National Institute for Public Health
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Ministry of Health, Welfare and Sport

Probit function technical support document

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substance name	CAS number
Carbon monoxide	**630-08-0**

This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have had the opportunity to comment on the derivation of the proposed probit function. The status of this document has now been raised to "interim", pending a decision on its formal implementation.

The decision on actual implementation depends on the results of a further consequence analysis.

Detailed information on the procedures for the derivation, evaluation and formalization of probit functions is available at
http://www.rivm.nl/en/Topics/P/Probit_functions

Technical support document carbon monoxide

1. Substance identification

CAS-number:	630-08-0
IUPAC name:	carbon monoxide
Synonyms:	carbon monooxide, carbonous oxide, carbon(II)oxide
Molecular formula:	CO
Molecular weight:	28.0 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	-191°C (at 101.3 kPa)
Vapour pressure:	3500 kPa (at 20°C)
Saturated vapor conc:	N/A
Conversion factor:	1 mg/m^3 = 0.859 ppm (at 20°C and 101.3 kPa)
	1 ppm = 1.165 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H331, H360D, H372

2. Mechanism of action and toxicological effects following acute exposure[1]

Acute effects: Carbon monoxide affects oxygen transport and cell metabolism through hypoxic and non-hypoxic mechanisms. These mechanisms are the result of the affinity of carbon monoxide to bind to haem in erythrocytes, muscle, brain, and cytochrome proteins. Because the affinity of haemoglobin for carbon monoxide is approximately 220 times that for oxygen, less oxygen will be carried by haemoglobin to tissues during CO poisoning.

The hypoxia is exacerbated by the inhibition of carbon monoxide on the dissociation of oxygen from haemoglobin as the blood reaches the tissues. The heart and brain are rapidly affected because of their high demand for oxygen. Muscles and cytochromes follow in terms of sensitivity to carbon monoxide. Acute poisoning is the result of tissue hypoxia.

The signs and symptoms of carbon monoxide poisoning are divided into three levels: 1) mild toxicity – headache, nausea, vomiting, dizziness, and blurred vision; 2) moderate toxicity – chest pain, dyspnea, weakness, tachycardia, and syncope (fainting); and 3) severe toxicity – cardiac arrhythmia, hypotension, myocardial ischemia, cardiac arrest, pulmonary edema, seizures, and coma.

Non-hypoxic mechanisms are attributable to carbon monoxide binding the myoglobin, neuroglobin, signalling pathways, and energy metabolism involving cytochrome proteins.

The unborn foetus and adults with coronary artery disease are considerably more susceptible for lethal effects of carbon monoxide than healthy adults. For non-lethal effects of carbon monoxide, subjects with coronary artery disease and children constitute the susceptible subpopulations.

Lethality results most likely from effects on the heart because the myocardial tissue is most sensitive to hypoxic effects of carbon monoxide.

Long-term effects: No morphological changes were observed in laboratory animals upon long-term carbon monoxide exposures. Human case reports of chronic exposure to carbon monoxide describe increased HbCO-levels with concomitant light-headedness with vertigo, nausea, headaches and palpitations.

3. Human toxicity data

Carbon monoxide's toxicity is generally correlated with the COHb level. The table below presents an overview of symptoms associated with COHb in healthy adult humans and susceptible subpopulations:

[1] AEGL 2010, ERPG 2014

Healthy adults		Susceptible subpopulations	
COHb (%)	**Symptoms**	**COHb (%)**	**symptoms**
~1	Physiological background concentration	2	During physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischemia in subjects with coronary artery disease
3-8	Background concentration in smokers	5-6	Increase in cardiac arrhythmias in subjects with coronary artery disease
		7	Headache, nausea in children
10	No appreciable effect, except shortness of breath on vigorous exertion, possible tightness across the forehead, dilation of cutaneous blood vessels	13	Cognitive development deficits in children
		15	Myocardial infarction in subjects with coronary artery disease
20	Shortness of breath on moderate exertion, occasional headache with throbbing in temples	25	Syncope in children
		25	Stillbirths
30	Headache, irritable, easily fatigued, judgement disturbed, possible dizziness, dimness of vision		
40-50	Headache, confusion, collapse, fainting on exertion		
60-70	Unconsciousness, intermittent convulsion, respiratory failure, death if exposure is long continued		
80	Rapidly fatal		

(adapted from WHO 1999)

The effects of carbon monoxide at specific concentrations for specific durations of exposure, as noticed in many studies, are summarized in the table below:

Concentration		**Duration**	**COHb**	**Effects**
ppm	**mg/m³**			
50	58	80 min	2%	Impaired vigilance. No effects on response latency, short-term memory, and ability to mentally subtract
26	30	135 min	2.30%	No effect on vigilance, heart rate, and minute volume
15	17	24 h/d, 8d	2.40%	Changes in P waves (3 of 16 subjects). Marked SBT changes in a subject who had localized myopathy in his heart
50	58	ca. 25 min	2.50%	Increased minute volume; reduction in the durations (from 21 min to 20 min) that the subjects could exercise maximally at 35°C
50	58	ca. 25 min	2.70%	No effects on maximal oxygen uptake, minute volume, and heart rate
35	41	4 h	3%	No effect on visual task performance
75	87	ca. 4.5 min	3.40%	A 5% decrease in the duration subjects can exercise maximally (from 24 min to 23 min). Reduced minute volume, but no effect on heart

Concentration		Duration	COHb	Effects
ppm	mg/m^3			
				rates.
100	117	N.S.	3.90%	In cardiac patients, impaired ability to visually trace a line through a bunch of entangles lines to the end of that line. No effects on time perception, number facility, reaction time, and perceptual speed
100	117	1 h	4%	A 5% decrease in exercise duration until exhaustion. Ischemic SBT segment depression after exercise (1 of 10 subjects)
100	117	> 1 h	4%	No ventricular arrhythmia
N.S.	-	ca. 10 min	4.5%	Decreased ability to detect flashes of light
114	133	2 h	4.80%	No effect on vigilance and alertness
300	350	45 min	Ca. 5%	Increased reaction time to visual stimuli. No effects on light detection sensitivity and depth perception
a bolus of CO, then maintained at 30	a bolus of CO, then maintained at 35	5 h		No effect on haemoglobin affinity for oxygen during exercise
50	58	4 h	5%	During exercise, there were higher heart rates, no effects on blood pressure, stroke volume, body temperature, minute volume, oxygen uptake, serum haemoglobin, lactate levels, and haematocrit
76	89	4 h	30%	Increase in tracking error and 12% increase in visual response time. Reduced ability to detect an auditory tone (impaired auditory vigilance) and to do two tasks simultaneously
100	117	2.5 h	5%	No decrement in motor performance (tapping and digit manipulation)
20,000	23,300	Several minutes	5.60%	Deficit in driving skills
200	233	> 1 h	6%	Increased frequency of ventricular premature depolarization
700	816	N.S.	6%	No effect on driving ability
111	129	135 min	6.60%	Impaired vigilance. No effect on heart rate and minute volume
125	146	15 min – 3 h	6.60%	No effect on tracking performance or ability to estimate time lapse
100	117	2.5 h	7%	Decrement in mental performance
50	58	24 h/d, 8 d	7.10%	Changes in P waves (6 of 15 subjects)
50	58	24 h/d, 8 d	7.10%	No effect on auditory vigilance
250	291	80 min	7.50%	No effects on vigilance, response latency, short-term memory, and ability to do subtraction
N.S.	-	15 min – 3 h	7.50%	23% reduction in duration subjects can exercise maximally
50	58	24 h	8%	No symptoms or toxic signs. No effect on manual dexterity, hand steadiness, reaction time, and

