a numerical value for an 8h-OEL, if necessary applying adjustment factors such as those described earlier.

The OEL Committee position

The value is set with the regulatory context in mind. Namely, the 8h-OEL can be exceeded for short periods during the workday, on condition that:

- The time-weighted average of values over the entire workday (8 hours) is not exceeded;
- The value of the STEL, if it exists, is not exceeded (cf. below).

The recommendation for each OEL will be justified in a summary report in sufficient detail for others working in the field to understand the arguments on which it is based. In particular, clear justification will be provided for the critical effect selected, the study chosen and the adjustment factors applied.

When it is not possible to calculate an 8h-OEL but the OEL Committee considers that critical effects can occur over the long term, it may recommend not exceeding 1/5th of the 15min-STEL over an 8-hour work period.

8.2 15min-STELs

In some cases, an 8h-OEL is not sufficient to protect the health of workers from the effects induced by inhaling the substance in question. For example, high concentrations occurring over short periods of a working day cannot be controlled through the use of an OEL time-weighted over 8 hours.

The OEL Committee then recommends a 15min-STEL. This corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical in the worker's breathing zone over a 15-minute reference period during the peak of exposure, irrespective of its duration.

Choice of the OEL Committee

15min-STELs are intended to protect the health of workers from short-term toxic effects by limiting the intensity of exposure peaks and from certain long-term effects due to repeated acute exposure. For substances with a non-threshold mechanism of action in particular, the basic postulate is that with exposure to any dose, even over a very short period of time, there is non-zero probability of the critical effect (cancer in most cases) occurring.

All of the data recorded in the toxicological profile (see 'General toxicity' section) are examined to identify effects related to short-term exposure (level, frequency, duration). The OEL Committee recommends basing the establishment of 15min-STELs on an analysis of all available scientific data.

Like for the 8h-OEL, a critical effect, source study and benchmark dose are identified. Adjustment factors can be applied when calculating the 15min-STEL using the same criteria as given above.

Sometimes however, the available data are not sufficient to calculate a 15min-STEL. The OEL Committee then recommends not exceeding five times the value of the 8h-OEL over a 15-minute period (pragmatic 15min-STEL). The OEL Committee has chosen to use the factor of five since it corresponds to the 90th percentile of French values with both an STEL and an 8h-OEL and is considered sufficiently protective (ANSES, 2009). Therefore, if there is no recommended 15min-STEL, workers should not be exposed, during a working day, to more than six 15-min. periods of maximum exposure to an intensity not exceeding five times the value of the 8h-OEL.

Note that for some substances, the repetition of an acute effect such as **irritation or corrosion** can result in chronic effects harmful to the health of workers such as chronic inflammation. If the OEL Committee considers that the critical effect in question can be prevented by limiting the intensity of exposure peaks, **it may decide to only set a 15min-STEL**. In this case, the recommended 15min-STEL will be intended to protect against an acute effect that could cause chronic effects to occur over the long term.

If the OEL Committee considers that the critical effect in question can be prevented by applying a short-term exposure limit, then it will not recommend an 8h-OEL.

The OEL Committee may recommend, as a preventive measure, not exceeding 1/5th of the 15min-STEL over the course of an 8-hour work shift (AFSSET, 2009; ANSES, 2010).

8.3 Ceiling values

The OEL Committee has studied the issue of measures to be recommended in cases when it would be relevant to limit the number of exposure peaks during a working day or set an exposure value that should never be exceeded (AFSSET, 2009; ANSES, 2010; ANSES, 2013b).

In this case, the OEL Committee will recommend a ceiling value, defined as an atmospheric concentration in workplaces, that should not be exceeded at any time during the day.

The ceiling value applies to substances for which the toxicological profile shows that exposure can instantly result in a **serious and potentially irreversible effect that cannot be controlled by application of an 8h-OEL or 15min-STEL**.

Position of the OEL Committee

The OEL Committee considers that only substances recognised as being highly irritating or

corrosive and those that may have potentially irreversible serious effects over the very short term should have a recommended ceiling value. The experts consider that a ceiling value does not conflict with an 8h-OEL. Depending on the substance, the OEL Committee may therefore recommend:

- a ceiling value only
- a ceiling value and an 8h-OEL
- a ceiling value and an 15min-STEL

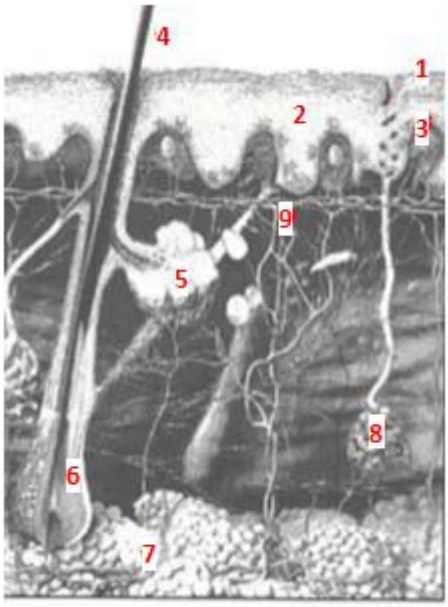
It is important to note that only continuous and specific measuring methods are appropriate for monitoring the ceiling value.

If there is no appropriate measuring method to monitor such a value, the OEL Committee will indicate this and will recommend encouraging research to be able to take continuous measurements. Moreover, for information, it will mention the methods that are currently available to monitor the proposed value, being sure to highlight their limitations and deviations from the OEL Committee's recommendations.

9 Assigning "skin" notation

9.1 General information on skin structure

The skin is the interface between the inside of the body and the environment. Not only is it an organ that provides mechanical, physical and biological protection from external stresses, it is also a target organ and the source of various metabolites. Through its epidermal barrier function, the skin prevents the loss of internal biological fluids and the penetration of xenobiotics into the body.
By its surface area (approximately 2 m^2) and weight (practically 13% of the body weight in adults), the skin is the most naturally widespread and heaviest organ (with the exception of the surface area of the pulmonary alveoli).
The skin has three major compartments: the epidermis, the dermis and the hypoderm. Multi-cellular, multi-layered and differentiated, the epidermis undergoes constant renewal. The tissue with the highest exposure to external damage, it consists of two main regions: the horny layer, or *stratum corneum* (SC), and the living epidermis.
The dermis is a connective fibrous tissue responsible for skin tonicity. It is separated from the epidermis by the dermo-epidermal junction, which serves as a diffusion filter for the circulating nutrient matter and metabolites. Blood and lymphatic vessels circulate in the dermis; a number of nerves also run through it.
These structures are associated with skin appendages such as sweat glands, hair follicles and sebaceous glands, as shown in the diagram below.



1 : stratum corneum

2 : living epidermis

3 : dermo-epidermal junction

4 : hair

5 : sebaceous gland

6 : hair follicle

7 : adipose panicle

8 : sweat gland

9 : capillaries

Figure 3: Schematic representation of the skin (Falson-Rieg, 2004)

9.2 Parameters of skin permeation

Percutaneous absorption, understood as a process of passive diffusion through a membrane, is quantified using the parameters described below.

The quantity of matter crossing the skin Q (g) by unit area S (cm^2) to ascertain the administered dose.

Flow J ($g.cm^{-2}.h^{-1}$) or speed of matter transfer per unit area. The flow depends on the diffusion coefficient D ($cm^{-2}.h^{-1}$) of the product transferred, the diffusion path δ (cm) and the difference in concentration ΔCm ($g.cm^{-3}$) of diffusing matter between entry from and exit into the diffusion environment as indicated in the equation below:

$$(dQ/dt)\ 1/S = J = D\ \Delta Cm / \delta$$

The diffusion path, δ, is often equated to the thickness of the skin or the *stratum corneum* (10 to 20 µm).

The distribution coefficient

The greater the affinity of the product for the skin, the easier the transfer. This affinity is evaluated using the substance's distribution coefficient K, which is the ratio of concentrations at equilibrium between the exterior environment (concentration Co on the external surface of the skin) and the skin (concentration Cm in the skin):

$$K = Cm/Co$$

This distribution coefficient is paramount because it induces the transfer process to the skin. It is often modelled by the octanol-water distribution coefficient with an approximate distinction of affinity toward either the lipid domain ($\log K > 3$) or the hydrophilic protein domain ($\log K < 3$)[8].

Permeability coefficient

A membrane's barrier performance is expressed by the permeability coefficient P ($cm\ h^{-1}$) where:

$$P = J/Co = DK/\delta$$

With K= Cm/Co

This parameter, which groups diffusion and distribution together, is used widely to compare:

- the absorption of various substances by a single membrane (subject to identical testing conditions),
- the resistance of various membranes to the passage of a permeant. This can be measured by comparing the penetration of a substance in healthy skin and in altered skin; the latter being either devoid of *stratum corneum*, or devoid of lipids due to the action of solvents or detergents, or modified by impregnation of exogenous substances.

Permeation parameters depend on the testing procedures used.

9.3 Place of "skin" notation in defining OELs

In the past, risk assessment of chemical substances at the workplace was based on an estimation of the atmospheric concentrations in a worker's breathing zone. The pulmonary route was thus the main (and often only) exposure pathway considered, and a specific methodological framework described by numerous bodies that set OELs explains the way in which they are defined (Boeniger, 2003).

[8] Traditional approach. Note that the guidelines of the GHS Regulation consider log K > 4

On the other hand, there are no commonly-accepted principles for the risk assessment of exposure by the cutaneous route. And yet, given the significant decrease in inhalation exposure levels for OELs over the past 50 years, or the replacement of a number of volatile agents with non- or low-volatile substances (Boeniger, 2003), this exposure pathway is taking on greater importance (Fenske, 2000; Semple, 2004). The International Programme on Chemical Safety's publication on the specific subject of dermal absorption in its Environmental Health Criteria series attests this development (WHO, 2006). When a substance can cause a systemic adverse effect, not only exposure by inhalation needs to be taken into account, but also cutaneous exposure, which can increase the substance's total body burden.

Dermal penetration notations accompanying the lists of limit values for inhalation [Skin for SCOEL, MAK and the ACGIH, R in Switzerland, and recently different notations for the NIOSH: SYS, Fatal, DIR, IRR, COR and SEN (NIOSH, 2009)] are currently the only tool for identifying the heightened risk potential by the cutaneous route.

Most of these notations were assigned based on a compilation of information from a variety of sources, according to data availability (Nielsen & Grandjean, 2004). The information used includes the observation of effects in humans following skin exposure, *in vivo* or *in vitro* measurements of dermal penetration, measurements of acute skin toxicity in animals and the use of modelling. Nielsen and Grandjean and Drexler have shown major discrepancies in the meaning and implications of "skin" notations and in the substances assigned notation depending on the institution responsible (Nielsen and Grandjean, 2004; Drexler, 1998). The authors underscore the fact that approximately one third of substances in the various OEL lists are assigned skin notation, which they feel reduces the notation's scope as a warning signal. The decision to assign skin notation is largely based on a substance's capacity to penetrate the skin. Sometimes the experience gained from work processes is also taken into account. Thus substances for which effects have been observed in the workplace following skin exposure are also assigned "skin" notation.

Lastly, as underlined by Bos et al. (1998), the absence of "skin" notation does not necessarily indicate the absence of risk by skin exposure, but may simply reflect the lack of relevant data on a substance.

Despite what is mentioned above, a consensus can be reached on the elements to be retained a minima for assigning "skin" notation. Thus, in most cases (US-EPA, 1992):

- The dermal absorption of gas and vapours is of little importance in relation to pulmonary absorption for the OEL;
- Direct skin contact with high-volatile, low-boiling liquids does not lead to significant dermal absorption due to the rapid evaporation of the liquid;
- Solids and liquids with a boiling point higher than the ambient temperature and a low vapour pressure can lead to skin exposure through both direct contact and aerosol deposit on the skin;
- The skin of the hands, forearms, face and neck enter into contact with a much higher volume of air than the volume inhaled over the course of a workday. That is why, in some circumstances, even a low deposit can lead to a significant increase in body burden.

Some of the accepted criteria for choosing suitable publications for assigning skin notation are indicated in Annex A5.

The OEL Committee position

There are prerequisites to take into account before assigning “skin” notation:

- “Skin” notation concerns the dermal absorption of the substance (whether solid, liquid or gas);
- Dermal absorption must only be taken into account in comparison with inhalation, at the same level of exposure as the OEL;
- “Skin” notation is only assigned if dermal absorption leads to a significant increase in the exposure and if it causes a systemic effect;
- “Skin” notation does not concern and is not intended to warn against direct effects on the skin of substances that have irritant properties, cause dermatitis or are sensitisers;

The OEL Committee deemed it necessary to implement a multi-step process to systematically identify the information to be sought and set qualitative and quantitative criteria for determining whether or not “skin” notation should be assigned.

