Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace.

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Appendix to Chapter R.8: Guidance for preparing a scientific report for health based exposure limits at the workplace.

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Preface

This document has two parts, the first addresses the findings of the ECHA/RAC – SCOEL Joint Task Force that examined alignment of methodologies for setting exposure limits at the workplace, while the second part outlines how to prepare a scientific report for identifying such exposure limits.

Part I Findings of the ECHA/RAC-SCOEL Joint Task Force on alignment of methodologies related to the exposure of chemicals at the workplace, including the inhalation and dermal routes, and in particular carcinogens with or without a threshold.

Part II How to prepare a scientific report for health based exposure limits at the workplace in accordance with the Joint Task Force reports.

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Part I. Alignment of methodologies in accordance with the ECHA/RAC-SCOEL Joint Task Force findings

As part of the REACH Review (2018), action 12 on the "*interface [between] REACH and OSH legislation*", the Commission requested ECHA in part 12.3 to "*align methodologies to establish safe levels of exposure to chemicals at the workplace by first quarter 2019*". This mandate under REACH is a follow-up action specific to the work of the ECHA/RAC-SCOEL Joint Task Force (JTF) conducted between 2015-2017

In 2015, the Commission requested[1] ECHA's Committee for Risk Assessment (RAC) and the Scientific Committee on Occupational Exposure Limits (SCOEL) to make a comparative assessment of the scientific methodologies that were used by the respective Committees for deriving'derived no effect levels' (DNELs) for workers or 'occupational exposure limits' (OELs).

These reports were delivered and published: the first in February 2017[2] on the comparative assessment of methodologies related to Derived No Effect Levels (DNELs) and Occupational Exposure Limits (OELs) and the methodologies for dermal OEL and skin notation; the second in December 2017 [3] in relation to the scientific evaluation of 'non-threshold' substances, mainly genotoxic carcinogens.

This Guidance Appendix is intended to capture the findings of the JTF from the above two reports on a number of scientific points, the main ones being:

- establishing mode of action based thresholds for genotoxic carcinogens
- sensory irritation
- dermal risk assessment and skin notations
- the use of human data in setting workplace limits and finally
- the use of uncertainty or assessment factors.

To put the above aspects further in context of REACH, cross references of these findings are made to the ECHA Guidance on IR&CSA Chapter R.8; and also to Chapter R.7 for some aspects on health effects.

This aligned methodology, reported in the JTF reports, can be applied to the establishment of safe levels at the workplace under both REACH and OSH. When limited to the above points, it should provide additional advice and allow RAC to proceed in a consistent way also when establishing safe levels of exposure to chemicals at the workplace on request of the Commission under the OSH legislation. However, it should be noted that it is not a comprehensive guidance on how to provide a scientific opinion on an OEL. This would require a separate mandate specific to OSH policy and legislation, e.g. CAD/CMD and is not envisaged at the present time.

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[1] **Joint Task Force request (6 July 2015)**
"*Request to the European Chemicals Agency (ECHA) and the Scientific Committee on Occupational Exposure limits (SCOEL) to create a joint task force on scientific aspects and methodologies related to the exposure of chemicals at the workplace and to prepare a report on their scientific evaluation.*"

Alignment of methodologies request (24 July 2018)
"*Request to the European Chemicals Agency to align the methodologies in accordance with the ECHA/RAC-SCOEL Joint Task Force and the REACH Review Communication*".

[2] https://echa.europa.eu/documents/10162/13579/rac_joint_scoel_opinion_en.pdf/58265b74-7177-caf7-2937-c7c520768216.

[3] https://echa.europa.eu/documents/10162/13579/jtf_opinion_task_2_en.pdf/db8a9a3a-4aa7-601b-bb53-81a5eef93145

Findings from the Joint Task Force supporting aligned methodology

The findings of the JTF from the two reports supporting aligned methodology on a number of scientific points are summarised below. On a general level, OEL and worker DNEL-setting follow the same basic principles and steps of toxicological hazard assessment, such as literature review, hazard assessment and characterization of dose-effect and dose-response relationships.

1. The use of human data in setting workplace limits

The JTF concluded that there was a preference for using good quality human data when available and used animal data as supportive evidence in a comprehensive approach taking account of the MoA. For worker DNEL derivation on less data rich substances, animal data is primarily used as the starting point with a standard modification of the dose descriptor to extrapolate to workers.

2. The use of uncertainty (UFs) or assessment factors (AFs)

The JTF concluded that where possible, default AF values should be replaced with chemical specific data; the justification of the AFs (RAC) and UFs (SCOEL) used by each Committee should be as transparent and consistent as possible. The JTF agreed that multiplication of default or specific AFs/UFs is a broadly supported and well-developed approach under REACH;

Subsequent to the work of the JTF, the SCOEL methodology (2017) adopted the standard factors described in Chapter R8 of the ECHA Guidance to adjust the dose from animals to humans. This significantly added to the alignment of the methodologies.

The final assessment factor used to address remaining uncertainties is generally seen as a matter of expert judgement and it is important to recognise this in transparent way when delivering a scientific opinion on limit values and comparing existing published limit values.

3. Sensory irritation

Chemo-sensory/irritant properties, are often the first sign of effect of some substances used at the workplace and can therefore often provide an important starting point when evaluating the proteciton of workers. The JTF agreed that the prevention of acute reversible effects such as pre-narcosis and respiratory tract irritation which may be caused by intermittent exposures above the 8 hour OEL are dealt with by SCOEL with the recommendation of a STEL (usually 15 minutes 4 times per work shift) which prevents or limits the occurrence of these peak exposures. This was recognised by the JTF as an important aspect to be considered, where acute exposure of workers is likely.

