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

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NOTE

Please note that the present document is a proposed amendment to Chapter R.8 of the Guidance on IR&CSA, limited to the development of a new Appendix (Appendix R.8-17)

This document was prepared by the ECHA Secretariat for the purpose of this consultation and includes only the parts open for the current consultation, i.e. :

- The new Appendix R.8-17 Guidance for proposing Occupational Exposure Limits

The full guidance document (version before proposed amendments) is available on the ECHA website at:

https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/ (version 2.1 published in November 2012).

After conclusion of the consultation and before final publication the updated Appendix will be implemented in the full document.

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Version	Changes	Date
Version 1	First edition	May 2008
Version 2	The present version includes the following new sections: - R.8.1.2.8 - Appendix R.8-15 - Appendix R.8-16 These new sections aim to explain in detail how to evaluate the data, extract the dose descriptors and derive the DNEL/DMEL when human data are used.	December 2010
Version 2.1	Corrigendum: (i) replacing references to DSD/DPD by references to CLP (ii) further minor editorial changes/corrections	November 2012
Version 3	Addition of an Appendix R.8-17: Guidance for proposing Occupational Exposure Limits	Xxxx 2019

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Appendix R.8-17: Guidance for proposing Occupational Exposure Limits

A.8-17.1 Introduction

A.8-17.1.1 Purpose of the guidance

This appendix to this Guidance on the "*Characterisation of dose [concentration]-response for human health"*, has been developed in order to provide specific advice on preparing proposals for Occupational Exposure Limits (OELs).

It is intended to incorporate and capture the findings of the ECHA-RAC/SCOEL Joint Task Force (2017 a, b) and the relevant parts of the revised SCOEL methodology (2018), so adding an important component to the existing ECHA Guidance.

A.8-17.1.2 Target audience for the guidance

This guidance for proposing OELs is aimed principally at:

- ECHA in drafting proposals (as the principle dossier submitter) on occupational exposure limits;
- members and Rapporteurs of the Committee for Risk Assessment (RAC) when evaluating proposed OELs;

In addition, the following stakeholders involved in the process

- Member State Competent Authorities and the regular stakeholders (industry, non-governmental organisations) involved in the process.
- The European Commission and the Advisory Committee of Safety and Health at Work (ACSH) and in particular it's Working Party on Chemicals at the workplace (WPC).

A.8-17.1.3 Background

The setting of OELs is for workplace air concentration of hazardous chemical agents and is an integral part of the EU mechanism for protecting the health of workers. OELs define effective control of exposure and provide a common objective for employers, workers and enforcement agencies.

The European Commission seeks the scientific advice of RAC in developing proposals for OELs. At EU level there are three types of OELs: the main types are the 'indicative' and 'binding' OELs (IOELs, and BOELs respectively). In addition there are binding 'biological' limit values (BLVs). The proposals for the IOELs, BOELs and BLVs prepared by ECHA for consideration by RAC follow the same procedure. However the regulatory administrative procedure is different for the three: this is further described below.

Indicative OELs are established in accordance with Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (Chemical Agents Directive; CAD)[1]. The process of establishing such limits does not include an assessment of the technical feasibility and socio-economic factors. Indicative OELs are intended as European objectives to assist employers in identifying and assessing risks and are

[1] OJ L 131, 5.5.1998, p. 11–23.

established following consultation of the tripartite Advisory Committee on Safety and Health at Work (ACSH) in Commission Directives implementing the CAD. For any chemical agent for which an indicative limit value is established at EU level, Member States must establish a corresponding national OEL taking this into account.

Binding OELs on the other hand, are set on the basis of the CAD, the Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Carcinogens and Mutagens Directive; CMD)[2] and the Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work"[3].

The process of establishing Binding limits also includes an assessment of the technical feasibility and socio-economic factors of applying the limit at the workplace. The setting of OELs for carcinogens at EU level follows the 'ordinary legislative procedure', which includes a recommendation from the ACSH, including an assessment of the feasibility issues and adoption of the final draft Commission's proposal (including an Impact Assessment), by the Council and Parliament. For any chemical agent for which a Binding limit value is established at EU level, Member States must establish a corresponding national binding OEL which can be stricter, but cannot exceed the EU limit value.

