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Manual for the
Simple European Calculator Of DNEL
(SECO-DNEL Tool 1.0)

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SECO DNEL ToolL

Simple European Calculator Of DNEL

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Content

Abbreviation

ABS:	Absorption fraction
AF:	Assessment factor
AS:	Allometric Scaling
CED:	Consumer Exposure Duration
CLP:	Classification, Labelling and Packaging
CMR:	Carcinogenicity, Mutagenicity, Reproductive toxicity
DMEL:	Derived Minimum Effect Level
DNEL:	Derived No Effect Level
EC:	European Commission
ECHA:	European Chemicals Agency
EU:	European Union
GLP:	Good Laboratory Practice
IOEL:	Indicative Occupational Exposure Limits
IPCS:	International Programme on Chemical Safety
Kow:	Octanol-water partition coefficient
LOAEC:	Lowest Observed Adverse Effect Concentration
LOAEL:	Lowest Observed Adverse Effect Level
MAK:	Maximale Arbeitsplatzkonzentration
NAEL:	No Adverse Effect Level
NOAEC:	No Observed Adverse Effect Concentration
NOAEL:	No Observed Adverse Effect Level
OECD:	Organisation for Economic Co-operation and Development
OEL:	Occupational Exposure Limits

RAC:	Risk Assessment Committee
REACH:	Registration, Evaluation, Authorisation and restriction of Chemicals
RIVM:	National Institute for Public Health and the Environment
SCOEL:	Scientific Committee on Occupational Exposure Limits
SDS:	Safety Data Sheet
SECO DNEL tool:	Simple European Calculator Of DNEL Values
SVHC:	Substances of Very High Concern
TG:	Testing Guidelines
WHO:	World Health Organization

diff. exp. cond.:	differences exposure conditions
derm:	dermal
inh:	inhalation
sRVhuman:	Standard Respiratory Volume, human
sRVanimal:	Standard Respiratory Volume, animal
wRV:	worker Respiratory Volume
M:	molar mass [g/mol]
p:	vapour pressure [Pa]
ρ:	density [kg/m³]
x_i:	molar fraction of the substance *i*
n_i:	amount of a substance *i* in a product [mole]
n_{tot}:	total amount of the substance [mole]

1 Introduction

According to Regulation (EC) No. 1907/2006 (REACH[1]), manufacturers and importers of substances are required to assess the human health hazard

- to determine the **classification** of the substance according to Regulation (EC) No. 1272/2008 (CLP[2]) and
- to derive levels of exposure to the substance above which humans should not be exposed. These exposure levels are referred to as **D**erived **N**o **E**ffect **L**evels (**DNEL**s) (see section 1.0.1. Annex I REACH).

1.1 Hazard assessment:

The human health hazard assessment according to Annex I REACH is a four-step procedure:

First step: Evaluate non-human information:

- Identify the hazard based on all available non-human information:
  - Toxicokinetic profile (absorption, metabolism, distribution and elimination)
  - Acute effects (e.g. acute toxicity, irritation and corrosivity)
  - Sensitisation (skin and respiratory sensitisation)
  - Repeated-dose toxicity
  - CMR effects (carcinogenicity, mutagenicity and reproductive toxicity)
  - Other effects, when necessary
- Establish the quantitative dose (concentration)-response (effect) relationship.
  - If not possible, give a justification and perform a semi-quantitative or a qualitative analysis.
- Present briefly all non-human information used to assess a particular effect on humans and the quantitative dose concentration)-response (effect) relationship:
  - In vitro, in vivo and other information
  - Test results: e.g. dose descriptors such as LD50, NOAEL/C, LOAEL/C, BMD(L)
  - Test conditions: e.g. test duration, route of administration, number of animals per dose group

[1] REACh: **R**egistration, **E**valuation, **A**uthorisation and restriction of **Ch**emicals

[2] Classification, Labelling and Packaging.

- Other information, when necessary
- Prepare a robust study summary giving rise to the highest concern:
  - If more than one test study is available for the same effect then the study giving the highest concern shall be used to establish a DNEL and a robust study summary shall be prepared for that/those study/studies.
  - Otherwise, if the study/studies with the highest concern is/are not used, a justification shall be given.

Second step: Evaluate human information:

The step 2 of the hazard assessment is, however, not implemented in the SECO DNEL tool. Only studies based on animal data will be considered in this version of the tool.

Third step: Classify and label the substance in accordance with the criteria as set out in Regulation (EC) No 1272/2008 (CLP).

Fourth step: Identify DNELs (see section 1.2 below for more details).

1.2 Definition of DNELs

REACH Annex 1 (1.0.1.) defines the Derived No-Effect Levels (DNELs) as levels of exposure to the substance above which humans should not be exposed. A DNEL should ensure that exposure to a specific substance does not lead to adverse health effects for humans.

- DNELs shall be established for all relevant exposure patterns associated with an exposure scenario. An exposure pattern is a specific combination of the likely exposure routes, exposure duration, exposure frequency and the relevant population.
- DNELs shall therefore be based on:
  - **Population:** workers and the general population (consumers and humans via the environment)
  - **Route:** oral, dermal and inhalation exposure
  - **Duration/Frequency:** acute (short-term) and chronic (long-term) exposure
  - **Effect type:** systemic or local
- DNELs are derived for substances that exert a **threshold effect**.
- DNEL are derived for the **leading health effect**. The leading health effect is defined as the toxic effect that leads to the lowest DNEL for a particular exposure pattern.
- Furthermore, the **uncertainty of the underlying data** shall be estimated, and the interspecies and the intraspecies variability, the nature and severity of the effect and the sensitivity of the human subpopulation (e.g. children) shall be taken into account.

1.3 When and why are DNELs needed?

The REACH legislation requires manufacturers and importers to calculate DNELs for (dangerous) substances produced in quantities above 10 tonnes/year. The **E**uropean **CH**emicals **A**gency (ECHA) has published a guidance document[3] (ECHA (2012)) that explains the concept and the procedure for deriving a no-effect level for human health. DNELs are used to evaluate exposure scenarios within the REACH legislation framework. Exposure scenarios show, for all relevant identified uses of a substance, under which operational conditions and risk management measures an adequate control of risks is reached. Risks are considered adequately controlled if exposure does not exceed the corresponding DNEL. Reference[4] DNELs are also derived by the ECHA's **R**isk **A**ssessment **C**ommittee (RAC) to evaluate the risks associated with the relevant uses of **S**ubstances of **V**ery **H**igh **C**oncern (SVCHs) that are subject to an authorisation process under the REACH legislation. The manufacturers and importers shall list the applicable DNELs under the section 8.1 in the **S**afety **D**ata **S**heet (SDS), together with the national occupational exposure limit values[5] that correspond to the Community OELs[6].

1.4 What are the current problems faced with DNELs?

Practical and regulatory experience show that registrants have different strategies and ways to derive DNELs.

Different problems are spotted regarding the derivation of DNELs:

- There is still a widespread belief that DNELs are conservative in nature[7]. Typically, legislative OELs are used to prove the conservativeness of the DNEL concept since they are considered to reflect a realistic level of exposure protecting the major part of the worker population. However, practical experience shows that:

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

[4] The Risk Assessment Committee of ECHA sets DNELs and dose-response curves for substances prior to receiving applications for authorization. This DNEL is referred to as reference DNEL.

[5] In Switzerland the national OEL corresponds to the SUVA MAK value (see Grenzwerte am Arbeitsplatz 2015 MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen, 1903D)

[6] In the absence of a Community OEL any relevant national limit must be listed.

[7] However, assessment factors applied are not necessarily conservative in nature but also a result of policy decision (see e.g. Falk-Filipsson (2007)).

    - Registrant DNELs are, for an equivalent percentage, higher or lower than the corresponding (national) OELs (see references below).
    - A significant number of DNELs are even higher, by more than a factor of 10, than the national or European Indicative OEL (see references below).
- Significant errors in calculating DNELs are made. For example, the wrong starting point correction formula, absorption rate or respiratory volume is used to calculate the DNEL.
- Different assessors may choose different leading health effects and corresponding dose descriptors based on the same dataset.
- Differences in the modification of the dose descriptor and in the individual assessment factors are applied.

For references see also Nies et al. (2013); Schenk and Johanson (2011); Schenk et al. (2014); Schenk, Deng et al. (2014)).

Problems that may appear for health practitioners:

- «High» DNELs may trigger protection measures that may unnecessarily increase the number of occupational diseases in a company.
- «Low» DNELs will generate unnecessary costs for the companies, and workers may be confronted with a disproportionately high level of personal protection measures.

➔ DNELs in the SDS should currently be interpreted cautiously!

1.5 What needs to be done?

Regarding the problems defined above, the following points need to be addressed:

- Calculation errors must be reduced.
- A consensus among different ways to derive DNELs has to be found.
- The scientific and legislative relation of DNELs to the national or European OELs needs to be intensively discussed.

This project offers a first step towards a solution to these problems. Concerning the high number of registrants and registered substances at ECHA[8], simple and pragmatic solutions need to be found.

[8] ECHA's database contains 13,052 unique substances and information from 50,405 dossiers (last updated 25 February 2015). However, it is expected that about 30,000 substances will be registered in 2018.

1.6 The SECO-DNEL tool

To this end, a DNEL calculator based on VBA Excel has been developed that includes a number of specific characteristics and features. The goal is to provide and promote a transparent platform that implements a consistent and well-accepted methodology for deriving DNELs. The tool is named the "**S**imple **E**uropean **C**alculator **O**f **DNEL**" (short-cut: SECO-DNEL tool 1.0). It is based on a clear set of criteria:

1. Simplicity
2. Transparency
3. Consistent methodological strategy for setting DNELs
4. Simple communication options

The SECO-DNEL tool (version) 1.0 has a simple structure that allows the user to calculate the relevant DNELs in an Excel spreadsheet according to a clear and well-accepted methodology. In general, the methodology used in the tool to calculate DNELs follows the rules established by ECHA (2012). All parameters that are used to adjust the (animal) dose descriptor, the assessment factors that are applied to the corrected dose descriptors and the corresponding calculation formula may be visualized and printed as a PDF file. This makes the calculation procedure of a DNEL transparent, because all relevant steps of the DNEL scenario are recorded in the «DNEL results sheet» of the tool. In addition, the communication process of a DNEL scenario via the PDF file is significantly simplified. This allows the manufacturers/importers, downstream users, regulatory bodies or risk assessors to fully comprehend the relevant steps of the DNEL calculation procedure of a registrant and compare them to other DNELs or OELs that are derived for the same substance. The primary reason for using an Excel spreadsheet is its well-known user interface and its possibility to be run without online access.

To promote this approach the tool will be provided free of charge on the website of the Swiss State Secretariat for Economic Affairs (SECO):

https://www.seco.admin.ch/seco/en/home/Arbeit/Arbeitsbedingungen/Chemikalien-und-Arbeit/Grenzwerte-am-Arbeitsplatz-DNEL.html

2 Methodology

The methodology used in this tool follows a clear procedure:

1. Substance-specific information should be used to derive the DNEL wherever possible.
2. If substance-specific information is not available, the default procedure shall be applied.

Priority should always be given to reliable substance-specific information when DNELs are derived (ECHA (2012); WHO/IPCS (2005)). A default approach shall therefore only be applied when no substance-specific data are available. The default approach used in the SECO-DNEL tool 1.0 follows the rules set out in ECHA (2012). Any substance-specific deviation from these rules must be stated and justified by the user. The quality of the data should always be critically evaluated in terms of its relevance, reliability and adequacy for a specific DNEL scenario (Klimisch (1997) and OECD (2005a)).

