Grenswaarden voor kortdurende blootstelling en acute DNELs: een gelukkig huwelijk?

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Acute exposure limits

STEL/peak limitation and emergency response limit values

OEL/STEL/peak limitation values

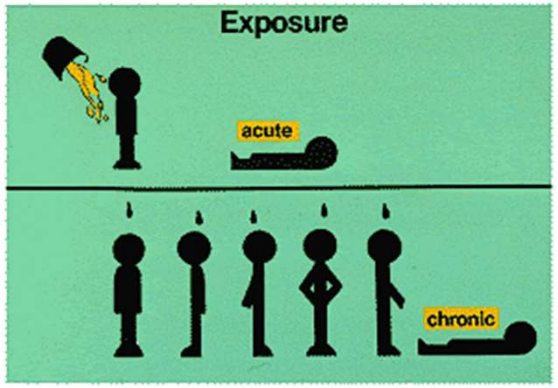
Considered to be safe levels, e.g. generally based on a no (adverse) effect level (generally obtained from animal studies) divided by safety/uncertainty factors

Acute/short term toxicity: used for workplace/occupational health

* *STEL/peak limitation value*
* *DNEL acute*

Long term toxicity: occupational health (8-h TWA)

* OEL / TLV / MAK / DN(M)EL



Emergency values

Threshold levels at which the effects start to occur and below which no such effects should be present

Acute/short term toxicity: used for a.o. emergency response, land use planning

* IDLH / AEGL / ERPG / EEI / AETL / Dutch intervention values (VRW, AGW, LBW)
* probits (C*t relationship)

Emergency Response Limit Values

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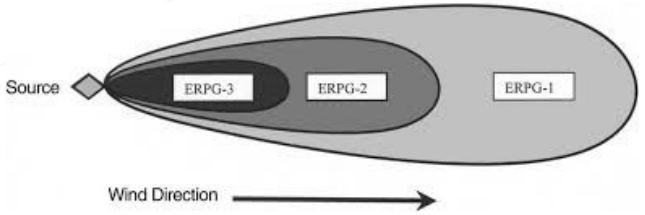
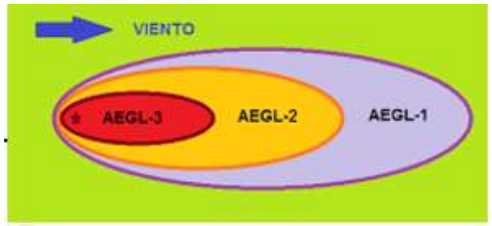
IDLH
IMMEDIATELY DANGEROUS to LIFE or HEALTH

* **IDLH values** (Immediately Dangerous for Life and Health; Am. NIOSH)
IDLH value = does not cause death, serious or irreversible health or impede the ability to escape
This is set for 30 min only

* **ERPG values** (Emergency Response Planning Guidelines; Am. Ind. Hyg. Ass.)
ERPG-1 = discomfort
ERPG-2 = incapacity
ERPG-3 = death and/or irreversible damage
These are set for 60 min only





* **AEGL values** (Acute Exposure Guideline Levels; US-EPA)
AEGL-1 = notable discomfort/irritation, effects are not disabling and are transient
AEGL-2 = irreversible or other serious, long-lasting adverse health effects/impaired ability to escape
AEGL-3 = life-threatening adverse health effects or death
These are set for 10, 30 and 60 min and 4 and 8 h

Emergency Response Limit Values (cont.)

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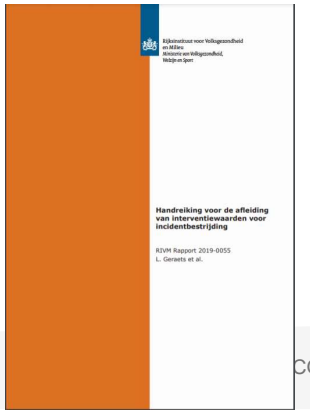
*** EEI values** (Emergency Exposure Indices; ECETOC)
Basic approach is similar to ERPG, but methodology is more clearly defined
These are set for 15, 30 and 60 min

*** AETL values** (Acute Exposure Threshold Levels; ACUTEX)
LDSA = level of distinct odour awareness
AETL-1 = discomfort, irritation and reversible health effects
AETL-2 = irreversible effects and impairment to escape
AETL-3a = death potential (1, 5, and 50% death)
AETL-3b = life-threatening conditions (usually 1/3 of the AETL-3a LC01 value)
These are set for 10, 30 and 60 min, and 2, 4 and 8 h