Biological Limit Values (BLVs) are set on the basis of the CAD. They constitute limits of the concentration in the appropriate biological medium of the relevant agent, its metabolite, or an indicator of effect. As for the BOELs, their adoption follows the ordinary legislative procedure[4].

Generally, since exposure to airborne chemical agents is the predominant route of exposure at the workplace limit values are set for that route. The oral route of exposure is generally of lesser importance in the occupational setting. The dermal route is also recognised as important in worker exposure to certain chemical agents; however, in the absence of methods to monitor dermal exposure alone, route specific limits are not proposed.

OELs are usually established as 8-hour time weighted average (TWA) limit values. There are, however, chemical agents for which an 8-hour TWA alone provides insufficient protection for workers. In such cases the establishment of a Short-Term Exposure Limit (STEL) may be recommended, usually involving a 15-minute reference period.

In addition to the above limit values, a notation can be added and may include a 'skin notation' for skin penetrating chemical agents, a 'sensitisation notation' for dermal and/or respiratory sensitizers and a 'noise' notation for those substances whose toxicity for the functioning of the ears and hearing, is exacerbated by noise (for further information see section A.8-17.2.3.5).

Biological Guidance Values (BGVs), can also be recommended in an advisory capacity for workers, employers and occupational physicians responsible for worker protections issues.

A.8-17.2 Preparation of the report for the derivation of OELs

A.8-17.2.1 Data collection

The report prepared on the derivation of an OEL should take into account recent published reviews of the chemical agent if available. These would be from established EU bodies, such as

[2] OJ L 158 30.4.2004, p. 50.

[3] OJ L 330, 16.12.2009, p. 28–36.

[4] To date there is only one binding BLV, for lead and its ionic compounds (blood-lead level) (CAD, Annex II).

SCOEL, EFSA, EU risk assessments reports (RAR), international organisations (such as, WHO, IARC), and relevant national scientific committees (such as DECOS, MAK, US EPA, ATSDR, US NIOSH). Furthermore, data should be collected from the REACH registration dossiers and the peer reviewed literature. Industry sectoral sources and market research can be used to gather information on the production and use of the chemical agent.

Data should be collected on:

- chemical agent identification and physico-chemical properties;
  Chapter R.7a of the guidance on IR&CSA gives further information sources on evaluation of physico-chemical properties.

- EU harmonised classification and labelling (CLP) according to Regulation (EC) No 1272/2008;

- existing OELs, BLVs, and BGVs (from EU and from relevant non-EU jurisdictions);
  Annex 1 of SCOEL (2017) lists the binding OELs and indicative OELs set by the EU up to end 2017 and data are available from databases, such as GESTIS for OELs and Biotox for BLV[5]

- toxicological information from epidemiological (observational) studies, experimental (human volunteer, animal, and in vitro) studies; and non-testing data (e.g. read-across);
  Human non-experimental data consists of case reports and epidemiological case-control, cohort and cross-sectional studies as further described in;
  - Chapter R.4 of the guidance on IR&CSA (section R.4.3.3),
  - This document, Appendix R.8-15 and SCOEL (2017), section F2-5.1

  Information on experimental studies consists of toxicokinetic studies and studies reporting on the toxicological endpoints:

  - SCOEL 2017, listed in section A.8-17.2.2.1(see also section F2-5.2).
  - Chapter R.7a of the guidance on IR&CSA gives further endpoint-specific guidance to information sources and evaluation of available information.
  - Chapter R.6 of the guidance on IR&CSA "QSARs and grouping of chemicals" provides information on the use of possible relevant non-testing data.

  Systematic approaches and tools are available for extracting studies from the literature e.g. PRISMA, OHAT (NTP 2015) and ROBINS-I (Sterne et al 2016) (see also Annex 2 to SCOEL 2017).

