
	<b>GUIDELINES TO ESTABLISH A SYENSQO ACCEPTABLE EXPOSURE LIMIT (SAEL)</b>	 IND-HSE-PRAS-05.01-GUI
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### List of Revisions

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V1.3		22/05/2024	<i>Update for Syensqo. 'Solvay' has been replaced by 'Syensqo'</i>

### Reference Documents

*IND-HSE-PRAS-05-PRO Procedure for establishing Syensqo Acceptable Exposure Limits (SAELs)*

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# **1. SUBJECT AND SCOPE**

## **1.1 Subject**

The purpose of this document is to provide guidance when setting **Syensqo** internal limits for exposure via the airborne route in order to protect workers and their progeny against adverse effects on health arising from occupational exposure to substances. In case of evidence of dermal absorption, a skin notation is assigned to the substance. On specific demand dermal SAEL values can be also calculated.

*'Syensqo Acceptable Exposure Limits' (SAELs) are internal Syensqo exposure limits aiming to ensure healthy and safe occupational conditions while working with hazardous substances. Syensqo establishes its own occupational exposure limit values (SAELs) when the company considers that the available regulatory or local values are not protective enough or they are not available for all substances. In general, SAELs are established for substances which are manufactured by Syensqo. However a SAEL may be derived for a substance which is not manufactured but used by Syensqo (purchased from suppliers).*

**An 8-hour TWA OEL** is the usual limit used for the purposes of preventing health effects arising from exposure to a specific substance; there will, however, be substances for which an 8-hour TWA OEL alone provides insufficient protection because a critical effect could be observed following a brief exposure. **In such cases, Syensqo could decide to recommend the establishment of short-term exposure limits (STELs), usually involving a 15 minute reference period, or even a ceiling value**, which is the concentration that should not be exceeded at any time.

**For genotoxic carcinogens** it may not be possible to define a threshold for the adverse effect. In such cases it must be assumed that any level of exposure, however small, might carry some finite risk and OELs must be established following **a risk-based approach ('probabilistic')**. **For such substances an acceptable risk and a corresponding concentration will be set.**

DNELs (and DMELs) have been introduced within the context of the REACH Regulation within the European Union to control the risks of workers exposed to substances. Nevertheless the EU Chemical Agents Directive (98/24/EC) refers to OELs (and not to DNELs) as criteria and therefore the OELs have a predominant legal effect in the context of the EU Chemical Agents Directive.

Furthermore the criteria for OEL and DNEL compliance are different. The DNEL/DMEL deriving in REACH is a standardized process, dividing the Point of Departure from animals, experimental studies by one or more fixed assessment factors. It differs from the more holistic, human health-based OEL setting by organizations like the EU regulatory bodies (**ECHA-RAC/SCOEL\***), the Dutch Health Council, the German DFG and the US ACGIH-TLV. The approach differences make that the DNELs/DMELs and OELs numbers can differ substantially despite that they are based in the same scientific data sets.

To ensure the same level of protection to **Syensqo** workers in all countries or regions related to activities involving substances with different national OELs and/or DNELs, a SAEL may be established for these substances manufactured by **Syensqo**. If a national OEL, TLV and/or DNEL is already available, the SAEL Committee will decide on a case by case assessment which limit value will be adopted as SAEL. This assessment will be based on the evaluation of the most recent available toxicological, epidemiological and medical data.

*\* The Scientific Committee on Occupational Exposure Limits (SCOEL) which established OEL values for Europe has been replaced by the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) from 2019.*

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In order to control total systemic exposure to chemicals at the workplace effectively, **it is necessary to take into account not only exposure by inhalation route, but also dermal exposure**, which may lead to skin penetration and a consequent increase in the total body burden. **For substances which are absorbed by the skin a ‘skin notation’ is recommended.**

## 1.2 Scope

The present document is intended for the use of SAEL committee members and toxicologists when preparing or reviewing dossiers on chemicals being evaluated for a [Syensqo](#) Acceptable Exposure Limit (SAEL).

*For the definition of **guideline**, refer to the Group’s policies glossary available on HSE teamsites doclib at [HSE managed documents/GLOSSARY-POLICIES.doc.](#); the latest, most recent issue of the present document is accessible on HSE teamsites doclib: [HSE managed documents](#).*

This document is part of [Syensqo](#)’s global policy approach, and in no event does it supersede, from a legal standpoint, any applicable legislation or regulation.

## 2. DEFINITIONS

BMD	Benchmark Dose
BMDL	Benchmark dose Lower confidence limit
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
ECHA	European Chemicals Agency
IND	Industrial function
IND-HSE	Department health Safety and Environment and its domains
IND-HSE-IH	Industrial Hygiene
IND-HSE-OH	Occupational Health
IND-HSE-PRAS	Product Regulatory Affairs and Stewardship
PPM	Policies and Processes Manager
LAEC	Lowest Adverse Effect Concentration
LD(C)50	Lethal Dose or Concentration (inducing 50% of mortality)
LOAEL / LOAEC	Lowest-Observed-Adverse Effect Level / Concentration
NOAEL / NOAEC	No Observed Adverse Effect Level / Concentration
NAEC	No Adverse Effect Concentration
OEL	Occupational Exposure Limit
RD50	exposure concentration producing a 50% respiratory rate decrease
SAEL	<a href="#">Syensqo</a> Acceptable Exposure Limit
STEL	Short Term Exposure Limit
T25	chronic dose rate that will give 25% of the animal’s tumors
TWA	Time Weighted Average

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### **3. PRINCIPLES USED IN SAEL VALUE DETERMINATION**

The derivation of occupational acceptable exposure levels based on animal and/or human data can ideally be split into four different phases:

- 1) Assemble and analyse all relevant data on the hazards of the substance. This will include human, animal data and other experimental information, as well as background data (e.g. physical properties) relevant to the establishment of a SAEL.
- 2) Establish whether the substance acts via a non-threshold mechanism or whether a threshold toxicological model can be used.
- 3) Assess the dose-response relationship. Establish 'no observed adverse effect levels/concentrations' (NOAELs/NOAECs) wherever possible, otherwise establish 'lowest observed adverse effect levels/concentrations (LOAELs/LOAECs) or benchmark dose (BMD) for threshold substances. Determine T25 (chronic dose rate that will give 25% of the animal's tumors) or BMD for non-threshold carcinogenic substances.
- 4) Establish a numerical value for an 8-hour SAEL TWA and/or for a 15-minute SAEL STEL if needed at or below the NOAEL/NOAEC (or, if this is not possible, below the LOAEL/LOAEC), applying appropriate assessment factors. However, for genotoxic carcinogens an acceptable risk and a corresponding concentration will be set.

### **4. OVERVIEW OF TOXICOLOGICAL AND HUMAN DATA**

The analysis of all relevant data on the hazards of the substance is performed by an extensive review of the data available for the substance. Information may derive from observations in humans, experiments in animals or laboratory investigations.

This analysis is focused on the definition of the most likely exposure route for the workers to the substance and the identification of one or more critical effects typical of the substance (toxicological endpoints).

In this phase, critical effects observed in animal studies have to be discussed for their relevance to human toxicology. If no information is available regarding the relevance of a specific effect for human health, it has to be considered as relevant under a conservative approach.

An overview of all relevant hazards data has to be made:

- Acute toxicity (oral, inhalation or dermal)
- Skin/eyes irritancy
- Skin/respiratory sensitization
- Subacute, subchronic or chronic toxicity (oral, inhalation or dermal)
- Genotoxicity/mutagenicity
- Carcinogenicity (oral, inhalation or dermal)
- Studies on reproduction and development
- Toxicokinetics
- Mechanism of action if available
- Human studies.

The observed effects should adequately be described, as well as the concentration and exposure time at which they occur.

The quality of the available data has to be evaluated. Based on Klimisch et al, 1997 scale, toxicological studies with reliability 1 or 2 should be retained. However, studies of lower reliability can

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be used to support the results of the SAEL calculation under a weight of evidence approach. In general, good quality human data are to be preferred to animal data, but human data is frequently either unavailable or scientifically inadequate.

When data on the compound under study are sparse or unavailable, a comparison with structural analogues should be examined in order to predict potential adverse effects of the substance. When a SAEL is derived based on data on analogue(s), an additional assessment factor can be applied based on an expert judgement (see chapter 6.2.7).

## **5. DOSE-RESPONSE RELATIONSHIP**

The dose-response relationship analysis has to be performed for each endpoint relevant to human health.

For effects where a threshold theoretically is expected, this phase is focused on the identification of the dose level at which no relevant adverse effects are observed. This level typically coincides with the NOAEC(L) (No Observed Adverse Effect Concentration or Level) of the toxicological study.

**The NOAEL/NOAEC is the highest concentration or dose of a chemical at which there are no statistically or biologically significant observed adverse effects between the exposed group compared with the control group for a given exposure period. Effects may be observed at this dose, but they are not considered to be adverse.**

In the absence of a NOAEL/NOAEC, an alternative value is needed. In this case an assessment factor is applied to the LOAEL/LOAEC (Lowest Observed Adverse Effect Level or Concentration) to derive the NOAEL/NOAEC. **The LOAEL/LOAEC is the lowest concentration or dose of a substance in a study, or group of studies, that produces statistically or biologically significant adverse effects in the exposed group compared with the control group.**

Alternatively, a benchmark dose (BMD) can be determined if possible, and is preferred over LOAEL/LOAEC to NOAEL/NOAEC extrapolation (ECHA R8 guidance, 2012 with Appendix on Occupational exposure limits (01/08/2019)).

A benchmark dose (BMD) is a dose or concentration that produces a predetermined change in the response rate of an adverse effect. This predetermined change in response is called the benchmark response (BMR). Normally, the default BMR is 5% or 10% change in the response rate of an adverse effect relative to the response of the control group depending on whether response data is continuous or quantal(dichotomous).

The benchmark dose (lower confidence limit) (BMDL) is defined as “the statistical lower confidence limit on the dose producing a predetermined level of changes in adverse response compared with the response in untreated animals”.

Notwithstanding that the BMD method is not widely used yet, it represents a novel approach which could replace the traditional threshold and non-threshold methods for the toxicological effect assessment in the future.