Step 1: Collecting data for qualitative assessment of possible dermal absorption

- The physico-chemical properties of the substance (physical state, lipophilicity, molecular weight, volatility);
- Hazard statements, particularly those relating to toxicity through dermal absorption;
- Effects observed following skin contact with the substance;
- Duration of exposure, etc.

Step 2: Collecting quantitative data

- Directly measuring dermal absorption in humans or animals using in vivo or in vitro models, flow through the skin (J in $mg.cm^{-2}.h^{-1}$). An extensive quantitative data compilation project on this subject was carried out in Sweden, and the OEL Committee refers to this research whenever possible to obtain data on cutaneous flow (Johanson and Rauma, 2008). Recent data from scientific literature must also be examined carefully;
- Finding the dose absorbed by the skin, which can be ascertained by the quantity of substance in direct contact with the skin by unit area;
- Applying ECETOC criteria: the quantity of compound absorbed following exposure to hands and forearms (2000 cm2) for 1h must contribute to more than 10% of the systemic dose absorbed by inhalation over an 8-hour workday at the 8h-OEL, considering an inhalatory absorption of 50% and a volume of inhaled air of 10 m^3 (ECETOC, 1993);
- When the chosen critical effect acts through a non-threshold mechanism (case of cancer), the 8h-OEL used for ECETOC calculations is the one that corresponds to the concentration of the substance inducing an excess risk of 10^{-4}.

Step 3: Choosing quantitative data

1. Data on human skin are preferable to data on animal skin
2. In vivo studies are preferable to in vitro data
3. The doses in question must be infinite or significant rather than low doses
4. As a last resort and if no data are available, physico-chemical data or Quantitative Structure-Activity Relationship (QSAR) data may be taken into account

The OEL Committee uses all of the information available to assess compliance with the application criterion of a skin notation. The expert judgement provides for certain sensitisers in particular.

10 Assigning “ototoxic” notation

This section has also been covered in a methodological report by ANSES that addresses the following points in detail (ANSES, 2013a).

10.1 General information on noise and hearing loss

Sound can disrupt work, sleep and communication and even damage physical health. When noise is measured in workplaces, it is always with the aim of assessing its intensity and frequency to determine whether it harms employee health and well-being. The best-documented physiopathological effects related to noise include irreversible hearing damage resulting in hearing loss and extra-auditory effects such as high blood pressure, stress, poorer performance and tinnitus (WHO, 2003).

The effects of exposure to noise on hearing partly depend on the characteristics of the noise and its ability to reach the sensory structures of the inner ear. However, there are also major differences in individual sensitivity.

In workplaces, daily exposure to high noise levels is a risk factor that can result in work-related deafness further to damage to the inner ear. Risks of hearing damage and its severity increase with the level of noise, exposure time and nature of the noise (ongoing, intermittent and/or impulse).

Noise is often present in the workplace along with chemical exposure. Consequently, the hearing disorders observed in several occupational categories are mostly attributed to noise exposure alone and do not take into account the possible involvement of other agents. The concept of occupational deafness has often been used as a synonym for hearing loss due to noise, which may not be accurate. Current standards for protection of hearing do not take into account the potential risk posed by chemical exposures.

10.2 General information on ototoxicity

An ototoxic agent is defined as a chemical that causes a functional impairment, hearing impairment or cell damage in the inner ear, especially to the hair cells, auditory or balance neurons, or the vestibulocochlear nerve.

Substances that impair hearing and balance by acting primarily on the trunk along the central auditory pathways are regarded as neurotoxic. Ototoxicity is systemic toxicity targeting cells involved in auditory function.

Chemical agents responsible for diseases of the ear may be in gaseous (gas, vapour), particle or aerosol form (dust, fumes, mist). Hearing damage results if exposure to these substances occurs at sufficiently high concentrations (which may, however, be lower than those at which the substance is considered toxic in other ways).

The ototoxic action of certain chemicals is heightened by the presence of noise (even at levels, for example, that are lower than those set by legislation as a threshold for initiating preventive action: 80 dBA) and/or by concomitant exposure to other ototoxic substances.

It has long been known that the effects of simultaneous exposure to numerous chemical agents cannot be predicted on the basis of their individual effects (Johnson et Morata, 2010). Often, the effects of exposure to multiple agents exceed the simple addition of the effects produced by single exposure to each agent (Humes, 1984). Since noise is the commonest exposure causing hearing

loss in humans, special attention has been paid to combined exposure to noise and ototoxic agents.

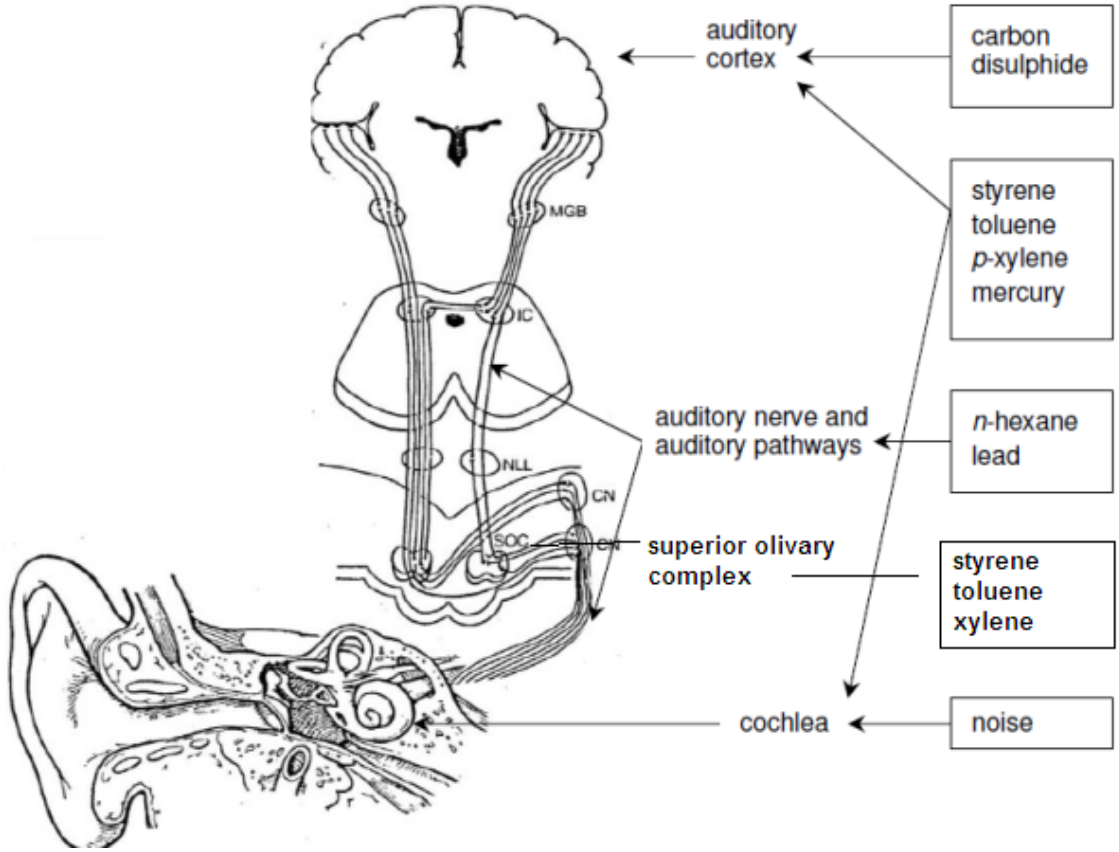


Figure 4: Diagram of the auditory system indicating the sites of action of certain chemicals (adapted from Johnson and Morata, 2010)

10.3 Place of “ototoxic” notation in defining OELs

The 'ototoxic' notation assigned by the OEL Committee indicates a risk of hearing impairment in the event of co-exposure to noise and the substance, to enable preventionists to implement appropriate measures (collective, individual and/or medical).

It thus clearly indicates the need to take into account, in the risk assessment of these substances, potential effects on the health of workers that may result from interactions between noise and the ototoxic substances, in accordance with the minimum health and safety requirements set out in Directive 2003/10/EC regarding the exposure of workers to noise and with Article R4433-5 of the French Labour Code.

The OEL Committee position

The OEL Committee recommends:

- Introducing an "ototoxic notation", indicating a risk of hearing impairment in the event of co-exposure to noise and the substance below the recommended OELs, to enable preventionists to implement appropriate measures (collective, individual and/or medical);
- Assigning this notation to chemicals for which there is a certain level of evidence on their possible ototoxic effect in the event of co-exposure to noise;

- Conducting research to better characterise the risks associated with co-exposure to noise and ototoxic agents;
- Conducting further studies to clearly determine the exposure limits, the effects of concentration peaks, the type of medical surveillance to propose, and the intervals between hearing tests required for any substance identified as ototoxic.

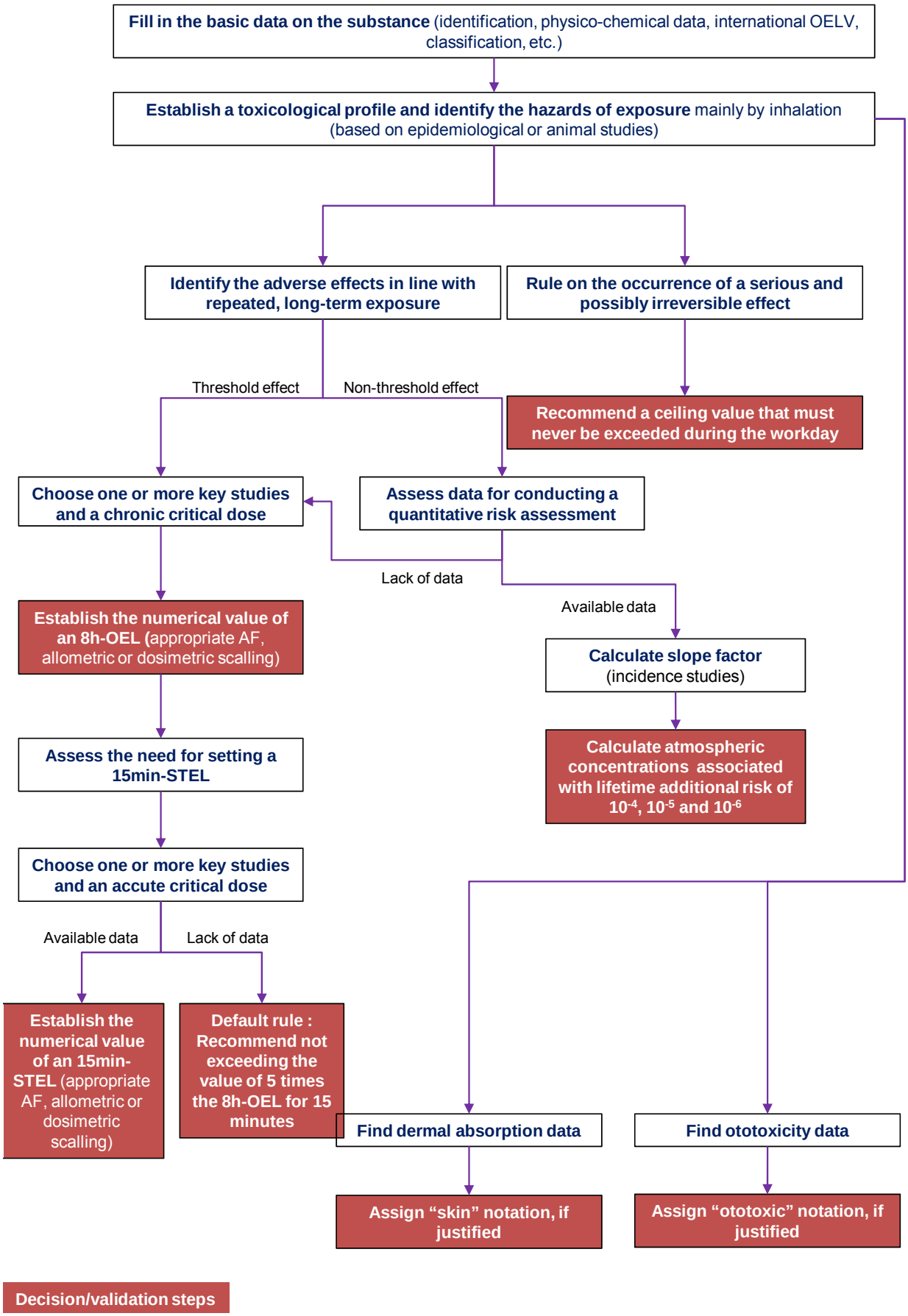


Figure 5: decision tree for the establishment of OELs

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Annex A1: Guidance for the reading of *in vivo* toxicological studies (Afsset, 2010)

For a description of toxicological studies, the Committee referred to a guide to toxicological studies inspired by the approach proposed by Lewandowski and Rhomberg (2004). The aim is to present the information to be reported in the data collection tables in a structured and systematic way.