- the occurrence, production and use of the chemical agent;

- exposure routes, exposure levels and characteristics in the population;

- exposure including measurements;
  Air measurements and biomonitoring at the workplace, and from the general population and/or non-occupationally exposed population should be gathered from peer reviewed journals, published reviews, REACH registrations, etc.

[5] http://limitvalue.ifa.dguv.de/

http://www.inrs.fr/publications/bdd/biotox.html

- information on requirements for methods on air- and biological monitoring.
  Explanations on the requirements for the methods and sources of information can be found in section A.8-17.2.4 of this Appendix.

A.8-17.2.2 Health effects

A.8-17.2.2.1 Evaluation of the hazard data and selection of points of departure

Information on toxicokinetics (absorption, distribution, metabolism and excretion - ADME) and on all toxicological endpoints relevant to workers exposure need to be assessed. The endpoints relevant for assessment are:

- Acute toxicity;
- Specific target organ toxicity/Repeated dose toxicity;
- Irritancy and corrosivity (skin + eyes);
- Sensitisation;
- Genotoxicity;
- Carcinogenicity; and
- Reproductive toxicity.

Evaluating experimental data includes an assessment of the adequacy, relevance and reliability for human health hazard assessment. The quality of experimental animal studies may be assessed using the Chapter R.4 of the guidance on IR&CSA, which includes a description of the reliability of the animal test data using Klimisch scores.

For epidemiological data, the considerations in sections F5 and F2-5.1 of SCOEL (2017) and the principles on evaluation of the quality and relevance of human data of ECHA guidance Appendix R. 8-15 are of relevance.

Although the focus of Chapter R.4 of the guidance on IR&CSA is on experimental animal data, it also includes considerations on the evaluation of human data, in vitro data and non-testing data.

Both ECHA guidance (e.g. Chapter R.4) and SCOEL (2017) stress the need to integrate all available evidence when drawing overall conclusions for each endpoint. ECHA guidance applies this principle in the form of a "Weight of Evidence" approach. This evidence based approach involves an assessment of the relative weights of different pieces of the available information (including information on the mode of action). The weight given to the available evidence will be influenced by factors such as the quality of the data, consistency of results, nature and severity of effects, relevance of the information for the given endpoint.

In integrating the available evidence, human data of good quality are particularly valuable (i.e. they are given preference or more weight than other data) because they apply directly to the human species, and the data may have been obtained from exposure conditions relevant to workers. However, in order to verify the good quality of such data, a proper assessment of the following aspects is needed: (1) the possibility and extent of various forms of bias; (2) confounding factors that were controlled for in the studies; and (3) the accuracy of the (quantitative) exposure assessment used in the studies (see SCOEL (2017) and Appendix R.8-15).

One of the key aims of the hazard assessment is to conclude on points of departure relevant for deriving an exposure limit value. If considered relevant, several points of departure may be

selected. Before derivation of the limits, it may not be clear which point of departure will lead to the lowest or most appropriate limit. The lowest limit(s) will normally be recommended, unless the weight of evidence does not support that selection (e.g., when supportive human data which may not be strong enough to be used in its own right, suggests such an approach would be too conservative).

A.8-17.2.2.2 Evaluation of Mode of Action

For chemical agents for which hazardous properties have been identified that are potentially relevant for the workplace, all evidence is evaluated with the aim of obtaining an understanding of the Mode(s) of Action (MoA) for each of the relevant hazardous properties.

Carcinogenicity

For carcinogens it is essential to determine whether a threshold for the carcinogenic action can be identified or not. In case a threshold can be identified, an OEL may be established (JTF 2017 b, chapter 5.3), if not, a cancer dose-response assessment should be performed (see 2.3.6). Application of the SCOEL grouping system for carcinogens (SCOEL 2017) is not considered a necessary step in the procedure (JTF 2017b).

There is agreement to generally distinguish between genotoxic and non-genotoxic carcinogens (SCOEL 2017).

For non-genotoxic carcinogens (for example tumour promoters), it is generally accepted that a threshold concentration exists and theoretically can be established below which the respective chemical agent will not be carcinogenic (SCOEL 2017).