*In some cases, BMD and BMDL have been already derived by Agencies (EFSA, US EPA, ATSDR, WHO, EU Existing Substances RAR), or published in the literature. Such values can be retained as the point of departure in order to set a SAEL value.*

*BMD/BMDL can be also calculated using the BMDS software available on different websites:*

- US EPA website: <http://www.epa.gov/ncea/bmds/>
  - EFSA website (PROCAST version 69.0): <https://r4eu.efsa.europa.eu/>
  - and RIVM website (PROCAST version 70.1, October 2020): <https://procastweb.rivm.nl/>
- Information and guidance on the use of BMD can be found on the same sites.*

It should be taken into account that the NOAEC(L)/LOAEC(L) approach is not applicable to a non-threshold effect. For more details on genotoxic carcinogenic effects see chapter 10.



Following the toxicological/human effect assessment, the SAEL value is extrapolated with different approaches, depending on the observed effects. The method of extrapolation for threshold, short-term and non-threshold effects are described in the following chapters.

## **6. SAEL CALCULATION FOR SUBSTANCES WITH THRESHOLD EFFECTS (SAEL TWA)**

For threshold substances the SAEL TWA value can be derived by applying a series of assessment factors to the identified dose descriptors: NOAEC, LOAEC or BMDL (Benchmark Dose Lower Confidence Limit). Assessment factors (AF) or uncertainty factors are values used in the process of extrapolating from a necessarily restricted human and/or animal database to wider human populations, in order to allow for uncertainties in the extrapolation process.

It should be noted that the assessment factors reflect a conservative approach, although based on practical experience and professional judgment. Despite attempts made to harmonise the use of assessment factors, different approaches are used at the moment by different authorities and scientific bodies.

Traditionally, a more or less standard assessment factor of 10 was used for every step of the extrapolation of a reference level from an animal N(L)O(A)EC(L). Recent approaches tend to define a tailored assessment factor for every specific extrapolation, based on default scientific assumptions as well as case-specific scientific evidence.

The approach presented in the following Sections is based on different guidance documents:

- Methodology for the Derivation of Occupational Exposure Limits. SCOEL, June 2013 and December 2017;
- Guidance for the implementation of REACH - Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. ECHA (2012);
- Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace. Version 1.0. ECHA (2019);
- Derivation of assessment factors for human health risk assessment. ECETOC Technical Report n.86 (2003);
- Guidance on Assessment Factors to Derive a DNEL – ECETOC, October, 2010;
- Guidelines for carcinogenic risk assessment. US EPA (2005);
- Overview of methodologies for the derivation of occupational Exposure limits for non-threshold carcinogens in the EU. RIVM, 2014.

Typically, four assessment factors are taken into account, based on:

- **Inter-species variability:** the inter-species biological and physiological differences between humans and the animal used for the toxicity tests.
- **Intra-species variability:** The existence of a human population with a different sensitivity to the considered adverse effect.
- **Duration extrapolation:** The extrapolation from short (non-chronic) exposure of the experimental study to the expected chronic exposure.
- **The point of departure used:** The extrapolation from a LOAEL/LOAEC to a NOAEL/NOAEC and use of a BMDL5 or a BMDL10.



A further assessment factor may be considered on a case-by-case basis, depending on:

- The presence of a shallow dose-response curve
- The quality of the study
- A general uncertainty on the adopted NOAEC(L)
- The use of analogues.

Before applying the assessment factors, a series of modifications of the dose descriptors, taking into account the differences existing between the exposure regimes adopted in the toxicological studies and the real-life exposure conditions need to be considered. Among them a route-to-route extrapolation needs to be carried out if available experimental data are based on administration routes not corresponding to the occupational exposure route.

## **6.1 Modification of the relevant dose descriptor to the correct starting point**

This modification is necessary when the effect assessment is not directly comparable to the exposure assessment in terms of exposure route, units and/or dimensions. This applies to 4 situations:

1. If for a given exposure route there is a dose descriptor for the same route in experimental animals but for that particular exposure route there is a difference in bioavailability between animals and humans at the relevant level of exposure.
2. Differences in worker and experimental exposure conditions.
3. Differences in respiratory volumes between experimental animals (at rest) and workers (light activity).
4. If for a given worker exposure route there is not a dose descriptor for the same route in experimental animals or in humans (workers).

### ***6.1.1 Difference in bioavailability***

The default situation, in the absence of information, is to assume the same bioavailability for experimental animals and humans for a particular exposure route. However, when available information indicates that at the relevant level of exposure humans absorb less or more than experimental animals, the dose descriptor needs to be corrected for this difference in bioavailability.

### ***6.1.2 Difference in human and experimental exposure conditions and in respiratory volumes between experimental animal (at rest) and humans (light activity)***

**For systemic effects**, exposure conditions between experimental animals and workers should be taken into account. In most cases, animals are exposed 6 hours per day, 5 days/week in an inhalation study whereas workers are usually exposed 8 hours per day, 5 days/week. Furthermore, it should be also taken into account that exposed animals are without activity whereas workers have light activity. Thus the correction is the following:

$$\text{Corrected N(L)AEC} = \text{inhalatory N(L)OAEC} \times (6\text{h/d} \div 8\text{h/d}) \times (6.7 \text{ m}^3 \div 10 \text{ m}^3)$$

6h/d: Usual exposure of animal in experimental inhalation studies

8h/d: Usual exposure time of workers

6.7 m<sup>3</sup>: respiratory volume if no physical activity for general population (8h)

10 m<sup>3</sup>: respiratory volume if light physical activity for workers (8h)

For respiratory tract irritation, the respiratory volume should be only taken into account in order to modify the starting point. For example in order to derive a SAEL for respiratory irritation, the conversion of an inhalatory rat NO(A)EC or LO(A)EC is the following:

$$\text{Corrected N(L)AEC} = \text{inhalatory N(L)OAEC} \times (6.7 \text{ m}^3 \div 10 \text{ m}^3)$$

6.7 m<sup>3</sup>: respiratory volume if no physical activity for general population (8h)

10 m<sup>3</sup>: respiratory volume if light physical activity for workers (8h)

### 6.1.3 Route to route extrapolation

*A route-to-route extrapolation is not appropriate for local effects.*

The toxic effect of a substance is influenced by route of exposure and concomitant rate of absorption, distribution, metabolism and excretion. These parameters control the resulting internal concentration.

When route-to-route extrapolation is considered appropriate (only for systemic effects), corrections should be made for differences in kinetics and metabolism. However, it is difficult to quantify differences in metabolism, excretion and distribution, thus in practice only differences between the different routes as determined by the percentages of absorption into the systemic circulation can be accounted for.

Substance-specific data on absorption via the different routes are to be preferred when available. *However, in case of no substance-specific data, default route-to-route extrapolation factors have to be applied.*

*For oral-to-inhalation extrapolation, ECHA (2012) proposes to use 50% for oral absorption and 100% for inhalation as defaults which is equivalent to an oral-to-inhalation ratio of 2.*

*In a recent publication, K.Schröder et al, 2016 analyzed pairs of oral and inhalation toxicity studies based on a big dataset (from RepDose® database) consisting of 246 study pairs on 110 chemicals and tried to identify oral-to-inhalation ratios. For systemic effects an oral-to-inhalation extrapolation factor of 2.2 (95% confidence interval: 1.2–3.1) was derived. For local effects, the extrapolation factor was 4.4 (95% confidence interval: 2.0–8.6). Calculation with LOELs instead of NOELs, exposure duration, intrinsic toxicological properties of the chemical and physicochemical properties of the chemical (vapor pressure, solubility in water, molecular weight, octanol-water partition coefficient and blood-air partition coefficient) did not influence the extrapolation factor significantly.*

*However, it is known that the state and the particle size have an influence on the absorption by inhalation (ECETOC TR-086, 2003). Based on this knowledge different default extrapolation factors can be proposed depending on the state of the substance (liquids or solids) and depending on the particle size of solids.*

**Solids:** *Solids with particles of a mass median aerodynamic diameter (MMAD) greater than 10 microns are retained (100%) in the upper respiratory tract (CIIT, 1999). Those particles are transported to the throat via the mucociliary escalator of the respiratory tract and are subsequently swallowed. This 'Secondary ingestion' is comparable to oral administration.*

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Therefore, for solid substances with particles size higher than 10 microns, no difference between oral and inhalation absorptions is expected and thus a default extrapolation factor of 1 is sufficient.

The rate and extent of deposition and absorption of respirable particles (MMAD less than 10 microns) via the alveoli could be higher than from secondary ingestion. Therefore, for such substances absorption via inhalation is considered to be higher than via oral route and a default extrapolation factor of 2 is recommended.

**Liquid:** in absence of specific data, a default extrapolation factor of 2 is proposed for liquids based on general ECHA recommendation and on the extrapolation factor of 2.2 derived for systemic effects in the publication of K.Schröder et al, 2016.

For nano-substances, a case by case approach, based on specific data will have to be followed.

The standard oral-to-inhalation extrapolation without taking into account the difference in absorption rates is the following:

$$N(L)AEC \text{ (human)} = N(L)OEL \text{ (rat)} \times 70 \text{ kg} \div 10 \text{ m}^3$$

**Body weight:** Body weight is usually assumed to be 70 kg (average for men). If exposures are expected to be to primarily women, 50 kg can be used.

**8 hour inhalation workers:** It is usually assumed that a person will inhale 10 m<sup>3</sup> of air in a typical 8 hour work day. A slightly higher or lower value can be selected if the known work environment would deviate significantly from the default value.

The table I, lists the parameters used for the modification of the dose descriptor in case of oral-to-inhalation extrapolation.

Table I: Parameters used for the modification of the dose descriptor (default and range values)

Assumption	Range for professional judgment	Default value
Body weight	50 - 70 Kg	70 Kg
8 Hour inhalation workers	7 - 15 m <sup>3</sup>	10 m <sup>3</sup>
<b>Absorption factors used for oral-to-inhalation extrapolation</b>		
For liquids	Specific rate if available	2
For solids with particles size smaller than 10 microns	Specific rate if available	2
For solids with particles size higher than 10 microns	Specific rate if available	1
For nano-substances	Only a specific approach is recommended	Only a specific approach is recommended

## 6.2 Assessment factors

The aim of this section is to recommend default assessment factors. However, it is to be noted that any relevant substance-specific or analogue-specific information on these assessment factors should be used to adjust or replace the default factors recommended in the following paragraphs.

### 6.2.1 Inter-species extrapolation

This assessment factor is used to extrapolate from an animal study to expected effects in humans. Interspecies differences result from variation in the sensitivity of species due to differences in toxicokinetics and toxicodynamics (US EPA, 1993).

If no substance-specific data are available, the standard procedure for threshold effects would be, **as a default, to correct for differences in metabolic rate** (allometric scaling factor) **and to apply an additional factor of 2.5 for other interspecies differences**, i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part) (ECHA R8 guidance, 2012; WHO, 2005).