Study design

- Toxicological study design: does it conform to a recognised methodological framework or a standard method (OECD guidelines, regulatory protocol, etc.)?
- Was the study conducted according to recommendations for Good Laboratory Practices (GLPs)?
- Was specific information given about the species, breed, strain, sex and age of the animals used?
- What was the number of animals tested?
- What were the ranges and number of doses tested? What was the duration and frequency of administration?
- Was the maximum tolerated dose (MTD) exceeded in the context of this study?
- What was the purity and volatility of the substance tested? What was its stability in the chosen exposure environment? What was its composition and origin?
- Was the route of administration defined? Was the vehicle used specified? In the case of oral exposure, did it involve administration by food intake or oral gavage? What was the composition of the animals' dietary regimen?
- What are the diseases or infections recorded in the animal population undergoing experimentation?
- Was the plan for conducting the study defined and described?
- Was exposure to the tested substance measured (for precision of the administered dose)?

Data collected in animals: measuring toxicological effects

- Which data were collected (haematological and biochemical analyses, organ weights, anatomopathological observations and characterisations, etc.)?
- Was the area of observation defined *a priori?* What are the degree of accuracy and definition of the effects measured?
- With regard to the means implemented for these measurements, was their suitability specified (certain detection, related uncertainties, etc.)? Were the analytical methods described?
- What was the degree of precision in recording the observed toxicity effects and clinical findings? To what extent were the observed effects described?

Study duration

- In the case of a carcinogenicity study, what was the exact duration of experimentation?
- Was information given on unexpected intercurrent events in animals (epidemics, premature deaths)? If so, how did these data influence the overall assessment of the results obtained?

- Was information given on unexpected intercurrent events related to how the study was conducted (failure in the regular administration of the substance, failure to maintain a controlled temperature, etc.)? If so, how did these data influence the overall assessment of the results obtained?

Interpretation of the results

- Did the observed results correspond to all initially defined areas of observation? If not, what were the reasons?
- Are concurrent control data from the study available?
- Are the laboratory's original records available?
- Is information available on the doses administered (if possible, with the results of chemical analysis verification)?
- Is there a dose-effect or dose-response relationship?

Annex A2: Guidance document for assessing epidemiological studies

Author, date, name of the study and other identification parameters	*Any information identifying the study so it can be referred to where necessary and quoted from*
Study objectives	*Analytical study, descriptive study;* *Background, objectives of the study and/or hypotheses tested* *Acute (sensitivity, irritation, sensitisation) or chronic toxicity (carcinogenicity, reproductive toxicity - fertility or development)*
Study type	*Choice of study type (cohort, case-control, cross-sectional study, meta-analysis, case report, etc.)*
Health parameters or pathology studied	*Definition of the health effect(s) studied* *Description of the indicator for the health effect*
Population	*Selection criteria for the study population:* *Cohort* *Inclusion/exclusion* *Industry* *Country* *Recruitment method: voluntary, etc.* *Socio-demographic description, sex-ratio, age* *Case-control* *Selection of cases and controls: precise description, group size, origin of subjects, etc.*
Substance studied	*Characterisation of the substance or substance group: definition, type of indicator (biomarker, metabolite, etc.)*
Description of the exposure groups (exposed, non-exposed according to levels of exposure)	*Numbers, age, sex, dose, etc.*
Route of exposure (and conditions if clinical trials)	*Respiratory, dermal, digestive route, etc.*
Methods of assessing exposure	*Job-exposure matrix, individual expert assessment of records, statements by subjects or relatives, quantitative assessment of exposure (sampling methods)*

Time sequence	*Exposure prior to observed effects?*
Exposure indicators (or parameters)	*Likelihood of exposure* *Frequency of exposure* *Level of exposure: semi-quantitative or quantitative data (geometric or arithmetic mean, confidence interval, range - maximum, minimum), etc.* *Duration of exposure* *Cumulative exposure*
Power of the study *a posteriori*	A posteriori *calculation of the study power* *Other discussion items: variability of exposure in the source population, mismatching or over-adjustment, etc.*
Additional information	*Methods of data processing, of retrieving missing data* *Mention of selection or classification bias, etc.* *Terms of the clinical trial (randomised, double-blind, etc.)…* *Discussion of uncertainties associated with exposure measurements*
Confounding factors	*Reporting of those which have been taken into account* *Control methods: stratification or other statistical methods*
Strength of the association observed	*Relative risks, odds ratio, etc.*
Dose-response relationship	*Any information related to the dose-response relationship*
Quality of the study	*Selection bias, misclassification, taking confounding factors into account, etc.*
Statistical analysis method	*Type of test, unilateral or bilateral*

Annex A3: Assessment of toxicity studies according to Klimisch

Toxicological studies should identify the effects resulting from exposure to the substance and the histological characteristics, and establish dose-effect relationships. Since 1981 the OECD has been developing guidelines for testing chemicals. One of the themes of this programme concerns the effects on health. The OECD proposes standard experimental protocols to properly assess the various effects involved and the dose-effect relationships, when they exist. Using these standard protocols helps to ensure a study's scientific quality and reproducibility.

By comparing studies with these guidelines, their quality can be assessed. Also, several studies can be compared with each other in order to select those considered of better scientific quality, or at least more weight can be given to those considered the most reliable and most relevant. When an OEL is being established, it is preferable that the selected experimental studies follow or are similar to the OECD guidelines. They can also follow other guidelines proposed by recognised organisations in the field of toxicology (e.g., the US National Toxicology Program).

However, the studies available in the literature may be old and do not necessarily adhere to the OECD guidelines. Faced with this situation, the quality of studies should then be considered on the basis of other relevant criteria, such as the purity of the test substance, the species of animals studied, the test conditions or the duration of exposure. This is advocated by the assessment according to Klimisch *et al.*, which comes from a 1997 publication [Klimisch *et al.* 1997]. Many other methods have been proposed in the scientific literature to assess the quality of studies, but they will not be detailed here. The decision to select the Klimisch assessment is based on the fact that this rating system is fairly recent, has been recognised and validated at European and international level, and is the most widely used in practice in the field of regulatory assessment of chemicals (TGD, OECD, US EPA, REACh).

In the approach of Klimisch *et al.*, when a study does not meet the OECD standard protocols, its reliability is determined by the following criteria:

- Type of animals tested (species, breed, sex, age);
- Composition, purity and origin of the substance;
- Purpose of the investigations (histopathological or clinical observations, etc.);
- Precision of the description of the lesions observed;
- Presence of a control group or historical control;
- Description of test conditions;
- Description of routes and doses administered;
- Identification of a dose-response relationship, if possible;
- Description and relevance of the statistical methods used;
- Information about the period of investigation during the animal's life;
- Information about the animals' living conditions (including diet).

Klimisch *et al.* (1997) therefore established a rating system for experimental studies that takes into account their reliability (standardised methods, GLPs (Good Laboratory Practices)), a detailed description of the publication and the relevance and usefulness of the data connected with the risk assessment. This rating is from 1 to 4, details of which are summarised below and Table 1 presents the associated criteria:

- Rating 1: Reliable without restriction
- Rating 2: Reliable with restrictions
- Rating 3: Not reliable

- Rating 4: Not assignable

The most relevant studies accurately describe the nature of the toxic effect, the number and percentage of animals concerned by the observed effects and the conditions of exposure (duration - concentration).

When establishing the OEL, any selected experimental studies that do not follow the OECD guidelines should be reviewed and rated according to the Klimisch method. It is therefore recommended that only those experimental studies rated 1 and 2 be taken into account.

Table 3 : Klimisch rating criteria

Rating	Category of validity
1	**Reliable without restriction**
1a	GLP study compliant with standardised tests (OECD, EC, US EPA, FDA, etc.)
1b	Comparable to guideline study
1c	Protocol compliant with a national standardised method (AFNOR, DIN, etc.)
1d	Protocol compliant with other standardised, scientifically accepted and sufficiently detailed methods
2	**Reliable with restriction**
2a	Standardised study without detailed documentation
2b	Standardised study with acceptable restrictions
2c	Comparable to a standardised study with comparable restrictions
2d	Protocol compliant with national standardised methods, with acceptable restrictions
2e	Well-documented study compliant with scientific principles, acceptable for evaluation
2f	Accepted calculation method
2g	Data derived from reference works and data collection
3	**Not reliable**
3a	Documentation inadequate for evaluation
3b	Significant methodological shortcomings
3c	Unrealistic protocol
4	**Not assignable**
4a	Summary
4b	Secondary literature
4c	Original reference not available
4d	Original reference in a language different from the international language (English)
4e	Documentation inadequate for evaluation

Annex A4: Guidance for the analysis of *in vitro* genotoxicity/mutagenicity tests

In order to assess the quality and relevance of genotoxicity tests, information and data are needed in the context of *in vitro* studies (excluding nationally or internationally recognised standard methods). These criteria are proposed in particular by the Klimisch rating system, a TGD (Technical Guidance Document) and by other international organisations.

What is the purity of the substance tested? What is its composition and origin?
Are the physico-chemical properties of the substance specified (pH, solubility of the substance, stability, volatility, etc.)?
Are the physico-chemical properties and the osmolarity of the mixture or vehicle used specified?
Has the choice of animal species or cell strain tested been defined and justified? Have the bioactivation conditions been specified? If a GMO is used, is qualitative or mechanistic information available to interpret another test?
Has the choice of equipment and the method been precisely defined?
Doses tested: are the mechanisms the same at all doses (presence of cytotoxicity at too high doses which is non-specific to the genotoxicity of the substance)?
Are there data on the dose-concentration ratio in the test system?
Where proliferative effects are demonstrated, are they due to an action on the regulation of mitosis (mitogenic effects) or regeneration following cytotoxicity?
Are data available on adverse effects that may have an impact on the results of the study (solubility, impurities, pH variation, impact on osmolarity, etc.)?
What is the level of validation of the test method? Does it respect the GLPs and the guidelines approved by the international scientific community?
Are references available that prove the method's suitability?
Are positive and negative controls used? What is the level of description of these controls?
Can a dose-response relationship be defined? What is the strength of the associations?

Annex A5: Guidelines for assessing the relevance of articles dealing with dermal absorption

In vivo assessment

- Human;
- Animal (pig, hairless rat, etc.);
- Condition of the skin;
- Known application surface area;
- Amount of substance applied per unit of skin surface area (*finite* dose, *infinite* dose);
- Physical state of the substance in the study (solid, liquid, gas);
- Donor vehicle: water, other (surfactant, solvent);
- Concentration of substance in the vehicle per unit of skin surface area;
- Occlusive or non-occlusive conditions on the skin;
- Study duration: 24h;
- Parameters measured:
    - Amount remaining on the skin surface at time t after application;
    - Distribution in the different structures of the skin (*stratum corneum*, epidermis, dermis) at time t if animal experimentation;
    - Kinetics of plasma concentration for the duration of the experiment;
    - Identification and assaying of metabolites.

Ex vivo assessment

- Two-compartment diffusion cells (Franz type cell) of known geometry (volume, contact surface area), static or dynamic;
- Whole skin: human, animal (pig, hairless rat);
- Application surface area;
- Amount of substance applied per unit of skin surface area (*finite* dose, *infinite* dose);
- Physical state of the substance in the study (solid, liquid, gas);
- Donor vehicle: water, other (surfactant, solvent);
- Concentration of substance in the vehicle per unit of skin surface area;
- Donor in occlusive or non-occlusive conditions;
- Recipient compartment: aqueous solution of sodium chloride (0.9%) and albumin if product is highly lipophilic, sink conditions maintained during the experiment, temperature 35-37°C, sufficient mixing;
- Study duration: 8h to 24h;
- Parameters measured:
    - Amount remaining on the skin surface at time t after application;
    - Distribution in the different structures of the skin (*stratum corneum*, epidermis, dermis) at time t;

- Kinetics of concentration in the recipient for the duration of the experiment;
- Transfer flux through the skin;
- Skin/vehicle, skin/recipient partition coefficients ;
- Metabolites in the dermis and recipient for short times (< 6h).

Work and results that are unnecessary for the objective of assigning the Skin-Dermal absorption notation:

- *Ex vivo* studies with synthetic membranes, reconstructed skin, the *stratum corneum* alone, stripped skin, snake shedding;
- *Ex vivo* studies with receiver containing ethanol, surfactant;
- Very short study time masking skin reservoir effect;
- Relative results:
  - % absorption referring to another absorption route (oral, pulmonary);
  - % absorption referring to an unspecified deposited dose;
  - Skin permeability coefficient (transcutaneous flow/concentration in the donor);
  - Comparison of enhancer effect with permeability coefficients.