The SECO-DNEL tool 1.0 follows a 3-step procedure as recommended by ECHA (2012).

The relevant methodological steps may be summarised as follows:

Step 1:

Step 1 requires the collection of all relevant dose descriptors for a given exposure pattern. ECHA (2012) defines a dose descriptor as corresponding to an exposure level (dose or concentration) with a quantified level of risk of a health effect in a specific study. For threshold effects, typical dose descriptors are NOAEL/C, LOAEL/C or the **B**ench**m**ark **D**ose[9] (BMD). For example, the NOAEL corresponds to an exposure (dose) level where no statistically significant adverse effects are observed in a particular test.

In the SECO-DNEL tool 1.0 the toxicological endpoints of concern are the

- reproductive toxicity and
- other non-reprotoxic effects (systemic or local) that arise from repeated exposure to a substance for a particular time span.

The user of the tool may select either a NOAEL/C or a LOAEL/C as a dose descriptor for a specific endpoint. In addition, for the reproductive toxicity a NOAEL/C or LOAEL/C has to be selected for either developmental or fertility effects.

[9] The BMD approach is not implemented in this version of the tool, because most current derivations of DNELs are based either on NOAELs or LOAELs. If more experience is gained with DNELs based on BMDs then the tool may be updated to include the BMDs as an alternative approach to the N(L)OAEL dose descriptors.

Step 2:

Modify, when necessary, the relevant dose descriptors for all endpoints of concern to the correct starting point. For example, the administration route (e.g. oral) or the experimental conditions (e.g. 7 days per week of exposure frequency) may differ from the real world exposure pattern (e.g. 8 hours per day of inhalation exposure and 5 days per week of exposure frequency at workplace).

Step 3:

Apply, when necessary, assessment factors (AF) to the correct starting point to obtain the DNELs for the relevant exposure pattern (e.g. worker-DNEL long-term for inhalation route-systemic-other effect). For example, the toxicokinetics and toxicodynamics may differ between animals and humans. Therefore, assessment factors may need to be applied to account for these differences. For more details on the assessment factors see section 4.3.

The last step may be formalised as follows:

Endpoint-specific DNEL = N(L)OAEL/C_{corr} / AF_1 x AF_2 x …. x AF_n = $NOAEL_{corr}$ / overall AF,

whereas AF_1, AF_2 etc. are referred to as the individual assessment factors applied to the starting point corrected N(L)OAEL/C and the overall AF is the product of all applied AFs.

3 DNEL scenarios

The SECO-DNEL tool has a modular design. Each module consists of a DNEL scenario. The DNEL scenario comprises a (derived) DNEL and a set of rules used to derive the DNEL. The adoption of these rules should be based on a broad methodological consensus and be consistent with the rules set out in ECHA (2012).

The current version 1.0 of the SECO-DNEL tool includes the DNEL scenarios for the reproductive toxicity and all non-reprotoxic effects (local or systemic) that arise from repeated exposure to a substance for a particular time span. DNELs may be derived for both workers and the general population. In total, version 1.0 of the tool contains 18 different DNEL scenarios (see Table 1-6). The general population includes both consumers and humans exposed via the environment (e.g. soil).

Tables 1 to 6 show all DNEL scenarios that are supported by the SECO-DNEL tool 1.0.

Table 1: DNEL scenarios for the worker population - reprotoxic effect.

worker - reproductive toxic effects
worker-DNEL long-term for oral route-reprotoxic effect
worker-DNEL long-term for dermal route-reprotoxic effect
worker-DNEL long-term for inhalation route-reprotoxic effect

Table 2: DNEL scenarios for the worker population - systemic - other effect.

worker - other effect - systemic
worker-DNEL long-term for oral route-systemic-other effect
worker-DNEL long-term for dermal route-systemic-other effect
worker-DNEL long-term for inhalation route-systemic-other effect

Table 3: DNEL scenarios for the worker population - local - other effect

worker - other effect - local
worker-DNEL long-term for oral route-local-other effect
worker-DNEL long-term for dermal route-local-other effect
worker-DNEL long-term for inhalation route-local-other effect

Table 4: DNEL scenarios for the general population - reprotoxic effect.

General population - reproductive toxic effects
General population-DNEL long-term for oral route-reprotoxic effect
General population-DNEL long-term for dermal route-reprotoxic effect
General population-DNEL long-term for inhalation route-reprotoxic effect

Table 5: DNEL scenarios for the general population - systemic - other effect.

General population - other effect - systemic
General population-DNEL long-term for oral route-systemic-other effect
General population-DNEL long-term for dermal route-systemic-other effect
General population-DNEL long-term for inhalation route-systemic-other effect

Table 6: DNEL scenarios for the general population - local - other effect.

General population - other effect - local
General population-DNEL long-term for oral route-local-other effect
General population-DNEL long-term for dermal route-local-other effect
General population-DNEL long-term for inhalation route-local-other effect

Generally, ECHA (2012) requires manufacturers and importers to calculate the DNELs listed in Tables 7 and 8 depending on the relevance of the corresponding exposure pattern. However, in this version 1.0 of the tool a DNEL for acute effects will not be supported since the derivation of an acute DNEL is considered highly uncertain (ECHA (2012)).

Table 7: Type of worker DNELs that may need to be derived according to ECHA (2012).

Worker - other effect - systemic
Worker-DNEL long-term for dermal route-systemic-other effect
Worker-DNEL long-term for inhalation route-systemic-other effect
Worker - other effect - local
worker-DNEL long-term for dermal route-local-other effect
worker-DNEL long-term for inhalation route-local-other effect
Worker – reprotoxic effect
worker-DNEL long-term for dermal route-reprotoxic effect
worker-DNEL long-term for inhalation route-reprotoxic effect
Worker - acute - systemic
worker-DNEL acute for dermal route-systemic-other effect
worker-DNEL acute for inhalation route-systemic-other effect
Worker - acute - local
worker-DNEL acute for dermal route-local-other effect
worker-DNEL acute for inhalation route-local-other effect

Table 8: Type of general population DNELs that may need to be derived according to ECHA (2012).

General population - other effect - systemic
General population-DNEL long-term for oral route-systemic-other effect
General population-DNEL long-term for dermal route-systemic-other effect
General population-DNEL long-term for inhalation route-systemic-other effect
General population - other effect - local
General population-DNEL long-term for dermal route-local-other effect
General population-DNEL long-term for inhalation route-local-other effect
General population – reprotoxic effect

General population-DNEL long-term for oral route-reprotoxic effect
General population-DNEL long-term for dermal route-reprotoxic effect
General population-DNEL long-term for inhalation route-reprotoxic effect
General population - acute - systemic
General population-DNEL acute for oral route-systemic-other effect
General population-DNEL acute for dermal route-systemic-other effect
General population-DNEL acute for inhalation route-systemic-other effect
General population - acute - local
General population-DNEL acute for dermal route-local-other effect
General population-DNEL acute for inhalation route-local-other effect

Table 9 shows the units for dose descriptors that are implemented in the SECO-DNEL tool 1.0. The user of the tool may select one of these units for the DNEL calculation.

Table 9: Units that are implemented in the SECO-DNEL tool 1.0.

DNEL long-term for oral route-systemic-other effect / reprotoxic effect	mg/kg bw/day µg/kg bw/day ng/kg bw/day
DNEL long-term for dermal route-systemic-other effect / reprotoxic effect	mg/kg bw/day µg/kg bw/day ng/kg bw/day
DNEL long-term for inhalation route-systemic-other effect / reprotoxic effect	mg/m³ µg/m³ ng/m³ ppm ppb
DNEL long-term for oral route-local-other effect	mg/cm²/day µg/cm²/day ng/cm²/day
DNEL long-term for dermal route-local-other effect	mg/cm²/day µg/cm²/day ng/cm²/day
DNEL long-term for inhalation route-local-other effect	mg/m³ µg/m³ ng/m³ ppm ppb

4 Explaining the relevant parameters and assessment factors of the three-step procedure

4.1 Step 1: Select the relevant dose descriptor

The first step requires the user to select the relevant dose descriptor for the toxicological endpoint of concern. For more details and literature see ECHA (2012) and ECHA Guidance R.7a.

4.2 Step 2: Starting point correction of the relevant dose descriptor

The experimental conditions from an animal test study may differ from the real world human exposure conditions. Therefore, first, the relevant experimental dose descriptors have to be converted to the correct starting point of human exposure.

In general, four factors are important when converting the dose descriptors to the correct starting point:

4.2.1 Bioavailability for the same exposure route:

Given the same exposure route (e.g. inhalation), the bioavailability of a particular substance may be different for experimental animals and humans. Therefore, if substance-specific data are available, a correction factor may have to be applied to account for the differences between the bioavailabilities of the experimental animals and humans.

Example:

Experimental oral absorption rate (rat): 30% based on toxicokinetic data;

Experimental oral absorption rate (human): 60% based on toxicokinetic data.

The absorption ratio applied to the dose descriptor is then calculated as

$ABS_{oral,rat} / ABS_{oral,human} = 0.5$.

If these experimental absorption data are considered to be reliable they would be preferred over the default factor of 1.

4.2.2 Route-to-route extrapolation

The relevant exposure route of the population (e.g. workers) may differ from the administration route of the experimental animal. For example, the relevant exposure route at the workplace is often inhalation or skin, whereas most toxicological studies are conducted for the

oral route of exposure. A frequently used approach to estimate the corresponding toxicity effect for other exposure routes (usually skin and inhalation at the workplace) is route-to-route extrapolation. The goal is to adjust for the differences in toxicokinetics between the experimental animal and humans. However, a full set of toxicokinetic data[10] for performing a comprehensive route-to-route extrapolation is rarely available. Therefore, often only absorption differences are accounted for route extrapolation. The toxicokinetic and toxicodynamic differences not related to absorption differences between the experimental animal and humans are estimated and quantified in step 3 of the DNEL calculation procedure. In practice, the route-to-route extrapolation may be defined as an equivalent external dose/concentration level for different exposure routes that produce the same toxicological effect at the corresponding internal dose/concentration level by allowing for absorption (de Raat (1997)). Where experimental data is lacking a default procedure is recommended, usually by assuming maximum human absorption and minimum animal absorption (see Figure 1 section 4.2.5). However, the scientific literature generally states that application of route-to-route extrapolation is highly uncertain and should only be applied with expert judgement (see Vermeire (1999), EC (1996), EPA (2002), WHO/IPCS (1994), ECETOC (2003), Wilschut (1998), Rennen (2004), Geraets (2014), IGHRC (2006), Bessems and Geraets (2013)).

4.2.3 Standard respiratory volumes of animals

Seven different experimental animals may be selected to apply the standard respiratory volumes in the tool. The standard respiratory volume [m³/kg bw] is needed to convert an inhalation exposure concentration (usually expressed in mg/m³ or ppm) to a dose per kg body weight (e.g. mg/kg bw/d), and vice versa to convert a dose in an inhalation exposure concentration. The standard respiratory volume of the experimental animal is calculated by applying an appropriate allometric scaling factor (e.g. 4 for rats) to account for the toxicokinetic differences between humans and animals.

For the worker population the differences in respiratory volumes between experimental animals (at rest) and humans (light activity) need to be adapted by a correction factor of 0.67. The factor of 0.67 corresponds to the ratio of the standard human respiratory volume (sRVhuman) of 6.7 m³/kg bw/8h to the worker respiratory volume (wRV) for light activity of 10 m³/kg bw/8h.

[10] Amount absorbed, absorption rate, distribution, metabolisation and excretion for experimental animal and humans.