The default allometric scaling factors resulting from the assumption that equitoxic doses (when expressed in mg/kg bw/day) scale with body weight to the power of 0.75, thus differ in function of species. Default allometric scaling factors for different species as compared to humans are indicated below in table II.

Table II: Allometric scaling factors for different species as compared to humans\*.

Species	Allometric scaling factor
Rat	4
Mouse	7
Hamster	5
Guinea pig	3
Rabbit	2.4
Monkey	2
Dog	1.4

\*Assuming the human body weight is 70 kg.

Allometric scaling should not be applied in cases where doses in experimental animal studies are expressed as concentration, i.e. mg/m<sup>3</sup> in air, as they are assumed to be already scaled according to the allometric principle, since ventilation rate and food intake directly depend on the basal metabolic rate. **Thus, allometric scaling should not be applied when setting a SAEL based on an inhalation animal study.**

**For local effects**, respiratory tract irritation, no assessment factor for interspecies differences is needed. Indeed, since the effects are not dependent on metabolic rate or systemic absorption, no allometric scaling factors should be applied.

Furthermore, several publications indicate that in general, laboratory animals have much more convoluted nasal turbinate systems than humans, and the length of the naso-pharynx in relation to the entire length of the nasal passage also differs between species. This greater complexity of the nasal passages, coupled with the obligate nose breathing of rodents, is generally thought to result in greater deposition in the upper respiratory tract.

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Therefore, based on these elements, no remaining factor is needed for irritation of the upper respiratory tract when this effect is observed on rodents. The pulmonary region is not affected by these particular features of the respiratory tract, thus a default factor of 2.5 for remaining difference should be applied for such an effect when no specific data are available.

**For systemic effects**, the default inter-species factor can be reduced to 1 when the effect in humans is expected to occur at about the same level of exposure or only at a slightly lower level than in the animal species. Similarly, when the effect appears at the same dose level in several different species (rodents and non-rodents species), the default inter-species factor should not be applied.

Where human data are used as the starting point for SAEL derivation, no extrapolation and no assessment factor is necessary for inter-species differences.

### 6.2.2 Intra-species extrapolation

This factor takes into account the uncertainty in the evaluation of the human sensitivity to toxicological effects based on individual variability. When considering the general population, the predicted variability is mainly related to human genetic polymorphism, but also several other factors, such as age, sex, health status, diet etc.

If the dose descriptor has been derived from a human study (epidemiological or occupational study) no additional factor is needed for intra-species variability.

If the dose descriptor has been derived from an animal study, animal intra-species variation has already to some extent been accounted for in that dose descriptor. However, since intra-species differences are greater in humans than in the more inbred experimental animal population, an additional factor is needed in order to take into account the human intra-species variability.

A review of the available literature on the variability of the human data for various toxicokinetic and toxicodynamic parameters (ECETOC Technical Report n.86, 2003) showed that the statistical variability estimable for the general population does not exceed a factor of 5. A default intra-species assessment factor of 3 is proposed in the ECETOC Technical Report for the worker population, because the worker population is continuously monitored and risk management procedures may be applied in order to minimise the risk (i.e. exclusion of susceptible sub-populations from specific exposures) (ECETOC Technical Report n.110, 2010). The ECHA R8 guidance for DNELs/DMELs gives a more conservative approach, setting intra-species assessment factors of 5 for workers.

**The value of 3 appears to be sufficient based on the fact that this sub-population does not cover children, old or very ill or susceptible people.**

However, **if a significant portion of the human population is known to be more susceptible** to a specific toxic effect seen in the key study, then an assessment **factor of 5** can be applied.

### 6.2.3 Exposure duration extrapolation

Differences in the experimental exposure and the duration of exposure for workers (usually 40 years for the whole working life) need to be considered taking into account that in general the experimental NOAEL/NOAEC will decrease with increasing exposure times and other and/or more serious adverse effects may appear with increasing exposure times. If no relevant substance-specific information on time-response is available, default assessment should be applied.

Since many chemicals may cause systemic adverse effects in a cumulative manner, the acceptable exposure is generally influenced by the duration of the exposure. The Haber's rule may be used as a default approach to estimate NOAEC(L) following chronic exposure from NOAEC(L) derived from less-than-chronic exposure studies.

The review of the ratios of subacute (subchronic) to chronic NOAEC(L) for a series of studies was carried out in the ECETOC Technical Report n.86, 2003 and confirmed substantially the approach derived from the Haber's rule for systemic effects. The assessment factors calculated according to this equation are about 6 and 2 for subacute-to-chronic and subchronic-to-chronic extrapolation, respectively. The assessment factors recommended in the Technical Report and in ECHA R8 Guidance on DNELs/DMELs are 2 and 6 when extrapolating chronic NOAEC(L)s from subchronic and subacute studies, respectively. Hence these can be considered as the default factor to be used for the less-than-chronic to chronic exposure extrapolation.

The following default assessment factors should be applied **for systemic effects**:

- Sub-chronic to chronic: **2**
- Sub-acute to chronic: **6**
- Sub-acute to sub-chronic: **3**

If the data (general toxicity) is coming from an OECD 422 guideline it is recommended to apply a default assessment factor of 6. Specific recommendations are indicated below in chapter 7 for deriving SAEL for fertility and developmental effects.

**For systemic effects**, a lower factor may for instance be used if there is specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects. For example, if there is clear evidence that based on 14, 28 day and 90 day studies the severity of the effect and the dose-response are similar, no assessment factor for time duration should be applied.

**For local effects** such as respiratory tract irritations mainly driven by the exposure concentration, no assessment factor for duration extrapolation is needed.

Information concerning **the toxicokinetics profile** of substances (e.g. detoxification rate, bioaccumulation potential) may influence the choice of this assessment factor. For example, a less-than-chronic to chronic exposure extrapolation assessment factor higher than the default factor could be warranted for a substance showing a relevant bioaccumulation potential.

#### **6.2.4 LOAEL/LOAEC-to-NOAEL/NOAEC extrapolation**

When there is no NOAEL/NOAEC observed in a study, the LOAEL/LOAEC can be used to extrapolate to the NOAEL/NOAEC. The size of an assessment factor should take into account the dose spacing in the experiment and the extent and severity of the effect seen at the LOAEL/LOAEC.

The ratio LOAEL/LOAEC to NOAEL/NOAEC was examined for a series of toxicological studies of different duration in the ECETOC Technical Report n.86, 2003. The results of the analysis showed that the average value is 3 and ratio rarely exceeds 5-6. The ECHA R8 Guidance is in agreement with the ECETOC vision concerning the default assessment factor to be used for LOAEL(C)-to-NOAEL(C) extrapolation. However, it is underlined that a higher assessment factor (up to 10) may be proposed, based on the slope of the dose-response curve and on the severity of the effects observed at the LOAEL/LOAEC.

The default assessment factor recommended is 3 in Faustman et al. 1994 publication. A higher assessment factor, generally 10, may be appropriate if serious adverse effects were noted at the LOAEL/LOAEC and if the spaces between the different tested doses are high. To the contrary an assessment factor smaller than 3 may be appropriate if only minor effects were seen at the LOAEL/LOAEC in a small number of the test animals and if the spaces between the different tested doses are small.

*For the LOAEL/LOAEC to NOAEL/NOAEC extrapolation, it is suggested to use an assessment factor between 3 (majority of cases) and 10 (as maximum). A default factor of 10 should be applied in*

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*exceptional cases where most animals present severe effects such as threshold carcinogenic effect, very severe irreversible effects, major offspring malformations and high offspring lethality at the LOAEL/LOAEC or in case of very high dose spacing.*

The BMD can be used in parallel to derivation of a NOAEL/NOAEC or as an alternative when there is no reliable NOAEL/NOAEC. Kalberlah and Schneider, 1998 considered the use of the BMD concept to be preferred to a general factor for LOAEL/LOAEC to NOAEL/NOAEC extrapolation. *A BMD calculated as the lower confidence limit of the dose that produces a response of 5% (BMD5) has, on average, been proposed to be comparable to a NOAEL (WHO, 2000). Therefore, if the starting point is a BMDL5 (benchmark-dose representing a 5% of response with a confidence level of 0.95) no additional assessment factor is needed.*

*If a BMDL10 (benchmark-dose representing a 10% of response with a confidence level of 0.95) is used it should be considered on a case-by-case basis whether an additional dose-response assessment factor is needed. If an additional assessment factor is required, a value of 3 is recommended.*

### 6.2.5 Quality of the study

In most cases no additional assessment factor is needed because data generally would not be considered if they were unreliable. In cases of limited data (such as a small number of test animals) it is implied that the results are of limited reliability and an assessment factor of 1 to 3 can be applied.

### 6.2.6 Severity of effect

An additional assessment factor is typically used for certain effects such as respiratory sensitisation, teratogenicity/developmental effects, reproductive or threshold carcinogenic effects.

*When the starting point for the SAEL calculation is a NOAEL/NOAEC an additional factor of 3 can be applied for serious effects such as severe irreversible effects, pup major malformations and high offspring lethality. In the exceptional case of a presumed threshold carcinogen an additional factor of 10 may be considered depending on the number of animals affected at the LOAEL/LOAEC (ECHA, 2012).*

*When the starting point for the SAEL calculation is a LOAEL/LOAEC the severity of the effects is already considered in the LOAEL/LOAEC to NOAEL/NOAEC extrapolation factor (see above chapter 6.2.4).*

### 6.2.7 Data on analogues

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. If the starting point has been derived by using read-across from one or more structural analogues, the additional uncertainty deriving from using these data may be addressed by selecting an additional assessment factor. Considering that the mode of action is very similar, **an assessment factor of 2 appears to be sufficiently conservative.**

In some cases where analogues induce slightly more severe effects than the substance, it is recommended to remove this additional assessment factor. For example, in the cyclopentanone REACH dossier some data gaps (repeated dose exposure toxicity) have been fulfilled by data performed on cyclohexanone. For the other endpoints, data available on both substances showed that cyclohexanone induces slightly more severe effects than cyclopentanone but in the same range of classification. Furthermore, some articles showed that the severity of the effects increases with the number of carbons. In such cases no additional assessment factor is needed.



The annex I (page 35) lists the recommended default factors and presents a range of values that can be used based on professional judgment depending on available data on the substance.

### 6.3 Adjusting SAEL TWA values for extended work shifts

The SAEL TWA of a substance is the time weighted average concentration of that substance in the workplace atmosphere to which nearly all workers may be exposed up to 8 hrs per day, 5 days per week, for up to a professional lifetime period of 40 years, without adverse health effects, attributable to that substance. In case of work schedules which are significantly different from the standard exposure schedule (e.g. 12 hrs shifts), the SAEL TWA value may be adjusted to provide protection for these workers equal to workers on conventional work shifts.