Concentration		Duration	COHb	Effects
ppm	mg/m³			
				estimation of time lapse
175	204	2.4 h	8-10%	No effect on mental capacity
100	117	4 h	8.20%	Increase in tracking error, but no effect on ability to monitor events
650	757	45 min	8.50%	Increased reaction time to visual stimuli. No effects on light detection sensitivity
200	233	3 h	9%	No degradation in night vision sensitivity. No effect on reaction time and visually evoked cortical responses
N.S.	-	4-6 h	10%	Increase in response time and decreased precision in maintaining separation distance in driving
200	233	3 h	10.4%	No symptoms. No effect on time perception and no effect on tracking performance
75	87	24 h/d, 7 d	11%	Change in P wave, SBT segment, or T wave (6 or 9 subjects). Supraventricular extra systoles (1 of 9 subjects)
700	816	N.S.	11%	Some decrement in driving performance
100	117	8 h	12%	No symptoms or toxic signs. No effect on manual dexterity, hand steadiness, reaction time, and estimation of time lapse
950	1107	45 min	12%	Increased reaction time. No effect on depth perception and light detection sensitivity
200	233	160 min	12.60 %	No effect on vigilance performance
500	583	1 h	13%	Mild headache
200	233	4 h	16%	Mild headache
11,600 as bolus, 142 maintenance	13,514 as bolus, 165 maintenance	135 min	17%	No effect on thresholds to visually detect motion, pattern, and contrast. No effect on luminance threshold
200	233	5 h	18%	No impairment in ability to estimate time lapse
11,000 bolus, 225 maintenance	12815 bolus, 262 maintenance	ca. 1 h	20%	Reduced maximal oxygen uptake
860	1002	N.S.	37%	Severe headache, dizziness, difficulty in concentrating and polycythemia
50	58	1.5 h	N.S.	Impaired ability to estimate time lapse
100	117	4 h	N.S.	No effect on tracking performance

N.S.: not specified *(adapted from ERPG 2014)*

According to AEGL (2010), various concentration-time combinations are reported as lethal exposures to CO: 40000 ppm (46600 mg/m^3) x 2 min, 16000 ppm (18640 mg/m^3) x 5 min, 8000 ppm (9320 mg/m^3) x 10 min, 3000 ppm (3495 mg/m^3) x 30 min, 1500 ppm (1748 mg/m^3) x 60 min. In addition, lethal exposure concentrations of 12000-16000 ppm (13980-18640 mg/m^3) for 5 minutes and 2500-4000 ppm (2913-4660 mg/m^3) for 30 minutes were described.

4. Animal acute toxicity data

During the literature search the following technical support documents and databases were consulted:

1. AEGL final TSD, ERPG document and EU RAR and reference database for carbon monoxide, covering references before and including 1995.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, ECHA, RTECS, IRIS and ToxNet with the following search terms:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit
3. Unpublished data were sought through networks of toxicological scientists.

Animal lethal toxicity data focused on acute exposure are described in Appendix 1. A total of 13 studies were identified -with 16 datasets for 3 species- with data on lethality following acute inhalation exposure. Two datasets were assigned status A for deriving the human probit function, one dataset was assigned status B and 13 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of one study was identified in which sensory irritation was studied. However, no full details are provided. In this study the following RD_{50} value was observed:

Table 1 *Sensory irritation data for carbon monoxide.*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
Rat, Crl:Cd strain, male	13980^{NS}	Not specified*	Lapin (1981)

NS: not specified if a plateau in response was reached.
* Lapin (1981) exposed animals for 5, 15, 30 or 60 min. It is however not clear for which exposure duration the RD_{50} applies.

5. Probit functions from individual studies

All available acute lethality data on carbon monoxide are displayed in Figure 1.

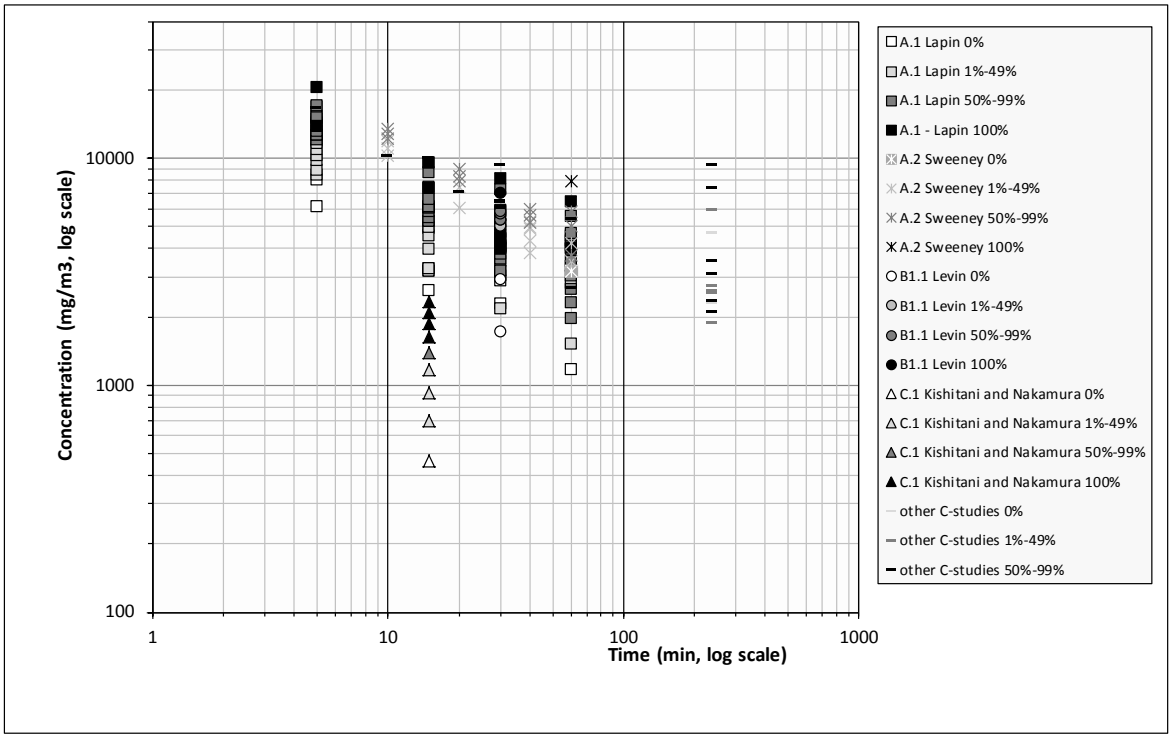


Figure 1 *All available acute lethality data for carbon monoxide.*

The data that were selected for initial analysis of the animal probit function are presented in Table 2 and Figure 2.