Example:

Calculation of the standard respiratory volume of rats (sRVrat); 8 hours exposure duration:

1. Standard respiratory volume, human (sRVHuman) = 6.7 m^3/person/8 h; worker weight: 70 kg

2. sRVHuman (per kg): 6.7 m^3/person/70 kg = 0.0957 m^3/kg bw/8h

3. sRVrat = sRVHuman x Allometric Scaling Factor (rat) = 0.0957 x 4 = 0.38 m^3/kg bw/8h

4.2.4 Differences in experimental and human exposure conditions

The exposure conditions for experimental animals in a test study may differ from that of the worker or general population. For example, in a repeated-dose inhalation study, exposure is usually 6 hours per day (see OECD TG 413), which differs from that for workers, which is usually assumed to be 8 hours per day. Furthermore, for humans via the environment the exposure duration is assumed to be 24 hours per day and, for consumers, 1 to 24 hours per day, depending on the specific exposure scenario. Particular caution must be exercised when the toxic effect is driven by the total accumulated dose, or depends on both total dose and the exposure concentration. In these cases, time corrections of the dose have to be applied. The modified Haber's law may be used to account for the different exposure (duration) conditions for animals and humans: $C^n \times t = k$, where C is the concentration, n is a regression coefficient, t is the exposure time and k is a constant. Time scaling is not appropriate when the toxic effect is mainly driven by the exposure concentration (as for irritation).

The user of the SECO-DNEL tool 1.0 will have to select whether the toxic effect is concentration-driven or dose-dependent. The dose-dependent default correction factor applied to account for the differences in experimental and human exposure conditions are depicted in Figure 1 section 4.2.5. The concentration-driven default correction factor is for all exposure patterns: 1.

Example:

- A NOAEC is available from a rat 6 h/d inhalation study.
- The working day lasts 8 hours.

For workers the experimental NOAEC needs to be corrected by a factor of 0.75 (= 6 h/d / 8 h/d, see also Figure 1 for the default factors). For this case the regression coefficient of n=1 has been considered as the most appropriate value.

4.2.5 Summary of all default factors that may need to be applied for the starting point correction of the relevant dose descriptors

Figure 1: Default adjustment factors that may need to be applied for the starting point correction.

1. Select human exposure route

Oral

Dermal

Inhalation

2. Select relevant population

worker

Consumer

Human via the environment

3. Bioavailability

Absorption animal		Absorption human
Oral - 100 %	→	Oral - 100 %
Oral - 100 %	→	Dermal - 100 %
Oral - 50 %	→	Inhalation - 100 %
Dermal - 100 %	→	Oral - 100 %
Dermal- 100 %	→	Dermal - 100 %
Dermal - 10 %	M > 500 g/mol & (logKow<-1 or logKow>4) →	Inhalation - 100 %
Dermal - 100 %	Not (M > 500 g/mol & (logKow<-1 or logKow>4)) →	Inhalation - 100 %
Inhalation - 100 %	→	Oral - 100 %
Inhalation - 100 %	M > 500 g/mol & (logKow<-1 or logKow>4) →	Dermal - 100 %
Inhalation - 100 %	Not (M > 500 g/mol & (logKow<-1 or logKow>4)) →	Dermal - 100 %
Inhalation - 100 %	→	Inhalation - 100 %

4. Experimental animal

starndard respiratory volume [m3/kg bw]	worker (70 kg) Exposure duration: 8 h	consumer exposure (60 kg) CED: Consumer Exposure Duration: 1 - 24 h	human via the environment exposure (60 kg) Exposure duration: 24 h
rat	0.38 m3/kg bw/8h	0.45 m3/kg bw x (CED/8h)	1.35 m3/kg bw/24h
mouse	0.67 m3/kg bw/8h	0.78 m3/kg bw x (CED/8h)	2.34 m3/kg bw/24h
hamster	0.48 m3/kg bw/8h	0.56 m3/kg bw x (CED/8h)	1.68 m3/kg bw/24h
guinea pig	0.29 m3/kg bw/8h	0.34 m3/kg bw x (CED/8h)	1.02 m3/kg bw/24h
rabbit	0.23 m3/kg bw/8h	0.27 m3/kg bw x (CED/8h)	0.81 m3/kg bw/24h
monkey	0.19 m3/kg bw/8h	0.22 m3/kg bw x (CED/8h)	0.66 m3/kg bw/24h
dog	0.13 m3/kg bw/8h	0.16 m3/kg bw x (CED/8h)	0.48 m3/kg bw/24h

5. Differences experimental and human exposure conditions

	Experimental conditions		Human exposure conditions								
			worker			consumer			human via the environment		
	hours/ day	days/ week	hours/ day	days/ week	correction factor	hours/ day	days/ week	correction factor	hours/ day	days/ week	correction factor
Oral	n.a.	7	n.a.	5	1.4 (=7/5)	n.a.	7	1 (=7/7)	n.a.	7	1 (=7/7)
Dermal	6	5	8	5	0.75 (=6/8x5/5)	CDE	7	=6/CDEx5/7	24	7	0.179 (=6/24x5/7)
Inhalation	6	5	8	5	0.75 (=6/8x5/5)	CDE	7	=6/CDEx5/7	24	7	0.179 (=6/24x5/7)

4.2.6 Calculation formulae for the starting point correction

In Figures 2, 3 and 4 the formulae for the starting point correction are presented for the exposure patterns that are supported by the tool. Note that the factor sRVhuman/wRV is only applied for the worker population scenarios.

Figure 2: Starting point correction formulae for other systemic effects (step 2).

Human		Animal
corr oral N(L)OAEL	→	oral N(L)OAEL
corr oral N(L)OAEL (human)	=	oral N(L)OAEL x (ABSoral,animal / ABSoral,human) x diff. exp. cond.
corr oral N(L)OAEL	→	derm N(L)OAEL
corr oral N(L)OAEL (human)	=	derm N(L)OAEL x (ABSderm,animal / ABSoral,human) x diff. exp. cond.
corr oral N(L)OAEL	→	inh N(L)OAEC
corr oral N(L)OAEL (human)	=	inh N(L)OAEC x sRVanimal (ABSinh,animal / ABSoral,human) x diff. exp. cond.
corr derm N(L)OAEL	→	oral N(L)OAEL
corr derm N(L)OAEL (human)	=	oral N(L)OAEL x (ABSoral,animal / ABSderm,human) x diff. exp. cond.
corr derm N(L)OAEL	→	derm N(L)OAEL
corr derm N(L)OAEL (human)	=	derm N(L)OAEL x (ABSderm,animal / ABSderm,human) x diff. exp. cond.
corr derm N(L)OAEL	→	inh N(L)OAEC
corr derm N(L)OAEL (human)	=	inh N(L)OAEC x sRVanimal x (ABSinh,animal / ABSderm,human) x diff. exp. cond.
corr inh N(L)OAEC	→	oral N(L)OAEL
corr inh N(L)OAEC (human)	=	oral N(L)OAEL x (1/sRV animal) x (ABSoral,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.
corr inh N(L)OAEC	→	derm N(L)OAEL
corr inh N(L)OAEC (human)	=	derm N(L)OAEL x (1/sRVanimal) x (ABSdermal,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.
corr inh N(L)OAEC	→	inh N(L)OAEC
corr inh N(L)OAEC (human)	=	inh N(L)OAEC x (ABSinh,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.

Figure 3: Starting point correction formulae for other local effects (step 2).

Human		Animal
corr oral N(L)OAEL	→	oral N(L)OAEL
corr oral N(L)OAEL (human)	=	oral N(L)OAEL x (ABSoral,animal / ABSoral,human) x diff. exp. cond.
corr derm N(L)OAEL	→	derm N(L)OAEL
corr derm N(L)OAEL (human)	=	derm N(L)OAEL x (ABSderm,animal / ABSderm,human) x diff. exp. cond.
corr inh N(L)OAEC	→	inh N(L)OAEC
corr inh N(L)OAEC (human)	=	inh N(L)OAEC x (ABSinh,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.

Figure 4: Starting point correction formulae for reprotoxic effects (step 2).

Human	Animal	
corr oral N(L)OAEL-reprotoxic	→	oral N(L)OAEL-reprotoxic
corr oral N(L)OAEL (human) -reprotoxic =		oral N(L)OAEL-reprotoxic x (ABSoral,animal / ABSoral,human) x diff. exp. cond.
corr oral N(L)OAEL-reprotoxic	→	derm N(L)OAEL-reprotoxic
corr oral N(L)OAEL (human)-reprotoxic =		derm N(L)OAEL-reprotoxic x (ABSderm,animal / ABSoral,human) x diff. exp. cond.
corr oral N(L)OAEL-reprotoxic	→	inh N(L)OAEC-reprotoxic
corr oral N(L)OAEL (human)-reprotoxic =		inh N(L)OAEC-reprotoxic x sRVanimal (ABSinh,animal / ABSoral,human) x diff. exp. cond.
corr derm N(L)OAEL-reprotoxic	→	oral N(L)OAEL-reprotoxic
corr derm N(L)OAEL (human)-reprotoxic =		oral N(L)OAEL-reprotoxic x (ABSoral,animal / ABSderm,human) x diff. exp. cond.
corr derm N(L)OAEL-reprotoxic	→	derm N(L)OAEL-reprotoxic
corr derm N(L)OAEL (human)-reprotoxic =		derm N(L)OAEL-reprotoxic x (ABSderm,animal / ABSderm,human) x diff. exp. cond.
corr derm N(L)OAEL-reprotoxic	→	inh N(L)OAEC-reprotoxic
corr derm N(L)OAEL (human)-reprotoxic =		inh N(L)OAEC-reprotoxic x sRVanimal x (ABSinh,animal / ABSderm,human) x diff. exp. cond.
corr inh N(L)OAEC-reprotoxic	→	oral N(L)OAEL-reprotoxic
corr inh N(L)OAEC (human)-reprotoxic =		oral N(L)OAEL-reprotoxic x (1/sRV animal) x (ABSoral,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.
corr inh N(L)OAEC-reprotoxic	→	derm N(L)OAEL-reprotoxic
corr inh N(L)OAEC (human)-reprotoxic =		derm N(L)OAEL-reprotoxic x (1/sRVanimal) x (ABSdermal,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.
corr inh N(L)OAEC-reprotoxic	→	inh N(L)OAEC-reprotoxic
corr inh N(L)OAEC (human)-reprotoxic =		inh N(L)OAEC-reprotoxic x (ABSinh,animal / ABSinh,human) x (sRVhuman / wRV) x diff. exp. cond.

*Abbreviations: sRV: standard respiratory volume; ABS: absorption; wRV: worker respiratory volume

Example 1:

Step 1 information:
- Toxicological endpoint: other effect;
- Effect type: systemic effects;
- Administration route: inhalation;
- Dose descriptor: inhalation NOAEC = 50 mg/m³.

Step 2 information:
- Relevant exposure route: inhalation;
- Relevant population: worker;
- Experimental animal: rat;
- Absorption animal: 60%;
- Absorption human: 80%;
- Experimental exposure conditions of the test study: 6 h/d; 5 d/w.

Starting point corrected inhalation NOAEC, human:

corr NOAECinh (human) =

NOAECinh x (ABSinh, animal / ABSinh, human) x (sRVhuman / wRV) x differences exp. conditions =

50 mg/m³ x (60% / 80%) x (6.7 m³ (8 h) / 10 m³ (8 h)) x (6 h/d / 8 h/d x 5 d/w / 5 d/w) = **18.8 mg/m³**

Example 2:

Step 1 information:
- Toxicological endpoint: other effect;
- Effect type: systemic effects;
- Administration route: oral;
- Dose descriptor: oral NOAEL = 250 mg/kg bw/d.