There are numerous mathematical models, some simple and some more complex, that can be used to adjust the TWA value to a different work schedule. The Brief and Scala model is recommended by ACGIH as a simpler model which reduces the TWA value by a factor that takes into account the hours worked daily and the periods of rest between them.

$$\text{Adjusted TLV} = \text{Reduction Factor} \times \text{TLV}$$

$$\text{Reduction Factor} = \frac{8}{\text{daily hours worked}} \times \frac{24 - \text{daily hours worked}}{16}$$

TLV = Threshold limit value (TWA set by ACGIH)

The number of days worked per week is not considered, except for a 7-day-workweek (e.g. for 56 workdays followed by 21 days off schedule). The formula to be applied for a 7-day workweek is:

$$\text{Weekly Reduction Factor} = \frac{40}{\text{hours worked per week}} \times \frac{(24 \times 7) - \text{hours worked per week}}{128}$$

For example, the modified TLV-TWA for toluene (TLV-TWA = 20 ppm) for a 12-hr/day 14-day pattern shift (five workdays one week and two workdays the next week) will be:

$$\text{Daily Reduction Factor} = \frac{8}{12} \times \frac{24 - 12}{16} = 0.5$$

$$\text{Adjusted TLV} = 20 \times 0.5 = 10 \text{ ppm}$$

It is recommended in a first instance to use the Brief and Scala model since it is a simple approach. This approach can be used by hygienists.

The toxicologists have to calculate first the SAEL TWA value for 8h of exposure and only the 8h SAEL value will be reported in the SAEL list. In the case of 12h work, since it is a specificity for some countries, the calculation will be done if needed by the hygienist, using brief and Scala method.

However this approach can be too conservative. If the risk does not appear to be controlled when using the Brief and Scala method, it is recommended to analyze the substance on a case-by-case basis according to their specificity and mode of action. In that case the adjusted TWA SAEL should be

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calculated by a toxicologist and has to be indicated in the SAEL rationale and it could also be included in the SAEL notification. The approach developed by Canada can be used by the toxicologist. For more information on this method, please see the following link: <http://www.irsst.qc.ca/media/documents/pubirsst/t-22.pdf>.

## **7. SAEL CALCULATION FOR SPECIFIC THRESHOLD ENDPOINTS (SAEL TWA)**

*In case that adverse effects are observed from reproductive toxicity studies a SAEL value for effects on fertility and/or for developmental toxicity should be derived. Usually, the various aspects of reproductive toxicity are considered to be effects with underlying dose threshold mechanisms and a NOAEL/NOAEC or LOAEL/LOAEC value should normally be provided from the available data. The methodology for reproductive SAEL calculation is similar to those described above for repeated dose toxicity. Calculations of SAEL<sub>fertility</sub> or SAEL<sub>development</sub> should be performed according to the general rules concerning conversion of the dose descriptor and the use of assessment factors. However, reproductive toxicity includes some specificities, especially for developmental effects, which are described in the following chapters.*

### **7.1 SAEL TWA calculation for fertility effects**

*Effects related to possible impairment of reproduction are assessed in reprotoxic screening studies OECD test guidelines n°421 and n° 422 and in complete reprotoxic studies OECD test guidelines n° 415, n°416 and n°443. Information from one or several of these guideline studies can be used to identify effects on fertility and for SAEL calculation.*

*For fertility effects, it is generally recommended to set a chronic SAEL value using the default assessment factors indicated in the chapter 6.2.3 for time duration extrapolation.*

- 6 for sub-acute to chronic extrapolation
- 2 for sub-chronic to chronic extrapolation.
- 3 for sub-acute to sub-chronic.

*Based on test guideline studies n°415, 416 and 443, no default assessment factors are required for the time duration extrapolation since these studies are considered as long term studies. They provide complete information on all aspects of reproduction and cover a full spermatogenic cycle and oogenesis cycle.*

*Reproduction/Developmental Toxicity Screening Test (OECD TGs n°421 and n°422) are not meant to provide complete information on all aspects of reproduction such as that obtained from a two-generation reproduction study (OECD TGs n° 416), from an extended-one-generation reproduction study (OECD TGs n°443) or from a one-generation reproduction study (OECD TGs 415). In addition, a limited number of animals is used in such studies. A positive result in OECD TG 421/422 may be considered sufficient for the calculation of a SAEL<sub>fertility</sub>. However, an additional assessment factor should generally be used to take account of the lower sensitivity of the study. Therefore, an assessment factor of 2 to 5, decided on a case-to-case basis, should generally be used to take account of the lower sensitivity of the study. A default factor of 3 is recommended in absence of specific data.*

*Since the exposure duration in the reprotoxic screening tests is not chronic, an additional factor for the time duration extrapolation is also recommended. A default assessment factor of 2 is considered sufficient since the time duration in these studies is between subacute and subchronic exposures and*

since the lower sensitivity of such studies is already taken into account by applying another assessment factor (see below).

No additional assessment factor for the severity of the effect is recommended in case of impairment on fertility.

Table III: Particular default assessment factors for SAEL<sub>fertility</sub> (chronic) derivation

	OECD TGs 421 and 422	OECD TGs 415, 443 and 416
Time duration extrapolation	2	1
Lack of sensitivity of the study	3	1

## 7.2 SAEL TWA calculation for development effects

For SAEL derivation developmental toxicity corresponds to the effects on the child resulting from parental exposure before conception, during embryo-fetal development or during the lactation period.

Development effects can be observed from Reproduction/Developmental Toxicity Screening Tests (OECD TGs n°421 and n°422), from a Prenatal Developmental Toxicity study (OECD TGs n° 414), from a two-generation reproduction study (OECD TGs n° 416), from an extended one generation study (OECD TGs n°443) or from a one-generation reproduction study (OECD TGs 415).

Screening tests does not provide complete information on all aspects of development such as that obtained from a Prenatal Developmental toxicity study, from a two-generation reproduction study (OECD TGs n° 416), from an extended-one-generation reproduction study (OECD TGs n°443) or from a one-generation reproduction study (OECD TGs 415). In particular, the post-natal effects associated with prenatal exposure (such as undetected malformations affecting viability or functional effects) or effects resulting from post-natal exposure or exposure during lactation are not covered in these studies. If a SAEL<sub>development</sub> is set based on a screening test, an additional assessment factor is recommended to cover the lack of information provided by such study. An assessment factor of 2 to 5, decided on a case-to-case basis, should generally be used to take account of the lower sensitivity of this type of study. A default factor of 3 is recommended in absence of specific data.

An additional factor for the time duration extrapolation can also be recommended depending on the type of study used, on the type of effects induced by the substance and on the type of population we would like to protect, pregnant woman, lactating mother or both.

Sub-chronic SAEL<sub>development</sub> appears sufficient to protect both pregnant women and lactating mothers.

- A Prenatal Developmental toxicity study offers a robust assessment of prenatal developmental toxicity. Therefore, an assessment factor for exposure duration is not necessary provided that experimental exposure adequately covered the pregnancy of the species under investigation. An OECD TG n°414 does not allow for any assessment of postnatal development, which may be identified as a data gap in the derivation of SAEL<sub>development</sub>. If additional information from other studies (OECD TGs 415, 416 or 443) indicated that the substance under evaluation can induce postnatal toxicity, such substances need to be evaluated on a case-by-case basis.
- If the SAEL<sub>development</sub> is derived based on a reprotoxic screening study (according to OECD TGs 421 or 422), the embryos and the fetuses are exposed throughout the gestation and effects of lactation are succinctly examined. Therefore, an assessment factor for the exposure duration is generally not recommended except if other available studies (OECD TGs 415, 416 or 443) indicated that the substance under evaluation can induce postnatal toxicity. In such a case, a specific assessment factor has to be applied.
- If the SAEL<sub>development</sub> is derived based on a two-generation reproduction study (OECD TGs n° 416), on an extended one-generation reproduction study (OECD TGs n°443) or on a one-generation reproduction study (OECD TGs 415), no exposure duration factor is

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recommended since such studies are long-term studies and covered both pre- and postnatal toxicities.

Developmental toxicity also includes effects which may occur after one single exposure in a susceptible window during foetal development (e.g. malformations and functional deficits). Most often it is not known from the data whether the development effect has occurred after single or repeated exposures. However, given the conservative nature of the proposed methodology (use of conservative assessment factors), a SAEL<sub>development</sub> value should be sufficient to ensure that adverse effects on development do not occur following high short-term exposures.

The extent and severity of the effects seen in reproductive/developmental toxicity studies may in some cases be very marked, e.g. extensive foetal or offspring death, major malformations, and severe functional defects in the offspring. When the starting point for the SAEL<sub>development</sub> calculation is a NOAEC(L) an additional factor of 3 for the severity of the effect can be applied for such serious effects.

For substances inducing only development effects, a specific SAEL<sub>development</sub> value has to be derived in order to protect specific sub-populations (pregnant woman, lactating mother or both).

For substances inducing both general toxic effects and developmental effects, two SAEL values have to be calculated, one protecting from developmental effects (for specific sub-populations) and the other one from the general toxic effects to protect all the workers. If the two SAEL values are similar, only the SAEL protecting all the workers (chronic one) has to be retained. If the SAEL<sub>development</sub> is lower than the general SAEL with more than 2-fold of magnitude, the two SAEL values have to be retained, the SAEL<sub>development</sub> in order to protect specific sub-population (sub-chronic SAEL) and the general SAEL in order to protect all the workers (chronic SAEL).

Table IV: Particular default assessment factors for SAEL<sub>development</sub> (sub-chronic) derivation

	OECD TGs 421 and 422	OECD TGs 414	OECD TGs 415 and 443 and 416
Time duration extrapolation	1	1	1
Lack of sensitivity of the study	3	1	1
Severity of the effects	3 (for extensive foetal or offspring death, major malformations and severe functional defects in the offsprings)		

## **8. SAEL CALCULATION FOR SHORT TERM SAEL VALUES (SAEL STEL)**

A specific SAEL STEL for a substance is defined as a 15 minutes average exposure which should not be exceeded at any time during a workday even if the 8-hour time weighted average exposure respects the SAEL TWA. Exposures above the SAEL TWA up to the SAEL STEL should not be longer than 15 minutes and should not occur more than four times per day. There should be at least 60 minutes between successive exposures in this range.