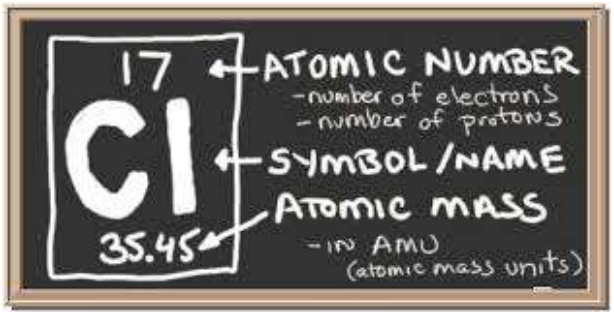
*** Dutch Intervention Values** (expert committee led by RIVM)
VRW = slight irritation (not discomfort)
AGW = reversible toxic effects including incapacity
LBW = death or severe/irreversible damage
These are set for 10, 30 and 60 min, and 2, 4 and 8 h



Example: Chlorine
Reported acute effects

1 ppm = threshold of odour perception
1-30 ppm = irritation of eyes, nose and upper airways, cough, shortness of breath, chest pain, choking and vomiting
> 30 ppm = tracheo-bronchial irritation, severe bronchospasm, bronchial and glottis oedema
220 ppm = 4-h LC50 in rats (650 mg/m3) - CLP acute inhalation cat. 2

Notes:
- No relationship with exposure duration (except for the 4-h LC50 value)
- What would be a protective value?



Gestis International Limit values
STEL 15-min: 0.5 ppm (1.5 mg/m3) or 1 ppm (3 mg/m3)
OEL 8-h TWA: 0.5 ppm (1.5 mg/m3)

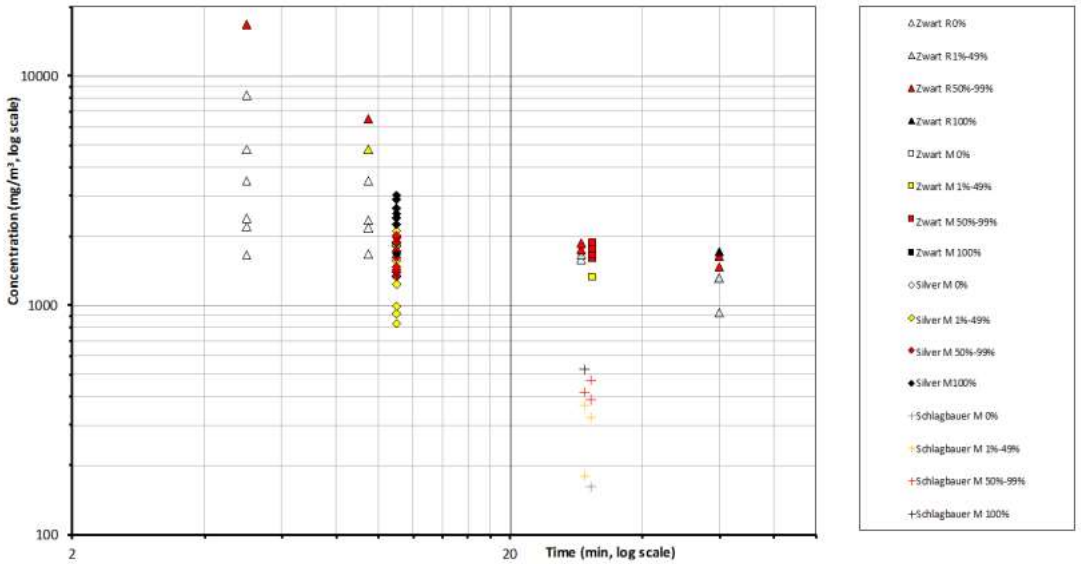
Dutch intervention values for chlorine (in ppm)

	10 min	30 min	60 min	2 h	4 h	8 h
VRW	0.5	0.5	0.5	0.5	0.5	0.5
AGW	5	2.8	2.0	1.4	1.0	0.7
LBW	100	36	20	11	6	3.2

for AGW n = 2 (based on a nuisance irritation response study in humans)
for LBW n = 1.1 (based on a mortality study; Zwart & Woutersen, 1988)

1 ppm	= threshold of odour perception
1-30 ppm	= irritation of eyes, nose and upper airways, cough, shortness of breath, chest pain, choking and vomiting
30 ppm	= tracheo-bronchial irritation, severe bronchospasm, bronchial and glottis oedema
220 ppm	= 4-h LC50 in rats (0.65 mg/L)

Chlorine – probit function (Cxt)



LC-vales calculated with the derived probit function compared with existing acute inhalation exposure guidelines.