Step 2 information:
- Relevant exposure route: inhalation;
- Relevant population: worker;
- Experimental animal: rat;
- Absorption animal: 50%;
- Absorption human: 100%;
- Differences experimental exposure conditions animal and human: 1.

Starting point corrected inhalation NOAEC, human:

corr NOAECinh =

NOAELoral x (1/sRV animal) x (ABSoral, animal / ABSinh, Mensch) x (sRVhuman / wRV) x differences exp. conditions =

250 mg/kg bw/d x (1 / 0.38 m³/kg bw/d) * (50% / 100%) * (6.7 m³ (8 h) / 10 m³ (8 h)) x 1 = **220.4 mg/m³**

4.3 Step 3: Apply assessment factors to the correct starting point

The differences between effect assessment data and the real human exposure situation need to be addressed, taking into account variability and uncertainty within and between species. In order to address these differences, assessment factors (AF) should be applied (ECHA (2012)). Note that the applied AFs only correct for uncertainties/variability in the effect data, not for exposure uncertainties.

The individual assessment factors used in the SECO-DNEL tool 1.0 that are applied to the correct starting point of the human dose descriptor are described in the following sections:

4.3.1 Interspecies differences

Toxicity results from exposure to a substance and a subsequent chain of events transporting the substance to the affected tissue or organ at a certain dose or concentration level that may cause an adverse effect. The potential toxic effect in a tissue or a specific target organ is a function of

1. the toxicokinetics of a substance, i.e. absorption, distribution, metabolism and excretion resulting in a certain dose or concentration of the substance at the target site, and
2. the toxicodynamics, i.e. the sensitivity of the tissues or organ to the substance.

The toxicokinetics and toxicodynamics of a particular substance are usually different for experimental animals and humans. The interspecies differences between the experimental animal and the humans are often quantified by an allometric scaling factor based on different body size of the species and the remaining differences not related to the metabolic rate, i.e. remaining toxicokinetics and toxicodynamics.

4.3.1.1 Allometric scaling

In general, allometric scaling relates a quantity of interest P (e.g. tissue dose causing an adverse effect, absorption or clearance rate) to a power function of body weight (bw) fitted across different species (see ECHA guidance R.7c):

$P = c \times bw^b$,

whereas *c* is a species-independent scaling coefficient and *b* is an allometric scaling coefficient. If, for example, the allometric scaling coefficient is set to be 1 then the quantity of interest would linearly scale with the body weight of the species. However, on empirical grounds (see e.g. Schneider (2004)) the equitoxic doses for different species scale approximately with the metabolic rate, i.e. on the body weight to the power of 0.75:

$$\frac{\text{basal metabolic rate (human)}}{\text{basal metabolic rate (animal)}} = \left(\frac{\text{body weight (human)}}{\text{body weight (animal)}}\right)^{0.75}$$

Different allometric scaling factors are therefore to be applied for different experimental animals to account for the metabolic difference between animals and humans. Table 11 in section 4.3.6 shows the allometric scaling factors recommended by ECHA (2012) if no substance-specific data are available. These allometric scaling factors are implemented as default values in the SECO-DNEL tool 1.0.

Allometric scaling is not applied for substances where the dose descriptors are expressed in concentration units such as mg/m³ or ppm. This is because respiratory rates depend directly on caloric demand. Thus, toxic study results are therefore (implicitly) extrapolated to humans based on metabolic rate scaling.

4.3.1.2 Remaining differences

The remaining differences of the interspecies variability that are not based on differences in toxicokinetics related to the metabolic rate need to be quantified. These remaining differences account for the differences in toxicokinetics not related to the metabolic rate and in toxicodynamics. ECHA (2012) suggests a default value of 2.5 to account for these remaining differences. This factor of 2.5 is also implemented in the SECO-DNEL tool 1.0 to account for the remaining differences in interspecies variability.

4.3.1.3 Total interspecies differences

The total interspecies differences are calculated by multiplying the allometric scaling factor (AS) with the remaining differences:

Total assessment factor for interspecies differences = AS factor x 2.5.

For example, for the rat the total interspecies differences are calculated as 4 (allometric scaling factor for rat) x 2.5 (remaining differences) = 10.

It is important to note that allometric scaling is not applied for local effects, because local effects are (generally) independent of the basal metabolic rate. Thus, the allometric scaling factor for local effects is 1. Furthermore, for local effects on skin, eye and GI tract via simple destruction of membranes, a factor of 1 (instead of 2.5) may be applied for the remaining differences in interspecies variability (ECHA (2012)).

4.3.2 Intraspecies differences

Humans differ in terms of their sensitivity to chemicals. For example, a group of workers exposed to an equivalent level of a chemical will show different sensitivities towards this chemical. Many biological factors such as genetic polymorphism, age, health status or gender may contribute to the different sensitivities in a population. In order to estimate the intraspecies variability it is, however, a common approach to separate the workers from the general population, because the worker population will usually not include the very young, the very sick and the very old, thus leading (potentially) to a lower susceptibility for workers compared to the general population.

In the SECO-DNEL tool 1.0 the intraspecies variability of 10 for the general population and a factor of 5 for workers are applied, as recommended by ECHA (2012).

When discussing intraspecies variability, special concern should be given to age and development, gender, disease, lifestyle and genetic polymorphism. Humans change anatomically, biochemically and physiologically throughout life. Therefore, at different stages of life humans may respond differently to chemical exposure. Especially (unborn) children are vulnerable to chemicals, because of their rapid growth and development (see Hattis (1999b)). Therefore, a higher intraspecies assessment factor may be considered for children.

4.3.3 Differences in exposure duration

Most animal testing experiments are performed only for a limited period of time (e.g. 28 days or 90 days) and not for the entire life of the experimental animal. Therefore, an extrapolation factor is applied to the time-limited dose levels obtained during the experiment to account for the effects that may arise during the entire lifetime of humans. Thus, the most relevant animal study is the chronic study, which accounts for the toxic effects over the entire life of the experimental animal.

It is generally believed that longer exposure durations will lead to lower NOAEL (ECHA (2012), Falk-Filipsson (2007)). There are several reasons for this:

- A chemical (e.g. lipophilic substances) may bioaccumulate and lead to an adverse effect after a specific threshold level is exceeded. ECHA (2012) suggest the use of a higher assessment factor for potential bioaccumulative (lipophilic) chemicals, or if the database does not contain sufficient information on the toxicokinetics of such bioaccumulative substances. Also, an uncertainty factor may be included for the assessment factor of the quality of the whole database.
- Long period of latency after which an adverse effect becomes apparent.

- Tissues or organs may be affected that were not affected during a shorter exposure period.
- Aging effects, because the toxicokinetic and toxicodynamics of humans may change during life.
- Statistical effects may play a major role, because more animals are used for the experiments in chronic studies, thus leading potentially to a lower and more accurate, i.e. less uncertain, NOAEL.

The SECO-DNEL tool 1.0 uses the default assessment factors for time extrapolation as depicted in Table 11 in section 4.3.6.

4.3.4 Issues related to dose-response

The uncertainty in the dose-response relationship quantified by a dose descriptor (e.g. NOAEL or LOAEL) should be assessed to account for the uncertainty of the true surrogate of the "**N**o-**A**dverse **E**ffect **L**evel" (NAEL). The default assessment factors suggested by ECHA (2012) are implemented in the SECO-DNEL tool 1.0 and are depicted in Table 7 in section 4.3.6 below.

For NOAELs, in the following cases the assessment factor should be greater than 1:

1. The dose-response curve is shallow,
2. in exceptional cases of serious adverse health effects (e.g. irreversible effects) and especially when this effect appears close to the NOAEL,
3. poor quality of the toxicological studies from which the NOAEL has been derived, and
4. for (e.g.) skin-sensitizing effects when it is not clear if the relevant dose descriptor is an NOAEL or an LOAEL.

4.3.5 Quality of the whole database

An additional assessment factor on the quality of the whole database should be applied to account for the remaining uncertainties in any of the factors discussed in sections 4.2 and 4.3 of the three-step procedure. ECHA (2012) suggests performing a completeness check of the database if all the tests and data requirements are met by the importer or registrant according to the relevant tonnage level. If gaps and deficiencies in the database are detected an assessment factor greater than 1 may be applied to account for the remaining uncertainties in the derived DNEL value. In particular, an additional assessment factor on the quality of the database shall be applied when serious adverse health effects and toxicological endpoints of high concern (e.g. respiratory sensitizers) are assessed. Furthermore, alternative data (e.g. in vitro, QSAR, read-across or chemical categories) shall be considered with caution, especially when quantitative dose descriptors (e.g. NOAEL) are extracted from these

studies to derive a DNEL. The database should also be assessed according to its adequacy, i.e. reliability and consistency of the dataset (ECHA (2012)).

The SECO-DNEL tool 1.0 implements the default assessment factor of 1 as suggested by ECHA (2012). A larger assessment factor needs to be applied if the criteria listed in Table 10 are not fulfilled:

Table 10: Default assessment factor to account for the quality of the whole database.

Quality of the whole database	Default assessment factor
Good/standard quality of the database: • Completeness • Consistency • Standard information requirements according to the relevant tonnage level	1

4.3.6 Summary table for the assessment factors applied to the correct starting point

In summary, the SECO DNEL tool 1.0 implements the following assessment factors listed in Table 11 below.

Table 11: Default assessment factors implemented in the SECO-DNEL tool 1.0.

1. Interspecies variability							
	rat	mouse	hamster	guinea pig	rabbit	monkey	dog
Allomteric scaling factor *not applied for inhalation route*	4	7	5	3	2.4	2	1.4
Remaining differences	2.5 - applied for all experimental animals						
2. Intraspecies variability							
worker	5						
consumer	10						
human via the environment	10						
3. Differences in exposure duration							
subacute to chronic N(L)OAEL(C)	6						
subacute to subchronic N(L)OAEL(C)	3						
subchronic to chronic N(L)OAEL(C)	2						
chronic N(L)OAEL(C)	1						
4. Issues related to dose-response							
NOAEL(C) to NAEL	1						
LOAEL(C) to NAEL	3 (default) *recommended range: 3 (majority of cases) to 10 (minority of cases)*						
5. Quality of the whole database							
Good/standard quality of the database *Completeness/Consistency/ Standard information requirements according to the relevant tonnage level*	1						

Note: For local effects on the respiratory tract, the same time extrapolation factors are used as for the systemic effects.

4.3.7 Apply an overall assessment factor to the correct starting point

On the assumption that all of the discussed assessment factors have been quantified:

1. interspecies differences
2. intraspecies differences
3. differences in exposure duration
4. issues on dose-response relationship
5. quality of the whole database

an overall assessment factor needs to be calculated:

$$AF_{Overall} = AF_{Interspecies} \times AF_{Intraspecies} \times AF_{Exposure\ duration} \times AF_{Dose\text{-}response} \times AF_{Database}$$

The relevant DNEL is then calculated by dividing the corrected dose descriptor (step 2) by the overall assessment factor (step 3). Table 12 below shows the formalised calculation procedure for the relevant DNEL based on the overall assessment factor calculated in step 3.

Table 12: The last step of the DNEL calculation procedure.