The aim of a STEL (short term exposure limit) is to prevent adverse short-term health effects (e.g. annoyance, irritation, central nervous system alteration) due to peaks in exposure that will not be controlled by the application of an 8-hour SAEL TWA limit.

When the review of the overall data-set shows that there is a need for a specific STEL, and sufficient data exist on which to make a scientifically based recommendation, a numerical limit will be proposed. A STEL value should be established in order to protect workers from an exposure of 15 minutes.

In principle, the STEL value is derived in the same way as TWA value, although special consideration needs to be given to the nature of the endpoint and the time of exposure.

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In certain cases it may not be possible to derive a SAEL TWA (lack of repeated dose studies) while it is possible to set a SAEL STEL.

## **8.1 Identification of the dose-response relationship**

Traditionally, acute toxicity tests in animals have primarily used mortality as the main observational endpoint, usually in order to derive a LC(D)50 value. Ideally, the sub-lethal toxicity occurring at lower doses should be considered as a more rational starting point than mortality for derivation of a STEL.

Human evidence, such as epidemiological studies, case reports of poisoning or episodes of acute toxicity at work, or information from medical surveillance, can be very important for the assessment of acute toxicity and can provide evidence of effects that are undetectable in animal studies, for instance induction of symptoms such as headaches and nausea. There may be case-reports of human poisoning incidents, which are usually single-exposure events, either deliberate ingestion or during incidents/accidents. The reliability of exposure assessments in such reports needs careful consideration as there is often substantial uncertainty, but these data may give valuable information on the acute toxicity in humans, allowing the identification of human NOAEL/NOAEC or LOAEL/LOAEC values.

In addition to acute systemic effects, some substances may cause local effects on the respiratory tract following a single exposure via the inhalation route. Acute local effects on the respiratory tract could be due to either or both of two different toxicological phenomena: sensory irritation or cytotoxicity/tissue damage. Only the derivation of a SAEL for acute cytotoxicity on the respiratory tract will be dealt with under this endpoint. The derivation of a SAEL for sensory irritation will be dealt with the endpoint of respiratory tract irritation (see chapter 6.2.1). For acute cytotoxicity on the respiratory tract, the severity of the local effects is usually proportional to the concentration/dose level; in such a situation, therefore it may be possible to identify a NOAEC or LOAEC for these effects from pathology or clinical observations from either animal studies or human data.

It is recommended not to derive a SAEL STEL value based on LC(D)50 since there is substantial uncertainty regarding the toxicity at lower doses or concentrations and no reliable basis to judge a dose which would not cause any toxicity in humans.

In the past, the RD50 calculated based on an Alarie test conducted in mice was used as a point of departure to derive a STEL value. Since this test is not performed any more, it was recommended not to use this test for setting a STEL value.

## **8.2 Modification of the starting point**

The most important modification is dealing with the time of exposure. STELs are established in order to protect from 15 minutes of exposure and generally inhalation acute studies are performed during 4 hours.

If time extrapolation is considered valid, then the most appropriate approach is to make use of the modified Haber's law ( $C^n \times t = k$ , where 'C' is the concentration, 'n' is a regression coefficient, 't' is the exposure time and 'k' is a constant) according to which the relationship between exposure concentration and exposure duration for a specific effect is exponential.

In order to estimate the value of the exponent n, empirical exposure concentration-exposure duration relationships for the relevant effect, which require the availability of good quality studies with several exposure durations, need to be established. In the absence of suitable data for deriving n, a default value of n=1 for extrapolating from shorter to longer exposure durations and a default value of n=3 for extrapolating from longer to shorter exposure durations should be used as these values lead to the most conservative estimates (ECHA, R8 guidance, 2012).



In addition to time scaling, it might be also necessary to convert the dose descriptor into a correct starting point to take into account the other differences such as: differences in routes of exposure between experimental animals and humans, possible differences in absorption rate and differences in respiratory volumes between experimental animals (usually at rest) and humans (light activity in case of workers). This conversion should be done as described in the general guidance for SAEL TWA (see chapter 6.1).

### **8.3 Application of assessment factors**

#### **Inter-species and intra-species extrapolations:**

The SAEL STEL value should be derived by applying the same assessment factors as described for SAEL TWA values (see 6.2.1 and 6.2.2 chapters).

#### **Exposure duration extrapolation**

This difference has been already taken into consideration with the modified Haber's law (see chapter above 6.2.3).

#### **LOAEL(C)-to-NOAEL(C) extrapolation**

In general, the investigation of toxicity is less extensive and detailed in acute toxicity studies compared to repeated-dose studies and reporting is in most cases limited to overt signs of toxicity (i.e. clinical signs) because histopathology, clinical chemistry, urinalysis, haematology and detailed motor activity are not normally performed. In view of this, one should consider the possibility that a lower NOAEL/NOAEC or LOAEL/LOAEC would have been determined if a more detailed investigation had been conducted. Overall, therefore, when a NOAEL/NOAEC or LOAEL/LOAEC from acute toxicity studies is used as the starting point for the derivation of the SAEL STEL for acute toxicity, careful consideration should be given as to whether an additional (over and above those described in the general guidance for a SAEL TWA) assessment factor should be applied to account for these deficiencies. **A default assessment factor of 5 can be applied instead of 3 for repeated dose studies.**

The other assessment factors, if any, are similar to those recommended for SAEL TWA values (Quality of the study, severity of effect and data used from analogues).

## **9. SAEL CEILING VALUE EXTRAPOLATION**

*Ceiling values (SAEL C) are maximal concentrations in the work atmosphere, which, due to a specific acute toxicity of the substance, should never be exceeded.*

Although the TWA concentration provides the most satisfactory practical way of monitoring airborne agents, there are certain substances for which it is inappropriate.

A substance may have certain toxicological properties that require the use of a ceiling value rather than a TWA or a STEL value. In the latter group are substances that are predominantly fast-acting and substances for which short-term peaks of exposure could result in serious health effects, for example, mortality after exposure to chlorine or to carbon monoxide. Such substances are best controlled by a ceiling value that should never be exceeded.

*A ceiling value has to be calculated for substances inducing effects immediately dangerous to life or health, for example substances classified Tox. Acute. Inhalation Cat. 1 or 2, H 330, strong respiratory tract irritants and substances inducing CNS suppressive effects.*

*Acute toxicity studies performed by inhalation are to be used for setting ceiling values. These values have to be derived in order to protect from irreversible effects that could occur immediately after exposure. The starting point to be used is a NOAEC or a LOAEC. If no starting point can be defined for irreversible effects, reversible effects can be used in a conservative approach. Because of its too great severity, lethality should not be selected as a critical effect. No modification of the starting point*

is required for the SAEL ceiling since there are instantaneous values never to be exceeded whatever the time of exposure.

### Assessment factors

Inter- and intra-species assessment factors have to be applied. For interspecies differences, a default factor of 3 is recommended only for systemic effects. No interspecies assessment factor has to be applied for local effects. For intraspecies differences, a default factor of 3 has to be used whatever the type of effects observed (systemic or local effects).

In case that a LOAEC has been chosen as a starting point, a factor of 3 or 10 is recommended depending on the severity of the effect and on the dose spacing.

No assessment factor for time extrapolation is necessary since instantaneous values have to be calculated.

Table V: Summary of default assessment factors to be applied for SAEL ceiling value derivation

	Systemic effects	Local effects
Default factors for interspecies differences	3	1
Default factor for intraspecies differences	3	
Default factor for LOAEL/LOAEC to NOAEL/NOAEC extrapolation	3 or 10	
Time extrapolation	Not applicable	

In the inhalation studies the effects and the lethality are observed for a given time exposure (generally 4 hours). The Haber law should be used for the extrapolation to other times of exposure. It is recommended to calculate the corresponding values for 1, 10, 20, 30 minutes and 1 hour.

### HABER LAW:

$$C^n * t = k$$

C= concentration of the substance (ppm)

T = time of exposure (minutes)

K = constant which represents a constant effect

n = Haber constant. With n = 1 for extrapolation to higher time of exposure and n= 3 for extrapolation to lower time of exposure.

The results can be given in a table with the corresponding calculated time. The more appropriate time is then to be chosen knowing that the aim of the ceiling values is to protect against instantaneous adverse effects. This most suitable time to be retained will be discussed within the SAEL committee based on the specific effect induced by the substance. For information, the value for 1 minute is only a calculated value without biological relevance.

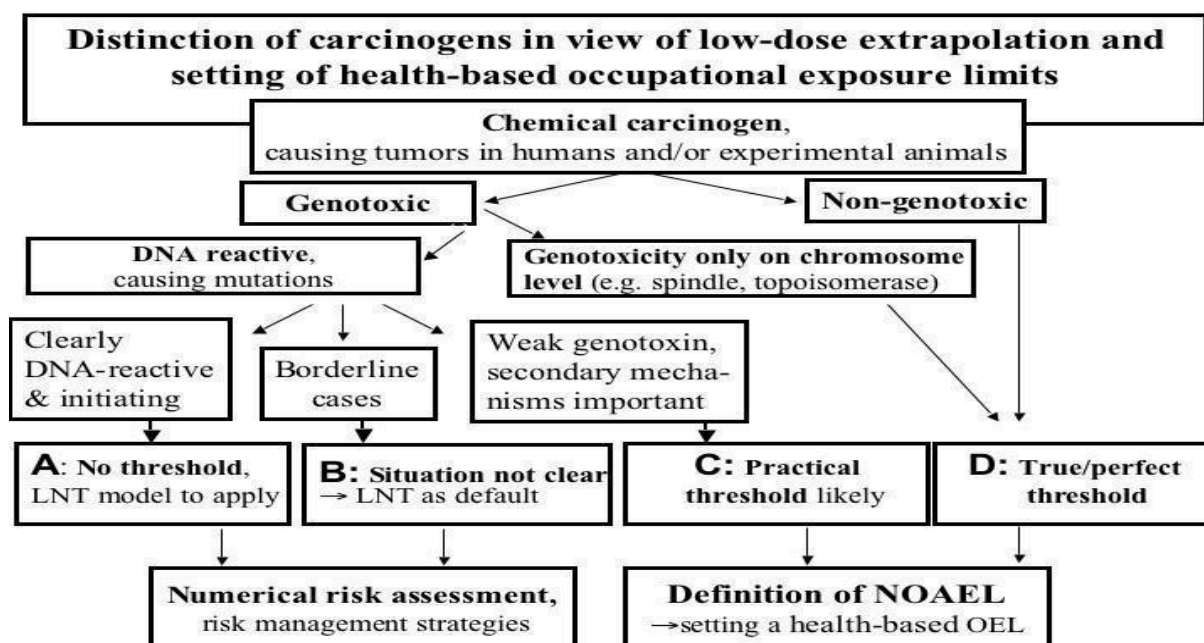


## **10. SAEL CALCULATION FOR SUBSTANCES WITH NON-THRESHOLD EFFECTS**

So far, there is agreement to distinguish between genotoxic and non-genotoxic chemicals, yet further differentiations seem appropriate. For genotoxic carcinogens, case studies of chemicals point to a whole array of possibilities. For a number of apparently genotoxic carcinogens, practical thresholds are a matter of discussion. For instance, positive data of chromosomal effects only, in the absence of mutagenicity, may support the characterisation of a compound that produces carcinogenic effects only at high, toxic doses (SCOEL, 2013, 2017). There is consensus that for non-DNA reactive genotoxicants, such as aneugens, thresholds should be defined. Specific mechanisms of clastogenicity have been repeatedly addressed as also having thresholds, such as topoisomerase II poisons or reactive oxygen species.