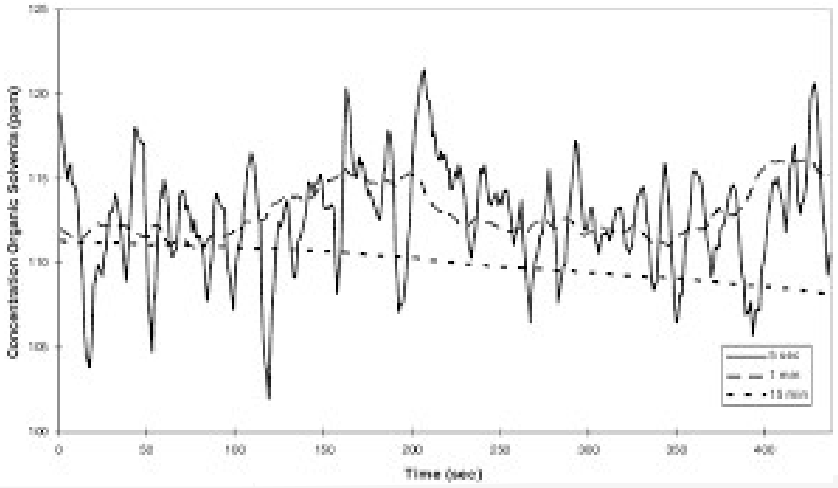
Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
0.1% lethality, this probit	86	44
1% lethality, this probit	126	65
AEGL-3[1] (2004, final)	83	59
ERPG-3[1] (2017)		59
LBW (2015)	110	59

$$Pr = -13.7 + 1.93 \times \ln (C^{1.04} \times t) \text{ with C in mg/m}^3 \text{ and t in min}$$

Peak exposure

Peak exposure - definition

The largest amount of a substance or radiation that a person is exposed to at one time. Peak exposure to a harmful substance or radiation may increase the risk of certain diseases or conditions. *(NCI Dictionary)*



Exposure standards

a. 8-hour time-weighted average (TWA) – adjustment needed for more than 8 h/day or 5 d/wk

b. short term exposure limit (STEL) – 15 min TWA – high short-term exposure – no time adjustment
intolerable irritation
irreversible tissue change
narcosis to an extent that could precipitate workplace incidents

A STEL should not be exceeded at any time during a working day even if the eight-hour TWA average is within the TWA exposure standard. Exposures at the STEL should not be longer than 15 min and not be repeated more than 4x per day. There should be at least 60 minutes between successive exposures at the STEL.

c. peak limitation – no time adjustment

Peak limitation exposure standards are a maximum or peak airborne concentration of a particular substance determined over the shortest analytically practicable period of time which does not exceed 15 min.
A Peak limitation exposure standard must not be exceeded at any time.

Examples: acetic anhydride, n-butyl alcohol, chlorine, ethyl acrylate, glutaraldehyde, and ozone