DNEL Calculation
DNEL = corr N(L)OAEL(C) / Overall Assessmment factor (AF)
Overall AF = AF(interspecies) x AF(intraspecies) x AF (Exposure duration) x AF (Issues related dose-response) x AF (Quality database)

Example of a DNEL scenario calculation:

Calculate the DNEL scenario: worker-DNEL long-term for inhalation route-systemic-other effect

Step 1:

Toxicological endpoint: Other effect

Effect type: Systemic effects

Administration route: oral

Dose descriptor: NOAEL (subchronic) = 200 mg/kg bw/d

Step 2:

see Figure 1 for default factors on the starting point correction

Relevant exposure route: inhalation

Relevant population: worker

Experimental animal: rat

Absorption rat: 50%

Absorption human: 100%

Differences experimental and human exposure conditions: 1.4 (= 7days/week / 5 days/week)

Starting point corrected inh NOAEC:

corr $NOAEC_{inh}$ =

NOAELoral x (1/sRV animal) x (ABSoral, animal / ABSinh, Mensch) x (sRVhuman / wRV) x diff. exp. cond. =

200 mg/kg bw/d x (1 / 0.38 m^3/kg bw/d) * (50% / 100%) * (6.7 m^3 (8 h) / 10 m^3 (8 h)) x 1 = **246.84 mg/m^3**

Step 3:

See table 15 for default AF:

Interspecies variability:

Allometric scaling: 1;

Note: No allometric scaling factor needs to be applied for the human inhalation route. Therefore, only a factor of 2.5 for the remaining differences needs to be applied for interspecies differences.

Remaining differences: 2.5;

Total AF on interspecies variability: 1 x 2.5 = 2.5

Intraspecies variability: 5

Differences in duration of exposure: 2

Issues related to dose-response: 1

Quality of the whole database: 1

Apply overall AF to derive DNEL value:

General formula: Endpoint-specific DNEL = $NOAEL_{corr}$ / AF_1 x AF_2 x …. x AF_n = $NOAEL_{corr}$ / overall AF

worker-DNEL long-term for inhalation route-systemic-other effect =

corr $NOAEC_{inh}$ / ($AF_{Interspecies}$ x $AF_{Intraspecies}$ x $AF_{exposure\ duration}$ x $AF_{dose\text{-}response}$ x $AF_{quality}$) =

246.8 mg/m^3 /((1 x 2.5) x 5 x 2 x 1 x 1) = 246.8 mg/m^3 / 25 = **9.87 mg/m^3**

Result: worker-DNEL long-term for inhalation route-systemic-other effect = 2.35 mg/m^3

5 How to use the SECO-DNEL tool 1.0

The SECO-DNEL tool 1.0 is introduced in the following sections. The main spreadsheet for the calculator is named «DNEL Calculation Animal Data», and this is where the entire calculation procedure is performed.

5.1 Three-step calculation procedure

The three steps of the DNEL derivation are briefly explained at the very top of the «DNEL Calculation Animal Data» spreadsheet:

General work flow for DNEL calculation - threshold effects
Step 1: Select the relevant dose descriptor for the endpoint concerned (e.g. NOAEL, LOAEL)
Step 2: Modify, when necessary, the relevant dose descriptor per endpoint to the correct starting point
Step 3: Apply, when necessary, assessment factors to the correct starting point
Results: Endpoint-specific DNEL values

5.2 Initial details of the substance and toxicological studies

The substance-specific information on the physical-chemical properties and the information on the (key) toxicological studies are provided in the table below:

Starting information on the substance and toxicological studies — Delete Starting Information

Product identifier: *i*

Substance name	CAS-Nr.	EC-Nr.

Please enter information on the physical-chemical properties of the substance: *i*

Physical state	Density [kg/m3]	Pure vapour pressure [Pa]	Typical concentration [%]	Log Kow	Molar mass [g/mol]	Temperature [ºC]	Pressure [hPa]
Please select:						20	1013

Please enter details on the leading health effect and the study guideline: *i*

Leading health effects (e.g. kidney effects)	Study guideline (e.g. OECD TG 413)	Study duration (e.g. 90 days)	Species (e.g. rat)	Number of animals per dose group

Note that this table is created only for information purposes. However, to perform the dermal-to-inhalation extrapolation in step 2, it is mandatory to enter the log Kow (octanol-water partition coefficient) and the molar mass of the substance.

Product identifier:

The user may enter the trade name of the substance or, alternatively, the name of the substance in accordance with Article 18(2) of Regulation (EC) No 1272/2008 (CLP):

1. if the substance is included in Part 3 of Annex VI (CLP), a name and an identification number as given therein (i.e.EC number and/or CAS number);

2. if the substance is not included in Part 3 of Annex VI (CLP), but appears in the classification and labelling inventory, a name and an identification number as given therein (i.e. EC number and/or CAS number);

3. if the substance is not included in Part 3 of Annex VI (CLP) or in the classification and labelling inventory, the number provided by the CAS, together with the name set out in the IUPAC nomenclature, or the CAS number together with another international chemical name; or

4. if the CAS number is not available, the name set out in the IUPAC nomenclature or another international chemical name.

Physical-chemical properties:

Physical state: The user may select four different states of matter: 1. gas, 2. liquid, 3. solid (non-powder) or 4. solid (powder). Definitions of physical states (gas, liquid, solid) can be found in section 1.0. of Annex I (CLP).

Density: The density (ρ) of a substance is defined as the quotient of the mass m and its volume V: $\rho = m/V$; SI units [kg/m^3]

Pure vapour pressure of the substance: The pure vapour pressure of a substance is defined as the saturation pressure above a solid or a liquid substance at constant temperature (usually 20 or 25 ºC). At the thermodynamic equilibrium, the vapour pressure of a pure substance is a function of temperature only. The tool uses the standard temperature of 20 ºC.

Typical concentration of the substance: Please enter the typical concentration of the main substance. For example, a substance A contains three components: the main component B [90%], an impurity C [4%] and an additive D [6%]. The typical concentration of 90% of the main substance must be entered in the corresponding cell.

Molar mass: The molar mass is defined as the mass [g] of the substance divided by its amount [mol]. The units are often expressed in [mg/mol] or [g/mol].

The tool uses the units of [g/mol] for the molar mass. The molar mass must be entered to calculate the default values for the dermal and inhalation absorption in step 2.

n-octanol/water partition coefficient, log Kow: The n-octanol/water partition coefficient (Kow) is defined as the ratio of the equilibrium concentrations of a dissolved substance in a two-phase system consisting of the largely immiscible solvents n-octanol and water. The property is moderately temperature-dependent and typically measured at 25 °C. The log Kow must be entered to calculate the default values for the dermal and inhalation absorption in step 2.

For further information on physical-chemical properties, please consult the ECHA guidance document R.7a: Endpoint specific guidance.

Information on toxicological studies:

Leading health effect: The leading health effect is the toxicological adverse effect that results in the most critical DNEL.

Study guideline: Good Laboratory Practice (GLP): mandatory for toxicological and ecotoxicological testing.

EU methods: Regulation (EC) No 440/2008 (Part B)
OECD method: Section 4: Health effects
For example: OECD guideline for testing of chemicals (No. 413): Subchronic inhalation toxicity: 90-day study.

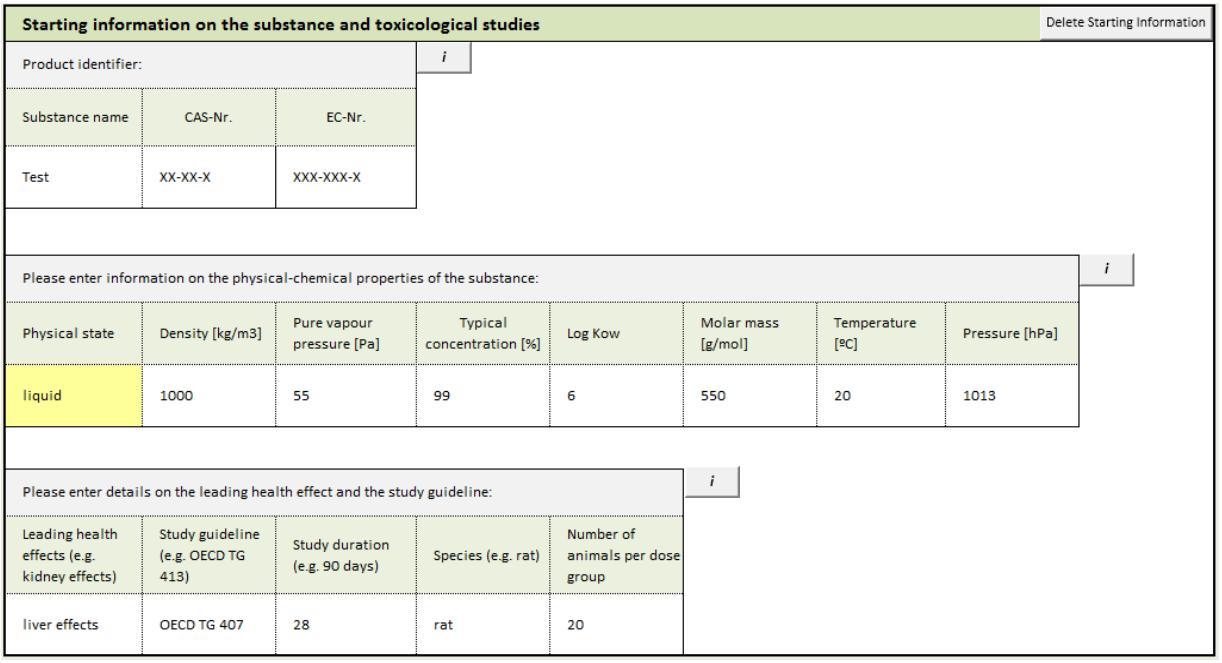
Study duration: The study duration refers to the duration of the experimental study. E.g. in OECD testing guideline No. 413, the study duration is 90 days.

Species: The species used to conduct the experiment. E.g. in the OECD testing guideline No. 413, the preferred species is the rat.

Number of animals per dose group: The number of animals used per dose group in the experiment. E.g. in the OECD testing guideline No. 413, at least 20 animals (10 males and 10 females) should be used for the experiment.

Administration route: The route of administration is the path by which a substance is brought into contact with the body. E.g., in the OECD testing guideline No. 413, the administration route is inhalation.

See below an example of how the information on physical-chemical properties and the toxicological studies may be given:



Starting information on the substance and toxicological studies — Delete Starting Information

Product identifier: *i*

Substance name	CAS-Nr.	EC-Nr.
Test	XX-XX-X	XXX-XXX-X

Please enter information on the physical-chemical properties of the substance: *i*

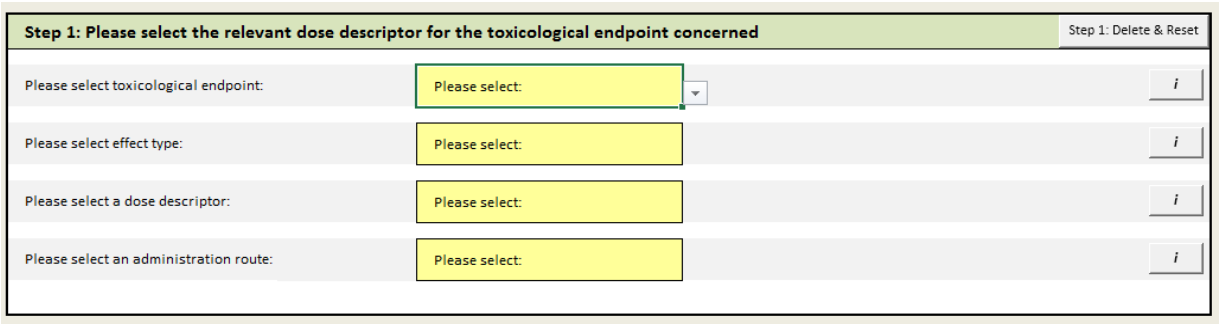
Physical state	Density [kg/m3]	Pure vapour pressure [Pa]	Typical concentration [%]	Log Kow	Molar mass [g/mol]	Temperature [ºC]	Pressure [hPa]
liquid	1000	55	99	6	550	20	1013

Please enter details on the leading health effect and the study guideline: *i*

Leading health effects (e.g. kidney effects)	Study guideline (e.g. OECD TG 413)	Study duration (e.g. 90 days)	Species (e.g. rat)	Number of animals per dose group
liver effects	OECD TG 407	28	rat	20

5.3 Step 1: Relevant dose descriptors for the toxicological endpoint concerned

In step 1 the following information on the toxicological endpoint and the dose descriptor needs to be selected:



Step 1: Please select the relevant dose descriptor for the toxicological endpoint concerned — Step 1: Delete & Reset

Please select toxicological endpoint:	Please select:	*i*
Please select effect type:	Please select:	*i*
Please select a dose descriptor:	Please select:	*i*
Please select an administration route:	Please select:	*i*

Toxicological endpoints:

Reproductive toxicity: The term reproductive toxicity is used to describe the adverse effects induced by a substance on sexual function and fertility in adult males and females, developmental toxicity in the offspring and effects on, or mediated via, lactation. For more details on reproductive toxicity, please consult section R.7.6. of ECHA guidance document R.7a.