All A and B1 studies were selected for derivation of the animal probit function for carbon monoxide.

Probit functions have been calculated and reported in Appendix 1 for each of the reported studies. The results of the calculations are presented in Table 2.

Table 2 *Data selected for initial analysis of the animal probit function of carbon monoxide.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 30 minutes (mg/m^3) 95% C.I.	n-value 95% C.I.
A.1*	Rat	-12.21 + 1.69×lnC + 0.90×lnt	4422 (3898 - 5000)	1.88 (1.49 – 2.28)
A.2	Rat	-36.5 + 3.87×lnC + 2.24×lnt	6311 (6037 - 6634)	1.73 (1.54 – 1.92)
B1.1 **	Rat	*30-min LC_{50}*	5283 (4133 - 5589)	N/A

* combined analysis of the restrained and unrestrained animals
** based on analysis of 'square-wave' exposure data (i.e. animals were placed in the chamber upon reaching the desired concentration)

The data of the two A studies and study B1.1 with rats are presented graphically below.

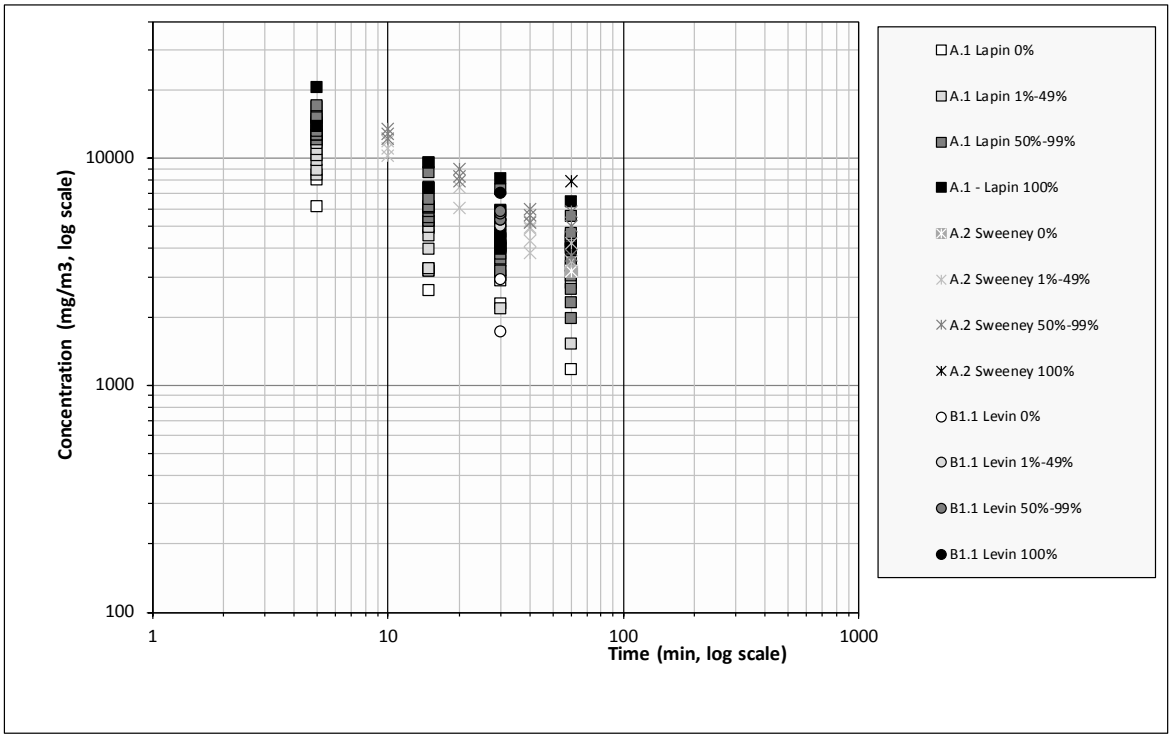


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of carbon monoxide.*

Based on criteria outlined in the guideline the data from rat studies A.1, A.2 and B1.1 were selected for the final dataset for the derivation of the animal probit function. The reason for including all these studies is that the studies are considered to be of sufficient quality, including sufficient C x t combinations.

Figure 3 provides an overview of LC_{50} values and LC_{50}-time relationships for all studies in the final analysis. The data that were selected for final analysis of the animal probit function are presented in Table 3 and Figure 4.

The final data eligible for calculating the animal probit function contain three datasets from three studies and include data from one animal species.