4. Dermal risk assessment and skin notations

The JTF shared the view that the current means under both OSH (skin notation) and REACH (dermal DNEL) legislation of identifying potential for dermal exposure can work in a complementary manner and that both trigger risk management measures as appropriate. The JTF also agreed that in the case of dermally absorbed chemicals biomonitoring, if available, would be a key component for the assessment of exposure, noting that biomonitoring generally allowed exposure from all sources to be assessed.

The JTF agreed that the assessment of dermal exposure remains problematic and measured exposure data are rarely seen in practice. Therefore, measures to prevent such exposures should have (within reason) a prevention/preventive character as achieved through a skin notation.

5. Establishing mode of action based thresholds for genotoxic carcinogens

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. The two Committees apply similar methodologies for such substances, assuming a linear relationship between exposure and effect and employing T25[4] and/or Bench Mark Dose (BMD) methodology. On reflection of recent opinions, it was found that there was often agreement within an order of two.

For those other carcinogens where it might be possible to adapt this threshold approach by taking into consideration a mode of action with a threshold, the following conclusions have been agreed:

1. In general, the SCOEL methodology and underlying principles for establishing MoA-based thresholds are appropriate and feasible for use under REACH with some adaptation.
2. Adaptation under REACH would be possible, provided that the focus remains on the scientific basis of determining a MoA-based threshold. Such adaptations would include:
   - the requirement to explain transparently the remaining uncertainty; it was agreed that this was needed to clearly indicate to the legislator that the limit/level proposed may contain some uncertainties as to a possible residual risk.
   - omission of the SCOEL grouping system as it was not considered a necessary step in the procedure;
   - the use of a transparent approach for correcting the PoD and the application of assessment factors;
   - use of allometric scaling and other adjustment factors as described in the recently revised SCOEL methodology, in the same way as described in the ECHA guidance. However, uncertainty factors used by SCOEL may differ from the assessment factors applied by ECHA.
3. The starting point/default is a non-threshold MoA and only when subsequent analysis of the data allows refinement in the sense that overall the data actually points to a threshold, then a threshold approach can be followed. Without (sufficient) data to conclude this, the default stays a non-threshold MoA.
4. With regard to the use of epidemiological data for risk assessment, both RAC and SCOEL have used such evidence for deriving limit values. However, differences exist in the way epidemiological evidence is used and applied in particular for risk calculations and this requires further harmonization.

6. Other aspects of alignment

The JTF considered in detail the selection of the Point of Departure, noting that REACH Guidance and the SCOEL methodology (2013) applied respectively a 'leading' effect and a 'critical' effect approach. The Joint Task Force acknowledged that the two approaches to selecting the point of departure can contribute to different numerical OEL and worker DNEL values but was unable to resolve this issue. Therefore further guidance on this important aspect is contained in section A.8-17.2.2.1, final paragraph. The Partner Expert Group that examined this Appendix made many useful comments on additional aspects directed at OEL setting, mainly derived from the recently revised SCOEL methodology (2017)[3], but incorporating the findings of the 'aligned methodology' as explained above. These are reflected in Part II – How to prepare a scientific report for health based exposure limits at the workplace.

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4 The T25 estimate of potency is defined as the daily dose (in mg per kg bodyweight) inducing a tumour incidence of 25 % upon lifetime exposure

[3] https://publications.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc-11e8-be1d-01aa75ed71a1/language-en

Part II. How to prepare a scientific report for health based exposure limits at the workplace

A.8-17.1. Introduction

Part II of the Appendix has been developed with the purpose to provide specific guidance on how to prepare recommendations for health based exposure limits at the work place, and more specifically Occupational Exposure Limits (OELs). Considering the alignment of the underlying methodologies described in Part 1, aspects may also be relevant for developing workplace Derived No Effect Levels (DNELs) and in particular to provide the advice when dealing with genotoxic carcinogens.

The European Commission seeks advice from independent scientific committees on the assessment of OELs in order to support proposed actions to amend Directive 2004/37/EC[5] and Directive 98/24/EC[6]. On request of the Commission, ECHA prepares a scientific report for OELs for chemical agents under both Directives; this scientific report is subsequently evaluated by RAC who adopt an opinion, recommending OELs when possible. The regulatory process is further described below in Section A8-17.2.1.

Appendix R8-17 is intended to advise a wide group of stakeholders such as those below:

- ECHA in drafting scientific reports on occupational exposure limits;
- Members and Rapporteurs of the Committee for Risk Assessment (RAC) when evaluating proposed OELs and preparing the Committees opinion;
- Member State Competent Authorities and the regular stakeholders (e.g. industry, non-governmental organisations).
- The European Commission and the Advisory Committee on Safety and Health at Work (ACSH) and in particular it's Working Party on Chemicals at the workplace (WPC).
- National relevant scientific committees/Member States.

A.8-17.1.1 Regulatory process for setting limit values

Council Directive of 89/391/EEC (Framework Directive) introduces measures to encourage improvements in the safety and health of workers at work. Based on Article 16(1) individual Directives are adopted for specific areas of worker protection. The setting limit values is covered by individual Directives, the Chemical Agents Directive (98/24/EC; CAD) and the Carcinogens and Mutagens Directive (2004/37/EC; CMD) and the Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work"[7]. These form

[5] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC), OJ L 158, 30.4.2004,p.50.

[6] Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC), OJ L 131, 5.5.1998, p.11.