TWA, STEL, Ceiling and Peak exposure

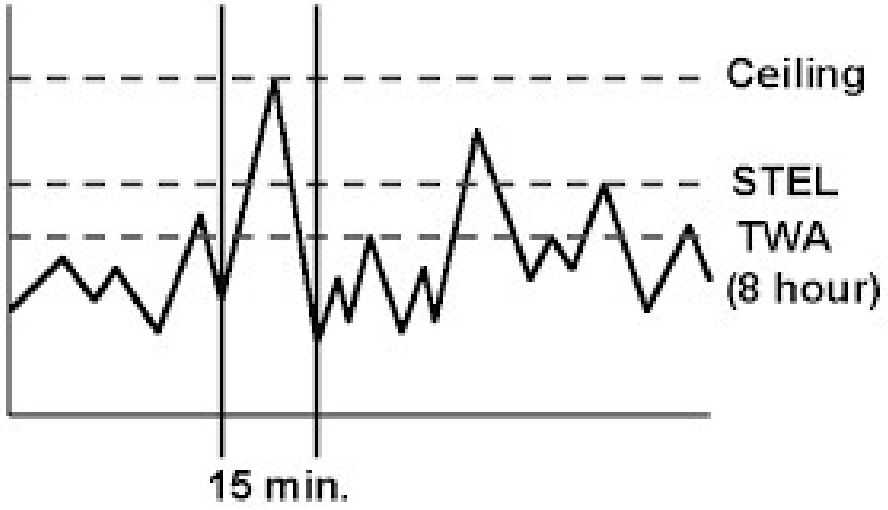


TABLE Z-2

Substance	8-hour time weighted average	Acceptable ceiling concentration	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hr shift	
			Concentration	Maximum duration
Benzene[a] (Z37.40-1969)	10 ppm	25 ppm	50 ppm	10 minutes.
Beryllium and beryllium compounds (Z37.29—1970) [d]	2 µg/m^3	5 µg/m^3	25 µg/m^3	30 minutes.
Cadmium fume[b] (Z37.5-1970)	0.1 mg/m^3	0.3 mg/m^3		
Cadmium dust[b] (Z37.5-1970)	0.2 mg/m^3	0.6 mg/m^3		
Carbon disulfide (Z37.3-1968)	20 ppm	30 ppm	100 ppm	30 minutes.
Carbon tetrachloride (Z37.17-1967)	10 ppm	25 ppm	200 ppm	5 min. in any 4 hrs.
Chromic acid and chromates (Z37.7-1971) (as CrO_3)[c]		1 mg/10m^3		
Ethylene dibromide (Z37.31-1970)	20 ppm	30 ppm	50 ppm	5 minutes.
Ethylene dichloride (Z37.21-1969)	50 ppm	100 ppm	200 ppm	5 min. in any 3 hrs.
Fluoride as dust (Z37.28-1969)	2.5 mg/m^3			
Formaldehyde; see 1910.1048				
Hydrogen fluoride (Z37.28-1969)	3 ppm			
Hydrogen sulfide (Z37.2-1966)		20 ppm	50 ppm	10 mins. once, only if no other meas. exp. occurs.
Mercury (Z37.8-1971)		1 mg/10m^3		
Methyl chloride (Z37.18-1969)	100 ppm	200 ppm	300 ppm	5 mins. in any 3 hrs.
Methylene Chloride: See §1919.52.				
Organo (alkyl) mercury (Z37.30-1969)	0.01 mg/m^3	0.04 mg/m^3		
Styrene (Z37.15-1969)	100 ppm	200 ppm	600 ppm	5 mins. in any 3 hrs.
Tetrachloroethylene (Z37.22-1967)	100 ppm	200 ppm	300 ppm	5 mins. in any 3 hrs.
Toluene (Z37.12-1967)	200 ppm	300 ppm	500 ppm	10 minutes.
Trichloroethylene (Z37.19-1967)	100 ppm	200 ppm	300 ppm	5 mins. in any 2 hrs.

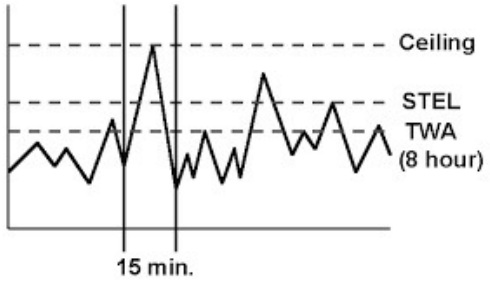
UNITED STATES DEPARTMENT OF LABOR

Occupational Safety and Health Administration

OSHA | STANDARDS | TOPICS | HELP AND RESOURCES

By Standard Number / 1910.1000 TABLE Z-2 - TABLE Z-2

- **Part Number:** 1910
- **Part Number Title:** Occupational Safety and Health Standards
- **Subpart:** 1910 Subpart Z
- **Subpart Title:** Toxic and Hazardous Substances
- **Standard Number:** 1910.1000 TABLE Z-2
- **Title:** TABLE Z-2
- **GPO Source:** e-CFR



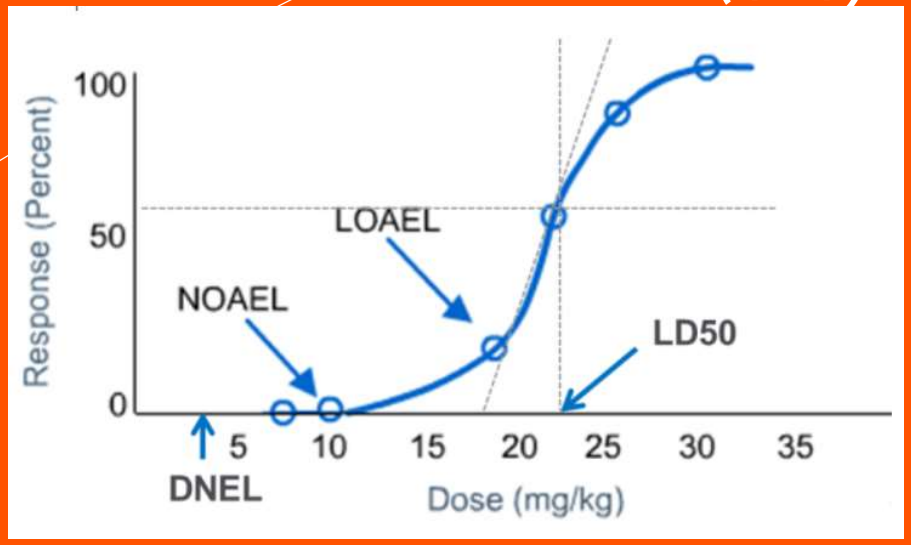
German MAK - Peak limitation: Limitation of exposure peaks and short-term exposures

Table 1 Excursion factors, the duration of peaks and number per shift, and the interval between peaks

Category	Excursion factor	Duration	Number per shift	Interval***
I Substances for which local irritant effects determine the MAK value, also respiratory allergens	1*	15 min, average value**	4	1 hour
II Substances with systemic effects	2*	15 min, average value	4	1 hour

* default value, or a substance-specific value (maximum 8)
** In certain cases, a momentary value (concentration which should not be exceeded at any time) can also be established
*** only for excursion factors > 1