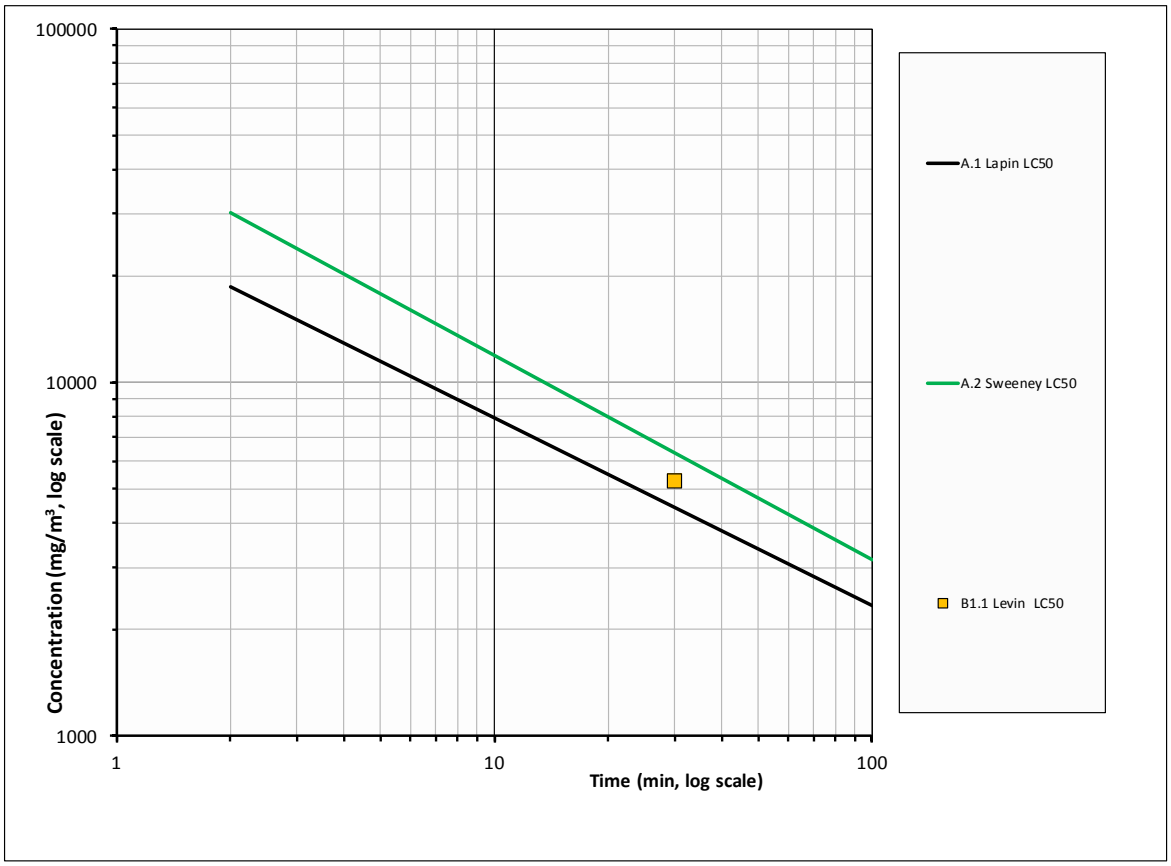


Figure 3 *LC_{50} values of A.1, A.2 and B1.1 rat datasets for carbon monoxide, over time where available.*

Table 3 *Data selected for the derivation of the animal probit function of carbon monoxide (identical to table 2).*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 30 minutes (mg/m^3) 95% C.I.	n-value 95% C.I.
A.1*	Rat	-12.21 + 1.69×lnC + 0.90×lnt	4422 (3898 - 5000)	1.88 (1.49 – 2.28)
A.2	Rat	-36.5 + 3.87×lnC + 2.24×lnt	6311 (6037 - 6634)	1.73 (1.54 – 1.92)
B1.1 **	Rat	*30-min LC_{50}*	5283 (4133 - 5589)	N/A

* combined analysis of the restrained and unrestrained animals
** based on analysis of 'square-wave' exposure data (i.e. animals were placed in the chamber upon reaching the desired concentration)

The data of the selected datasets are presented graphically below.

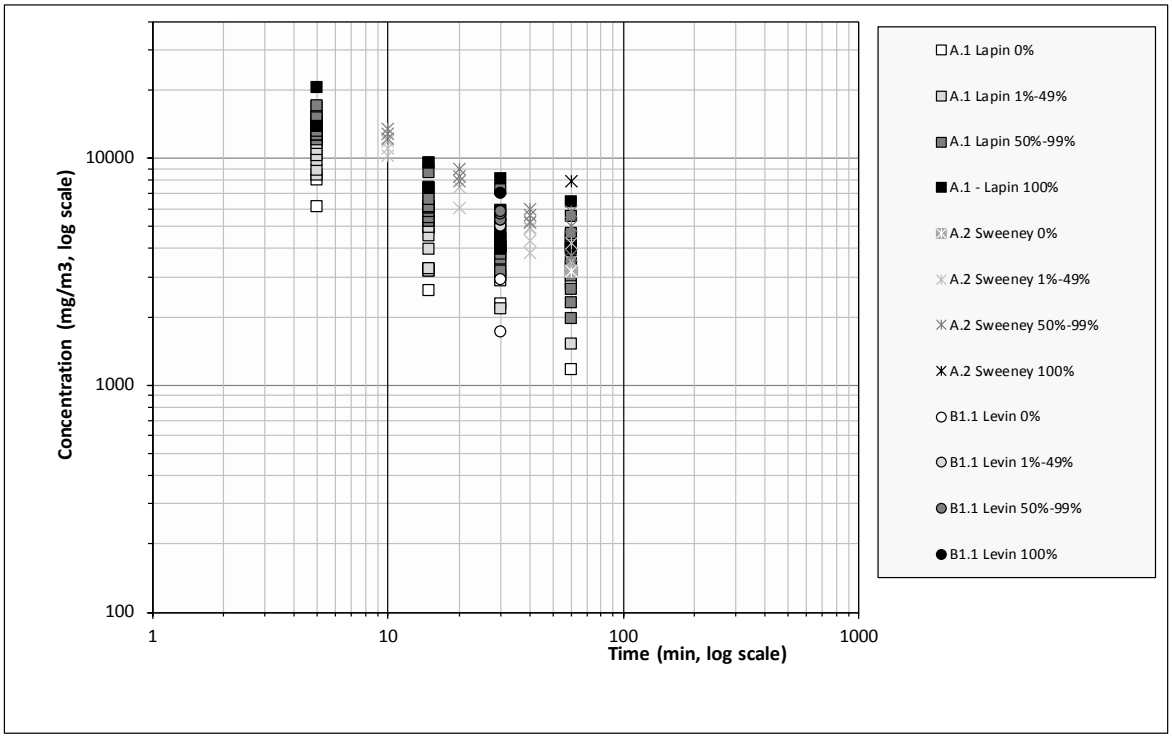


Figure 4 Final data selected for derivation of the animal probit function of carbon monoxide (identical to figure 2).

6. Derivation of the human probit function

To derive the human probit function the results from rat studies A.1 (Lapin, 1981), A.2 (Sweeney et al., 2016) and B1.1 (Levin et al., 1987) have been used to derive a point of departure as outlined above. The results of study A.1 were based on a combined analysis of the restrained and unrestrained animals.

First, the arithmetic mean n-value was calculated from studies A.1 and A.2. The arithmetic mean species-specific rat n-value was calculated to be 1.805.
Second, the LC_{50}-values of all applicable rat A- and B1-studies were calculated for a common exposure duration of 30 minutes.
Finally, the rat-specific geometric mean LC_{50}-values were calculated from all available (time-scaled) LC_{50} values of studies A.1, A.2 and B1.1. The species-specific 30-min LC_{50}-value was 5283 mg/m^3 for the rat.

The formula for the geometric mean of time-scaled LC_{50}-values from 1 species is as follows:

$$\overline{LC_{50}} = \left[\prod_{i=1}^{m} LC_{50,i}\right]^{(1/m)}$$

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value
$LC_{50,i}$ = LC_{50}-value of study i.
m = number of observations on LC_{50}-values (i=1…m).

The Point of Departure for the human probit function is a 30-minute geometric mean animal LC_{50} value of 5283 mg/m^3 and an arithmetic mean n-value of 1.805.

Application of an overall assessment factor of 3 (determined by an interspecies factor of 3) would result in a 60-min LC_{01} of 362 mg/m^3, which is in conflict with human data. For example, a 45-min exposure to 950 ppm (1107 mg/m^3) resulted in an increased reaction time and no effect on depth perception and light detection sensitivity. Further, slight headache was observed upon a 1-h exposure to 500 ppm (583 mg/m^3). See section 3 for an overview of the human data.