[7] Directive 2009/148/EC of the European Parliament and of the Council of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance) Directive 2009/148/EC of the European Parliament and of the Council of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance). OJ L 330, 16.12.2009, p. 28–36

an integral part of the EU mechanism for protecting the health of workers.

At EU level there are two main types of limits: 'indicative' and 'binding' OELs (IOELs, and BOELs respectively). In addition there are 'biological limit values' (BLVs).

CAD and CMD state that *'Occupational exposure limit value[s]' means ….. , the limit of the time-weighted average of the concentration of a chemical agent or carcinogen or mutagen respectively in relation to a specified reference period;* OELs are usually established as 8-hour time weighted average (TWA) limit values).

Binding OELs, are set on the basis of the CMD and the CAD and the Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work"[8]. The process of establishing Binding limits involves a scientific assessment, but also includes an assessment of the technical feasibility and socio-economic factors of applying the limit at the workplace. The setting of BOELs 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.

Indicative OELs are established in accordance with the CAD. The process of establishing such limits does not include an assessment of the technical feasibility and socio-economic factors. IOELs are intended as European objectives to assist employers in identifying and assessing risks and are 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. They set threshold levels of exposure below which, in general, no detrimental effects are expected (Commission Directive 2009/161/EU).

Short-Term Exposure Limit values (STEL): There are chemical agents for which an 8-hour TWA alone provides insufficient protection for workers. In such cases Short-Term Exposure Limit values (STEL) may be set according to CAD or CMD, usually relating it to a 15-minute reference period (for further information see Section A.8-17.2.3.2).

Biological Limit Values (BLVs) are currently set in accordance with the CAD. They constitute limits of the concentration in the appropriate biological medium of the relevant agent, its metabolite, or an indicator of effect. The adoption of the BLVs follows the ordinary legislative procedure (for further information see Section A.8-17.2.3.3).

Biological Guidance Values (BGVs) are exposure-related values, representing 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. They may be useful for workers, employers and occupational physicians when dealing with worker protections issues. For instance they can be an indicator of occupational exposure that may require attention to consider the need for additional risk management measures (for further information, see Section A.8-17.2.3.4).

Notations can be added and may include a 'skin notation' for chemical agents that can be absorbed through the skin, a 'skin sensitisation' or 'respiratory sensitisation' notation for

[8] Directive 2009/148/EC of the European Parliament and of the Council of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance) Directive 2009/148/EC of the European Parliament and of the Council of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance). OJ L 330, 16.12.2009, p. 28–36

dermal or respiratory sensitisers, 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).

Generally, since exposure to airborne chemical agents via inhalation is the predominant route of exposure at the workplace, limit values are set for that route. The oral route of exposure, usually via unintentional ingestion and addressed through application of good occupational hygiene practice, 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, as the legal basis, i.e. CAD and CMD, refer to OELs as "…concentration of the chemical agent in the air within the breathing zone of the worker…" and in the absence of methods to directly measure exposure via the dermal route alone, dermal OELs have not been proposed by SCOEL. Skin notation is recognised by CAD and CMD and has been proposed by SCOEL when appropriate (see A.8-17.2.3.5). However, BLVs (reflecting exposure via all routes combined) have also been considered in numerous SCOEL opinions (SCOEL 2014).

A.8-17.2. Preparation of the report for the derivation of workplace exposure limit values

A.8-17.2.1 Data collection

Recent published reviews of the chemical agent should be used for overview if available, e.g. from established EU bodies, such as SCOEL, EFSA, ECB (EU Risk Assessment Reports), international organisations (such as, WHO, IARC), and relevant national scientific committees (such as AGS, DFG (MAK), DECOS, NEG, ANSES, ACGIH, US NIOSH). When using reviews, adequate consideration should be given to assess also the relevant source studies. If relevant REACH registration dossiers[9] are available, they should be examined for relevant hazard and exposure data and supplemented by the peer reviewed literature, where needed. In the case of exposure data provided in REACH registrations, measured data is likely to be more informative than modelled data. 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 Information requirements and Chemical Safety Assessment) 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 relevant EU and non-EU jurisdictions and organisations (e.g. ACGIH));
  Annex 1 of SCOEL (2017) lists the binding OELs and indicative OELs set by the EU up to the end of 2017 and data are available from databases, such as GESTIS for OELs and Biotox for BLV[10]

[9] For substances of very high concern on Annex XIV of REACH, the published applications for Authorisation and RAC opinions may provide an important source of occupational exposure data.

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

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

- published reports of organisations developing OELs, BLVs and BGVs.
  Different organisations (e.g. ACGIH, DFG (MAK) etc) publish a "documentation" that explains the rationale behind the limit value (AF applied etc) and considerations made (e.g. whether feasibility has been taken into account etc)

- relevant information from epidemiological (observational) studies, case reports (e.g. accidental acute poisoning), 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),
  - Appendix R.8-15 and SCOEL (2017), section F2-5.1

  Information on experimental studies consists of toxicokinetic studies, studies reporting on the toxicological endpoints of relevance (see section A.8-17.2.2.1) and mechanistic studies, as further described in:

  - SCOEL (2017), sections F2-5.2, F2-6 and F2-7.
  - Chapter R.7a of the guidance on IR&CSA gives further endpoint-specific guidance to information sources and evaluation of available information.
  - Chapter R.7.c of the guidance on IR&CSA, section R.7.12 provides guidance on toxicokinetics.
  - ECHA's Read-Across Assessment Framework (RAAF) and Chapter R.6 of the guidance on IR&CSA "QSARs and grouping of chemicals" provide information on the use of possible relevant non-testing data.