Lists of current recommendations concerning dermal absorption (methodological references)

OECD 427 (2004): OECD Guidelines for the Testing of Chemicals; skin absorption: *in vivo* method

OECD 428 (2004): OECD Guidelines for the Testing of Chemicals; skin absorption: *in vitro* method

OECD Series on testing and assessment Number 28: Guidance document for the conduct of skin absorption studies

European Commission/Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Products /0970/06: Opinion on “Basic criteria for the *in vitro* assessment of dermal absorption of cosmetic ingredients” (28 March 2006)

Annex A6: Examples of some substances known for their ototoxicity (Johnson and Morata, 2010)

Chemicals with confirmed ototoxic properties, and which are commonly used in the workplace, are listed in the table below.

Class of chemical	Examples
Organic solvents	Styrene, toluene, p-xylene, ethylbenzene, chlorobenzene, trichloroethylene, n-hexane, n-heptane, carbon disulphide, solvent mixtures
Metals	Lead, mercury, organotins
Asphyxiants	Carbon monoxide, hydrogen cyanide, acrylonitrile, 3,3'-iminodipropionitrile
Other substances	Pesticides (organophosphates, paraquat, pyrethroids, hexachlorobenzene), polychlorinated biphenyls

Part B – Drafting the assessment report of exposure measurement methods in the workplace

1 Objectives and general principles

1.1 Definitions

Protocol

This term designates the operating procedures published by recognised bodies.

Method

This term designates the principle of a method for measuring a pollutant in the air of the workplace. It encompasses the sampling technique and the analysis technique.

For example: sampling using a pump through an activated charcoal adsorption tube, CS_2 desorption and analysis by GC/FID.

The same method can be described in different protocols.

1.2 Objectives

The OEL CES assesses the methods for measuring the concentration of a substance in the air of the workplace so as to recommend one or more benchmark methods for measuring the concentration of the substance for comparison with occupational exposure limit values established by the OEL CES.

The objective is not to classify all of the studies according to a quantified grading system, but rather to give a structured and systematic presentation of the criteria for making a final, scientifically-based decision. Methods can be classified into four categories depending on their level of validation:

- Category 1A: recognised and validated methods;
- Category 1B: partially validated methods;
- Category 2: indicative methods (essential criteria for validation are not clear enough);
- Category 3: the method is not suitable, essential criteria for validation are lacking or inappropriate.

Having a validated physical measuring method or having the possibility of developing a validated method with a relatively precise timetable (entry into force of the OELV based on this timetable) is one of the three criteria used by the Steering Committee on Working Conditions (COCT) to establish a binding occupational exposure limit. This criterion means that:

- methods classified in Categories 1A and 1B are those that are preferably recommended for monitoring exposure in reference to binding regulatory OELVs;
- methods in Category 2 require additional validation to assess their applicability for monitoring exposure in reference to binding regulatory OELVs. When there are no additional studies, they are recommended for monitoring exposure in reference to indicative regulatory OELVs;
- Methods in Category 3 cannot be used to monitor exposure in reference to binding or indicative regulatory OELVs.

1.3 Overall principle

The general methodology involves:

- Documenting the various protocols for measuring the pollutant in workplace atmospheres;
- Identifying the various methods that are available by grouping together similar protocols;
- Pre-screening the methods by searching for exclusion criteria that automatically result in a Category 3 classification so as to avoid unnecessary further analysis;
- For methods not pre-classified in Category 3:
    - Listing various parameters for evaluating the sampling technique, analytical technique and performance of the overall method;
    - Evaluating each method in terms of compliance with the performance requirements given in the NF EN 482 Standard[9] and the decision-making criteria presented later in this document;
    - Classifying each method into one of three categories based on the evaluation undertaken:
        - Category 1A: recognised and validated methods
        - Category 1B: partially validated methods
        - Category 2: indicative methods (essential criteria for validation are not clear enough).
    - Recommending the most appropriate method(s) for measuring concentrations for comparison with the OELs.

[9] The NF EN 482 Standard stipulates general requirements for the performance of procedures for the measurement of chemical agents in workplace atmospheres.

2 Detailed methodology

2.1 Inventory of protocols

The sampling and analysis protocol for the assessment of occupational exposure must have been published in a reliable source.

Protocols specifying measurements at fixed workstations only, environmental measurements or measurements of indoor air quality are not taken into account. However, they may be documented and presented if no individual measurement protocols have been sufficiently validated.

The main sources consulted are the following (non-exhaustive list):

- France: INRS (National Research and Safety Institute – MétroPol database)
- http://www.inrs.fr/metropol/sommet.htm
- Europe: Gestis database: groups together validated European methods, centralised in the BGIA (Berufsgenossenschaftliche Institut für Arbeitsschutz) Germany
- http://www.dguv.de/ifa/en/gestis/analytical_methods/index.jsp
- Spain: INSHT (Instituto Nacional de Seguridad e Higiene en el Trabajo)
- http://www.insht.es/portal/site/Insht/menuitem.a82abc159115c8090128ca10060961ca/?vgnextoid=f6a8908b51593110VgnVCM100000dc0ca8c0RCRD
- UK: HSE (Health and Safety Executive)
- http://www.hse.gov.uk/pubns/mdhs/index.htm
- Germany: IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) : IFA-Arbeitsmappe Messung von Gefahrstoffen http://www.ifa-arbeitsmappedigital.de/sg/9/inhalt.html
- BGIA-Arbeitsmappe Messung von Gefahrstoffen:
- http://www.bgia-arbeitsmappedigital.de/sg/9/_sid/_@,dA1te-vql5KCW/inhalt.html
- USA: NIOSH (National Institute for Occupational Safety and Health)
- http://www.cdc.gov/niosh/nmam/default.html
- USA: OSHA (Occupational Safety and Health Administration)
- http://www.osha.gov/dts/sltc/methods/toc.html
- International scientific literature if necessary

Standard-setting bodies:

- AFNOR: Standards prepared or examined by Commission X43C "Workplace atmospheres" (ICS code 13.040.30): http://www.afnor.fr
- ISO: Standards prepared or examined by Sub-Committee TC 146/SC 2 “Workplace atmospheres” (ICS code 13.040.30): http://www.iso.org

2.2 Identification of available methods

Various methods are identified through the documented protocols.

Protocols are said to be similar when they use the same measuring method, meaning that the sampling systems, desorption or mineralisation techniques and analytical techniques are similar.

2.3 Search for exclusion criteria

Exclusion criteria are criteria that cause a method to be classified in Category 3, which means that the method is not suitable for the assessment of occupational exposure against the OELs recommended by the OEL Committee.

Except for the case of ceiling values (see monitoring of ceiling values below), these exclusion criteria are as follows (also see Tables 6 and 7):

- for sampling:
    - sampling not individual
    - sampling medium not suited to the states of the chemical at atmospheric pressure and ambient temperature (20-25°C): case in particular of mixed gas-vapour/solid or liquid aerosol phases
    - sampling medium not suited to the fraction to be sampled
    - no studies of trapping or retention capacity
    - sampling rate for passive media calculated and not determined experimentally
    - no data on the storage of samples (or insufficient recovery rate) or storage life of samples less than 2 days.
- for analysis:
    - analytical technique not suited to the chemical to be assayed
    - inappropriate measurement range and limits of quantification
    - adsorption/desorption efficiency not determined or insufficient
- for performance of the overall method:
    - no data on the uncertainty of the method or expanded uncertainty not compliant with the requirements of the NF EN 482 Standard.

Whenever one of these criteria is met, the method is classified in Category 3 and is not evaluated in detail.

2.4 Inventory of the various parameters required for assessment

If no exclusion criteria have been found, then the method is evaluated in detail.

To undertake this evaluation, various parameters are documented based on similar protocols describing the method.

This inventory is drawn up using the following three tables:

Table 4: Descriptive parameters

METHOD X		Brief description of the method	
DESCRIPTION			
Parameters		Protocol 1	Protocol 2
Gas/vapour Aerosol Mixed		*Specify whether it is the gaseous or particulate form, or both. In the case of aerosols, specify the conventional fraction sampled.*	
Sampling	Active / passive	*Specify whether the sample is active (passage of a flow of air by means of a pump) or passive (diffusion of air through the media)*	
	Sampling system	*Specify the sampling system (closed cassette, tube, cyclone, etc.), the nature of the sampling media (glass fibre filter, activated carbon, etc.) and its characteristics (diameter, amount of adsorbent, etc.)*	
	Rate	*Specify the recommended rate.* *For passive sampling, specify the sampling rate (if the sampling rate is given by the manufacturer, note (M), or if experimental validation data are available, note (Ex))*	
	Volume	*Specify the recommended air volume*	
	Duration	*Specify the recommended sampling duration*	
Analysis	Sample preparation	*Specify the conditions of sample preparation: desorption/dissolution* *(nature of the solvent, dissolution of the filter/cassette, thermal desorption, etc.)*	
	Analytical technique	*Specify the analytical technique used: GC, HPLC, ICP, ion chromatography, etc.*	
	Analytical parameters	*Specify the main analytical parameters*	

Table 5 : Validation data

METHOD X	Brief description of the method	
VALIDATION DATA		
Parameters	**Protocol 1**	**Protocol 2**
Field of validation	*Specify the measurement range over which the method was validated*	
Coefficient of desorption / Desorption efficiency	*Specify the values of the coefficients of partition and adsorption-desorption, and their acceptance criteria*	
Recovery rate	*Specify the technique used (controlled atmosphere, spiking of tube or sampling media, etc.)* *Specify the conditions: mass of analyte used, rate, etc.*	
Experimental validation data on the sampling rate	*To be completed if passive media is used*	
Capacity / Breakthrough volume	*For adsorbent tube sampling, specify the conditions of determination*	
Linearity of detector response (analysis instrument)	*Ability to provide responses proportional to the concentration of analyte to be assayed*	
Conservation and storage tests prior to analysis	*Study of loss of analyte as a function of time, storage (and transport) conditions to be respected.*	
Environmental conditions	*Specify, where necessary, the influence of environmental parameters: temperature, pressure, humidity, wind speed, direction of the sampling device, etc.*	
Selectivity	*Specify the influence of possible interfering compounds (interfering with sampling or analysis)*	
Speciation	*Can the method be used to identify the chemical form in which the substance occurs?*	

Table 6 : Characteristics

METHOD X		Brief description of the method	
CHARACTERISTICS			
Parameters		**Protocol 1**	**Protocol 2**
Conditions for determination of the 8h-OEL	**Estimated expanded uncertainty**	*Include if possible sampling uncertainty + analytical uncertainty* *Detail as far as possible the different components of the uncertainty*	
	Limit of detection	*Converted to concentration in the air mg.m^{-3}* *Specify the method of determination and the volume sampled*	
	Limit of quantification	*Converted to concentration in the air mg.m^{-3}* *Specify the method of determination and the volume sampled*	
Conditions for determination of the STEL (or five times 15-min 8h-OEL[(2)])	**Estimated expanded uncertainty**	*Include if possible sampling uncertainty + analytical uncertainty* *Detail as far as possible the different components of the uncertainty*	
	Limit of detection	*Converted to concentration in the air mg.m^{-3}* *Specify the method of determination and the volume sampled*	
	Limit of quantification	*Converted to concentration in the air mg.m^{-3}* *Specify the method of determination and the volume sampled*	
ADDITIONAL INFORMATION			
Additional information		*Give any additional information for supplementing the assessment of a given method:* *practical nature* *availability of materials or reagents* *ease of implementation…*	

2.5 Performance requirements for the evaluation of each method

The evaluation of measurement methods is based on:

- the general performance requirements set out in the NF EN 482 Standard
- the additional requirements that must be met for certain specific types of measurement procedures and systems. These include:
  - diffusive samplers (NF EN 838)
  - pumped samplers for gases and vapours (EN 1076)
  - detector tubes (NF EN 1231)
  - sampling pumps (NF EN 1232 and NF EN 12919)
  - dust sampling systems (NF EN 13205)
  - metals and metalloids (NF EN 13890)
  - direct-reading instruments (NF EN 45544 all parts)

If there are several protocols that use the same method, this method is studied against the validation data described in each protocol. It may turn out that some protocols are not very detailed and do not have all of the required validation data. In this case, the OEL Committee ensures that the method does indeed have the validation data through the data available in each protocol.

2.5.1 Origin of the methods

The method must have been published in a reliable source (see 2.1).

2.5.2 Description of the measurement procedure

The procedure must include all of the information necessary for successfully conducting the procedure and indicate, among other things, the expanded uncertainty obtainable, the measuring range, the duration of sampling, interferences and information relating to environmental or other conditions that can influence performance of the measurement procedure.

2.5.3 Sampling conditions

Selectivity

The measurement procedure must specify the relevant information on the nature and extent of interferences, as well as the various means of mitigating their effects.

Procedures for measuring chemicals in the form of atmospheric particles must stipulate a method for sampling the size fraction corresponding to the limit value set for the chemical. Size fractions are defined in the NF EN 481 Standard.