For most genotoxic carcinogens the available data are likely to be inadequate for an effective threshold to be identified with sufficient confidence. The default, or starting assumption, for these carcinogens will be that there is no threshold for the carcinogenic hazard. However, for some genotoxic carcinogens for which sufficient information is available, it may be possible to conclude on a threshold based on the mode of the carcinogenic action (MoA based threshold). Such cases can be carcinogens which are only weakly genotoxic and for which there is sufficient information that the carcinogenicity is not primarily driven by the DNA reactivity, but mainly arises from other mechanisms, and where the evidence suggests that any relevant (usually indirect) genotoxicity is occurring only at doses above the MoA based threshold.

Examples of indirectly acting genotoxic carcinogens are (i) increase in the background level of oxidative DNA damage; (ii) interaction with the cellular response to DNA damage (e.g. by inactivating DNA repair mechanisms, or by epigenetic effects); or (iii) acting on the chromosomal level alone (e.g. induction of numerical chromosomal aberration), in the absence of gene mutations.

Also for some specific genotoxic carcinogens a MoA based threshold could be identified. For example when such a substance occurs endogenously, a threshold may be derived below which it can be concluded with sufficient confidence that there is no additional cancer risk.

Reproductive toxicity

The current state of scientific knowledge considers substances interfering with fertility or with pre-/postnatal development as likely to act by threshold mechanisms, thus permitting the determination of NOAELs (SCOEL 2013).

However, it should be noted that some substances show adverse effects on reproduction at exposure levels considerably lower than those causing other forms of toxicity. Because of the relative sensitivity of the rapidly developing individual (from conception to puberty) to specific toxic effects, OELs established to protect adults cannot *a priori* guarantee the absence of pre- or post-natal adverse effects. Thus pregnant or lactating women may represent a special risk group in the workplace (SCOEL 2013).

When recommending an OEL, information on reproductive and developmental toxicity are taken into consideration. In case such information is missing, the uncertainty needs to be addressed.

Other endpoints

Knowledge of the mode of action of relevant effects other than carcinogenicity and reproductive toxicity is of importance for a better understanding of the effects and their biological relevance and for the establishment of an OEL. Of specific relevance are eye irritation (including serious eye damage), sensory irritation, skin irritation (including skin corrosion), skin sensitisation, airway toxicity (including respiratory irritation and sensitisation), and specific organ toxicity (including immunotoxicity and neurotoxicity).

A.8-17.2.2.3 Outcome of the hazard assessment

The possible outcome of the hazard assessment is:

1) One or more hazardous properties are relevant for the workplace and the available evidence is adequate to establish exposure limit value(s). This includes carcinogens for which sufficient information is available to conclude on a MoA based threshold for the carcinogenic action and for which the evidence is adequate to establish an exposure limit value. For such carcinogens it is recommended to additionally present the dose-response for carcinogenicity above the threshold as this may inform the decision makers of the health risks above the threshold level.
2) The chemical agent is a genotoxic carcinogen for which no threshold can be identified and therefore no exposure limit values can be derived. In such cases, if possible, a dose-response for carcinogenicity will be presented. In addition, OELs can be derived for other relevant endpoints than carcinogenicity as applicable to inform decision makers about the applicable thresholds for these other endpoints. However, no overall OELs would be recommended.
3) There is a relevant hazardous property other than carcinogenicity but the available data are insufficient to derive a reliable exposure limit value for that property.
4) Based on the available evidence the chemical agent is not hazardous for occupational exposures.

A.8-17.2.3 Exposure limit values and notations

A.8-17.2.3.1 Occupational Exposure Limits

Occupational exposure limits (OELs) are generally established in relation to a reference period of a typical 8-hour working day, i.e. as 8-hour time weighted average (TWA) exposure limits. Further, they are generally set on the basis of a nominal 40-hour working week and for a

working lifetime of 40 years (48 weeks/year; 5 days/week; i.e. 9600 days or 76,800 hours) (SCOEL 2017). OELs can be derived for non-carcinogenic substances and for carcinogenic substances for which a MoA based threshold could be identified.