  In addition to traditional literature searches to identify relevant scientific articles, systematic approaches and tools are available for obtaining studies from the literature e.g. PRISMA, OHAT (NTP 2015). These, as well as other tools, e.g. ROBINS-I (Sterne et al 2016), also include approaches to assess the quality of the studies (see also Annex 2 to SCOEL 2017).

- the occurrence, production and use of the chemical agent;
  Identification of potential occupational exposure during the whole life cycle of the substance (i.e. including downstream use, and waste treatment or collection) and potential environmental (background) exposure.
  See also section F2-8 of SCOEL (2017).

- exposure routes, exposure levels and characteristics; including measurements

  When collecting information on background exposure levels (including biomarkers in biological media), information on possible co-exposures and confounding factors should also be gathered.
  See also section F2-9 of SCOEL (2017).

- information on the available methods on air- and biological monitoring.
  For air, this should include methods based on sampling and analysis but may also include mobile/hand-held instrumental methods (e.g. PID) for direct measurement in the workplace, especially when accessing confined spaces. Explanations on the requirements for the methods and sources of information can be found in Section A.8-17.2.4.

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. This includes local and systemic effects also occurring during time of pregnancy and lactation. The endpoints relevant for assessment include:

- Acute toxicity / Specific target organ toxicity single exposure;
- Repeated dose toxicity / Specific target organ toxicity repeated exposure/
- Irritancy (including sensory irritation) and corrosivity (respiratory tract, skin, eyes);
- Sensitisation (respiratory tract, skin);
- Genotoxicity;
- Carcinogenicity; and
- Reproductive including developmental toxicity.

Evaluating data includes an assessment of the adequacy, relevance and reliability for human health hazard assessment in the occupational context. 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 for example Klimisch scores.

For epidemiological data, please see the quality, validity and relevance considerations in sections F5 and F2-5.1 of SCOEL (2017) and in ECHA guidance Appendix R. 8-15 and R.4.

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 and the 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 humans, and the data are more likely to have been obtained from exposure conditions relevant to workers. In order to verify the good quality of such data, a proper assessment of the following aspects is needed (see SCOEL (2017) and Appendix R.8-15 for details):

(1) confounding factors that were controlled for in the studies;

(2) the accuracy of the (quantitative) exposure assessment used in the studies.

(3) the possibility and extent of various forms of bias (including also the ones related to the above bullets, i.e. from uncontrolled confounding and from non-differential or differential error in exposure assessment)

Similarly, more weight is generally given to *in vivo* data of good quality than to *in vitro* data, and more weight is generally given to experimental data of good quality than to non-testing data when integrating the available evidence in a weight of evidence approach.

The key aim of the hazard assessment is to identify hazardous properties relevant to the

workplace and, if possible, to conclude on points of departure (PoD) (e.g. BMD or NOAEL) relevant for deriving limit values (i.e. OELs, STELs, BLVs). The most relevant adverse effect(s) are taken as a basis for the PoD(s). If considered relevant, several points of departure for a single endpoint may be selected (e.g. when more than one study of similar quality are available for the most relevant route exposure, usually the inhalation route). Similarly, a PoD may be selected for different endpoints (e.g., a PoD for respiratory irritation and for reproductive toxicity). Before derivation of the respective limit values, it may not be clear which PoD will lead to the most appropriate limit[11] or if a STEL will be needed in addition to an 8-hour TWA OEL[12]. The process of selecting the final recommended limit values may be iterative and should take into consideration all available evidence in a weight of evidence approach, in contrast to basing a limit value on a single study result. If the weight of evidence does not allow to select one limit value over another, the lowest limit value(s) will normally be recommended.

A.8-17.2.2.2. Specific considerations on health effects and Mode of Action

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

OELs are established to protect workers from adverse effects on health, as defined by (SCOEL 2017, F3-2), that would arise from exposure to the respective chemical agents.

More detailed information on specific health effects and MoA relevant for OEL derivation can be found in Section F3-2 of SCOEL (2017). In the following, an overview is provided.

A.8-17.2.2.2.1 *Respiratory tract and sensory irritation*

Many chemical agents elicit local irritant effects on the eyes or the respiratory tract producing symptoms ranging from trivial to serious. Approximately 40% of the OELs have been set on the basis of this endpoint (Brüning et al 2014).

There is likely to be a threshold of effects for irritants and responses can be viewed as a continuum (SCOEL 2017):

1) no effects observed; no awareness of exposure;
2) very slight effects; awareness of exposure (e.g., smell);
3) slight irritant effects or nuisance (e.g., odour, sensory irritation); easily tolerable;
4) significant irritation or nuisance, overt health effects; barely tolerable;
5) serious health effects (e.g. pulmonary oedema); intolerable.

Slight symptoms, such as slight irritation, sensory irritation, ocular and/or nasopharyngeal discomfort, decreased performance and headache are regarded as adverse effects on the health and well-being of workers and, hence, as a 'hazardous property'. Consequently, when establishing OELs, nuisance (or sensory irritation) and somatic adverse health effects should be considered. However, a distinction between nuisance and a mere perception or awareness of exposure (e.g. smell) needs to be made.

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[11] For example, it may not be immediately obvious from comparison of the selected PoD for respiratory irritation and the selected PoD reproductive toxicity which POD will lead to the most appropriate 8h TWA OEL that is sufficiently protective for both properties because different assessment factors may be applied to the POD, see also section A.8-17.2.3.1.

[12] Before 8h TWA OELs are derived for the relevant chronic effects it may not be clear whether these 8h TWA limits will also protect against possible acute harmful effects.