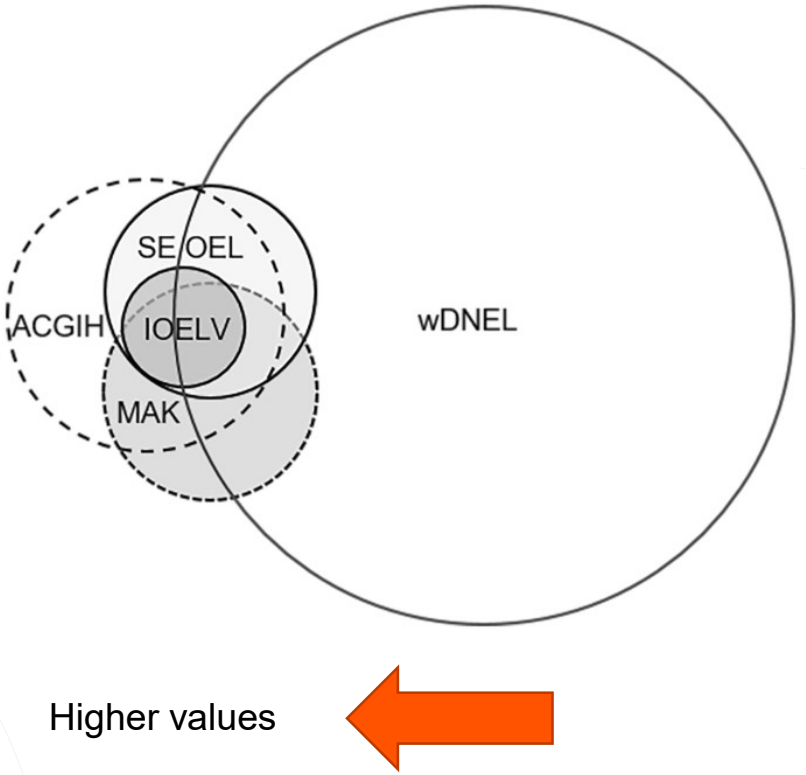
Acute DNELs (REACH)



OELs versus DNELs

So far, OELs have been usually set for data-rich substances for which human data are available.

For worker DNEL derivation on less data rich substances, animal data is primarily used as the starting point with a standard modification of the dose descriptor to extrapolate to workers.



Acute DNELs aim?

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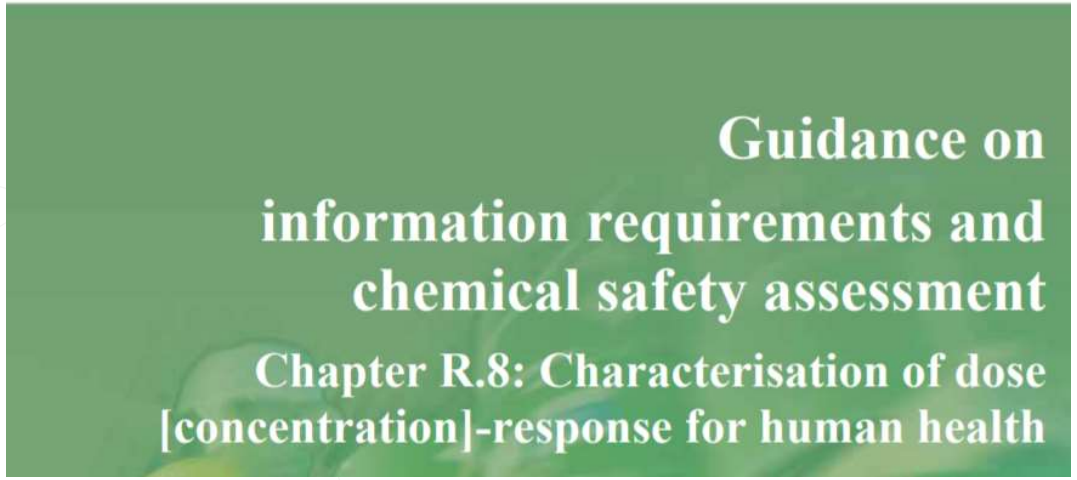
ECHA
http://echa.europa.eu

"There is no established accepted methodology"

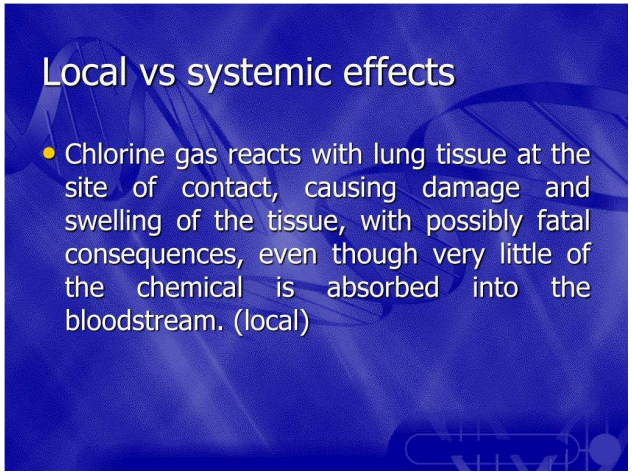


Acute inhalation toxicity effects (Reach guidance R.8)

Acute toxicity includes effects which occur after a single exposure

- Narcosis (transient and reversible)
- Irreversible organ damage
- Irreversible effects on the developing foetus
- CNS depression
- Decrease in activity
- Change in normal behavior
- Signs of distress

Systemic effects



Local effects

- Cytotoxic/tissue damage – proportional to concentration x time (dosage)
- Sensory irritation – proportional to concentration only

Acute inhalation DNEL – REACH guidance - when?