The human equivalent LC_{50} was calculated by applying the following assessment factors:

Table 4 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	1	Default value of 3 was reduced to 1, see text above
Nominal concentration	1	Studies with analytically determined concentrations available
Adequacy of database:	1	Two A studies and one B1 study available

The estimated human equivalent 30-minute LC_{50} value is 5283 / 1 = **5283 mg/m^3**.

The experimentally determined n-value was **1.81** (arithmetic mean of n-value of studies A.1 and A.2). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.11**.

The human probit function is then calculated on the human equivalent 30 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.11 \times \ln (1761^{1.81} \times 30)$ resulting in the a-value of **-15.91**.

$Pr = -15.9 + 1.11 \times \ln (C^{1.81} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically sound basis. The probit function is based on two studies in the rat with A quality and one study in the rat with B1 quality. Further, these data included in total 125 C x t combinations, including durations from 5 to 60 minutes and lethality in the range of 0-100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 737 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 1076 mg/m^3.

Table 1 *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	1081	737
1% lethality, this probit	1578	1076
AEGL-3[2] (2010, final)	699	384
ERPG-3[2] (2014)	-	583
LBW (2016)	700	390

[2] AEGL and ERPG values were converted from ppm to mg/m^3 with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m^3 can deviate slightly from those reported in the AEGL and ERPG TSDs.

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are slightly higher.

Appendix 1 Animal experimental research

Study ID: A.1

Author, year: Lapin, 1981[3]
Substance: carbon monoxide
Species, strain, sex: rat, CrL:CD, male
Number/sex/conc. group: 4-8 for restrained animals and 6-10 for unrestrained animals
Age and weight: age not specified, weights 250 ± 25 gram
Observation period: 14 days

Evaluation of study quality

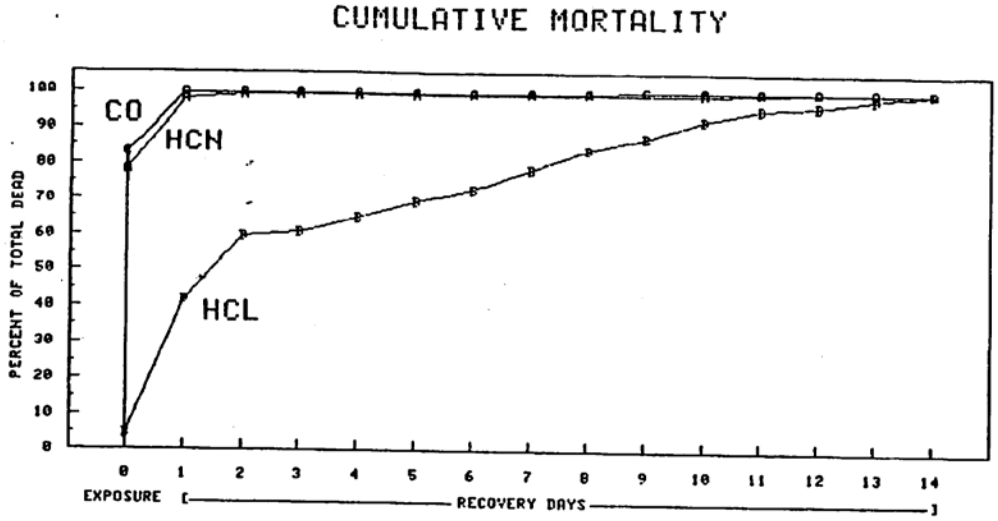
Criteria	*Comment*
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Restrained: head only* *Unrestrained: whole body*
Type of restrainer	*In case of head-only exposure, rats were restrained in whole body holders inside the chamber (175 l). By using a switch a hinged box was swung down to start an exposure (see figure below) after the required concentration was reached.* *In some cases restrained animals were simultaneously exposed with unrestrained animals*
Pressure distribution	*Not specified*
Homogeneity of test atmosphere in breathing zone of animals	*The test-gas atmospheres were obtained with continuous flow-through generation. Gas concentrations were generated by dilution of commercial bottled gas*
Number of air changes per hour	*Unknown*
Equilibration time (t95)	*Insufficient information to calculate*
Start of exposure relative to equilibration	*Whole body: no information* *Head-only (in chamber): it was stated that exposure started "once a satisfactory steady state chamber concentration of the test material was obtained."*
Actual concentration measurement	*Continuous measurements with infrared spectrophotometry*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*NA*

[3] This study is sometimes also presented as E.I. du Pont de Nemours and Co., 1981

Assessment of Reliability	**A** *Data were suitable to derive a probit function. Multiple concentration levels and durations were tested, resulting in a good concentration response relation with mortality of 0-100%.*

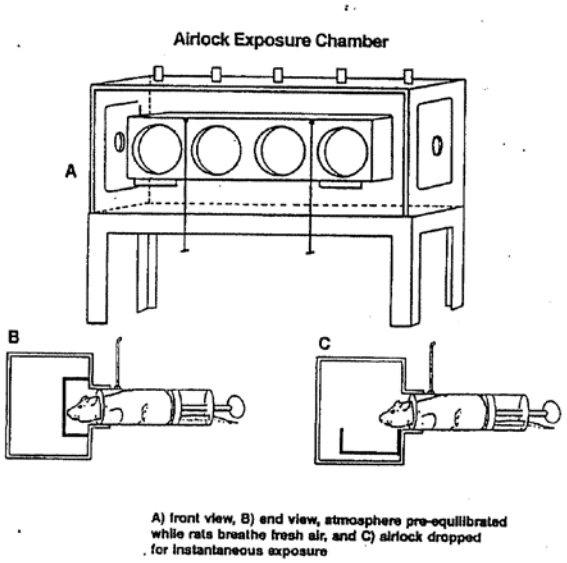
Additional information on time points of mortality

The results of this study of Lapin (1981) show that mortality occurred mainly during exposure. Approximately 80-85% died during exposure, the remaining deaths occurred one day post-exposure. See figure below (copied from study report).



The figure below (copied from study report) shows how the restrained animals were exposed. Figures B and C show respectively a closed and opened hinged box. The authors claim that animals receive a true 'square wave' exposure pattern without a (significant) equilibration period.

For the probit calculations it is assumed that the exposure of the animals is almost instantaneously to the measured concentration, even though some dilution may have been present.