If different limit values are defined for various species of a chemical, the measurement procedure must determine each species concerned.

Speciation

It must be specified whether the method identifies the chemical form in which the substance is found.

Description of the sampler

For sampling an aerosol, the sampling apparatus must comply with the requirements of standard EN 13205 for the type of aerosol sampled (inhalable or respirable), and the conventional fraction sampled must be specified.

Additional requirements specified in standards EN 838, EN 1076, EN 1231, EN 1232, EN 12919, EN 13205, EN 13890 and EN 45544 must be met for particular types of measurement procedure and apparatus.

Volume of air recommended (or sampling duration)

The sampling duration must be as close as possible to the reference period of the limit value.

While some methods are validated for very short sampling durations, the CES will verify the possibility of extending the duration of sampling based on validation data and particularly information on the capacity of the sampling medium.

The recommended sampling volume must be less than two-thirds of the breakthrough volume measured in accordance with the NF EN 1076 Standard in the case of gas or vapour sampling.

Diffusive uptake rate

For passive sampling, tests must have been performed to validate the diffusive uptake rate in compliance with standard EN 838 or an equivalent procedure.

Influence of environmental conditions

The influence of environmental parameters must be specified: temperature, humidity, pressure, air velocity, orientation of the sampling apparatus.

2.5.4 Transport and storage

A detailed description of transportand storage conditions (packaging, temperature, duration, etc.), as well as information on the stability of samples, must be included for critical samples.

In other cases, a brief description must be provided. The storage life of samples prior to analysis must be specified.

Details of studies on sample stability and storage must be provided. The recovery rate after storage will be used to evaluate optimal storage conditions.

Average recovery rates after storage must not have differences greater than 10% of the initial concentration for gas and vapour sampling in accordance with the NF EN 1076 Standard.

2.5.5 Analysis conditions

Sample preparation:

Sample handling conditions must be described: desorption, mineralisation, etc.

In the case of aerosols, the method of sample dissolution must specify whether deposits on the sides of the sampling apparatus are taken into account.

Analysis technique:

The analysis technique and conditions must be specified.

Detector linearity must be verified on the minimum measuring range.

2.5.6 Validation data

Minimum measuring range

The measuring range must cover at least 0.1 to 2 times the 8h-OEL and 0.5 to 2 times the STEL.

If a protocol has not been validated on these concentration intervals, the CES takes account of quantification limits, as well as data on the sampler's capacity, to assess the extent to which the protocol can be used on the required concentration range.

Desorption efficiency

Desorption efficiency must be mentioned and the method of determination specified.

According to NF EN 1076 desorption efficiency must be:

- ≥ 75% (with coefficient of variation ≤ 10%) for type A sampling systems[10]
- ≥ 95% (with coefficient of variation ≤ 10%) for type B sampling systems[11]

According to the NF EN 13890 Standard, the analytical recovery rate must be ≥ 90% (with coefficient of variation ≤ 5%)

Breakthrough volume/capacity

For active sampling through an adsorption tube, the breakthrough volume or capacity must have been determined.

The conditions for determination must be specified.

Detection limit

The limit of detection and conditions of determination must be specified.

Quantification limit

The limit of quantification must be specified and must be such that one-tenth of the 8h-OEL and half of the 15min-STEL can be measured. The conditions of determination must be specified.

Unless otherwise mentioned, it is considered equal to approximately 3.33 times the limit of detection if this was determined as being three times the standard deviation of the blank measurements.

Uncertainties

Data enabling an assessment of the uncertainty of the measurement procedure (sampling and analysis) must be mentioned.

Standard EN 482: 2006 specifies that the expanded uncertainty must be:

- ≤ 50% at 0.5 to 2 times the STEL,
- ≤ 50% at 0.1 to 0.5 times the 8h-OEL,
- ≤ 30% at 0.5 to 2 times the 8h-OEL.

For mixtures of airborne particles and vapours, the relative expanded uncertainty must be

- ≤ 50% at 0.5 to 2 times the STEL,
- ≤ 50% at 0.1 to 0.5 times the 8h-OEL,
- ≤ 50% at 0.5 to 2 times the 8h-OEL

In the event the expanded uncertainty is not specified, the CES compares the uncertainty data available (precision, bias, etc.).

[10] Type A sampling system: system based on adsorption on a solid or a medium impregnated with reagent, desorption with a solvent and then analysis of the desorption product

[11] Type B sampling system: system based on adsorption on a solid or a medium impregnated with reagent, thermal desorption and then analysis of the desorption product

2.5.7 Other characteristics of the method

Adaptability of the method in case of significant decrease in the 8h-OEL

The CES verifies whether the conditions for sampling and analysis can be adapted in the case of significant decrease in the 8h-OEL, particularly with regard to quantification limits, sampling conditions, etc.

Capacity of the method to monitor an STEL

If the protocols for implementing a method do not clearly specify whether they are applicable to monitoring an STEL, the CES will examine the data on sampling, quantification limits, sampler capacity, desorption efficiency and recovery rate to verify the method's applicability for monitoring STELs.

In the absence of an STEL, the CES will adopt the same approach to determine whether the method can be used to measure a threshold of five times the 8h-OEL with a sample taken over a 15-minute period.

Ease of implementation (cost, required materials, etc.)

Where applicable, if the method requires specific materials or special conditions to be implemented, these conditions are clearly mentioned.

Implementation safety

Implementation of the method (sampling and analysis) must not be a source of potential risk to the health and safety of workers.

2.6 Decision-making criteria and classification of methods

2.6.1 Decision-making criteria

Methods must fulfil the criteria and requirements presented in the previous section.

However, so as to refine the evaluation of methods and be able to classify them into the four categories defined above, various decision-making criteria have been established.

These criteria vary slightly depending on the purpose of the method, i.e. monitoring 8h-OELs, 15min-STELs or ceiling values. They are broken down in the following paragraphs.

Monitoring 8h-OELs

For the classification of methods, the OEL Committee refers to the previous evaluation (see 2.5) and the decision-making criteria shown in Tables 6 and 7.

Table 7: Decision table for the classification of methods – sampling parameters

Parameters related to the sampling method	Decision-making criterion	Classification of the method			
		1A	1B	2	3
The method applies to OEL controls by individual sampling	Yes	X			
	No				X
Sampling medium suited to the states of	Yes	X			

Parameters related to the sampling method	Decision-making criterion	Classification of the method			
		1A	1B	2	3
the chemical at atmospheric pressure and ambient temperature (20-25°C): case in particular of mixed gas-vapour/solid or liquid aerosol phases	Partially (1 phase)		X		
	No				X
Sampling medium suited to the conventional fraction to be sampled	Yes	X			
	No				X
Trapping capacity (breakthrough volume) studied in a controlled atmosphere in a concentration interval of 0.1 to 2 times the 8h-OEL over a period of:	>4 hrs.	X			
	>1 hr. and < 4 hrs.		X		
	<1 hr.			X	
	If study with a concentration interval greater than 2*8h-OEL?			X	
	Not studied	see if retention study			
Trapping capacity (retention) studied by injection of an aliquot directly on the medium or in an air flow in a concentration interval of 0.1 to 2 times the 8h-OEL over a period of:	>4 hrs.		X		
	>1 hr. and < 4 hrs.			X	
	If study with a concentration interval greater than 2*OEL?			X	
	Not studied				X
Identification and study of the influence of the environmental conditions on trapping capacity: relative humidity (80%) at ambient temperature (20-25°C), stability of the medium in light for a reactive medium (drift) Passive: air speed	Identification and study	X			
	Identification		X		
	No information			X	
Determination of the sampling rate for passive media	Experimental over the range of 0.1 - 2 times the 8h-OEL	X			
	Experimental over a different concentration range			X	
	Calculated				X
Identification and study of interferences (influence on trapping capacity in particular)	Identification and study	X			
	Identification		X		
	No information			X	
Sample storage	≥ 8 days	X			
	4- 8 days		X		
	2-4 days				
	< 2 or no tests				X

Table 8: Decision table for the classification of methods – analytical parameters

Parameters related to the analytical method	Decision-making criterion	Classification of the method			
		1A	1B	2	3
Analytical technique suited to the chemical to be assayed (e.g. assaying a VOC with colorimetry *versus* GC)	Suited	X			
	Not suited				X
Limits of quantification, measurement range suited to concentrations corresponding to the OELs (see Figure 1)	Suited	X			
	Partially suited		X		
	Adaptable			X	
	Not suited				X
Adsorption/desorption efficiency	Several concentrations over the range of 0.1-2 times the 8h-OEL	X			
	1 point or concentration range >		X		
	Not determined or insufficient				X
Identification and study of interferences	Identification and study	X			
	Identification		X		
	No information			X	
Uncertainty data (sampling + analysis)?	Expanded uncertainty compliant with the NF EN 482 Standard	X			
	Other uncertainty data		X		
	No data or expanded uncertainty not compliant with the NF EN 482 Standard				X

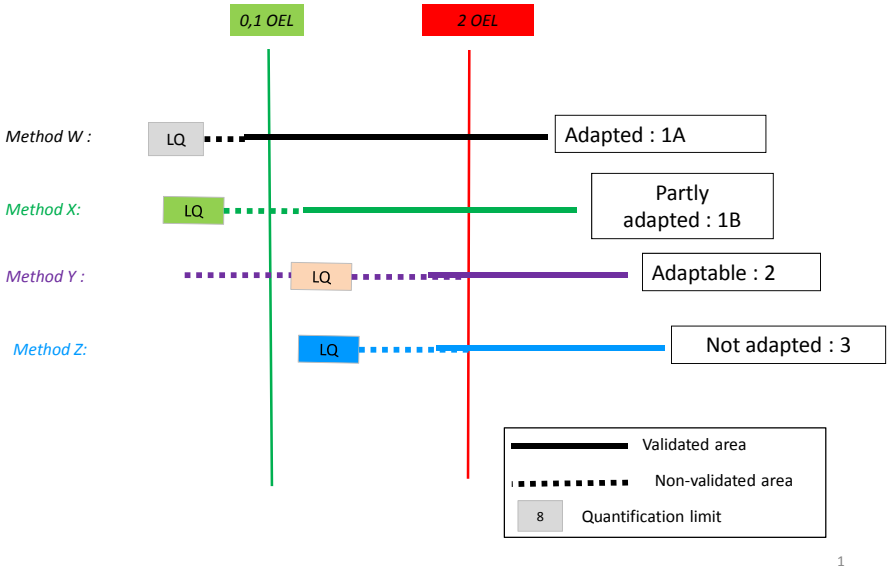


Figure 6 : Graphical representation of quantification limits and of range of measurements

15min-STEL monitoring

For the evaluation of methods for an STEL, the criteria defined above also apply. The exception is the method's interval of applicability which must cover 0.5 to 2 times the 15min-STEL. Thus, the decision-making criteria for the classification of methods involving trapping capacity, sampling rate for passive media, limits of quantification, adsorption/desorption efficiency and uncertainty data must apply over the range of 0.5 to 2 times the 15min-STEL.

Under the French regulations[12], for technical monitoring of the limit value, the measurement method must be able to measure one-tenth of the 15min-STEL. Indeed, "during the initial evaluation, OEL compliance can be assessed from the first measurement campaign if all the results of the homogeneous exposure group are less than one-tenth of the monitored OEL".

As such, when a method cannot measure one-tenth of the 15min-STEL, it cannot be classified in Category 1A or 1B for regulatory monitoring of the 15min-STEL. However, it may be classified in Category 1A or 1B solely for assessing occupational exposure.

Monitoring ceiling values

Given the definition and purpose of ceiling values, measurement methods that involve taking a sample of air and then conducting a post-analysis are not suitable for the monitoring and control of this type of limit value.

For the monitoring of ceiling values, the priority therefore should be to determine whether there are specific and individual systems for measuring concentrations continuously with real-time results.

These systems must meet the general requirements of the NF EN 482 Standard and the special requirements of the NF EN 45544 Standard relating to gases and vapours only. Special attention will need to be paid to the following characteristics (see Annex B1):

- Issue of measurable concentration range;
- Sensitivity;
- Response time;
- Selectivity (particularly with the use of an electrochemical cell)

If there are no individual portable continuous concentration measurement systems, then the OEL Committee will also evaluate portable, transportable and fixed continuous concentration measurement systems. If there are no continuous concentration measurement systems, then the Committee can mention other concentration measurement methods, clearly indicating that these methods are not suitable for monitoring a ceiling value. Therefore, these methods will be classified in Category 3.