A.8-17.2.2.2.2 *Respiratory sensitisation*

Evidence relating to respiratory sensitisation in the workplace is predominantly derived from experience in humans. Although such data would rarely enable identifying thresholds or dose-responses for induction of respiratory sensitisation, they might provide information relevant for dose-response related to markers of clinical manifestation of respiratory sensitisation. It is generally accepted that no validated methods exist to predict experimentally the risk of "respiratory sensitisation" to chemical agents (SCOEL 2017, F6-2.2.).

The criteria for classification of a chemical agent for respiratory sensitisation comprise the induction of sensitisation by immunological and non-immunological mechanisms. For some chemical agents (for example, those causing respiratory sensitisation via a non-immunological mechanism) it might be possible to identify a threshold of exposure below which a state of sensitisation is unlikely to be induced. For chemical agents acting via immunological mechanisms, thresholds have often not been identified or could not be observed (Section F6-2.2 of SCOEL 2017).

Chemical agents identified as respiratory sensitisers are assigned a "respiratory sensitisation" notation (see also Section A.8-17.2.3.5).

A.8-17.2.2.2.3 *Skin sensitisation*

Allergic contact dermatitis is one of the most frequently reported occupational illnesses which can only be handled by allergen avoidance. For the assessment of the skin sensitising potential of a chemical agent human data may be available. Case reports, especially from occupational settings, may be sufficient to raise a concern, but, in general, do not allow a clear assessment to be made. Most frequently, *in vivo* animal test data will only be available (SCOEL 2017, F3-2).

Chemical agents identified as skin sensitisers, including those classified according to the criteria of the CLP Regulation (EC No 1272/2008) criteria, are assigned a "skin sensitisation" notation (see also section A.8-17.2.3.5).

A.8-17.2.2.2.4 *Specific target organ toxicity*

Specific target organ toxicity covers effects occurring as a result of acute, short-term or long-term exposure such as significant functional changes, more than transient in nature, in the respiratory system, central or peripheral nervous systems, other organs or other organ systems, including signs of central nervous system depression and effects on special senses (such as sight, hearing and sense of smell) (see CLP Regulation EC No 1272/2008).

Adverse effects on organs are usually considered as relevant PoD for OEL derivation for non-carcinogenic substances and for non-genotoxic carcinogens.

A.8-17.2.2.2.5 *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 where the available data is adequate and sufficient (see A.8-17.2.3.6).

The Joint Task Force (JTF 2017b) considered that there is agreement to generally distinguish between genotoxic and non-genotoxic carcinogens. For genotoxic carcinogens two groups were identified:

i. where genotoxicity is caused by direct interaction of the respective substance or its metabolite with the DNA, the risks are usually assessed using a linear dose response relationship unless substance-specific data are available that allow deviation from linearity and/or to derive a MoA-based OEL;

ii. where genotoxicity may occur through indirect mechanisms that cause damage to DNA or chromosomes, frequently by interactions with proteins and there is sufficient evidence that a threshold can be identified, then a health-based occupational exposure limit may be derived.

It may be useful for understanding the rationale for the OEL to refer to the SCOEL grouping system for carcinogens (SCOEL 2017), but to note that this scheme is not considered a necessary step in the procedure (JTF 2017b).

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 (JTF 2017b; 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 is 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 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 (JTF 2017b; SCOEL 2017).

Examples of mechanisms of indirect genotoxicity include (JTF 2017b; SCOEL 2017):

i. increase in the background level of oxidative DNA damage, overload the system/change metabolism and exceed of natural protective mechanisms in the body such as stimulation of cell proliferation due to irritation, chronic inflammation or change in homeostasis;

ii. interaction with the cellular response to DNA damage (e.g. by inactivating DNA repair mechanisms, or by epigenetic effects); or

iii. effect on the chromosomal level alone (e.g. induction of numerical chromosomal aberration), in the absence of gene mutations.

Also for some specific direct acting genotoxic carcinogens a MoA-based threshold could be identified. For example when DNA repair mechanisms protect from the induction of mutations at low exposure levels (JTF 2017b), or when a substance (such as formaldehyde; SCOEL 2016) occurs endogenously for which a threshold may be derived below which it can be concluded with sufficient confidence that there is no relevant additional cancer risk beyond the typical biological range.

A.8-17.2.2.2.6 Reproductive and developmental 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 a point of departure such as a no observed adverse effect level (NOAEL; SCOEL 2017). However, when it is known that genotoxicity is the underlying mechanism for the reproductive toxicity of a substance, it is prudent to assume that a threshold dose/concentration cannot be identified (ECHA Guidance R.8-12).

In case a substance shows adverse effects on reproduction, the OEL should protect workers from such adverse reproductive effects.

Because of the relative sensitivity of the rapidly developing individual to specific toxic effects (especially during pregnancy and lactation), pregnant or lactating women may also represent a special risk group in the workplace. For pregnant workers or workers who have recently given birth or are breastfeeding, any risks to the safety or health and any possible effect on the pregnancy or breastfeeding of workers has to be assessed and decided what measure should be taken to avoid exposure of that workers to such risks (Council Directive 92/85/EEC).

However, at the beginning of pregnancy, workers might not be aware of the pregnancy with the consequence of possible adverse effects on the offspring. Hence, OELs should also protect the offspring of workers from adverse developmental effects.

When recommending an OEL, available information on reproductive and developmental toxicity needs to be taken into consideration in considering the appropriate point of departure for deriving an OEL. Where such information is not available, the consequential uncertainty should be recognised and identified so far as possible.