As summarised in the figure I below, these and other mechanistic arguments, taken together, led to the distinction of the following four main groups of carcinogens and mutagens in relation to setting SAEL values:

**Figure I: Distinction of carcinogens based on their mode of action (SCOEL, June, 2013 and 2017)**



**Group A:** Non-threshold genotoxic carcinogens; for risk low-dose assessment the linear non-threshold (LNT) model appears appropriate.

**Group B:** Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases the LNT model may be used as a default assumption, based on the scientific uncertainty.

**Group C:** Genotoxic carcinogens for which a practical threshold is supported.

**Group D:** Non-genotoxic carcinogens and non-DNA reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly found NOAEL/NOAEC.

Genotoxic carcinogens substances belonging to groups A and B act via a non-threshold mechanism, thus, no acceptable exposure level can be set, under which no adverse effect could be expected. **In this case, the risk characterisation is carried out by establishing the probability that an adverse effect may occur at a certain exposure level.**

Basically two semi-quantitative risk assessment formats can be followed: the 'Linearised approach' and the 'Large Assessment Factor' approach.

- The 'Linearised approach' is driven by the assumption of a linear dose-response relationship between cancer formation and exposure, using a high-to-low-dose extrapolation factor. *It is described in ECHA R8 Guidance, 2012, which should be used for further information and reference.*
- The 'Large Assessment Factor' approach is formally similar to the overall assessment factor approach applied for threshold effects and results in values representing exposure levels where the likelihood that effects (cancer) are avoided is appropriately high and of low concern from a public health point of view (this method is also described in the ECHA R8 guidance).

*The following chapters describe the approaches to be used for deriving non-threshold SAEL values.*

## 10.1 Risk-related concept

### 10.1.1 Introduction

Since there is no EU legislation nor worldwide document setting the 'acceptable' risk level for carcinogens, the SAEL committee adopted the 'Risk-related concept' developed by German authorities for setting MAK values for non-threshold carcinogens. This concept is described in the document TRGS 910 titled 'Risk-related concept of measures for activities involving carcinogenic hazardous substances'. For more details on this approach see below the web link to the TRGS 910 document.

<https://www.baua.de/EN/Service/Technical-rules/TRGS/TRGS-910.html>

For this concept, limits of risk are defined and substance-specific concentration values are derived corresponding to tolerable and acceptable risks. Two acceptable risks and one tolerable risk are defined.

This German approach is similar to the approach developed by the Netherlands government with the same level of risk. The Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands derives in the first step so-called health based calculated occupational cancer risk values (HBC-OCRVs). HBC-OCRVs are exposure levels corresponding to an extra risk of cancer that is predefined by the government. Two general reference risk levels have been defined in the Netherlands: a target risk level of  $4 \times 10^{-5}$  (4 additional cases per 100,000) for 40 years of occupational exposure and a prohibitive risk level of  $4 \times 10^{-3}$  (4 additional cases per 1,000) for 40 years of occupational exposure.

For non-threshold carcinogens, ECHA requires (where data allow) the calculation of a 'Derived Minimal Effect Level' (DMEL) which expresses an exposure level corresponding to a low, possibly theoretical, risk at which workplace exposures should be controlled. In their guidance, ECHA refers to  $1 \times 10^{-5}$  as indicative of a tolerable risk level when setting a DMEL for workers (ECHA, 2012). The ACGIH develops 'Threshold Limit Values' (TLVs®) as guidelines for levels of chemicals to which it is believed a worker can be exposed, on a daily basis for a working lifetime, without adverse health effects. These recommendations or guidelines are not developed for use as legal standards. The methodology employed by the MAK Commission has been used by ACGIH since 1995.

Other countries or bodies decided not to recommend a level of risk. For non-threshold substances ECHA-RAC/SCOEL followed the risk concept approach but doesn't give a view on the acceptability of risks, as that is not within its remit. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) develops OELs on the basis of scientific data. For non-threshold substances, cancer risk values are calculated for three different risk levels, i.e.  $10^{-4}$ ,  $10^{-5}$  and  $10^{-6}$  (presumably for 40 years of exposure, but not clearly stated) using linear extrapolation as a default method. Getting these three so-called individual excess risk (IER) values presented by the OEL Committee, it is then the responsibility of risk managers to establish an acceptable risk level.

An ECHA Workshop took place in November 2016, in order to discuss how to determine acceptable levels of exposure and related risks for workers and the general public in order to have a coherent approach. The workshop examined existing procedures and methodologies in the Member States and at European level. For workers, the Dutch model for setting risk based OEL for non-threshold chemical was presented as well as the German approach.

Ruth et al., 2017 publication concludes that unless proper differentiation is made between threshold and non-threshold carcinogens, inappropriate risk management measures may be put in place and lead also to difficulties in translating carcinogenicity research findings into appropriate health policies. This article recommends that clear differentiation between threshold and non-threshold carcinogens should be made by all expert groups and regulatory bodies dealing with carcinogen classification and risk assessment (<https://www.sciencedirect.com/science/article/pii/S027323001730003X>).

Another article written by Boobis et al. (2016) strongly criticizes current approaches to the classification of carcinogens, proposing a risk rather than hazard-based decision framework to avoid health scares and unnecessary economic costs.

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For developing internal non-threshold values and based on the information described above, Syensqo recommends therefore, to follow a risk-based approach and to adopt the method developed by the German authorities in their TRGS 910 document 'Risk-related concept of measures for activities involving carcinogenic hazardous substances'.

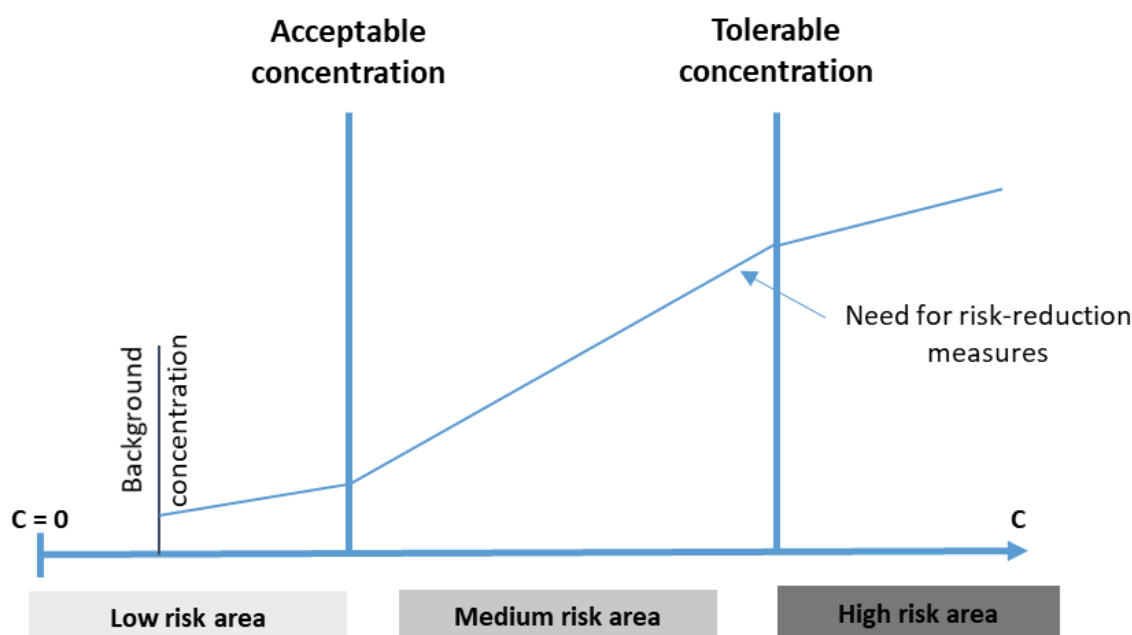
### 10.1.2 Principle

In the SYENSQO SAEL risk concept (similar to the TRGS 910 document), three different risk areas emerge on the basis of the acceptable and tolerable risks.

1. **Low risk area** (the exposures lie below the acceptable concentration),
2. **Medium risk area** (the exposures lie between the acceptable and tolerable concentrations) and,
3. **High risk area** (the exposures lie above the tolerable concentration).

The aim of the risk concept is to ensure that exposures lie below the acceptable concentration. According to this concept, the employer must prioritize the various measures to be taken. The higher the concentration of a non-threshold carcinogenic substance at the workplace, and so the risk, the more urgent is the necessity to take additional operational risk-reduction measures. The need for risk-reduction measures which increases with the risk, and its relation-ship to the three risk areas is depicted in the figure II below.

**Figure II: Relation between risk areas and measures**



C: Airborne concentration at the workplace

The area of low risk includes the area up to the acceptable risk. In this area, the need to carry out additional measures is low.

The medium risk area covers the area between the acceptable and the tolerable risk. In this area, the need for additional measures increases considerably as the respective concentration approaches the tolerable concentration.