A stepwise approach for selection of the point of departure and application of adjustment, variability and uncertainty factors is explained in Frame 6 of the SCOEL methodology for derivation of OELs (2017): "*To derive an OEL, an effect (or mechanism) and the corresponding concentration at which this occurs, identified from an experimental or epidemiological study, is selected as the point of departure (POD). Both, the concentration and the effect observed in the study may not exactly match the exposure and/or response of workers. In this case, the experimental data are adjusted to the workers' situation using adjustment factors. The variability among workers (intraspecies variability) is accounted for by a variability* factor*. Moreover, the data obtained from any study are usually imprecise and the impact of this inherent uncertainty within the data is considered and may require the use of uncertainty factors when recommending an OEL*" (SCOEL 2017).

Section R.8.4.3 of this guidance, provides guidance on the use of assessment factors: "*In principle, all data on a specific substance need to be reviewed thoroughly in order to use, as far as possible, substance-specific information for the establishment of appropriate values for the various assessment factors. When substance-specific information is not available, data on analogues, which act with the same mode of action as the chemical under consideration, should be taken into account. However, when the available data do not allow the derivation of substance-specific or analogue-specific assessment factors, default assessment factors should be applied. Although very often necessary to rely upon, the default assessment factors represent a fall back position rather than the starting point*". Detailed information on default assessment factors is available in Section R.8.4.3 of this guidance

For consistency, the term 'assessment factor' (AF) is used in this document. This term covers the 'adjustment factors', 'variability factors' and 'uncertainty factors' of SCOEL (2017) and the 'assessment factors' of Section R.8.4.3 of this guidance.

In the JTF report (2017a) it is concluded "*where possible, default AF values should be replaced with chemical specific data; the justification of the AFs […] should be as transparent and consistent as possible*".

The selection of the POD, its adjustment to the worker's situation and the application of factors in the derivation of an OEL have to be transparently reported and should take into account all relevant information on the substance.

Where a MoA-based threshold can be confidently established for a carcinogen, the resulting recommendation for an OEL sets a level of exposure where it is assumed that there will be no expectation of a significant residual cancer risk. In practise the level of confidence will vary case-by-case and although a carcinogen may have one or more MoA-based thresholds, it does not necessarily mean that the indicated level is safe - some uncertainties with regards to residual cancer risk may remain. In all cases the remaining uncertainties as to a possible residual cancer risk need to be clearly described: firstly, the uncertainty surrounding the identification of a MoA threshold itself and secondly, the uncertainty in identifying the actual level (value) of the threshold. In some cases, especially for the second type of uncertainty, the remaining uncertainties may lead to the application of an assessment factor. (See JTF 2017b, chapter 4.3 and 5.4)

It is recommended to express OELs in units of mg/m^3, providing the equivalent ppm-expressed values in brackets when applicable. Although, it is recognised that in some industrial sectors a rounded ppm value may be preferred. Furthermore, in order to avoid the impression of an unjustifiable precision of the proposed value, as a general rule (SCOEL, 2017), OELs are expressed as preferred values, i.e. decimals of the integers 1, 2 or 5 mg/m^3. Further

discrimination, resulting in proposals falling in-between any two of these integers, suggests a precision that, in reality, is usually unjustifiable, given the uncertainties involved in the whole process and the limitations of the databases for the vast majority of the chemical agents considered. Deviation from the use of preferred values may be justified in specific cases; in these instances, the OEL will be expressed using only one significant figure".

A.8-17.2.3.2 Short Term Exposure limits

Commission Directives implementing CAD acknowledge that "*It is also necessary to establish short-term exposure limit values for certain substances to take account of effects arising from short-term exposure"* and then define in their Annexes the reference time-period for such limit values (usually 15 minutes as explained below) (see e.g. Commission Directive 2009/161/EU establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC).