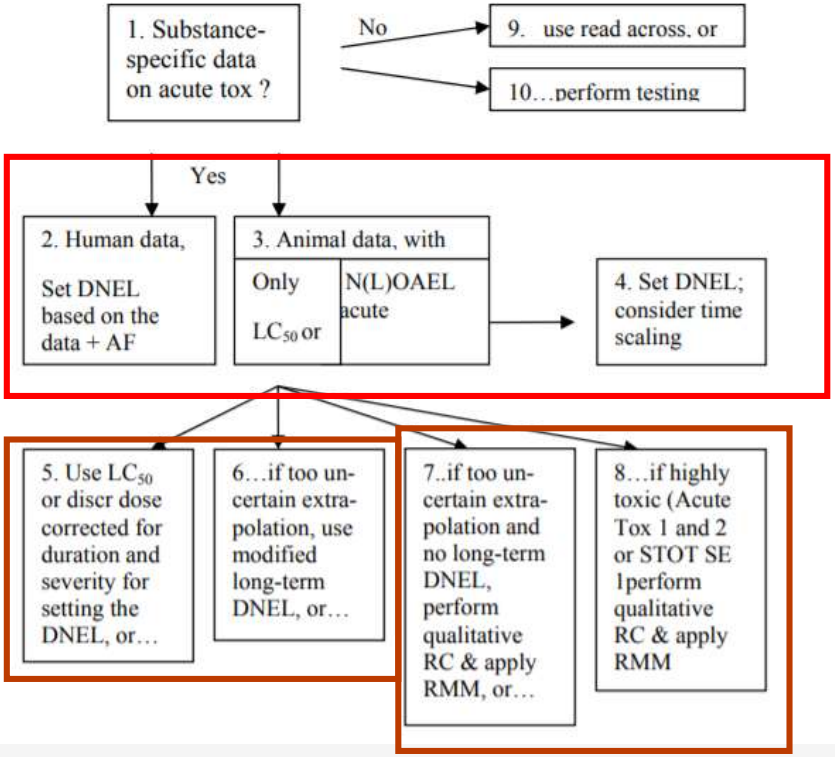
- For some substances, with an acute toxicity hazard (leading to C&L), **AND** for which the tentative exposure assessment has predicted high peaks (e.g. high volatility or specific use patterns), the long-term DNELs may not ensure a sufficient level of protection after peak exposure.
- As a rule of thumb, a DNEL acute should be set for acutely toxic substances if **actual** peak exposure levels significantly exceed the long-term DNEL. For such cases, a DNEL acute need to be set and assessed in relation to the peak exposure levels that humans may experience.

Thus:

1. **Actual** peak exposure determines an acute DNEL? Measurements needed?
2. Hazard based on acute toxicity – long-term DNEL too high? Acute DNEL lower than long-term DNEL?
3. What about respiratory sensitisation, sensory irritation or narcosis?
4. How?

Acute inhalation DNEL – REACH guidance - how?

Figure R. 8-5 Decision tree for setting an acute inhalation toxicity DNEL.



The reference period of the acute toxicity DNEL is e.g. 15 minutes

If relevant effect is deemed to be concentration- rather than dose-dependent time extrapolation would be inappropriate

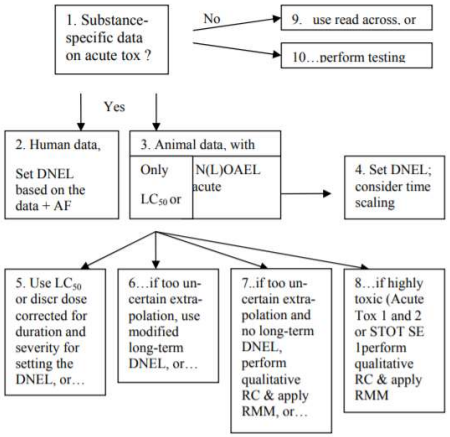
If time extrapolation considered valid: modified Haber's law (C^n x t = k, where 'C' is the concentration, 'n' is a regression coefficient, 't' is the exposure time and 'k' is a constant

A default value of n=1 for extrapolating from shorter to longer exposure durations and n=3 from longer to shorter exposure durations

Acute inhalation toxicity DNEL – in case of lack of human data – according to the guidance