The following table presents the various types of methods and their possible classification based on their performance for the monitoring and control of ceiling values:

Type of method	Maximum classification	Requirements
Continuous measurement of exposure using an individual analyser	1A	Compliance with the NF EN 45554 Standard
Continuous measurement of exposure or concentration in the workplace atmosphere using a portable analyser	1B	Compliance with the NF EN 45554 Standard
Continuous measurement of concentration in the	2	Compliance with the NF EN

[12] Ministerial Order of 15 December 2009 on technical monitoring of occupational exposure limits in the workplace and conditions for accrediting organisations responsible for monitoring, published in the French Official Journal on 17 December 2009

workplace atmosphere using a fixed or transportable device		45554 Standard
One-time measurement using an immediate-response device or system (e.g. detector tubes)	3	Compliance with the NF EN 1231 Standard
One-time measurement using a delayed-response device or system requiring laboratory analysis	3	-

2.6.2 Classification of methods (ranking of criteria)

The method will be classified according to the lowest score assigned to one of the assessment criteria.

However, depending on the criterion concerned, and based on expert judgement, it is not impossible for the method to be classified at a higher level, subject to this being clearly justified.

2.7 Developing recommendations

A detailed comparative study of the methods is then conducted with regard to the various validation data and their technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for the purpose of comparison with the different recommended limit values (8h-OEL, 15min-STEL, ceiling value).

The OEL Committee may recommend one or more methods. In each case, it clearly specifies each method's conditions of applicability, and in particular states for which type of value (8h-OEL, 15min-STEL, ceiling value) the methods are recommended.

If it becomes clear that no method has been sufficiently validated, the OEL Committee may recommend the use or development of a measurement method, stressing its limitations and stating in particular the parameters that need further validation.

When a method poses a particular hazard, whether during the sampling or analysis phase, the OEL Committee shall stress this in its report and may issue recommendations on the implementation of this method or on possible improvements to be made to it.

In the event that no method has been described for the studied substance, the OEL Committee may issue recommendations based on information drawn from the literature.

3 Metrology summary report

3.1 Development

A metrology summary report is written by the WG on Metrology and submitted for validation to the OEL Committee.

3.2 Content

3.2.1 General information

The first section of the report presents general information about the substance to be studied, i.e. information on the identity of the substance and its physico-chemical properties.

3.2.2 OELs

Current OELs

The aim of this section is not to present all of the current limit values but rather to review, when applicable, the French values together with the European and international values, especially if they are very different from the French values.

These values should be considered against the documented methods since the methods have generally been established and validated for concentration levels corresponding to these OELs.

OELs recommended by the OEL Committee

The OELs recommended by the OEL Committee are reported.

The methods are evaluated based on the recommended concentration level and the nature of the value (8h-OEL, 15min-STEL, ceiling value).

3.2.3 Occupational uses

The most common uses of the substance are mentioned; this list is not exhaustive.

3.2.4 Presentation and discussion of methods for measuring substance X in workplace atmospheres

Inventory and classification of measurement methods

The methods and related protocols are presented. The classification of the methods is specified, using the following table for example:

No.	Method	Similar protocols	Category

Discussion of measurement methods

- Methods classified in Category 1:

The evaluation that led the methods to be classified in Category 1A or 1B is presented.

- Methods classified in Category 2:

The evaluation that led the methods to be classified in Category 2 is presented.

- Methods classified in Category 3:

The evaluation that led the methods to be classified in Category 3 is presented.

3.2.5 Conclusion and recommendations

The conclusion of the expert appraisal report should clearly highlight the method recommended by the OEL Committee as well as the criteria that led to the choice of this method.

The recommendations of the OEL Committee regarding the method(s) recommended or to be developed should be written. Likewise, the types of values (8h-OEL, 15min-STEL, ceiling value) for which the methods are recommended should be clearly specified, for example using the following table.

Method	Type of OEL	Classification
Active sampling in an active charcoal tube – CS_2 desorption – GC/FID analysis	8h-OEL 15min-STEL	1B
Passive sampling in a badge – CS_2 desorption – GC/FID analysis	8h-OEL	1B
	15min-STEL	3 (not applicable for monitoring the 15-min STEL)
Active sampling in a Tenax tube – thermal desorption – GC/FID analysis	8h-OEL	1A
	15min-STEL	2

The various tables used to collect data for methods 1A, 1B and 2 are included in the annexes of the summary report.

4 Bibliography

EN 482: 2006 - Workplace atmospheres. General requirements for the performance of procedures for the measurement of chemical agents.

Pr NF EN 482: 2011 - Workplace atmospheres – General requirements for the performance of procedures for the measurement of chemical agents

EN 838: 2010 - Workplace atmospheres. Diffusive samplers for the determination of gases and vapours. Requirements and test methods.

in 1076 2010 - Workplace exposure. Procedures for measuring gases and vapours using pumped samplers. Requirements and test methods.

EN 1231: 1997 - Workplace atmospheres. Short-term detector tube measurement systems. Requirements and test methods.

EN 1232: 1997 - Workplace atmospheres. Pumps for personal sampling of chemical agents. Requirements and test methods.

in 12919 1999 - Workplace atmospheres. Pumps for the sampling of chemical agents with a volume flow rate of over 5 L/min. Requirements and test methods.

EN 13205: 2002 - Workplace atmospheres. Assessment of performance of instruments for measurement of airborne particle concentrations.

EN 13205: 2010 - Workplace atmospheres. Assessment of performance of instruments for measurement of airborne particle concentrations.

EN 13890: 2009 - Workplace exposure. Procedures for measuring metals and metalloids in airborne particles. Requirements and test methods.

EN 45544: 2000 - Workplace atmospheres. Electrical apparatus used for the direct detection and direct concentration measurement of toxic gases and vapours.

- Part 1: general requirements and test methods.
- Part 2: performance requirements for apparatus used for measuring concentrations in the region of limit values.
- Part 3: performance requirements for apparatus used for measuring concentrations well above limit values.
- Part 4: guide for selection, installation, use and maintenance.

Annex B1: Summary of the general requirements from EN 45544 (Parts 1 and 2)

Table 9 : General requirements for mechanical construction, indications given by the system, fault signals, adjustments, batteries, marking and gases to be detected (NF EN 45544 Standard, Parts 1 and 2)

Mechanical construction	Suitable devices for application of test gas
	Resistance to substances
Indication	Indication of values below the lower end of the scale
	Indication if upper limit of the measuring range is exceeded
	Precision required to measure the performance requirements of the Standard
	Shall operate at concentrations above the alarm
Fault signals	Power supply failure
	Loss of electrical continuity of sensing system
	Flow failure alarm for aspirated apparatus
	Disconnection of the sensor
Adjustments	Adjustment of the gain does not affect the 0 point
Batteries	Indication of low battery condition
Marking	
Gases to be detected	Label

Table 10 : General requirements for the instruction manual (NF EN 45544 Standard, Parts 1 and 2)

Instruction manual	Information about testing (gases, measuring range, accessories, test laboratory)	
	Installation (orientation)	
	Operating instructions and adjustments	
	Description of the measuring principle	
	Instructions for checking and calibration	
	The calibration gas, the procedure and frequency and warning notes	
	Response factors of the gases	
	Information on instrument drift	
	Operational conditions	Gases and measuring range
		$T°_{amb}$ range
		RH_{amb} range
		Supply voltage
		Characteristics and type of cable with remote sensors
		Need to shield cables?
		Battery data
		T° range for storage
		P limits and correction
		0 variation ($\Delta 0$)
	Interferences from other gases	
	Min/max flow rate, response times	
	Flow verification	
	Statements of nature of alarms and signals	
	Malfunction and corrective procedures	
	Battery operating time	
	Recommended replacement parts	
	Storage life and conditions	
	Optional accessories	
	Limitations of a sampling probe	
	Warm-up time, time of response, time of recovery, averaging time for OEL	
	Action to take if subjected to a concentration above the measuring range	

Table 11 : General requirements for the test conditions (NF EN 45544 Standard, Parts 1 and 2)

Test conditions	Test sequence
	Preparation of apparatus before test
	Environmental conditions: T, RH, P
	Test gas
	Supply voltage
	Stabilisation time
	Orientation
	Calibration

Table 12 : General requirements for the test method (NF EN 45544 Standard, Parts 1 and 2)

Test method	Unpowered storage	After storage test, carry out all the tests described below	
	Measurement of deviations	Overall uncertainty in relation to a test gas in a range of 5 concentrations	**Uo < 50%** for 0.1*[STG] < [gas] < 0.5*[STG] **Uo < 30%** for 0.5*[STG] < [gas] < 10*[STG]
		0 variation (Δ0)	**lower limit of measuring range ($L_{low}MR$)** **< manufacturer range** $L_{low}MR = 0.5*\Delta0$ if $\Delta0 <$ 0.25*[STG] $L_{low}MR = 0.8*\Delta0$ if $\Delta0 >$ 0.25*[STG]
	Mechanical tests	Vibration	see Basic requirements
		Drop test	see Basic requirements
Overall uncertainty **$[(X_{av}-X_{st})+2s]*100 / X_{st}$** 0 variation **$X_{av}+2s$** X_{av} = average of repeated n measurement results s = standard deviation of the measurements	Environmental tests in air and in the standard gas	T°	0 air **($m_{20°C}-m_{5°C}$) and ($m_{20°C}-m_{40°C}$) < Δ0 or 5% of [STG]** **($m_{20°C}-m_{-10°C}$) < 2*Δ0 or 5% of [STG]** STG **see basic requirements (modified for ($m_{20°C}-m_{-10°C}$))**
		P	see Basic requirements
		RH	see Basic requirements
		Air speed	see Basic requirements
Basic performance requirements (45544-2) **$(m_b-m_a)/m_b * 100 < (30-2s_{STG}/m_b*100)$** ($s_{STG}$ = standard dev. concentration meas. stand. test gas) **$m_b-m_a <$ variation 0** (measurements before and after test)	Performance tests	Audible alarm	> 70 dB at 0.3m
		Alarm set points	Activation at each set point
		Alarm response time	T_{alarm} < 20s
		Flow failure warning	see Basic requirements
		Warm-up time	see Basic requirements for STG
		Time of response: measurement of T_{90} (90% [STG])	T_{90} < 2.5min (or T_{50} < 1 min for some gases)
		Time of recovery: measurement of T_{10} (10% [STG])	T_{10} < 5min (or T_{50} < 1 min for some gases)
		Concentrations above measuring range	< 20% [STG] or Δ0
		Extended operation in test gas	see Basic requirements
	Orientation tests		see Basic requirements
	Electrical tests	8h-OEL function for $[gas]_{av}$ = 50% (3 levels over 8 hrs.: 100%, 50%, 0%)	45% - 55% see Basic requirements for the rest
	Drift tests		see Basic requirements
Test report			

STG = standard test gas; [gas], [STG] = concentration of gas and standard test gas; Δ0 = 0 variation; m = measurement

Part C – Criteria for choosing biomarkers of exposure (BME) and defining biological limit values (BLV)

1 Preamble

Biomonitoring and atmospheric metrology are two complementary approaches to assessing the occupational exposure levels of substances. Biomonitoring is used to assess a worker's exposure to a given chemical agent, considering all its routes of entry into the organism (lungs, skin, and digestive tract). It is especially relevant when the substances have a systemic effect and:

- when routes other than inhalation contribute largely to absorption;
- and/or when the pollutant is cumulative;
- and/or when working conditions not accounted for in the atmospheric metrology (respiratory protection, inter-individual differences in breathing ventilation, etc.) cause major differences in internal dose among individuals.

The working group on Biomarkers thus determines its programme based on these considerations.

2 Definitions

2.1 General definition of a biomarker of exposure (BME)

A BME is a parent substance, or one of its metabolites, determined in a biological matrix, whose variation is associated with exposure to the agent targeted.

Biomarkers of early and reversible effects are included in this definition when they can be specifically correlated to occupational exposure.

Figure 6 clarifies the definition by presenting the continuum between exposure and the occurrence of health effects.

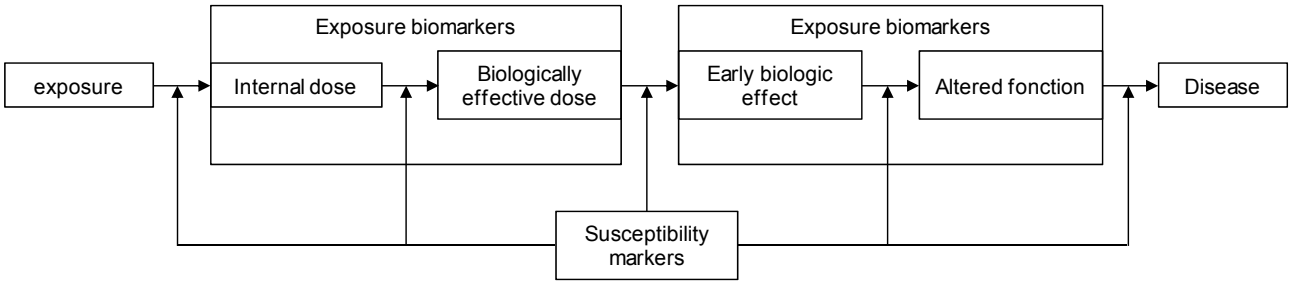


Figure 6 : exposure continuum – health effects

2.2 Definition of a biological limit value (BLV)

This is the limit value of relevant biomarkers of exposure. As for the 8h-OEL, it aims to protect workers exposed to the chemical agent in question regularly and over the course of a working life from the adverse effects related to medium- and long-term exposure.