A) front view, B) end view, atmosphere pre-equilibrated while rats breathe fresh air, and C) airlock dropped for instantaneous exposure

1
2 **Results**

Species	Concentration (mg/m^3)		Exposure duration (min)	Restrained?	Lethality	
	Measured	Adjusted			Male	
					Dead	Tested
Rat	6151	NA	5	yes	0	7
Rat	11860	NA	5	yes	3	8
Rat	12034	NA	5	yes	5	8
Rat	12640	NA	5	yes	4	8
Rat	12745	NA	5	yes	4	8
Rat	13957	NA	5	yes	6	7
Rat	14306	NA	5	yes	7	8
Rat	14912	NA	5	yes	4	8
Rat	15087	NA	5	yes	5	8
Rat	15273	NA	5	yes	5	8
Rat	16823	NA	5	yes	4	8
Rat	17114	NA	5	yes	6	8
Rat	20457	NA	5	yes	8	8
Rat	2615	NA	15	yes	0	8
Rat	3169	NA	15	yes	3	8
Rat	3250	NA	15	yes	3	8
Rat	3973	NA	15	yes	1	6
Rat	4567	NA	15	yes	1	6
Rat	4881	NA	15	yes	0	8
Rat	4980	NA	15	yes	1	8
Rat	5295	NA	15	yes	6	8
Rat	5476	NA	15	yes	4	6
Rat	5802	NA	15	yes	7	8
Rat	6035	NA	15	yes	4	8
Rat	6064	NA	15	yes	4	8
Rat	6128	NA	15	yes	7	8
Rat	6571	NA	15	yes	6	8
Rat	7363	NA	15	yes	8	8
Rat	9547	NA	15	yes	8	8
Rat	2182	NA	30	yes	2	6
Rat	2295	NA	30	yes	0	6
Rat	2901	NA	30	yes	0	4
Rat	3017	NA	30	yes	1	8
Rat	3190	NA	30	yes	3	4
Rat	3200	NA	30	yes	4	6
Rat	3501	NA	30	yes	2	6
Rat	3588	NA	30	yes	5	6
Rat	3772	NA	30	yes	5	6
Rat	3976	NA	30	yes	6	6
Rat	4005	NA	30	yes	4	5
Rat	4052	NA	30	yes	5	6
Rat	4104	NA	30	yes	4	6
Rat	4454	NA	30	yes	6	6
Rat	4544	NA	30	yes	6	6
Rat	5252	NA	30	yes	6	6
Rat	5803	NA	30	yes	6	6
Rat	1168	NA	60	yes	0	6

Rat	1526	NA	60	yes	1	6
Rat	1961	NA	60	yes	3	6
Rat	2308	NA	60	yes	3	6
Rat	2631	NA	60	yes	4	6
Rat	3017	NA	60	yes	5	6
Rat	3523	NA	60	yes	5	6
Rat	4016	NA	60	yes	6	6
Rat	8039	NA	5	no	0	10
Rat	8388	NA	5	no	2	10
Rat	8901	NA	5	no	1	10
Rat	9763	NA	5	no	2	10
Rat	10252	NA	5	no	2	10
Rat	10963	NA	5	no	1	10
Rat	11603	NA	5	no	2	10
Rat	12652	NA	5	no	6	10
Rat	13083	NA	5	no	8	10
Rat	13817	NA	5	no	10	10
Rat	3169	NA	15	no	0	10
Rat	3250	NA	15	no	0	10
Rat	5295	NA	15	no	2	10
Rat	6035	NA	15	no	4	10
Rat	6128	NA	15	no	3	10
Rat	6571	NA	15	no	4	8
Rat	7363	NA	15	no	6	10
Rat	7497	NA	15	no	7	10
Rat	8621	NA	15	no	9	10
Rat	9547	NA	15	no	10	10
Rat	4005	NA	30	no	0	10
Rat	4052	NA	30	no	2	6
Rat	4372	NA	30	no	3	10
Rat	4718	NA	30	no	3	10
Rat	5068	NA	30	no	1	8
Rat	5881	NA	30	no	6	10
Rat	7270	NA	30	no	8	10
Rat	8084	NA	30	no	10	10
Rat	2806	NA	60	no	0	10
Rat	3360	NA	60	no	0	10
Rat	3963	NA	60	no	3	10
Rat	4102	NA	60	no	2	10
Rat	4314	NA	60	no	1	10
Rat	4568	NA	60	no	8	10
Rat	4694	NA	60	no	6	10
Rat	5522	NA	60	no	6	10
Rat	6430	NA	60	no	10	10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times lnC + c \times lnt + d \times R$

with C for concentration in mg/m^3, t for time in minutes and R is a variable for restrainment (1=restrained, 0=unrestrained).

First, the data were analysed for restrained and unrestrained animals separately. Subsequently the data were analysed with both restrained and unrestrained animals, with a variable to account for restrainment.
To assess the influence of including the 5-min data and the use of restrainment, the calculations were performed:

- with and without the 5-min data.
- for restrained and unrestrained animals separately.
- all animals in the model, with and without a variable to account for restrainment.

Probit function	Species	a	b	c	d	n-value
Only restrained animals, INCL 5 min data	Rat	-23.3	2.67	1.99	-	1.341 (1.196-1.486)
Only restrained animals, EXCL 5 min data	Rat	-25.3	2.97	1.85	-	1.604 (1.215-1.993)
Only unrestrained animals, INCL 5 min data	Rat	-37.1	4.23	1.61	-	2.629 (2.289-2.968)
Only unrestrained animals, EXCL 5 min data	Rat	-36.9	4.43	1.09	-	4.076 (2.880-5.273)
All animals, restrainment as covariate, INCL 5 min data	Rat	-17.9	2.19	1.19	0.945	1.831 (1.568-2.095))
All animals, INCL 5 min data	Rat	-12.21	1.69	0.90	-	1.884 (1.493-2.275)

All LC_{50} values calculated with the probit model are presented below. For comparison the LC_{50} values as calculated by the study authors are also presented (calculated per exposure duration).

1. Restrained animals only

Duration (min.)	*LC_{50} (mg/m^3) 95%-C.I. (Restrained)*	*LC_{50} (mg/m^3) 95%-C.I. (Restrained, excl 5 min.)*	*LC_{50} (mg/m^3) presented by study authors (Restrained)*
10	7194 (6578-7755)	6384 (5407-7469)	*
30	3171 (2874-3454)	3218 (2919-3492)	3367
60	1891 (1643-2152)	2089 (1750-2443)	2200

* Lapin (1981) only reported LC_{50} values for the experimental exposure durations

2. Unrestrained animals only

Duration (min.)	*LC_{50} (mg/m^3) 95%-C.I. (Unrestrained)*	*LC_{50} (mg/m^3) 95%-C.I. (Unrestrained, excl 5 min.)*	*LC_{50} (mg/m^3) presented by study authors (Unrestrained)*
10	8649 (8185-9192)	7247 (6594-7930)	*

30	5695 (5390-6042)	5535 (5306-5785)	5487
60	4375 (4045-4748)	4669 (4380-5007)	4606

* Lapin (1981) only reported LC_{50} values for the experimental exposure durations