Consequently SCOEL states that *"STELs are needed where adverse health effects (immediate or delayed) are not adequately controlled by compliance with an 8-hour TWA. Usually, the STEL involves a 15-minute reference period (that should not occur more than four times per 8-hour work shift, with a minimum of one-hour intervals in-between the occurrences). The need for a STEL likely arises for chemical agents for which a relevant effect is observed following a brief exposure (e.g. nuisance, irritation, central nervous system depression, cardiac sensitisation) and where the 8-hour TWA OEL is established at a level not very much lower than exposures at which there might be a risk of short-term (acute) effects occurring".* (SCOEL 2017)

A.8-17.2.3.3 Biological Limit Value

In order to set standards on biomonitoring Biological Limit Values can be based either on a direct relationship between a biomarker of exposure and an early reversible adverse health effect or, on a relationship between a biomarker of exposure and the chemical agent's OEL (SCOEL 2017). However, currently the only binding BLV listed in Annex II of CAD concerns blood-lead level. Nevertheless, SCOEL has also, where appropriate, included in its recommendations "health–based BLVs" (see SCOEL 2014 for an overview).

"BLVs relate to a chemical agent's concentration in the respective biological medium (e.g. blood, urine, breath). Exposure concentrations equivalent to the BLV generally do not affect the health of the worker adversely, when they are attained regularly under workplace conditions (8 hours/day, 5 days/week)" (SCOEL 2017).

Biological monitoring is primarily used as an aid to the assessment of systemic exposure by inhalation, ingestion and absorption through the skin (SCOEL 2017). It is a complementary approach to air monitoring and is particularly useful for chemical agents with a 'skin' notation or where control of exposure relies on personal respiratory protection equipment, where air monitoring alone may not give a complete picture of exposure.

A.8-17.2.3.4 Biological Guidance Value

Where the available data do not support deriving a BLV, e.g. in the case of non-threshold carcinogens, a Biological Guidance Value (BGV) may be established.

"BGVs are exposure-related guidance values in that they represent the upper concentration of

the chemical agent or one of its metabolites in any appropriate biological medium corresponding to a certain percentile (generally the 90th or 95th percentile) in a defined reference population. It is preferred to use a non-occupationally exposed working population as defined reference population, but in practice this may not be possible. As such, the defined reference population may vary from task to task" (SCOEL 2017, SCOEL 2014).

If background levels cannot be detected, the BGV may be equivalent to the detection limit of the biomonitoring method, which then is to be specified in the document.

A.8-17.2.3.5 Notations

'Skin'

In order to effectively control total systemic exposure to chemical agents at the workplace, it may be necessary to take into account that chemical agents may also penetrate the skin and thereby increase the total body burden. If the skin penetration of a given chemical agent is likely to make a substantial contribution to the total body burden, a 'skin' notation will be assigned in addition to the establishment of the OEL. According to SCOEL (2017) 'Substantial contribution' to the total body burden will be, in general, in the order of 10 % or more of the uptake from respiratory exposure at the 8-hour TWA.

Skin penetration will also have a greater relative impact on total body burden (and thus present a greater health risk) when exposure by the inhalation route is controlled to relatively low levels, i.e. when the established OELs are very low.

A 'skin' notation may in certain cases be assigned although no OEL is set (e.g. some non-threshold carcinogens). See SCOEL 2017, Chapter F6-2.1

'Sensitisation'

Dermal and/or respiratory sensitisation notations are assigned based upon the availability of evidence on either skin or airway sensitisation leading to the conclusion that the chemical agent under investigation may elicit such effects in the occupational setting (Sartorelli et al., 2007). See SCOEL 2017, Chapter F6-2.2. Such evidence would be available for substances classified as skin or respiratory sensitizers in Annex VI of the Regulation (EC) 1972/2008 on Classification, Labelling and Packaging of substances.

'Noise'

If a chemical agent is likely to interact synergistically with noise or potentiate the effects of noise on the auditory system, a 'noise' notation may be assigned as a warning that hearing impairment may occur even at exposures below or close to the established OEL if there is also exposure to noise. See SCOEL 2017, Chapter F6-2.3

A.8-17.2.3.6 Cancer dose-response assessment

In case the chemical agent is known to act via a non-threshold MoA, or when it is not possible to conclude on an MoA based threshold, a cancer dose-response assessment is presented. This cancer dose-response will typically present the cancer risk as a function of the air concentration. However, the cancer risk may be presented as a function of relevant biological indicators that are used in biomonitoring of exposure in the workplace as well.