- If an acute toxicity hazard (leading to C&L) has been identified
- Classified as Acute Tox 1 and 2 or STOT SE 1 according to the CLP Regulation; a qualitative risk characterisation is recommended
- Starting point; a NOAEC(L) or LOAEC(L) for sub-lethal effects or an LC(D)50 value
- The acute oral N(L)OAEL could be modified into an inhalation N(L)OAEC using route-to-route extrapolation
- If the acute animal inhalation study (normally 4 hours exposure time) includes dose-response relationships for relevant sub-lethal effects, a N(L)OAEC for these effects may be identified. In a first step, the N(L)OAEC is corrected to a dose descriptor representing 15 minutes exposure using the modified Haber's law
- There is no scientific basis for a default value of the assessment factor (for the extrapolation of a lethal concentration into a NOAEC). Still, a default AF of 100 is suggested as a starting point
- When only an LC(D)50 value is available or when all the dose/concentration levels tested produced mortality, there is substantial uncertainty regarding the toxicity at lower doses and no reliable basis to judge a dose which would not cause any toxicity in humans

Figure R. 8-5 Decision tree for setting an acute inhalation toxicity DNEL.



Thus……?????

Acute inhalation toxicity chlorine
Zwart et al (1988)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Fatal	Exposed
	1654		5	0	10
	2201		5	0	10
	2399		5	0	10
	3485		5	0	10
	4798		5	0	10
	8241		5	0	10
	16801		5	7	10
	1680		10	0	10
	2186		10	0	10
	2363		10	0	10
	3485		10	0	10
	4798		10	1	10
	6519		10	6	10
	1586		30	0	10
	1665		30	3	10
	1757		30	5	10
	1870		30	6	10
	935		60	0	10
	1325		60	4	10
	1473		60	6	10
	1651		60	8	10
	1725		60	10	10

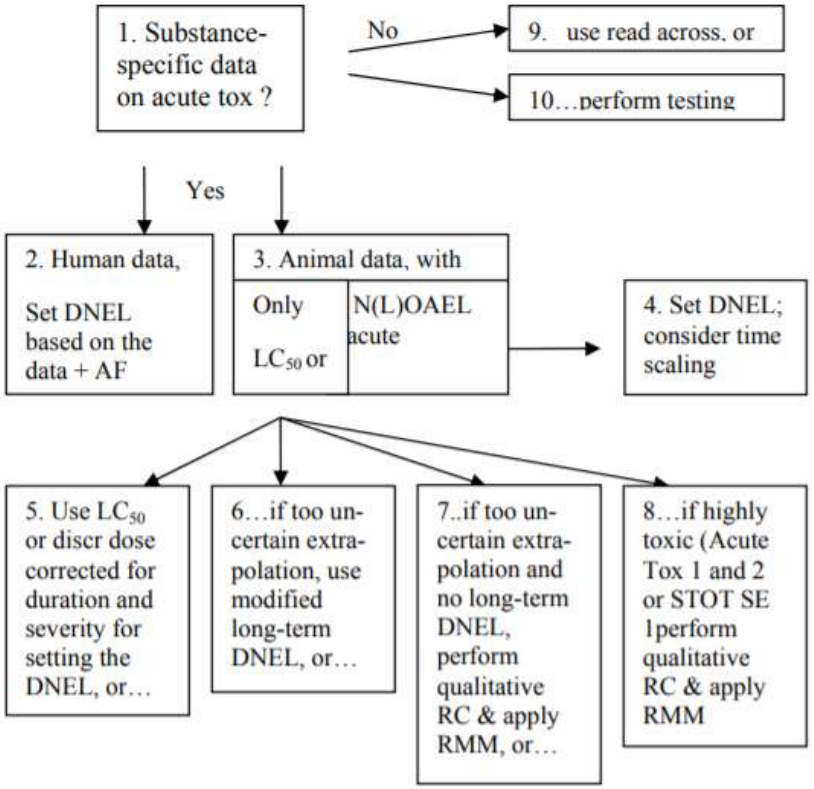
LC0 10 min: 3485 mg/m3
LC0 30 min: 1586 mg/m3
LC0 60 min: 935 mg/m3

For the acute 15-min DNEL:
LC0 10 min: 3485 mg/m3
Haber's rule; n=1 to longer durations

LC0 15 min ~ 2600 mg/m3
AF LOAEC/NOAEC: 3
AF respiratory volume 6.7/10
AF intraspecies 2.5
AF interspecies 5
DNEL acute 46 mg/m3

NB Gestis International Limit values
STEL 15-min: 1.5 mg/m3 (0.5 ppm)
3 mg/m3 (1 ppm)

Figure R. 8-5 Decision tree for setting an acute inhalation toxicity DNEL.



How to relate a 4-h **TWA** LC50/LC0 to peak exposure(s)?