Other effects: Other effects comprise all non-reprotoxic effects (local or systemic) that arise from repeated exposure to a substance for a particular time span. Repeated-dose toxicity studies provide information on possible general toxicological effects such as body weight gain, relative organ and tissue weight or functional disturbances in organs and tissues in general. For more details on repeated-dose toxicity (other effects), please consult section R.7.5. of the ECHA guidance document R.7a.

Effect type:

Systemic effect: Effect that is normally observed distant from the site of first contact, i.e. after the substance has passed through a physiological barrier (mucous membrane of the gastrointestinal tract or of the respiratory tract, or the skin) and become systemically available.

Local effect: Effect that is observed at the site of first contact, caused irrespective of whether a substance is systemically available.

Dose descriptors:

NOAEL (No Observed Adverse Effect Level): The highest dose used in a toxicity study without any sign of an adverse effect. The NOAEL is usually set for the oral or dermal route of exposure.

NOAEC (No Observed Adverse Effect Concentration): The highest exposure concentration used in a toxicity study without any sign of an adverse effect. The NOAEC is usually set for the inhalation route of exposure.

LOAEL (Lowest Observed Adverse Effect Level): The lowest dose used in a toxicity study which indicates an adverse effect.

LOAEC (Lowest Observed Adverse Effect Concentration): The lowest exposure concentration used in a toxicity study which indicates an adverse effect.

N(L)OAEL(C) fertility: N(L)OAEL(C) related to adverse effects on fertility.

N(L)OAEL(C) development: N(L)OAEL(C) related to developmental toxicity.

Adverse effect: An adverse effect is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system, or (sub) population that results in an impairment of functional capacity, or an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (OECD, 2003).

Units: The appropriate unit of the dose descriptor value should be selected for the route of administration (bw = body weight). The following units may be selected:

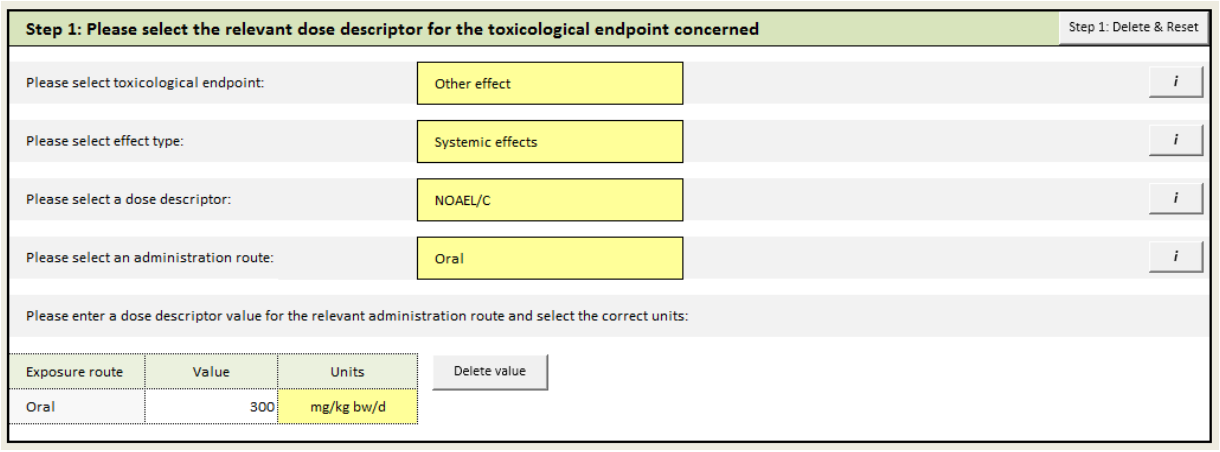
Oral: mg/kg bw/day; µg/kg bw/day; ng/kg bw/day;

Dermal (systemic effects): mg/kg bw/day; µg/kg bw/day; ng/kg bw/day

Dermal (local effects): mg/cm²/day; µg/cm²/day; ng/cm²/day

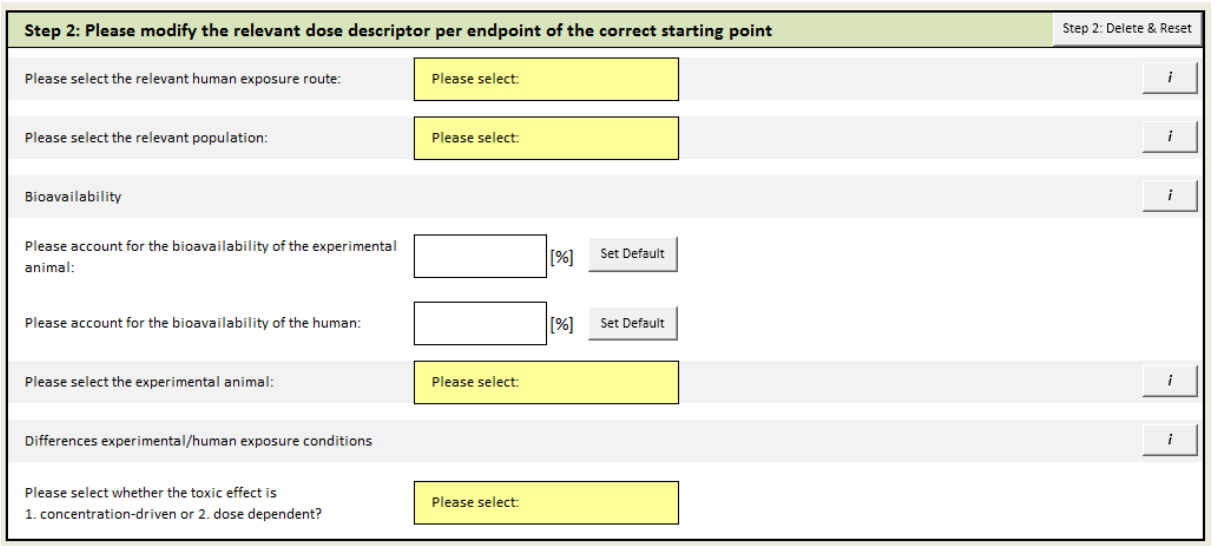
Inhalation: mg/m³; µg/m³; ng/m³; ppm; ppb

An example of a step 1 entry is given below:



5.4 Step 2: Starting point correction

In step 2 the following information for the starting point correction of the dose descriptor (step 1) needs to be entered or selected:



Exposure route:

DNELs may have to be derived for:
- oral,
- dermal and
- inhalation exposure.

The user of the tool is only required to derive DNELs for the relevant routes of exposure. In all cases, it must be justified why the selected exposure routes have been considered as relevant and others as irrelevant. For local effects, the tool does not support route-to-route extrapolation. In order to proceed with the calculation, the same human exposure route must be selected as for the experimental animal.

Relevant population:

DNELs may have to be derived for:
- workers and
- general population. The general population includes consumers and humans exposed via the environment.
- Under certain circumstances it may also be necessary to derive DNELs for certain sub-populations, to cover a particular higher sensitivity (e.g. for children, pregnant women).

It is not always necessary to derive DNELs for all mentioned populations. However, in all cases, it must be justified why the selected population has been considered as relevant and others as irrelevant.

Bioavailability and route-to-route extrapolation:

Absorption fractions [%] must be entered for the experimental animal and humans in order to calculate the differences in bioavailability for one route or to perform a route-to-route extrapolation for different exposure routes between the animal and humans. The default values for the bioavailability and route-to-route extrapolation are depicted in Figure 1 in section 4.1.5.

For dermal-to-inhalation extrapolation, the default mode of the SECO-DNEL tool 1.0 implements the cut-off points at a molecular weight of 500 g/mol and log Kow values below -1 or above 4 to set a dermal absorption factor at 10% (EC, 2007). Otherwise, a default dermal absorption factor of 100% is set. The inhalation absorption factor is set at 100%. Please do not forget to enter the molecular weight and log Kow in the information part at the very top of the tool.

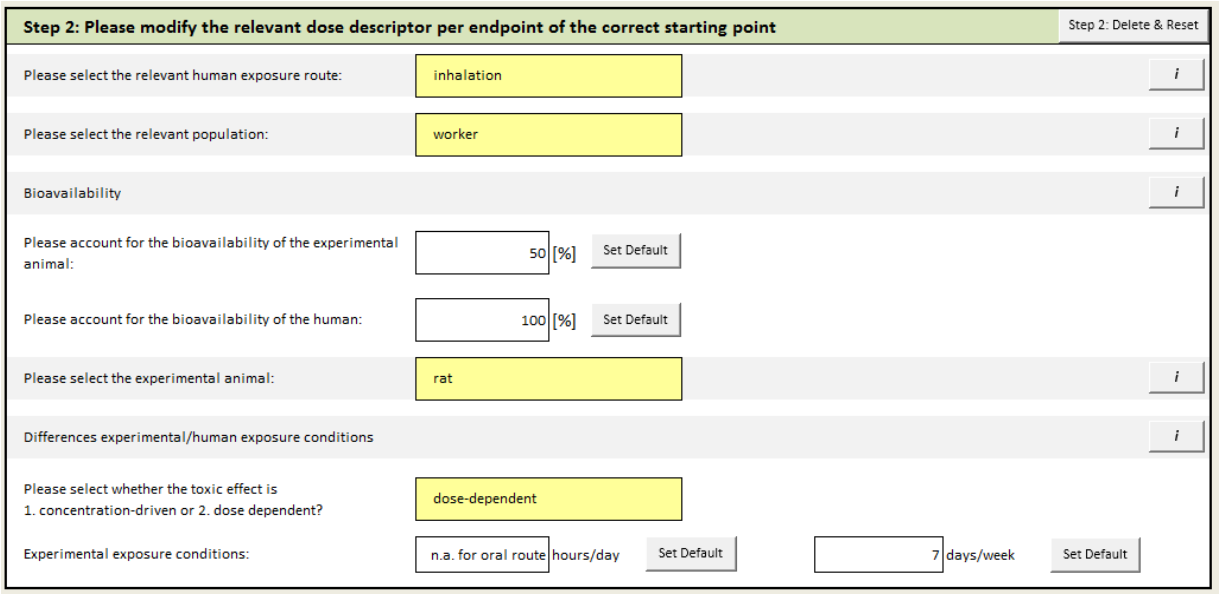
Experimental animals:

Seven different experimental animals may be selected in the tool: rat, mouse, hamster, guinea pig, rabbit, monkey and dog. Each of them has a specific standard respiratory volume [m^3/kg bw] and will be used to convert doses [e.g. mg/kg mw/d] to concentrations [e.g. mg/m^3] and vice versa.