3. Restrained and unrestrained animals in one analysis

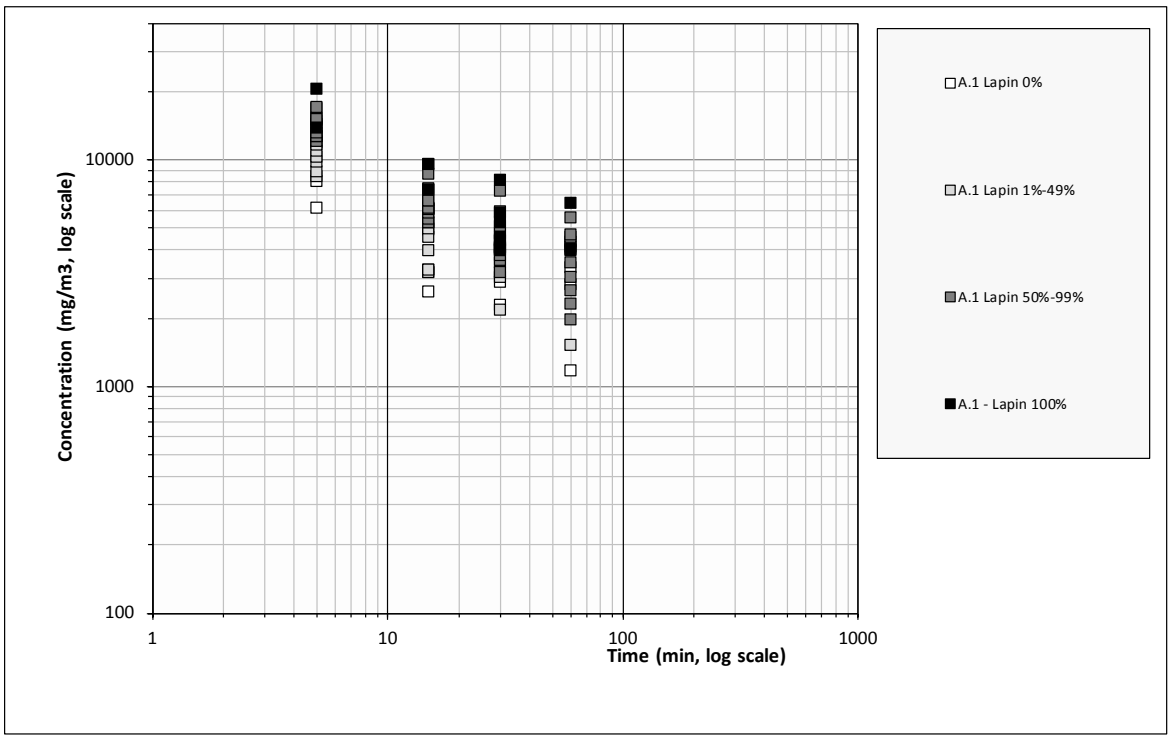
Results for restrained/unrestrained animals in the table below were taken from the combined analysis, by applying a variable for restrainment.
Combined animals are restrained and unrestrained animals taken together.

Duration (min.)	*LC_{50} (mg/m^3) 95%-C.I. (Restrained)*	*LC_{50} (mg/m^3) 95%-C.I. (Unrestrained)*	*LC_{50} (mg/m^3) 95%-C.I. (combined animals)*
10	6458 (5756-7175)	9950 (8925-11240)	7921 (7038-8923)
30	3545 (3141-3945)	5461 (4926-6115)	4422 (3898-5000)
60	2428 (2075-2789)	3740 (3271-4305)	3061 (2544-3662)

The calculated LC_{50} values were systematically higher (lower toxicity) in unrestrained vs restrained animals by a factor 1.5-2.2. Stress or inability to avoid exposure in restrained animals may have contributed, although there is no definitive explanation for the difference.

Data from the combined analysis were selected for human probit derivation.

A graphical overview of the data is presented below. Each concentration-time combination (with 4-10 male rats) represents one point in the plot



Study ID: A.2

Author, year: Sweeney et al., 2016
Substance: carbon monoxide
Species, strain, sex: rat, Sprague-Dawley, male
Number/sex/conc. group: 6-10 males/group
Age and weight: age 48-58 days, weight 220-373 g at time of exposure
Observation period: 24 hours *

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to OECD 403 guideline(s)	*No, however follows similar protocol, where the observation period was shorter in the study than stated in the OECD guideline. Study was performed for research of the toxic load model in acute inhalation toxicology. Only continuous exposure profiles were considered for current probit function derivation*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Nose-only*
Type of restrainer	*In house constructed 12-position Cannon style nose-only exposure tower, included in a vented hood. Before exposure, animals were placed in a nose-only cone for a 30-min acclimatization period*
Pressure distribution	*The nose-only system was operated under a slight, negative static pressure, as a safety procedure to minimize the risk of exposing laboratory personnel (due to the toxicity and high concentrations tested).* *The authors stated** that air could leak past the animal and could pass through the outer portions of the breathing zone along with the excess test chemical. However, they further stated that this is highly dependent on the operating static pressure, in this case -0.05" H_20, which is very low. Based on this low static pressure, only a minimal leakage will take place, and this will have minimal effect on the exposure concentration presented in the breathing zone of the animal.* *This rationale is considered acceptable*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by CO derived from prefilled cylinders diluted with clean air to attain the target concentrations*

Number of air changes per hour	*Average flow rate through the nose-only exposure unit was 6.0 L/min*
Equilibration time (t95)	*Insufficient information to calculate t95. However, Sweeney et al. (2016) state that the t95 is 10.5 s.*
Start of exposure relative to equilibration	*Not specified*
Actual concentration measurement	*Continuous measurements with a Nicolet 380 Fourier Transform Infrared Spectrometer (FT-IR). The FT-IR sampled from a total system flow of 6.5 L/min at the inlet to the nose-only exposure unit at a flow rate of approximately 0.5 L/min*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***A*** *Well-performed study, including multiple exposure durations and exposure concentrations.* *Although the observation period of 24 h is quite short, in view of the mechanism of action of CO, the fact that 94% of the animals in this study died during exposure, and the data of Lapin (1981) show that mortality occurs during exposure or shortly thereafter (i.e. within one day), this is considered acceptable.*

* Sweeney et al. (2016) considered it adequate to limit the postexposure observation of exposed rats to 24 h rather than the guideline duration of 14 d. As support for their decision they stated: "*As noted by Lapin (1981) and Levin et al. (1987), deaths due to acute exposure of rats to CO typically occurred during exposure or shortly thereafter (e.g. within minutes), likely due to the rapid clearance of CO (i.e., blood half-life of 23 min, Andersen et al., 1991)*". They further stated: "*In the course of the study, no deaths occurred in the 1 h – 24 h postexposure window, confirming the adequacy of the observation protocol.*" and "*Among the 600 rats exposed, 51% (306) died during or within 1 h of exposure. Of those deaths, 94% were during exposure. No deaths occurred during the 1 h -24 h postexposure period*."