OECD GD 39:
Individual chamber concentration samples should deviate from the mean chamber concentration
by no more than ±10% for gases and vapours, and by no more than ±20% for liquid or solid aerosols

Acute inhalation DNEL – Reach guidance

REFERENCES

- US NRC. National Research Council 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC, USA.

Default value of n=1 for extrapolating from shorter to longer exposure durations and n=3 from longer to shorter exposure durations

- ten Berge WF, Zwart A, Appelman LM (1986) Concentration-time mortality response relationship of irritant and systemically acting vapour and gases. J Hazardous Materials 13:301-309.

Based on the observation that n lies in a range of 1 to 3 from an analysis of approximately 20 structurally diverse chemicals with established concentration-time relationships for lethality

TABLE Z-2

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Cadmium fume[b] (Z37.5-1970)	0.1 mg/m^3	0.3 mg/m^3		
Cadmium dust[b] (Z37.5-1970)	0.2 mg/m^3	0.6 mg/m^3		
Carbon disulfide (Z37.3-1968)	20 ppm	30 ppm	100 ppm	30 minutes.
Carbon tetrachloride (Z37.17-1967)	10 ppm	25 ppm	200 ppm	5 min. in any 4 hrs.
Chromic acid and chromates (Z37.7-1971) (as CrO_3)[c]		1 mg/10m^3		
Ethylene dibromide (Z37.31-1970)	20 ppm	30 ppm	50 ppm	5 minutes.
Ethylene dichloride (Z37.21-1969)	50 ppm	100 ppm	200 ppm	5 min. in any 3 hrs.
Fluoride as dust (Z37.28-1969)	2.5 mg/m^3			
Formaldehyde; see 1910.1048				
Hydrogen fluoride (Z37.28-1969)	3 ppm			
Hydrogen sulfide (Z37.2-1966)		20 ppm	50 ppm	10 mins. once, only if no other meas. exp. occurs.
Mercury (Z37.8-1971)		1 mg/10m^3		
Methyl chloride (Z37.18-1969)	100 ppm	200 ppm	300 ppm	5 mins. in any 3 hrs.
Methylene Chloride: See §1919.52.				
Organo (alkyl) mercury (Z37.30-1969)	0.01 mg/m^3	0.04 mg/m^3		
Styrene (Z37.15-1969)	100 ppm	200 ppm	600 ppm	5 mins. in any 3 hrs.
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Toluene (Z37.12-1967)	200 ppm	300 ppm	500 ppm	10 minutes.
Trichloroethylene (Z37.19-1967)	100 ppm	200 ppm	300 ppm	5 mins. in any 2 hrs.

How to establish these values based on an acute (4-h) LC50 or an oral LD50 study????

Acute DNEL (15 min) at 1-5 times the value (default 3) of the long-term DNEL

Acute inhalation toxicity DNEL – in case of lack of human data

- For some substances, with an acute toxicity hazard (leading to C&L), **AND** for which the exposure assessment has predicted high peaks (because of e.g. high volatility or specific use patterns), the long-term DNELs may not ensure a sufficient level of protection after peak exposure.
  Acute toxicity hazard – Inhalation? Oral? Dermal?
  Why would the long-term DNEL not be sufficient in case of acute toxicity?

- Particular account should be taken of health effects which are not of the same type as those which drive the long-term DNEL.
  Applicable to sensory irritation, respiratory cytotoxicity, sensitization – but no tests or data available for many chemicals

- Still, all of the available evidence and not only the acute toxicity studies should be used to determine the most appropriate toxicological effect on which to base the derivation of the DNEL for acute toxicity.
  What if only long-term oral toxicity studies are available, and only an acute oral and dermal toxicity study?

- As a rule of thumb, a DNEL acute should be set for acutely toxic substances if **actual** peak exposure levels significantly exceed the long-term DNEL. For such cases, a DNEL acute need to be set and assessed in relation to the peak exposure levels that humans may experience.
  How do I know if actual peak exposure levels significantly exceed long-term DNEL?
  How to measure these peak exposure (next session?) – but how to set an appropriate, meaningful acute DNEL?

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Conclusions

For many HPV chemicals lots of data available incl. human health hazard data; as such STEL, peak limitation and ceiling limits set on these

But even for many of such chemicals **peak** exposure data with related human health effects is lacking

Peak limitation and/or STEL data are needed to protect workers against peak exposure

But how to set a relevant/appropriate/meaningful acute DNEL in case of 'simple' REACH dossiers; chemicals with no human data, only (oral) animal data?

The REACH guidance APPENDIX R. 8-8 Acute toxicity provides a lot of non-useful 'guidance'

"The establishment of an acute toxicity DNEL set for effects occurring after a single exposure of a few minutes up to 24 hours is not only cumbersome (there is no established accepted methodology) and resource-intensive but probably unnecessary" - I would like to conclude it is, and thus acute DNEL setting only proposed in case human data available, preferably as STEL value!

Thanks for your attention

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