A.8-17.2.2.3. Outcome of the hazard assessment

The hazard assessment can have one of the following main[13] outcomes:

1) A health-based OEL can be derived

One or more adverse effects[14] are relevant for the protection of workers and the available evidence is adequate to establish health-based OEL(s) based on a threshold mode of action. Adverse effects for which health-based OEL(s) can be established may include for example irritancy, reproductive toxicity, or carcinogenicity in cases where 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. In case of the latter, it is recommended to additionally present the dose-response for carcinogenicity (i.e. cancer risk estimates) above the threshold, if possible, as this may inform those involved in the decision making process (i.e. ACSH, European Commission, Council and European Parliament) of the health risks above the threshold level (e.g. for impact assessment). If it is not possible to derive the dose-response for carcinogenicity, the reasons should be stated.

2) No health-based OEL can be derived

a) The chemical agent is a genotoxic carcinogen for which no threshold can be identified and therefore no safe exposure limit values can be derived for the carcinogenicity endpoint. In such cases, if possible, a dose-response for carcinogenicity providing cancer risk estimates will be presented (see section A.8-17.2.3.6). In case no such dose-response can be derived, the reasons will be presented. In addition, OELs can be derived for other endpoints than carcinogenicity to inform decision makers about the applicable thresholds, or absence thereof, for these other endpoints. However, no overall OEL would be recommended as there are currently no accepted reference cancer risk levels established on an EU-wide basis (a binding OEL can be adopted by the decision makers)[15].

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[13] In addition, STELs, BLVs, BGVs and notations may be outcomes of the hazard assessment.

[14] Adverse effects on health as defined by section F3-2 in SCOEL (2017). Similarly to SCOEL (2017), ECHA considers adverse effects on health in the broad sense, which includes the concept of 'nuisance' or sensory irritation.

[15] A binding OEL can be adopted by the decision makers in the 'ordinary legislative procedure' under the Carcinogens and Mutagens Directive, see Section A.8-17.1.1.

b) The main outcome of the hazard assessment does not fall under 2a and there is one or more relevant adverse effects but the available data are insufficient to derive a reliable exposure limit value. Thus, no overall OEL would be recommended for the chemical agent. The data gaps and uncertainties that lead to such an overall conclusion must be described.

c) Based on the available evidence the chemical agent is not hazardous for workers, or the available information does not allow a conclusion on whether the chemical agent is hazardous. Since a proposal for OEL is initiated the chemical agent will usually be known to be hazardous for workers, thus making this option an unlikely outcome in practise. This outcome of the hazard assessment is unlikely in practice since the Commission will normally request ECHA to develop a proposal for occupational exposure limits only when a chemical agent is identified to be hazardous for workers.

A.8-17.2.3 Exposure limit values and notations

A.8-17.2.3.1. Occupational Exposure Limits

Indicative or binding OELs are established, based on sufficient evidence, 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). The assumed respiratory volume is 10 m^3/8 hours (SCOEL 2017). OELs can be derived for non-carcinogenic substances and for carcinogenic substances for which a MoA based threshold can be identified.

A stepwise approach for selection of the point of departure and application of adjustment factors (extrapolation from animals to humans, in case animal data is used), variability factors (variability among workers) and uncertainty factors (considering uncertainties related to individual studies or to a set of studies) 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).

Furthermore, it is relevant to notice that "*The PoD, adjustment, variability and uncertainty factors are specific for a given chemical agent and based on the entire available database, considering consistency and interdependence of effects and mechanisms […] without using specific defaults. The SCOEL applies this comprehensive approach that considers the importance of interdependence which may not result in the simple product of the individual parts"* (SCOEL 2017).

Section R.8.4.3 of this guidance, provides guidance on the use of assessment factors for Derived No-Effect Levels (DNELs): "*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 and further reported in Table R.8-6 of this guidance.

In the Joint Task Force 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*". 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. The selection of the PoD, its adjustment to the worker's situation and the application of AFs (specifying the factors used for adjustment, uncertainty and variability) have to be transparently reported and should take into account all relevant information on the substance. Chemical specific data, including an evaluation of the size and quality of the data set, should always be considered first when deciding on AFs. Default AFs should only be used as a last option. The selection of PoD should include consideration, and if necessary adjustment, of the relevant exposure metric.

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 relevant residual cancer risk. In practice 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 absolutely safe - some uncertainties with regards to residual cancer risk may remain.

In all cases the remaining uncertainties need to be clearly described, including the uncertainty surrounding the identification of a MoA threshold and the uncertainty in identifying the PoD. 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 5.3 and 5.4).

It is recommended to express OELs in units of mg/m^3, providing the equivalent ppm-expressed values in brackets for gases and vapours. It is also useful to include conversion factors to translate between mg/m^3 and ppm. OELs can also be expressed in other units, e.g., fibres/ml or particles/ml. The OEL should be rounded to a value taking into account the uncertainties in deriving and measuring the OEL. Where relevant (e.g. to protect from different types of effects due to the size of inhaled particles and their location in the respiratory tract), the OEL should be defined as corresponding to the respirable, thoracic and/or inhalable fractions as defined by EN 481.

A.8-17.2.3.2. Short Term Exposure limits

In situations where the 8-hour TWA alone provides insufficient protection for workers, STELs are set according to CAD or CMD, usually relating to a 15-minute reference period. Typical examples are chemical agents causing acute harmful effects, such as respiratory sensitisation, irritation or narcosis after short-term (peak) exposure situations. Based on a 15 minutes exposure estimate, the STEL is defined as the exposure limit for 4 peak exposures per work-shift for 15 min each at maximum. The STEL should reflect the upper bound of the exposure variability. Both the TWA and the STEL must be complied with in the workplace, because the one does not substitute for the other (JTF 2017a).