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*The high risk area begins above the tolerable risk. In this area, there is a direct necessity for additional measures in order to return at least to the medium risk area.*

*The acceptable and tolerable risks are values not associated with a specific substance that express the statistical probability of cancer. The acceptable and tolerable risks defined in this approach are the following:*

**Acceptable risk:** 4: 10000 or 4:100000 (Below which a low, acceptable risk exists)

**Tolerable risk:** 4: 1000 (above which there is a high risk that is evaluated as intolerable).

*These risk values refer to a working lifetime of 40 years and exposure for 8 h every working day.*

*Substance-specific concentrations are then set corresponding to the three risks defined above. These concentrations are then used as an assessment criterion of risk assessment and for the implementation of measures to reduce exposure to non-threshold carcinogenic substances as explained in the figure II.*

*The acceptable concentration is a substance-specific value. It refers to the concentration of an airborne substance at the workplace, which corresponds to the acceptable risk. The tolerable concentration is also a substance-specific value, and it refers to the concentration of an airborne substance at the workplace, which corresponds to the tolerable risk.*

### **10.1.3 Recommendation for setting non-threshold SAEL values**

*Currently, for setting non-threshold SAEL values it is recommended to follow the 'Risk-related concept' described above and to establish three different SAEL values corresponding to the three following 'acceptable and tolerable risks':*

**Acceptable risk:**

- 4 out of 10,000 cases (4: 10,000),
- 4 out of 100,000 cases (4: 100,000)

**Tolerable risk:**

- 4 out of 1,000 cases (4: 1,000).

The choice of the applicable SAEL values based on the acceptable risk will be done within the SAEL committee after discussion with the GBU and sites. The final value targeted will be the one linked to the lowest acceptable risk (4 out of 100 000).

## 10.2 Methodology for SAEL extrapolation for substances with non-threshold effects

*The calculation of the SAEL for risk management purposes will be done using the 'Risk-related concept', and taking as basis the 'Linearised approach'.*

The *linearised* approach essentially results in values representing exposure levels where the likelihood that effects (as assessed by the lifetime cancer risk) are avoided is appropriately high and considered to be of very low concern. In order to derive such values, the accepted criterion for the risk characterisation of genotoxic carcinogens is to derive a human dose at which the cancer incidence probability would be of an excess incidence of  $1/10^5 - 1/10^6$  on a lifetime basis compared to a non-exposed population. The derivation of this acceptable dose implies the extrapolation of the cancer incidence at low doses from the incidence at experimental doses in animals.

*In the case of the SAEL methodology, the linearised approach have to be used in order to derive three different SAEL values corresponding respectively to the three level of risk:*

**Acceptable risk:**        - 4 out of 10,000 cases (4: 10,000),  
                                     - 4 out of 100,000 (4: 100,000)

**Tolerable risk:**         - 4 out of 1,000 cases (4: 1,000).

This approach follows a procedure consisting of the following steps:

- Step 1 : Selection of relevant dose-descriptor(s)
- Step 2 : Modification, when necessary, of relevant dose descriptor(s) to the correct starting point
- Step 3 : Application of assessment factors.
- Step 4: Calculation of the three different values corresponding to the three levels of risk defined.

### **10.2.1 Step 1: Selection of relevant dose-descriptor(s)**

The T25 should be used as the default dose-descriptor in relation to linear extrapolation. The linear approach is used when there is an absence of sufficient information on modes of action or when mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. The BMD10 i.e. the Benchmark-dose representing a 10% response should be used in certain cases in addition to the T25 when data are adequate for modeling purposes.

T25 is a dose-descriptor defined as the chronic (daily) dose that will give 25% of the animals' malign tumors at a specific tissue site after correction for spontaneous incidence, within the standard lifetime of that species. T25 is a linear extrapolation from observed cancer incidence in one experimental dose in animals. The selected dose for T25 calculation is generally the lowest tumorigenic dose showing a significant response (on statistical or biological basis). A statistical significance of  $p < 0.05$  or  $< 0.001$  may be considered for the selection of the dose, based on the tumor type. A lower statistical relevance is sufficient for rare tumor types having an extremely low background incidence, while  $p < 0.001$  is needed in the case of tumors that have a relatively high spontaneous incidence. The general derivation of T25 is reported in the equation below:

$$T25 = D (25/I)$$

I: the malign tumor incidence (cancer) (reported as a percentage)

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D: the experimental dose at which I was measured.

In case that spontaneous tumors are observed in the control group, correction for baseline tumors should be done in the calculation of the T25. The net % of tumors have to be calculated as followed:

Net % of tumors = I - malign tumor incidence at the control group

$T25 = D (25 / \text{Net \% of tumors})$

BMDL10 is the lower limit of the one-side 95% confidence interval on the Benchmark-dose representing a 10% cancer increase over background upon lifetime exposure (confidence level of 0.95). BMDL10 is calculated by fitting a mathematical dose-response model to data using appropriate statistical procedures. The fitting model for the BMDL10 calculation should be chosen on the basis of the goodness of fit (in terms of P and Chi-square values, as proposed in the EPA guideline on Benchmark dose), although the multistage model is proposed by EU TGD as a widely accepted model for the dose-response relationship. In contrast to the T25 approach, the BMDL10 approach takes into consideration all the experimental data and thus gives more reliable information about the dose-response relationship. On the other hand, the reliability of BMDL10 modeling is significantly limited by the quality of the experimental dataset. BMDL10 can be calculated by software available in the US EPA site (see page 7).

### **10.2.2 Step 2 : Modification, when necessary, of relevant dose descriptor(s) to the correct starting point**

This modification is necessary in the following situations:

1. If for a given human exposure route there is a dose descriptor for the same route in experimental animals but for that particular exposure route there is a difference in bioavailability between experimental animals and humans at the relevant level of exposure.
2. If for a given human exposure route there is not a dose descriptor for the same route (in experimental animals or humans).
3. Differences in respiratory volumes between experimental animals (at rest) and humans (light activity) when the starting point is an inhalation study.
4. Differences in human and experimental exposure conditions.

The corrections for situations 1 to 3 are performed in the same way as described in Section 6.1 for the derivation of threshold limit values.

#### **Case 4: Differences in human and experimental exposure conditions**

In case of oral carcinogenicity studies, both a correction factor taking into account the differences in the exposure regimes and a route-to-route extrapolation need to be considered. The accepted criterion is that the exposure conditions of the (oral) 2-year carcinogenic studies (1 administration/day, 7 days/week for 2 consecutive years) adequately represent the conditions of exposure for the general population. This means that, when the risk is assessed for the worker population, a correction factor is needed in order to take into account the different exposure period of workers (5 days/week, 48 weeks/year for 40 years of working life). This correction factor is then:

$$7/5 \times 52/48 \times 75/40 = 2.8$$

In case of inhalation carcinogenicity studies, since animals are exposed for 6 hours/day, 5 days/week for 2 consecutive years in the carcinogenicity studies by inhalation, whereas the occupational exposure is 8 hours/day, 5 days/week, 48 weeks/year for 40 years of working life, the following correction factor is to be considered:

$$52/48 \times 75/40 \times 6/8 = 1.5$$

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### 10.2.3 Step 3: Application of assessment factors

For non-threshold limit derivation, **the assessment factors** to be considered are the following:

- Inter-species differences
- Intra-species differences
- Differences in duration of exposure
- Issues related to dose-response
- Quality of whole database
- And, high to low dose extrapolation

For the variability concerning intra-species differences, differences in duration of exposure and issues related to dose-response, in contrast to threshold effects, no assessment factor is to be applied for this extrapolation step for non-threshold effects. The reason for this approach is that the linear model used for high to low dose extrapolation (see part on high to low dose extrapolation below), which is over about four orders of magnitude, is considered sufficiently conservative to also cover intra-species, duration of exposure and dose-response differences.

#### Inter-species differences

For systemic non-threshold effects, only an assessment factor for differences in metabolic rate (allometric scaling) is to be applied. However, this assessment factor is not needed for non-threshold effects that are induced locally at the ports of entry, or when a respiratory study is used as a starting point for deriving a non-threshold SAEL in air for humans.

It should be noted that it is the dose unit (original or transformed), and not the (experimental) route of application, that triggers the necessity for a species-specific factor for allometric scaling. This follows, for instance, that an assessment factor is needed also in chronic studies once the concentration (e.g., ppm in food) is transformed into a body burden or dose (mg/kg/day), which is then used in the risk assessment.

The above implies that, in contrast to threshold effects, as a default there will be no assessment factor for remaining uncertainty (i.e. in the absence of substance-specific information) for both systemic and local non-threshold effects. The reason for this approach is that the linear model used for high to low dose extrapolation (see part on high to low dose extrapolation below), which is over about four orders of magnitude, is considered sufficiently conservative to also cover these differences in interspecies sensitivity.

### 10.2.4 Step 4: Calculation of the three different values using the risk-related concept and the linear high-to-low dose extrapolation

The steps described in the above chapters (correction of the starting point, and application of assessment factors) have resulted in relevant (i.e. with regard to route and absorption) human equivalent lifetime daily doses:

- HT25 ('Human T25') if the starting point is the T25 (assumed to represent human daily exposures associated with tumour incidences of 25%) or,
- HBMD10 ('Human BMD10') more occasionally when the starting point is the BMD10 (assumed to represent human daily exposures associated with tumour incidences of 10%)

This high-to-low dose extrapolation step is to arrive at an exposure level that is considered to represent a risk level where the likelihood that effects (cancer) are avoided is appropriately high and of very low concern, acknowledging the fact that for non-threshold carcinogens a dose level without any residual cancer risk cannot be identified.

Since there is no EU legislation nor worldwide document setting the 'acceptable' risk level for non-threshold carcinogens, SAEL committee adopted the pragmatic and also fully recognized German 'Risk-related concept' for exposure management.

*Table VI: Recommended risk extrapolation factor depending on the dose descriptor*

	Risk level	Default multiplying value for high-to-low extrapolation to be applied on the 'Linearised approach'	
		Based on T25	Based on BMD10
<b>Tolerable risk</b>	4 : 1,000	4 / 250	4 / 100
<b>Acceptable risk n° 1</b>	4 : 10,000	4 / 2,500	4 / 1,000
<b>Acceptable risk n° 2</b>	4 : 100,000	4 / 25,000	4 / 10,000

*Three values corresponding to the three different levels of risk defined in the German 'Risk-related concept' should be calculated by the toxicologist. The final choice of the SAEL value will be done in the SAEL committee and after discussions with the sites. The final target value will be the one linked to the lowest risk defined (4 out of 100 000).*

Annex II (page 36) shows examples of SAEL derivation for non-threshold effects according to the 'Linearised approach'.

## **11. SKIN NOTATIONS**

Substances which can substantially contribute to the daily absorbed dose by dermal penetration receive a "skin" notation. For such substances, on a case-by-case basis, optimal protective measures will be recommended to minimise skin contacts.

A 'skin notation' relates specifically to dermal absorption of the material, i.e. it is determined by the toxicokinetic properties of the material. It does not relate to and is not intended to give a warning for direct effects on the skin such as corrosivity, irritation and sensitisation.