Differences in experimental and human exposure conditions:

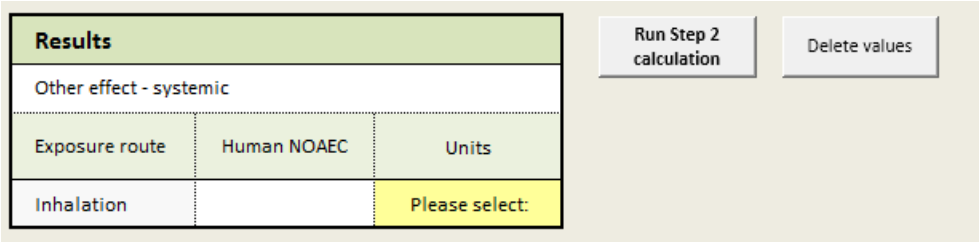
The exposure conditions for experimental animals in a toxicity study may differ from those of the target populations. Therefore, the experimental exposure conditions need to be adapted to the real word conditions (e.g. at workplace). First, one must select whether the toxic effect is concentration-driven or dose-dependent. If the toxic effect is concentration-driven then the default correction factor for the differences in experimental and human exposure conditions is 1. If the toxic effect is dose-dependent, the user has to enter a value for the exposure duration in hours per day and in days per week. Note: if the administration route is oral then the hours per day entry is not applicable since in oral test studies the substances are administrated once per day. For default factors see Figure 1 in section 4.1.5.

An example for a step 2 scenario is shown below:

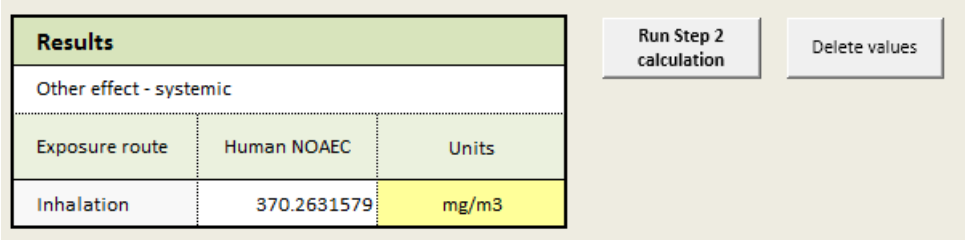


After finishing the selection and entry part of the step 2 procedure, the modified dose descriptor for humans needs to be calculated. To run the calculation, it is only required to select an appropriate unit for the corrected dose descriptor. The run button needs to be pressed

only when a factor, e.g. an absorption fraction, has been changed in step 2 to recalculate the corrected dose descriptor.

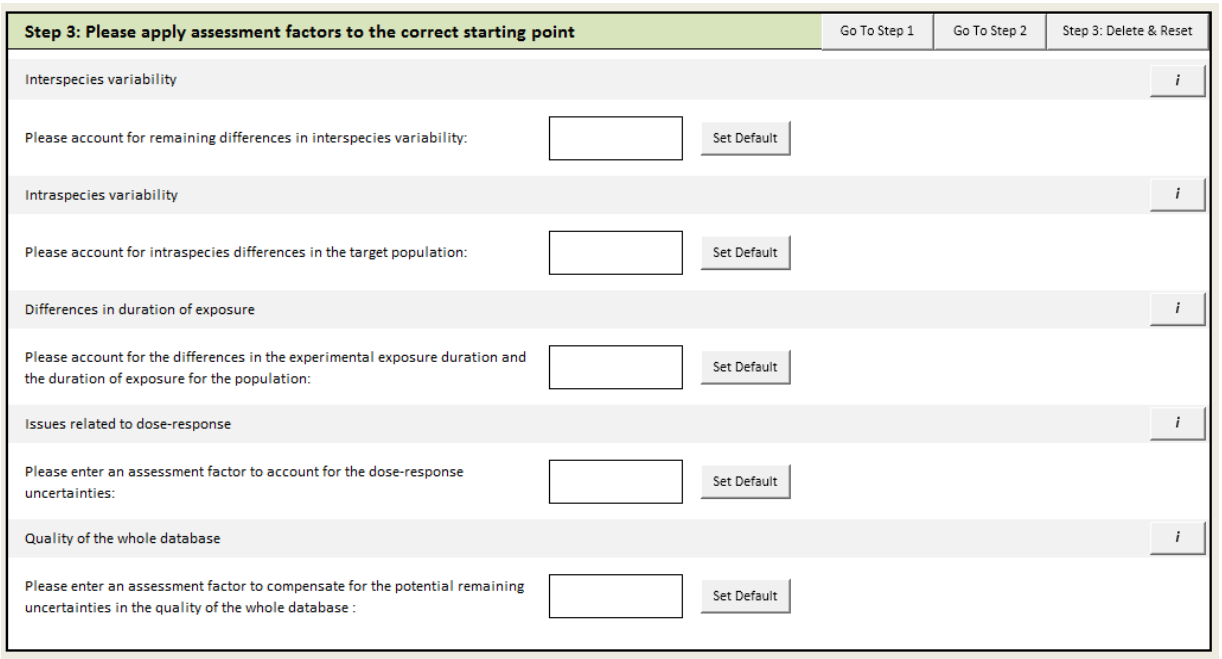


The dose descriptor modification for the inhalation route in mg/m³ has been performed for the example described above.



5.5 Step 3: Apply assessment factors to the correct starting point

In step 3 of the DNEL calculation procedure, the assessment factors depicted below need to be entered in the corresponding cells. When no substance-specific data are available, the default button «Set Default» may be pressed to directly insert the default value for the corresponding assessment factor:



The following individual assessment factors are supported by the tool:

Interspecies variability: An allometric scaling factor for oral or dermal exposure and the remaining differences in interspecies variability for all routes must be entered in the corresponding cells.

Allometric scaling: The default allometric scaling factors depend on the experimental animal that has been selected in step 2 of the calculation procedure: rat: 4; mouse: 7; hamster: 5; guinea pig: 3; rabbit: 2.4; monkey: 2; dog: 1.4. Note that only for systemic effects of the dermal and oral route does an allometric scaling factor need to be applied to account for the interspecies differences. For systemic effects of the inhalation route, a default factor of 1 is set (ECHA (2012)). In addition, for local effects no allometric factor is applied.

Remaining differences: For all DNEL scenarios the remaining differences are quantified by a default factor of 2.5.

Intraspecies variability: For workers, as a standard procedure for threshold effects, a default assessment factor of 5 is to be used, based on the fact that this subpopulation does not cover the very young, the very old or the very ill.

For the general population (i.e. consumers and humans via the environment), as a standard procedure for threshold effects, a default assessment factor of 10 is applied. This factor is assumed to be sufficient to protect the larger part of the population.

Differences in exposure duration: When the default button is pressed a pop-up window (i.e. Excel userform) will appear, from which the user may select four different options:

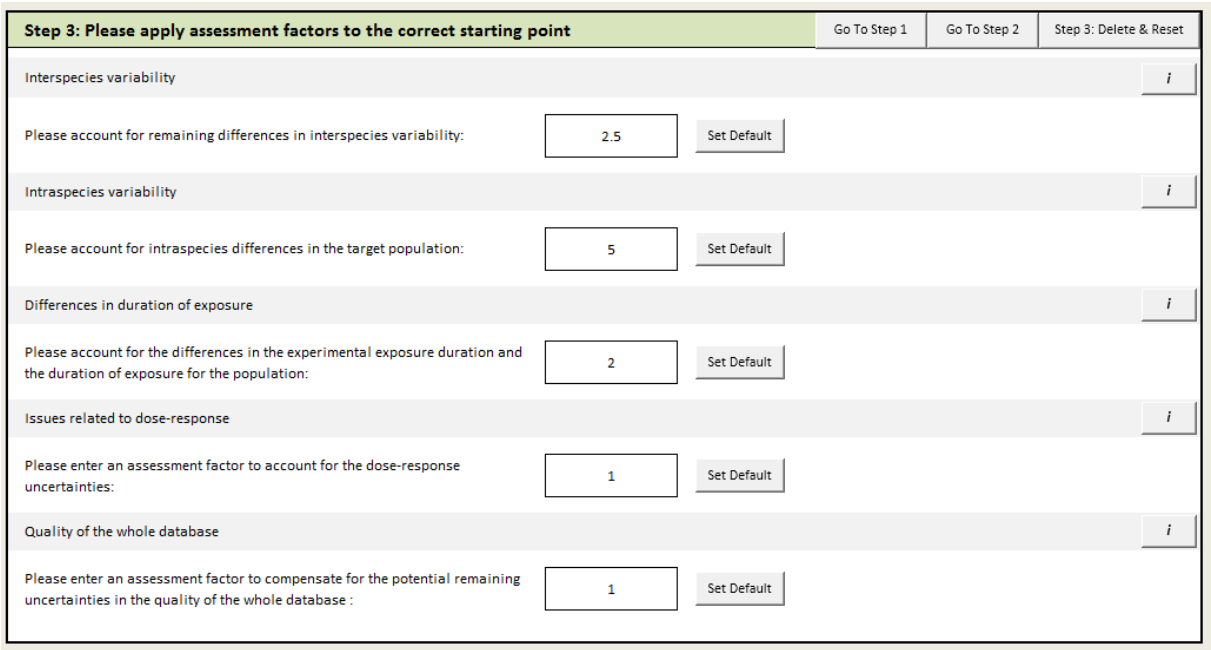
If an adequate chronic toxicity study is available, this is the preferred starting point, and no assessment factor for duration extrapolation is needed: 1
sub-acute to chronic extrapolation: 6
sub-acute to sub-chronic extrapolation: 3
sub-chronic to chronic extrapolation: 2

Dose-response relationship: For the dose-response relationship, consideration should be given to the uncertainties in the dose descriptor (e.g. NOAEL, LOAEL) as the surrogate for the true no-adverse-effect-level (NAEL), as well as to the extrapolation of the LOAEL to the NAEL.
A default factor of 1 is set for the NOAEL dose descriptor.
A default factor of 3 is set for the LOAEL dose descriptor.

Quality of the whole database: An assessment factor on the quality of the whole database should, if justified, be applied to compensate for the potential remaining uncertainties in the derived DNEL. The default assessment factor should take into account completeness, consistency and the standard information requirements. A larger database assessment factor should, where relevant, be applied and justified on a case-by-case basis.

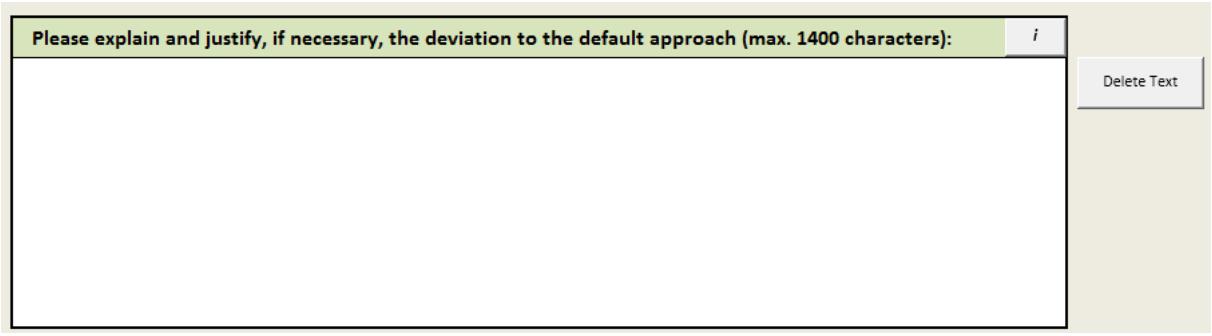
The default assessment factor to be applied for good/standard quality of the database: 1.