For substances which would necessitate a STEL over a very short exposure duration (i.e. less than 15 minutes) the concept of a 'ceiling value' might be used, provided appropriate instantaneous measurement techniques are available, such as direct-reading instruments. These values must not be exceeded during any part of the working exposure. Such values with shorter reference period (e.g. one minute) have been implemented under CAD.

A.8-17.2.3.3. Biological Limit Value

Biological Limit Values (BLVs)[16] are limit values which relate to a chemical agent's concentration in the respective biological medium (e.g. blood, urine, breath).

A BLV is a tool for the control of potential health risks in the practice of occupational health. For a health based BLV derived directly from human studies containing data on cohorts with dose response effects or early biological effects, the BLV may not necessarily have a relationship with the OEL but rather with the levels at which the potential adverse health effects are observed in the study(ies). Another option is to derive the BLV from the OEL on the basis of established correlations between air levels and biomarker level. Background contextual information such as time of sampling, analytical method etc. are essential to interpret biomonitoring data. BLVs have similarity to Biological Exposure Indices (BEI values) in the US (ACGIH) and Biological Tolerance Values (BAT values) in Germany. (JTF 2017a).

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. Occasionally exceeding a BLV is unlikely to be associated with any adverse health effect whereas regularly exceeding a BLV should trigger improvement of exposure control.

When a BLV is proposed it should be indicated when the sample should be collected (e.g. post-shift, at the end of the work week, etc). Biological monitoring is primarily used as an aid to the assessment of systemic exposure by all routes (i.e. inhalation, ingestion and absorption through the skin) (SCOEL 2017) and sources of exposure (including non-occupational). It is a complementary approach to air monitoring and is particularly useful for chemical agents with a 'skin' notation, chemical agents that accumulate and/ or other situations where air monitoring alone may not give a complete picture of exposure. In cases where a skin notation is assigned, a biological limit value should also be derived, if feasible.

In cases where there is an identified exposure from other sources (e.g. water, food) biomonitoring can act as a useful means to identify potential for occupational exposure to cause exceedance of any pre-existing limit. As biological monitoring results reflect total exposure to the substance through any relevant route and from any source, in some cases, it may be difficult to link biological monitoring data to occupational exposure, as opposed to exposure through diet and the environment.

The methodology to derive BLVs and BGVs is out of the scope of this document. Recognised methodologies regarding derivation of BLVs are available (see for instance ANSES 2014 and MAK 2012)

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 often also called reference values. 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 population of a working age as defined reference population, but in practice this may not be possible. (SCOEL 2017, SCOEL 2014).

A value exceeding the BGV suggests occupational exposure and might require attention to identify the need for specific risk management measures, e.g. an expert consideration of the working conditions. BGVs do not represent a limit for health effects. If background levels cannot be detected, the BGV may be equivalent to the detection limit of the biomonitoring

[16] 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).

method, which then should be specified in the document (SCOEL 2017).

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 be absorbed through the skin and thereby increase the total body burden. Skin absorption 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 indicates a possible significant uptake through the skin. It alerts risk assessors and occupational hygienists in the interpretation of workplace air monitoring results that may not reflect the total uptake of the substance. This can for example occur in situations when the skin is in contact with a liquid. Simply put, keeping worker exposure below the OEL may not be adequately protective in such cases. It should be noted that the skin notation relates specifically to potential for dermal absorption and is not intended to give warning of direct effects on the skin such as corrosivity, irritation or sensitisation.

The assessment whether a skin notation is required considers various types of information and is necessarily qualitative. It can include the following:

- health effects observed in workers following skin exposure;
- where it is estimated (e.g. estimated through biomonitoring) that systemic exposure may to a large extent be due to dermal exposure;
- dermal absorption studies (*in vitro*, *in vivo*, and human);
- physicochemical properties – mainly solubility properties (e.g. aprotic solvents dissolving in both lipid and water).

Usually, a skin notation is applied where it can be assumed that dermal exposure may contribute to about 10 % or more of the body burden by inhalation exposure at the OEL (JTF, 2017a).

'Sensitisation'

'Skin sensitisation and '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, SCOEL 2017, Chapter F6-2.2). For chemicals at the EU market, such evidence would be available for substances classified as skin or respiratory sensitisers according to the Regulation (EC) 1272/2008 on Classification, Labelling and Packaging of substances. For other chemical agents that are not included in CLP, it will be necessary to look for evidence from other sources, e.g. published literature.

'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 excess noise. See Section F6-2.3 of SCOEL 2017.

A.8-17.2.3.6. Cancer dose-response assessment

Where the chemical agent is known to act via a non-threshold MoA, or when it is not possible to conclude on a MoA based threshold, a cancer dose-response assessment is presented if adequate and sufficient data are available. This cancer dose-response will be derived based on the appropriate dose response from human or animal data and using the relevant dose metric. Typically, in its final form, the cancer dose-response will present the excess cancer risk estimates as a function of the air concentration, assuming exposure during the entire working life. However, the excess cancer risk may also be presented as a function of a relevant biomarker of exposure in the workplace, or directly as a function of biomarkers of effect. If the available data indicate a deviation from linearity, a modification of the default linear approach should be considered.