For substances with an effect threshold, the value will ideally be determined based on a relationship with an effect considered critical (BLV based on a health effect). The health effect will usually be the one that was used to establish the 8h-OEL. Failing that, the value will be given by the average concentration corresponding to exposure to the 8h-OEL when examining the direct correlation between the concentration of the biomarker and the atmospheric concentration of the substance in question (BLV based on exposure to the 8h-OEL).

In the case of non-threshold carcinogens, when the scientific information available allows for a quantitative risk assessment, BLVs will be expressed as a scale of three concentrations corresponding to lifetime additional risks 10^{-4}, 10^{-5} and 10^{-6} (BLVs based on risk levels). When the information does not allow the derivation of biomarkers concentrations corresponding to these lifetime additional risks, pragmatic BLVs based on an effect other than cancer may be proposed. These will not be intended as values below which there are no health effects but rather will provide preventionists with tools to limit exposure to these substances in workplaces.

There may be one or several biomarkers with no associated BLVs.

2.3 Definition of biological reference values

Biological reference values can be defined based on values found in a general population whose characteristics are similar to those of the French population or in a control population not occupationally exposed to the substance in question.

For biomarkers of exposure, BRVs should be established for the general population as a priority, primarily to highlight concentrations unrelated to occupational exposure to the chemical agent in question. It is therefore necessary to ensure that there is no exposure. However, this is not certain and/or cannot be verified in field studies, even if workers are considered unexposed. For biomarkers of exposure, BRVs will preferably be established based on data in the general population[13]. However, for biomarkers of effects, it is more important to ensure that the population in which the biomarker is measured has physiological characteristics similar to the target population, which is not the case for studies in the general population. For biomarkers of effects, BRVs will preferably be established based on data in workers not exposed to the pollutant in question.

These values cannot be considered as providing protection against the onset of health effects; they can be used for comparison with concentrations of biomarkers of exposure and/or effects measured in exposed workers.

These values are particularly useful in cases where it is not possible to establish a BLV.

[13] As an example, major national surveys may be cited to the extent that they use numerous biomarkers of exposure: ENNS (France), GerES (Germany), NHANES (United States)…

3 Methodology for determining OEL Committee recommendations on biomonitoring of one or more biomarkers for exposed workers

3.1 Drafting a summary report

The bibliographic review is analysed and relevant information is summarised. This information concerns:

- The toxicokinetic and toxicodynamic data of the parent substance;
- The specificity (other substances that can produce the same biomarker, exposure outside the workplace);
- The data that can affect the interpretation of results of the biomarker(s) identified as relevant to the biomonitoring of exposed workers;
- The toxicokinetic and toxicodynamic data of the chosen biomarkers;
- The relationship between biological levels and health effects;
- The relationship between atmospheric concentrations and biomarkers concentrations, derived from exposure data from field studies or studies on volunteers;
- The toxicokinetic models used to predict the relationship between exposure and the concentration of chosen BMEs;
- The values found in the general population and/or in controls not occupationally exposed to the substance studied, separating the values found in smokers and non-smokers when possible;
- Sampling conditions (matrix, invasiveness or non-invasiveness of the method, sample contamination, etc.);
- Essential conditions to sample stability (equipment, transportation, storage) and conditions pertaining to the analytical methods, etc.

These same points will be covered in a 'discussion' section to put forward the justifications for recommending the monitoring of one or several relevant exposure biomarkers for which BLVs were derived. Sampling times and any remarks (background and biomarkers of exposure specificity, etc.) will also be included in this section.

Lastly, a concluding section of the expert appraisal report covers OEL Committee recommendations on biomonitoring for exposed workers:

- Selection of one or more biomarkers;
- Biological matrix and time of sampling;
- Nature and levels of chosen values:
    - For substances with an effect threshold: BLVs based on a health effect, BLV based on exposure to the 8h-OEL, biological reference value in the general population, biological reference value in a control population not occupationally exposed;
    - For non-threshold substances: BLVs based on risk levels, biological reference value in the general population, biological reference value in a control population not occupationally exposed, pragmatic BLV.
- Elements that can interfere with interpretation of results (any remarks on background, specificity, etc.).

The analysis methods described in scientific literature for measurement of chosen BMEs are also included in the summary report. All of the publications with the same separation and analysis techniques are grouped together. The objective of this section is not to recommend a measurement method, but to provide succinct information on certain characteristics of the analysis methods (detection limit, quantification limit and variation coefficient for results, etc.).

3.2 Collective appraisal

A presentation before a multi-disciplinary group of experts is required at this stage. The report is thus examined and then discussed by the other experts and, depending on the remarks, it is amended to produce a summary report from a collective expert appraisal.

4 Relevance criteria for recommending monitoring of one or several biomarkers for exposed workers

4.1 Determining biological limit values for substances with an effect threshold

4.1.1 There is a relationship between internal concentration and health effect

If there is sufficient data, a BLV may be calculated based on the biomarker concentration, associated with the critical effect chosen by the Committee when establishing the 8h-OEL, or with any other effect deemed relevant. The calculation of a health-based BLV is outlined in the chapter 5 of this part.

The choices of biomarkers concentrations, pharmacokinetic data and safety factors to obtain a BLV are submitted for collective expert appraisal and substantiated.

4.1.2 There is no available relationship between internal concentration and health effect

If it is not possible to quantify the relationship between concentrations of biomarkers and health effects, the alternative approach is to try to quantify the relationship between concentrations of biomarkers and atmospheric concentrations. Thus, once the OEL has been established, it will then be possible to recommend biomarker levels corresponding to exposure to the 8h-OEL. In this case however, extrapolations should be limited so as to minimise uncertainties about the recommended biological values where applicable.

Correlation between atmospheric concentration and BME concentration

When a strong correlation (linear or logarithmic) can be found between the concentrations of the chosen BME and the atmospheric concentrations of the substance studied, a BLV may be derived that corresponds to the 8h-OEL using the regression line equation, as shown in Figure 7.

The value will be given by the concentration corresponding to exposure to the 8h-OEL. BLVs can be derived from studies on volunteers or from field studies. It has to be noticed that adjustments may be necessary in studies on volunteers to take account of occupational exposure scenarios.

A brief description of the advantages and limits of these types of study can be found in Annex C1.

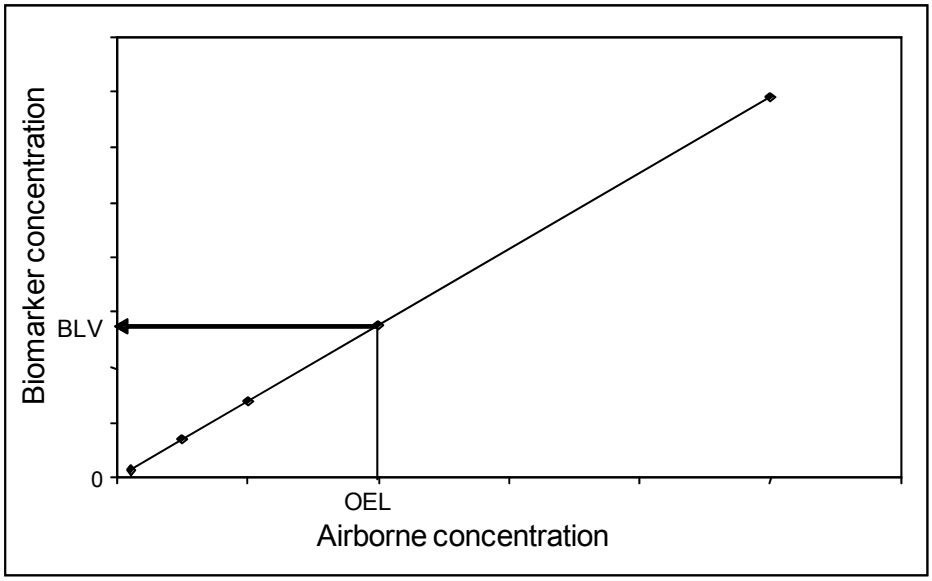


Figure 7: Determining a BLV from the 8h-OEL

Relationship between exposure and internal concentration based on pharmacokinetic modelling

In some cases, provided that there are adequate data, it is possible to extrapolate concentrations of biomarkers of exposure based on exposure (atmospheric concentrations, ingestion) and therefore the critical dose used for the establishment of the OEL, relying on the pharmacokinetic data (compartmental models, physiologically based pharmacokinetic modelling, mass conservation equations). The use of this type of approach introduces many uncertainties in the establishment of BLVs and so extrapolations should be limited and only kinetic data compatible with scenarios of occupational exposure should be used (exposure route and time)[14].

The choice of equations correlating exposure data to biological levels or pharmacokinetic models are submitted for collective expert appraisal and substantiated.

4.2 Determining biological limit values for non-threshold carcinogens

It is recognised that using a biomarkers can help prevent occupational risks in the same way as atmospheric measurements. BLVs based on risk levels and pragmatic BLVs may be proposed. BME concentrations found in exposed workers may be compared to biological reference values in the general population or in a control population not occupationally exposed to the substance in question.

4.2.1 Determining BLVs based on risk levels

In some cases, BLVs may be defined in keeping with the procedure for establishing an 8h-OEL for the substance in question. As seen earlier in the case of a BLV based on exposure to the 8h-OEL, these relationships may be derived from pharmacokinetic modelling, or correlations from exposure data (studies on volunteers, field studies). BLVs will correspond to BME concentrations or 8h-OELs identified for individual excess risks (IER) 10-4, 10-5, 10-6.

[14] animal-to-human, ingestion-to-inhalation, acute-to-chronic exposure (for the critical dose)

4.2.2 Pragmatic BLVs

When there is a relationship between exposure biomarkers concentrations and a health effect other than cancer, a pragmatic BLV is determined in the same way as BLVs for substances with an effect threshold (cf. 5.1).

4.3 Summary and decision tree for determining a BLV

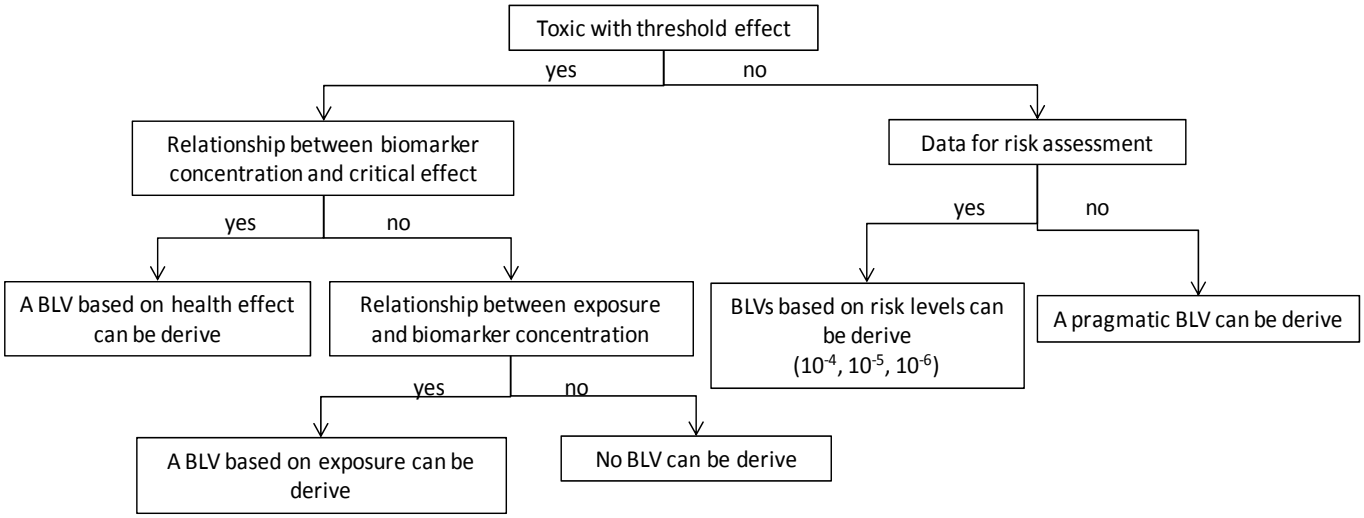


Figure 8: Decision tree for determining a BLV

5 Calculation of a BLV

5.1 Calculation of a health-based BLV

For substances with a threshold effect, the epidemiological and experimental data are examined in order to seek a relationship between the biomarkers concentrations and the appearance of the critical effect chosen.