Acceptable cancer risk levels have been adopted in some countries such as Germany and The Netherlands. However, there are currently no accepted reference cancer risk levels established on an EU-wide basis. The cancer dose-response therefore aims to inform the decision maker of

the relationship between cancer risk and exposure, enabling an appropriate occupational exposure limit to be derived on such considerations as feasibility and health impact; such limits will however not reflect a safe level.

Human epidemiological data

When available, good quality human epidemiological data with sufficient statistical power should be used for dose-response assessment of non-threshold carcinogens, (i.e. for estimating the excess cumulative (lifetime) cancer risk associated to a given level of exposure) in preference to other data. Two main methods are used, the conditional method and the unconditional method (also known as life-table method).

In short, the conditional method calculates the excess life-time risk (ELR) for one or more exposure levels from ELR =RR*P-P, in which P represents the cumulative (lifetime) risk in the non-exposed target population and RR is exposure-related relative risk (per a given exposure level) (Rothman and Greenland 1998). This approach does not take into account the population dynamics, i.e. the fact that there are other causes of death than the disease under study (See e.g. Goldbohm et al 2006 for illustration of this effect).

The unconditional method calculates the excess risk using a life-table by age category that takes into account what fraction of the (hypothetical) original population cohort would still be available to experience the excess risk in each age category and then sums up these to a life-time risk. (Goldbohm et al. 2006, Seidler et al. 2013, Steenland et al 1998, SCOEL 2017, Section 8.B.1 of Appendix R8-15 of this guidance)

The conditional method produces higher life-time excess risk estimates than the unconditional method (when equal parameter choices are applied). Regardless of the choice of method, one needs to decide e.g. until which age it is relevant to calculate the risk following occupational exposure. The higher the age selected, the larger the difference in the excess risk produced by the two methods (see Goldbohm et al 2006).

The life-time method is considered the state-of-the-art method and is preferred by SCOEL (2017) and several other regulatory bodies (e.g. US EPA, NIOSH and DECOS). It also allows calculations restricted to a given time-window of exposure if such a restriction is considered relevant. However, the conditional method is simpler in the sense that no specific software and life-table data are needed, thus allowing to easily verify the calculations. As the differences between the two methods are relatively small if not extended to very old age categories some (e.g. Seidler et al 2013) prefer it as a less complex approach.

Regardless of the method, one has to consider that some cancers have a good prognosis because of modern treatment opportunities. This leads to considerable differences between the incidence and mortality for a specific cancer. SCOEL (2017) therefore prefers the use of incidence data in calculations of lifetime risk. The ECHA/RAC-SCOEL Joint Task Force Report (2017b, Appendix 2) also supported this preference. If studies are based on mortality data, some modifications may thus be needed in the risk assessment.

Animal data

When good quality human epidemiological data with sufficient power are not available, experimental animal data can be used to derive a dose-response for carcinogenicity. Use of animal data requires extrapolating cancer risks of generally in the order of 25 to 10% in animals exposed at high dose levels to low human occupational exposure levels.

The high to low dose response assessment may be performed using the following steps:

1) Derivation of the relevant dose descriptor(s). The dose response in the observable range for the tumour type under consideration is assessed. The BMD10 (the benchmark-dose representing a 10% response above background) or the T25 (dose representing 25% response above background) may be used as a point of departure.
2) Modification of the dose descriptor(s) to the correct starting point if needed (e.g. when there are differences in human and experimental exposure conditions).
3) Application of assessment factors when necessary. Usually only an allometric scaling factor is applied in this step. The linear model used for high to low dose extrapolation is generally considered sufficiently conservative to also cover differences in intra- and interspecies sensitivity.
4) Linear extrapolation (default) from the dose descriptor to lower dose levels in the range of actual worker exposures. For example, a linear extrapolation from 10^{-1} to 10^{-5} risk is obtained by dividing the BMD10 (10% response) by 10 000. Similarly, a linear extrapolation from 25% to 10^{-5} risk is obtained by dividing the T25 by 25 000. If the available data indicate a deviation from linearity, a modification of the default linear approach should be considered.