The figure below shows an example of the default assessment factor settings based on step 1 and step 2 entries:



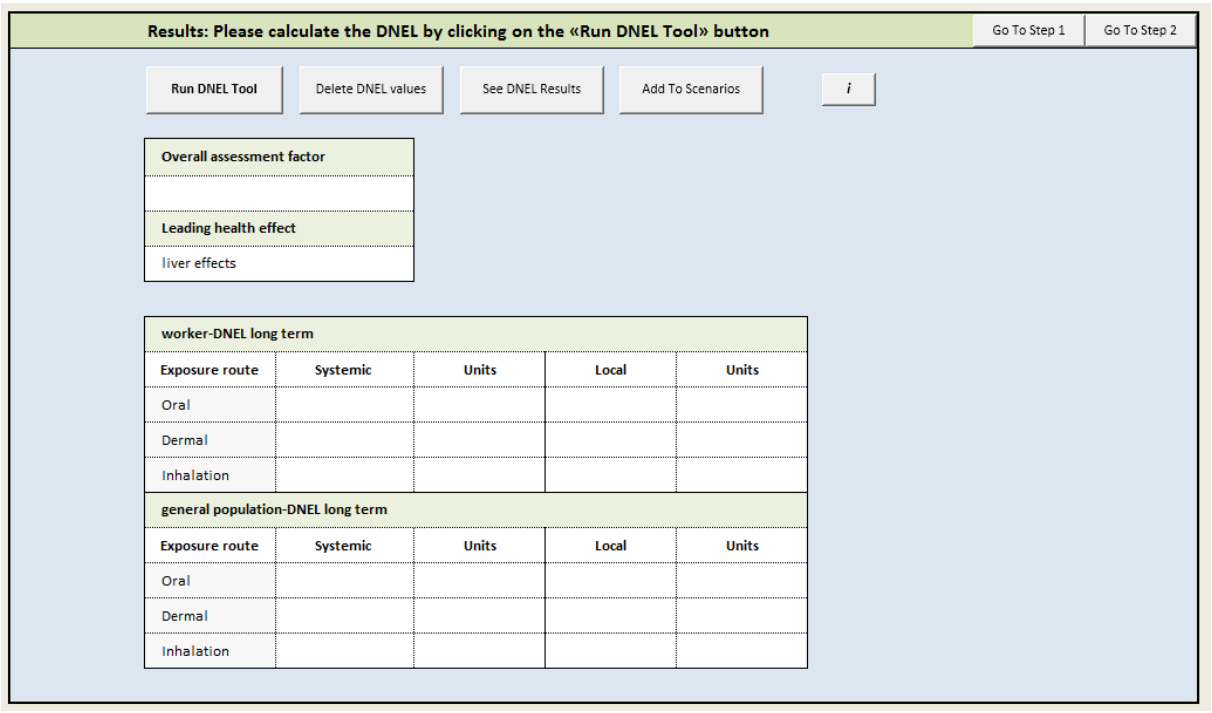
Please note, in order to successfully calculate a DNEL in every Excel cell of steps 1, 2 and 3, either a value must be entered (white coloured cell) or a selection has to be made (yellow coloured cell). Otherwise, an error will result (in red).

Use the comment box below to (briefly) explain and justify as clearly as possible each deviation from the default process (e.g. by using substance-specific data), including any assessment factor values chosen. A link or reference can also be given, e.g. to the chemical safety report (CSR) or studies where the deviation from the default approach is explained in more detail.

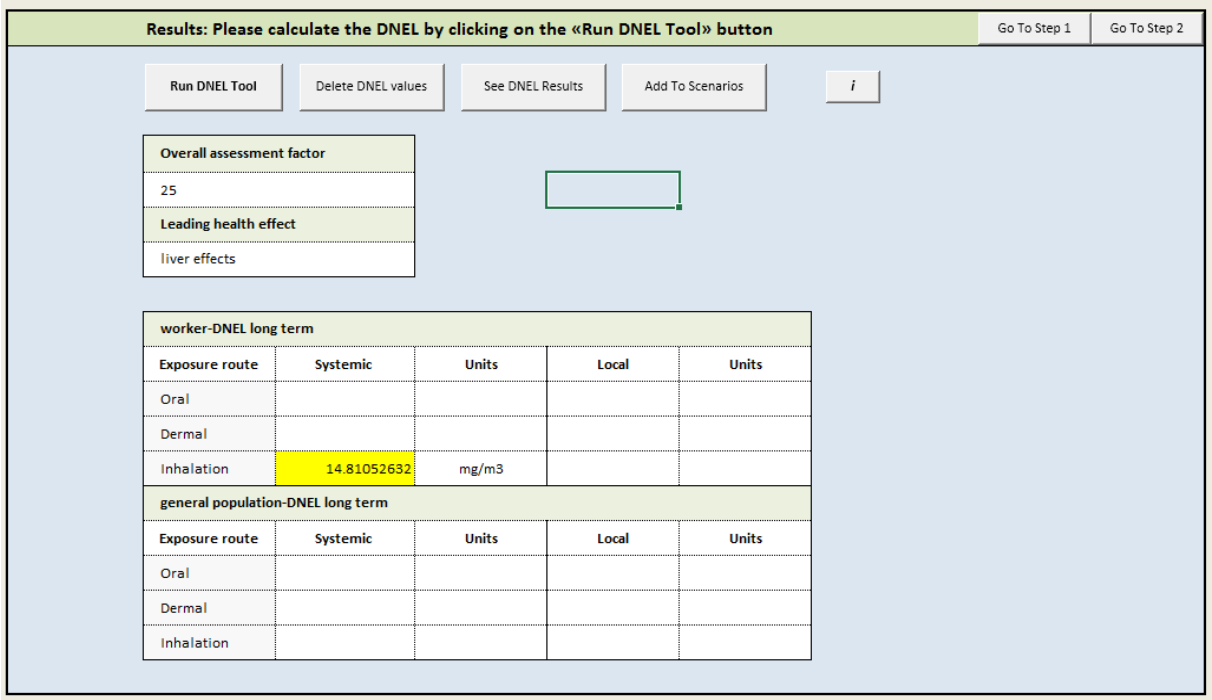


5.6 Calculation results

To calculate the DNEL please press the «Run DNEL tool» button to calculate the DNEL. The calculated DNEL value will be presented in the table below (yellow cell). To delete all DNEL values and the overall assessment factor, please press the «Delete DNEL values» button.



For the example above (steps 1 to 3) the results would be depicted in the following way:

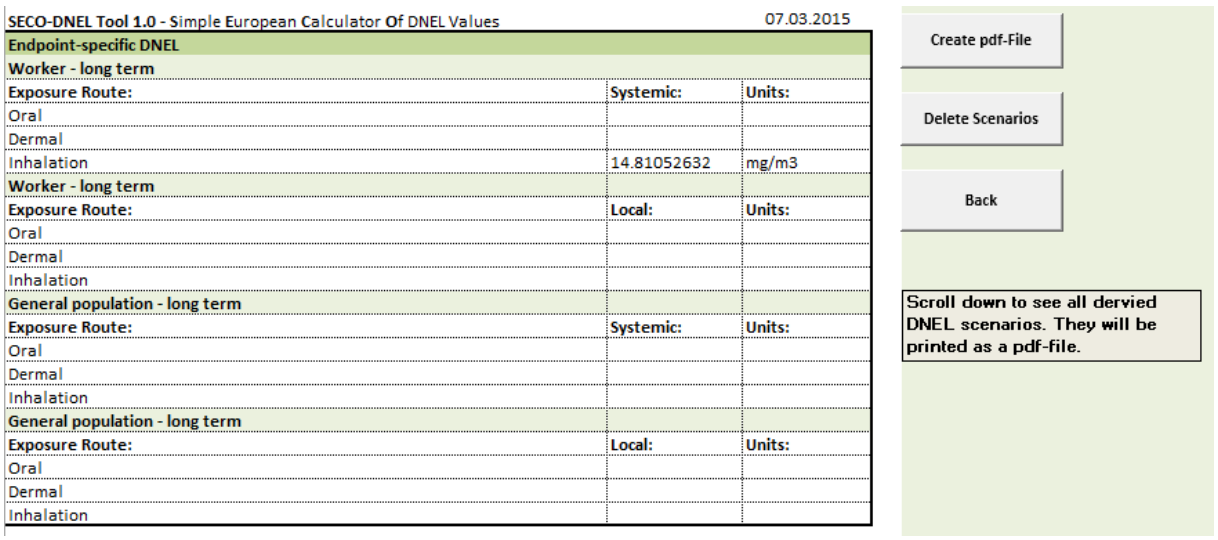


To show all the relevant factors, parameters and formulae that were used to derive the DNEL, please press the «See DNEL results» button. See figure below for the example discussed above:

Physical-chemical information		
Physical state of the substance/product	liquid	
Density	1000	kg/m3
Pure vapour pressure	55	Pa
Molar fraction	99	
Molar mass	550	mg/mol
Log Kow	6	
Study information		
Leading health effect	liver effects	
Study guideline	OECD TG 407	
Study duration	28	days
Species	rat	
Number of animals in the study	20	
Administration route	Oral	
Step 1: Select the relevant dose descriptor for the toxicological endpoint concerned		
Toxicological endpoint:	Other effect - systemic	
NOAEL - oral route:	300	mg/kg bw/d
Step 2: Modify the relevant dose descriptor per endpoint of the correct starting point		
Starting point correction formula:		
corr inh NOAEC = oral NOAEL x 1/sRVan x Diff. exp. cond. x (ABSoral,an/ABSinh,hu) x sRVhu/wRV		
Relevant human expsoure route:	inhalation	
ABSoral,an/ABSinh,hu	0.5	
Experimental animal:	rat	
Standard respiratory volume, animal (sRVan)	0.38	m3/kg bw/8 h
Standard respiratory volume, human (sRVhu)	6.7	m3 / person
Worker respiratory volume (wRV)	10	m3 / person
Differences experimental/human exposure conditions	1.4	
Corrected dose descriptor		
corr inh NOAEC:	370.2631579	mg/m3
Step 3: Select assessment factors		
Interspecies, AS	1	
Interspecies, remaining differences	2.5	
AF1: Interspecies, total	2.5	
AF2: Intraspecies	5	
AF3: Exposure duration	2	
AF4: Dose response-relationship	1	
AF5: Quality of the whole data base	1	
Overall AF (= AF1xAF2xAF3xAF4xAF5)	25	
DNEL Results		
worker-DNEL long-term for inhalation route-systemic-other effect:	14.81052632	mg/m3

To add the DNEL scenario to the «Scenarios» spreadsheet please press the «Add To Scenarios» button, which allows you to print all added scenarios in a PDF file.

By clicking on «Create pdf-File» a pdf-file can be created for all the DNEL scenarios calculated with the tool:



SECO-DNEL Tool 1.0 - Simple European Calculator Of DNEL Values 07.03.2015

Endpoint-specific DNEL		
Worker - long term		
Exposure Route:	**Systemic:**	**Units:**
Oral		
Dermal		
Inhalation	14.81052632	mg/m3
Worker - long term		
Exposure Route:	**Local:**	**Units:**
Oral		
Dermal		
Inhalation		
General population - long term		
Exposure Route:	**Systemic:**	**Units:**
Oral		
Dermal		
Inhalation		
General population - long term		
Exposure Route:	**Local:**	**Units:**
Oral		
Dermal		
Inhalation		

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