Acceptable excess cancer risk levels have been adopted in some countries such as Germany[17] and The Netherlands[18]. 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 the decision maker to derive an appropriate occupational exposure limit based on such considerations as feasibility and health impact; such limits will however not reflect a safe level.

Human data

When available, good quality epidemiological data with sufficient statistical power should be used for excess cancer risk estimation of non-threshold carcinogens, (i.e. for estimating the excess cumulative (lifetime) cancer risk associated with 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 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-table 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 easy verification of 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. The JTF states that "*the use of*

[17] AGS (2016). The Technical Rules for Hazardous Substances (TRGS 910), dated 22.11.2016. Available at: https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/pdf/TRGS-910.pdf?__blob=publicationFile&v=2

[18] Health Council of the Netherlands (2012). Guideline for the calculation of occupational cancer risk values. Report No. 2012/16E. The Health Council, The Hague, 2012. Available at: https://www.healthcouncil.nl/documents/advisory-reports/2012/10/26/guideline-for-the-calculation-of-occupational-cancer-risk-values

Life table analysis (unconditional risk) is often, but not always, preferred from a scientific point of view above the so called conditional method since it takes into account shrinking of the population at risk due to other causes of death. The conditional method should be avoided as it is overestimating risk at a given exposure, leading to too conservative exposure estimates at which a certain risk occurs, especially when the analysis is extended to entire life-time or very old ages." (JTF 2017b)

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 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.

It is also important to consider other critical choices like (1) if a dose-response from an individual study or from secondary (meta or pooled) analyses of several studies is used, (2) what exact method is used to identify the dose-response (or slope) in the study, (3) until which age the calculations are done, (4) if the risk is restricted to a certain time window after exposure, and (5) which reference (incidence) rate is used (gender, geographical area) (see SCOEL 2017 and Goldbohm et al 2006 for details).

No assessment factors are typically applied when human data is used to derive the cancer excess risk function. This is by analogy to animal data, where generally only the assessment factor for allometric scaling between the animal species and humans is applied.

Animal data

When good quality epidemiological data with sufficient statistical power are not available, experimental animal data can be used to derive the excess cancer risk in function of exposure. 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 derivation of excess cancer risk estimates based on animal data 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) Apply an allometric scaling factor if necessary. 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^{-4} risk is obtained by dividing the T25 by 2 500. If the available data indicate a deviation from linearity, a modification of the default linear approach should be considered.

Further guidance on the derivation of excess cancer risk estimates based on animal data is available in ECHA Guidance R.8.5 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 the feasibility to monitor

the external exposure to the given chemical agent to assess compliance against the recommended OELs 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[19] "*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 fulfil other requirements in terms of, for example expanded uncertainty[20], selectivity, etc.

The report for the derivation of OELs should include a list of available methods that have the potential to fulfil the relevant standards (EN 482)[6] and include information on:

- Working range and limit of quantification (LOQ)
- Sampling, including:
  - Sampling time and,
  - where relevant, flow rate used and health related fraction(s) sampled (e.g. inhalable, respirable).
  - Selectivity/interferences
  - Type of sampling. Methods for OEL compliance should use personal sampling. Type of sampling in terms of active/ passive should also be detailed in the report.
  - Whether there is information from the published l methods, literature or databases.

Measurement procedures, including sampling and analysis, 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[21] provides an overview on the existing methods for a given chemical, including a rating of the method against the requirements of the relevant European standards.

However, it should be considered that when the GESTIS rating was made, the limit value may have been different.

.Care should be taken when applying the rating of a method to a new/revised OEL which may

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[19] 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.

[20] Statistical parameter to account for uncertainty of measurement: it consider sthe uncertainty of all steps of process (combined standard uncertainty) and adds a coverage factor. In the case of this standard to have a confidence level of approx. 95%, the coverage factor is 2)

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

be significantly lower care should be taken before considering applicability of the methods to a new OEL.

When a new OEL limit is proposed, a validated method may not yet be available. This does not necessarily mean that reliable measuring is not feasible, as normally the methods have been validated and optimised for substances having a OELs already in place. In such cases it is useful to assess whether the available 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). If no there is no method available able to reliably measure the OEL concentration this should be stated in the report.

For some chemical agents (and sectors), direct reading hand held (mobile) devices are used for routine check that exposure controls are working properly, e.g. when entering confined spaces. In those cases information on direct reading/ mobile methods (including measuring range) can be added to help assessing the impact of the new OEL on sector practices.

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 and sources 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 when a BLV or BGV is proposed. The information should describe the chemical agent (e.g. the substance of interest or a relevant metabolite) and the biological matrix (e.g. blood, urine or exhaled breath) and any known interferences of the analytical method. This information serves to describe the feasibility to monitor the internal exposure to the given chemical agent to detect the BLV or BGV concentration.

The biomonitoring method should be able to detect concentrations well below (e.g. 0.1 times) the BLV. In case the biomarker is detected also in the biological tissues of the general population, and especially in the case of bioaccumulative substances, the biomonitoring method should be able to detect the levels below the BGV concentrations (or established 90th /95th percentiles of the general population levels). In the case of substances, which BLV levels are very close to general population 95th percentile levels there might be a need to make e.g. pairwise comparisons (comparing pre-shift values to post-shift values) to identify occupational exposure. In these cases the biomonitoring method should be able to detect even lower level than levels just below the BGV.

In the absence of background exposure, or when background exposure is negligible, a BGV may be set at the limit of quantification, in which case the limit of detection should be as low as technically and practically possible.

Potentially suitable analytical methods can be found in the literature, but require an in-house validation, 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)[22] (SCOEL 2017).

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

A.8-17.3. References

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