If no experimental data on dermal absorption are available, one of the following criteria will be used to assign a "SKIN" notation:

- 1) Dermal, oral, IV LD50 and LC50 values in the same species are available. If the dermal LD50 lies within the same range of the LC50 (converted to dose in mg/kg), or if the dermal LD50 is smaller than the oral LD50, further evaluation is needed to determine whether a skin notation is assigned (on a case-by-case basis). The same principle is valid if the dermal LD50 is similar to or smaller than 10 x the IV LD50.
- 2) Specific skin absorption data are available (e.g. topical pharmaceuticals). If the dose necessary to entail a systemic effect is such that contact of hands/forearms/face during occupational exposure is likely to reach this dose (before the correction with gloves), then a "SKIN" notation is assigned.
- 3) Biomonitoring data are available. If from biomarkers of exposure (urinary or blood concentration of a substance or its metabolites) it can be deduced that the internal dose is greater than the calculated absorbed dose by inhalation at steady state conditions, then further evaluation is needed to determine the contribution of the skin to the absorbed dose.
- 4) Case reports and practical experience on the work site is available (e.g. when substance elicits taste or urine odour after dermal contact). In this case an evaluation of dermal contribution to the total absorbed dose will be made on a case-by-case basis, whereby other

toxicological and physico-chemical data will have to be taken into consideration, or whereby additional data will have to be generated.

- 5) If the chemical structure of the substance suggests a similarity with other molecules having a relevant percutaneous absorption, then the "SKIN" notation has to be evaluated.

In absence of data described above, an indication of likely skin penetration may be inferred from physico-chemical data, including volatility, molecular weight and lipophilicity.

The diffusion of a molecule is much easier as its size is small. A molecular weight greater than 500 Da is a very limiting factor for dermal absorption. If it exceeds 1000 Da, the passage is almost impossible through healthy skin.

By its hydrolipidic nature, the stratum corneum enables the absorption of molecules of amphiphilic nature and moderately lipophilic molecules, which are characterized by its partition coefficient K or logP. It is recognized that the passage is promoted if the molecule has a log P between -1 and 4, a log P greater than 6 will be a very limiting factor. A 'Skin' notation is recommended in the different following situations (Kroes et al., 2007):

- Molecular weight between 150 and 250 and Log P between 1.0 and 2.0
- Molecular weight between 60 and 200 and Log P between 0.5 and 3.5
- Molecular weight less than 150 and Log P between -0.5 and 2.

Cases 1 and 2 are extensively discussed in an ECETOC document (ECETOC Special Report n.15, 1998).

This 'SKIN notation' corresponds to the 'notation Sp2' (Skin penetration 2) described in the Standard IND-HSE-IH-05.01-STA regarding hazard banding and OEBs and IND-HSE-IH-05.06-GUI regarding skin exposure management".

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## Annexes

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**Annex I: Recommended assessment factors in order to set a *general* SAEL TWA value (default and range values)**

Assessment factors		Range for professional judgment	Default value
<b>Interspecies variability</b>	Metabolic differences (Allometric scaling)	1 - 7 Depending on animals species, see table II  Not needed when the point of departure is an <u>inhalation study</u>  Not needed for <u>local effects</u>	1.4 – 7  Depending on animals species, see table II
	Remaining differences (mostly toxicodynamic differences)	1 - 2.5  Not needed for <u>local effects</u> <u>excepted for local effect on lung</u>	2.5
<b>Intraspecies variability</b>		2 – 5  <u>5</u> for substances with <u>severe effects</u> or substances for which a significant portion of population is known to be more <u>susceptible</u>	3
<b>Difference in duration of exposure</b>		Not needed for <u>local effects</u>	
Sub-chronic to chronic		1 - 2	2
Sub-acute to chronic		1 - 6	6
Sub-acute to sub-chronic		1 - 3	3
<b>Dose-Response relationship</b> LOAEL/IOAEC to NOAEL/NOAEC  BMD10 / BMD5		1 - 10  1 for BMD5 and case by case for BMD10	3  1 for BMD5
<b>Severity of effect</b>		1 - 10	1
<b>Reliability of data</b>		1 - 3	1
<b>Use of analogues</b>		1 - 2	2

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## Annex II: Examples of SAEL derivation for non-threshold effects according to the 'Linearised approach'.

**Example 1: Derivation of a SAEL for inhalation based on an oral rat carcinogenicity study (see next pages)**

STEP 1: Derivation / Identification of the relevant dose descriptor for carcinogenicity		
Based on the results of an oral rat carcinogenicity study a T25 of 10 mg/kg/d and a BMDL10 of 2.9 mg/kg/d are assumed.		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Relevant Dose descriptor	T25 (rat, oral) = 10 mg/kg/d	BMDL10 (rat, oral) = 2.9 mg/kg/d
STEP 2: Modification of the relevant dose descriptor		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Route-specific bioavailability: specific data: Assuming 100% of absorption for oral route and inhalation	* 1	* 1
Adjustment of route of exposure: Multiplying by 70 kg (average human weight) and dividing by 10 m <sup>3</sup> (average of respiratory volume rate for 8h with slight activity)	* 70 /10	* 70 /10
Differences between occupational and lifetime exposure conditions $7/5 * 52 /48 * 75/ 40 = 2.8$	* 2.8	*2.8

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Calculation of modified dose descriptor	T 25 of 10 mg/kg/d multiplied by $1 * 70/10 * 2.8$ <b>= 196 mg/m<sup>3</sup></b>	BMDL10 of 2.9 mg/kg/d multiplied by $1 * 70/10 * 2.8$ <b>= 56.84 mg/m<sup>3</sup></b>
<b>Corrected Dose Descriptor</b>	<b>Corrected T25 = 196 mg/m<sup>3</sup></b>	<b>Corrected BMDL10 = 56.84 mg/m<sup>3</sup></b>

STEP 3: Application of assessment factors		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Inter-species extrapolation (Allometric scaling)	4 (default allometric scaling factor for rat)	4 (default allometric scaling factor for rat)
Intra-species extrapolation	not applied	not applied
Differences in duration exposure	not applied	not applied
Quality of whole data	not applied	not applied

STEP 4: Calculation of SAEL as the "Acceptable risk" (Traffic light method)		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
High-to-low dose extrapolation (multiplicative value)	4/250 (for 4:1.000) 4/2,500 (for 4:10.000) 4/25,000 (for 4:100.000)	4/100 (for 4 :1000) 4/1,000 (for 4:10.000) 4/10,000 (for 4:100.000)

Calculation of <i>the 3 values</i> (corrected T25 or BMDL10 divided by overall assessment factor)	<p><i>For</i> tolerable risk: <math>196 \times 4 / 4 \times 250 = 0.784 \text{ mg/m}^3</math></p> <p><i>For</i> acceptable risk <i>n°1</i>: <math>196 \times 4 / 4 \times 2,500 = 0.0784 \text{ mg/m}^3</math></p> <p><i>For</i> acceptable risk <i>n°2</i>: <math>196 \times 4 / 4 \times 25,000 = 0.00784 \text{ mg/m}^3</math></p>	<p><i>For</i> tolerable risk: <math>56.84 \times 4 / 4 \times 100 = 0.5684 \text{ mg/m}^3</math></p> <p><i>For</i> acceptable risk <i>n°1</i>: <math>56.84 \times 4 / 4 \times 1,000 = 0.05684 \text{ mg/m}^3</math></p> <p><i>For</i> acceptable risk <i>n°2</i>: <math>56.84 \times 4 / 4 \times 10,000 = 0.005684 \text{ mg/m}^3</math></p>
<b>SAEL value</b>	<i>The choice of the applicable SAEL values based on the acceptable risk will be discussed in the SAEL committee.</i>	<i>The choice of the applicable SAEL values based on the acceptable risk will be discussed in the SAEL committee.</i>

**Example 2: Derivation of a SAEL for inhalation based on an inhalation rat carcinogenicity study**

STEP 1: Derivation / Identification of the relevant dose descriptor for carcinogenicity		
Based on the results of an oral rat carcinogenicity study a T25 of 176 ppm and a BMDL10 of 42 ppm are assumed.		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Relevant Dose descriptor	T25 (rat, inhalation) = 176 ppm	BMDL10 (rat, inhalation) = 42 ppm
STEP 2: Modification of the relevant dose descriptor		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Route-specific bioavailability: specific data: Assuming 100% of absorption for oral route and inhalation	1	1
Activity-driven differences At rest/slight activity: 6.7/10	* 6.7 /10	* 6.7 /10
Differences between occupational and lifetime exposure conditions $52/48 \times 75/40 \times 6/8 = 1.5$	1.5	1.5
Calculation of modified dose descriptor	T 25 of 10 mg/kg/d multiplied by 6.7/10 * 1.5 = 176.88 ppm	BMDL10 of 2.9 mg/kg/d multiplied by 6.7/10 * 1.5 = 42.21 ppm
Corrected Dose Descriptor	Corrected T25 176.88 ppm	Corrected BMDL10 42.21 ppm
STEP 3: Application of assessment factors		

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	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
Interspecies extrapolation	1 (The starting point is an inhalation study)	1 (The starting point is an inhalation study)
Intraspecies extrapolation	not applied	not applied
Differences in duration exposure	not applied	not applied
Quality of whole data	not applied	not applied

STEP 4: Calculation of SAEL (Traffic light method)		
	"Linearised" approach based on T25	"Linearised" approach based on BMDL10
High-to-low dose extrapolation (multiplicative value)	4/250 (for 4:1.000) 4/2,500 (for 4:10.000) 4/25,000 (for 4:100.000)	4/100 (for 4 :1000) 4/1,000 (for 4:10.000) 4/10,000 (for 4:100.000)
Calculation <i>of the 3 values</i> (corrected T25 or BMDL10 divided by overall assessment factor)	<i>For</i> tolerable risk: $176.88 \times 4 / 250 = 2.83$ ppm <i>For</i> acceptable risk n°1: $176.88 \times 4 / 2,500 = 0.283$ ppm <i>For</i> acceptable risk n°2: $176.88 \times 4 / 25,000 = 0.0283$ ppm	<i>For</i> tolerable risk: $42,21 \times 4 / 100 = 1.688$ ppm <i>For</i> acceptable risk n°1: $42,21 \times 4 / 1,000 = 0.1688$ ppm <i>For</i> acceptable risk n°2: $42,21 \times 4 / 10,000 = 0.01688$ ppm
<b>SAEL value</b>	<i>The choice of the SAEL value will be discussed in the SAEL committee.</i>	<i>The choice of the SAEL value will be discussed in the SAEL committee.</i>