Further guidance is available in section R.8.5 of this guidance and Section F6/CM.3 of SCOEL (2017).

A.8-17.2.4 Methodological aspects of exposure monitoring

The information on validated monitoring methods serves to assess and describe the feasibility to monitor the external exposure to the given chemical agent at the recommended OEL using appropriate monitoring methods.

A.8-17.2.4.1 Air monitoring

The sampling and analysis methods used to compare exposure concentrations with a limit value should fulfil certain requirements in terms of uncertainty and measuring range among other parameters.

The standard EN 482[6] *"Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents"* provides requirements for methods for sampling and analysis used to compare exposure concentrations with a limit value. In terms of measuring ranges the method should be able to measure:

- 0.1-2 times the OEL for 8-hour TWA
- 0.5-2 times the OEL for 15 min STEL

The methods should also fulfill other requirements in terms of, for example expanded uncertainty, selectivity, etc.

The report for the derivation of OELs should include a list of available analytical methods that have the potential to fulfil the relevant standards and include information on:

[6] Specific International Standards and European Standards are available for different types of measuring procedures and measuring devices. These include standards for airborne particle samplers [EN 13205 (all parts)], diffusive samplers (ISO 16107 and EN 838), pumped samplers (EN 1076), short-term detector tubes (ISO 17621), personal sampling pumps (ISO 13137), metals and metalloids in airborne particles (EN 13890), mixtures of airborne particles and vapour (EN 13936) and direct reading instruments for toxic gases and vapours [EN 45544 (all parts)]. In these specific standards, additional requirements have been included for the procedure or device in question, so that the general requirements of this document are not compromised. Where no specific International and/or European Standard exists, only the general requirements apply.

- Working range and LOQ
- Sampling time and where relevant flow rate used
- Whether there is information from the published or databases such as GESTIS on validation

Measurement procedures, including monitoring and analytical methods, for chemical agents in workplace atmospheres are available from many sources (normally OSH national institutes) in both Europe (e.g. France, Germany, Spain and UK) and in the US (the Occupational Safety and Health Administration (OSHA) and NIOSH). These methods normally have validation data available.

The GESTIS database[7] provides an overview on the existing analytical methods for a given chemical, including a rating of the analytical methods against the requirements of the relevant European standards.

When a new OEL limit is proposed, a validated analytical method may not yet be available. This does not necessarily mean that reliable measuring is not feasible, as normally the analytical methods have been validated and optimised for the OELs already in place. In such cases it is useful to assess whether the available analytical method(s) can be modified to be applicable for the new OEL (e.g. via modifications on sampling times/ flow rate or volume of extraction).

A.8-17.2.4.2 Biological monitoring

Biological monitoring is a way of estimating exposure by measuring the chemical agent or its metabolites in a biological sample (usually urine, blood or breath). The advantage of biological monitoring is that it integrates all routes of exposure. It is therefore a complementary approach to air monitoring and is particularly useful for chemical agents with a 'skin' notation or where control of exposure relies on personal respiratory protection equipment, where air monitoring alone may not give a complete picture of exposure (SCOEL 2017, EU-OSHA 2016, HSE 1997, MAK 2018).

Information on validated biomonitoring methods of the workers' internal exposure needs to be given. The information should describe the chemical agent (e.g. the substance of interest or a metabolite) and the specimen chosen (e.g. blood, urine, or saliva). This information serves to describe the feasibility to monitor the internal exposure to the given chemical agent at the recommended BLV or BGV using the defined monitoring methods.

For a BGV the minimum is that the method is able to reach the BGV concentration.

Suitable analytical methods can be found in the scientific literature but a good source of validated methods is available from the German MAK Commission (Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area)[8] (SCOEL 2017).

[7] http://www.dguv.de/ifa/gestis/gestis-analysenverfahren-fuer-chemische-stoffe/index-2.jsp

[8] https://onlinelibrary.wiley.com/doi/book/10.1002/3527600418

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