The aim is to identify a maximum concentration at which the effect is not observed and/or a minimum concentration at which the critical effect is observed. The concentration selected will then be weighted by safety factors. The identification of a critical concentration and application of safety factors must follow the procedure described for the establishment of an 8h-OEL.

5.2 Calculation of a BLV based on exposure to the 8h-OEL

It is not always possible to establish a BLV based on human data, and animal data seldom associate the onset of health effects with the measurement of biomarkers of exposure. It may then be necessary to calculate BME concentrations from a point of departure (atmospheric concentration, daily dose) used to establish the 8h-OEL. Depending on the key study chosen to establish the 8h-OEL, certain parameters lead to many uncertainties:

- route of exposure other than inhalation
- observation period not compatible with the timing of the effect and a scenario of occupational exposure (8 hours/day; 5 days/week; 48 weeks/year for 40 years).

In this case, some organisations sometimes add statements to the BLVs obtained in this way depending on the soundness of the database and the substance's predominant type of toxic effect.

ACGIH (American Conference of Governmental Industrial Hygienists) uses the 'semi-quantitative' notation when Biological Exposure Indices (BEIs) are based on data considered not convergent enough or too few in number.

For carcinogenic substances, DFG (Deutsche Forschungsgemeinschaft) has chosen to only extrapolate concentrations from data on inhalation in humans; failing that, it establishes a BLW[15], a pragmatic value, based on the concentration levels found in the general population. Moreover, DFG has introduced the notion of biological value for populations not occupationally exposed (BAR).

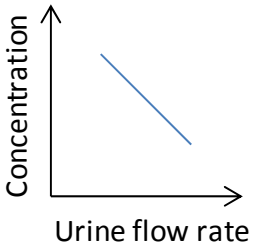
In some cases, when there are no adequate studies to establish a BLV, only BRVs may be recommended.

15 BLWs are set for hazardous substances for which the available data are insufficient to establish a BAT value; they are established for substances whose toxic effects appear at low doses, whether the substances are carcinogenic or not and recognised or suspected, and for substances whose toxicological data are insufficient

5.3 Urine creatinine value used by default for the adjustment of urinary BME concentrations

It should be noted that the relevance of adjusting urinary concentrations of chemical substances is affected by renal physiology (according to Boeninger et al. 1993).

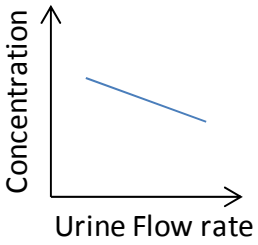
Glomerular filtration is the primary mechanism of renal elimination for many small compounds such as urea and excess sodium and free water. It plays a key role in homeostasis. Various physiological mechanisms help maintain glomerular filtration at a near-constant rate irrespective of blood flow to the heart. Many xenobiotics and their metabolites are also eliminated by glomerular filtration. When this mechanism is predominant in the elimination of a given compound, its concentration will vary depending on diuresis.



Active secretion is the two-way transport (against the electrochemical gradient) of compounds (in ionic form or not) between the peritubular capillaries (blood) and the lumen of the proximal tubules (secondary urine).

Urinary concentrations of compounds excreted by active secretion are influenced by diuresis.

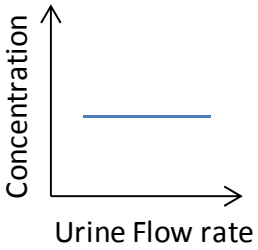
Most organic bases are secreted in urine, including conjugated organic compounds (glucurono-, glyco- and sulpho-conjuguated). Some examples of secreted compounds are penicillin, uric acid, certain sulphonamides and *para*-aminohippuric acid.



Passive diffusion (tubules) involves water-soluble substances. They are diffused from plasma to urine (through tubules) or vice-versa. Urine flow rate does not play an essential role in this mechanism. The ionisation of compounds and therefore the urinary pH for weak acids or bases is the most limiting factor.

Urinary concentrations of compounds that can easily move passively through biological membranes are not influenced by diuresis.

Some compounds such as toluene, methanol and methylmercury are known to move through tubular membranes.



In the case of filtered and secreted compounds, the influence of diuresis makes measurements difficult to interpret. It is obvious that when the urine flow rate is high, compounds are more 'diluted' in the urine, even for similar exposure levels and internal doses. In this case, and when urine is sampled over a 24-hour period, it is more relevant to adjust urinary concentrations of the compound of interest to a daily rate of creatinine excretion. Indeed, since little creatinine is reabsorbed, its excretion is influenced, in more or less the same way as the compound of interest, by diuresis.

This daily rate of creatinine has been empirically determined based on a person's age and weight (Selberg and Sel, 2001; Boeninger et al., 1993; Harris et al., 2000; Fournier and Achard, 2000).

The case of measurements taken in workplaces is more complex insofar as urine is sampled periodically and not over a 24-hour period. It is then necessary to adjust urinary concentrations of the compound of interest to urinary concentrations of creatinine. Thus, as indicated above for concentrations adjusted to the daily creatinine excretion rate, concentrations adjusted to the creatinine concentration compensate for the state of dilution and for variability related to the person's age and weight (Viau et al., 2004).

The field studies published in the literature do not always report the average concentration of urinary creatinine in the population of workers. And yet to be able to compare the results of several studies, it has to be possible to express concentrations, whether adjusted to urinary creatinine or not, based on a default value.

An average urinary concentration was therefore evaluated through large-scale studies in populations of active workers and the general population. This value will be used by default when the average creatinine concentration is not reported in the publication of interest.

Study in the general population (between the ages of 20 and 60 years)

A publication on the results of the American national survey NHANES (1988 to 1994) reports measured creatinine concentrations for over 11,000 people between the ages of 20 and 60 years (Barr et al., 2005). The authors report that the mean creatinine concentration, all ages and sexes combined, is 1.30 $g.L^{-1}$ with the following distribution:

		Creat (g/L)					
		Median			Mean		
		(95% confidence interval)					
n		All	Men	Women	All	Men	Women
22,245	All ages	1.18 (1.11 – 1.21)	1.37 (1.34 – 1.41)	0.99 (0.97 – 1.02)	1.30 (1.28 – 1.32)	1.48 (1.45 – 1.51)	1.13 (1.10 – 1.16)
3,438	20 - 29	1.53 (1.47 – 1.61)	1.73 (1.62 – 1.85)	1.33 (1.26 – 1.41)	1.62 (1.57 – 1.67)	1.83 (1.75 – 1.91)	1.41 (1.35 – 1.47)
3,259	30 - 39	1.29 (1.21 – 1.36)	1.50 (1.40 – 1.62)	1.07 (1.01 - 1.14)	1.38 (1.32 – 1.43)	1.58 (1.50 – 1.66)	1.19 (1.13 – 1.25)
2,542	40 - 49	1.19 (1.12 – 1.25)	1.47 (1.40 – 1.54)	0.90 (0.80 – 0.97)	1.25 (1.20 – 1.30)	1.50 (1.43 – 1.56)	1.01 (0.96 – 1.05)
1,823	50 - 59	0.98 (0.93 – 1.03)	1.23 (1.14 – 1.36)	0.73 (0.66 – 0.81)	1.08 (1.04 – 1.12)	1.32 (1.24 – 1.40)	0.86 (0.81 – 0.91)

Thus, mean creatinine concentrations can be calculated for the 20-59-year age group based on the means reported for each age group. The mean creatinine concentrations for the 20-59-year age group would be 1.33 $g.L^{-1}$ (both sexes combined), 1.56 (for men) and 1.12 (for women).

Studies in the workplace

Two studies report creatinine concentrations measured with urine samples taken in the workplace.

The study by Bader et al. (2012) covered a sample of approximately 6,440 workers (6,148 men and 290 women). The mean urinary concentration of creatinine was 1.45 $g.L^{-1}$ with the following distribution:

		Creat (g/L)					
		Median			Mean		
n		All	Men	Women	All	Men	Women
1,040	20 - 29	1.60	1.64	1.02	Not specified		
1,588	30 - 39	1.45	1.46	1.05			
1,827	40 - 49	1.29	1.30	0.91			
1,755	50 - 59	1.28	1.29	0.73			
6,438	16 - 69	1.36	1.37	1.00	1.45 ± 0.80	1.46 ± 0.80	1.12 ± 0.76

A study by Cocker et al. (2011) covered 20,433 workers (15,111 men, 1,558 women and 3,764 people whose sex was not reported) and urinary concentrations of creatinine were reported based on 49,506 urine samples taken between 1996 and 2007. The mean urinary concentration, both sexes combined, was 12 $mmol.L^{-1}$ (1.36 $g.L^{-1}$), and so was the median. For men (39,610 samples), the mean was 13 $mmol.L^{-1}$ (1.47 $g.L^{-1}$) and the median was 12 $mmol.L^{-1}$ (1.36 $g.L^{-1}$). For women (3,207 samples), the mean was 9.8 $mmol.L^{-1}$ (1.11 $g.L^{-1}$) and the median was 8.8 $mmol.L^{-1}$ (0.99 $g.L^{-1}$).

The two studies in the workplace and the study in the general population (aged 20 to 60 years) show that on average, both sexes combined, the urinary concentration of creatinine is 1.4 $g.L^{-1}$.

This is therefore the value that has been chosen by default to adjust urinary concentrations of BMEs to creatinine concentration when it is not specified in a publication or more simply to compare values taken from several studies in order to obtain the same units.

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The Expert Committee 'Expert appraisal for recommending occupational exposure limits for chemical agents in the workplace' (OEL Committee) adopted on 10 October 2013 the 'Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs) as a whole and informed ANSES's general directorate.

Date of validation of thereport by the OEL Committee : 10/10/2013

On behalf of the experts of the Committee

François Paquet
Chairman of the Committee

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Annexe C1 : Description of data

Studies on volunteers

Studies on volunteers, in which exposure is controlled and the biomarkers concentrations measured, enable relationships to be established more easily between exposures and biomarkers concentrations.

The oldest of these studies were conducted for exposure that, at the time, was close to the values applicable in the occupational environment. Usually only a few atmospheric concentrations were studied and since then the exposure limits applicable in the workplace have been reassessed and sometimes lowered. Extrapolation to lower atmospheric concentrations thus leads to uncertainty. However, it is most often assumed that extrapolation can be linear, despite the possibility in some cases of there being mechanisms resulting in the saturation of transformation and elimination pathways.

In the case of substances with significant dermal absorption, studies in which the biomarkers concentrations have been studied for both inhalation and dermal exposures (vapours) will be preferred.

Field studies

Field studies conducted in occupationally exposed subjects provide a more accurate picture of exposure and enable a wide variety of exposure situations to be studied (tasks, industry sectors, atmospheric levels, etc.). An increasing number of publications are reporting results from such studies.

Particular attention must however be paid to the relationship between exposure and internal concentrations. It may be that studies involving very different exposure situations reveal strong correlations. These correlations, however, can turn out to be weaker once the exposure situations have been broken down (by industry sector, by order of magnitude for atmospheric concentrations, when there is another related route of exposure, etc.). In the case of exposure to metals, bioavailability associated with particle size and speciation can also lead to differences particularly in relationships between atmospheric exposure and concentrations of biomarkers of exposure.

Description of physiologically based pharmaco/toxicokinetic (PBPK) modelling

PBPK models are multi-compartmental pharmacokinetic models in which each tissue or organ is represented by a compartment. The compartments are interconnected by blood flow, thus describing the circulation of the test substance and possibly also its metabolites. The substance enters an arterial compartment where it is distributed to other compartments (tissue or organs), then secondarily enters a venous compartment.

The development of a PBPK model is divided into four phases. The first phase is the conceptual representation of the organs and tissues presumably involved in the distribution of the substance and/or its metabolites; the compartments are also interconnected by flows. Then, values from experimental data obtained *in vivo* or *in vitro* are assigned to all the parameters of differential equations (pulmonary ventilation, cardiac output, partition coefficient of the substance between air and blood, etc.). There are many uncertainties associated with these experimental data. The third phase corresponds to simulations performed using specific software. The final phase is the evaluation of the model by comparing, for a given exposure, the modelling results with the experimental results.

This phase may lead to reconsideration of the model representation and/or the values of its various parameters, as the modelling is totally based on a number of assumptions that may be relatively far from the physiological reality.

PBPK models will only be used to establish a BLV if 1) they have been published in the scientific literature and therefore submitted to peer review and 2) they have been validated (with independent data) for inhalation and for exposure scenarios compatible with occupational exposure and the kinetics of the substance and for the biomarker of exposure in question (no extrapolation of concentrations for one BME based on another BME).

Annexe I - Monitoring of report updates

Date	Version	Description of the change
10/10/2013	01	Version validated by the OEL Committee
08/01/2014	02	Section 7.5.2 “Animal/human dosimetric adjustments for gases” Change to the equations added for the extrathoracic, tracheobronchial and pulmonary regions following verification in the document quoted as a reference (US-EPA, 1994)