** Personal communication Sweeney *et al*. (d.d. May 2017)

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	10314	N/A	10	2/10
Rat	10999	N/A	10	2/10
Rat	11849	N/A	10	2/10
Rat	12236	N/A	10	5/10
Rat	12809	N/A	10	9/10
Rat	13462	N/A	10	8/10
Rat	6030	N/A	20	2/10
Rat	7455	N/A	20	3/10
Rat	7916	N/A	20	6/10

Rat	8382	N/A	20	5/10
Rat	9021	N/A	20	9/10
Rat	3851	N/A	40	2/8
Rat	4329	N/A	40	3/10
Rat	4891	N/A	40	4/10
Rat	4958	N/A	40	1/10
Rat	5240	N/A	40	4/6
Rat	5270	N/A	40	3/10
Rat	5613	N/A	40	7/10
Rat	5954	N/A	40	7/8
Rat	3182	N/A	60	0/10
Rat	3507	N/A	60	3/10
Rat	3743	N/A	60	5/10
Rat	4216	N/A	60	4/10
Rat	5051	N/A	60	6/10
Rat	5853	N/A	60	8/10
Rat	7936	N/A	60	10/10

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

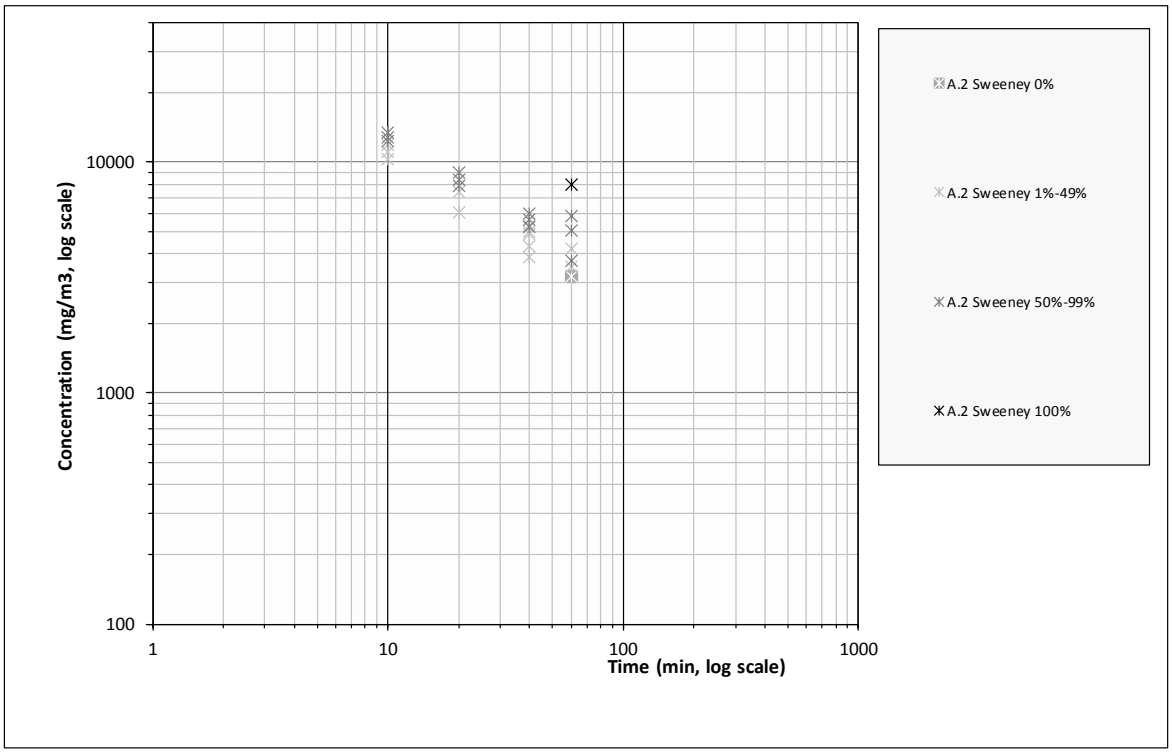
$Pr = a + b \times lnC + c \times lnt$

with C for concentration in mg/m^3, t for time in minutes.

Probit function	Species	a	b	c	n-value
	Rat	-36.5	3.87	2.24	1.73 (1.54-1.92)

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
10	11910 (11020 - 12890)
30	6311 (6037 - 6634)
60	4227 (3948 - 4563)

A graphical overview of the data is presented below. Each concentration-time combination (with 6-10 male animals) represents one point in the plot.


Concentration (mg/m3, log scale)
10000
1000
100
1
10
100
1000
Time (min, log scale)
A.2 Sweeney 0%
A.2 Sweeney 1%-49%
A.2 Sweeney 50%-99%
A.2 Sweeney 100%

1

Study ID: B1.1

Author, year: Levin et al., 1987
Substance: carbon monoxide
Species, strain, sex: rat, Fischer 344, male
Number/sex/conc. group: 6 males/group
Age and weight: age not specified, weight 200-300 g
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to OECD 403 guideline(s)	*No statement of compliance with OECD guideline 403 provided*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*Air or nitrogen **
Whole body / nose-only (incl. head/nose-only) exposure	*Head-only*
Type of restrainer	*Animals were placed in restrainers that were then inserted into six portholes, located along the front of the exposure chamber, such that only the rats' heads were exposed. No further detail on type of restrainer presented*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by mixing CO with nitrogen and/or air in the animal exposure chamber, and a fan in the chamber provided adequate mixing of the gases*
Number of air changes per hour	*No information on number of air changes per hour* *A 200 L animal exposure chamber was used*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*Animals were inserted into the chamber when the desired concentrations were reached*
Actual concentration measurement	*CO was measured continuously by nondispersive infrared spectroscopy throughout the exposures and recorded by an on-line computer every 15 s*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***B1*** *Well-performed study. Limited to one exposure duration*

* Dependent on the commercially supplied CO (i.e. 1.2% CO in air, 3.2% in nitrogen, and 100% CO)

Levin et al. (1987) studied the toxicological interaction of CO and CO_2; not only exposure to CO but also exposure to CO_2 and combined exposure to CO and CO_2 were

included in their study. For current probit evaluation, only the exposure groups with single CO exposure were selected.
Further, they included two types of exposure in this study, i.e. a square-wave exposure and a gradual exposure. In the square-wave exposure, animals were placed in the chamber upon reaching the desired concentration. In the gradual exposure, gas was introduced in the chamber during a 5-min period. Both types of exposure are included in the initial evaluation of this study.
It is noted that part of the exposed animals were cannulated in order to determine a.o. blood HbCO-levels during and following the exposure.

With respect to the time of death, the authors stated: “All deaths except one occurred during the 30-min exposure period; the exception was a death noted at 40s postexposure.”

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Square-wave exposure				
Rat	1470		30	0/6
Rat	2520		30	0/5
Rat	4330		30	1/6
Rat	4570		30	5/6
Rat	4610		30	3/6
Rat	4860		30	5/6
Rat	5030		30	4/6
Rat	5990		30	6/6
Gradual exposure				
Rat	3280		30	0/6
Rat	3620		30	1/6
Rat	3720		30	0/6
Rat	4080		30	0/6
Rat	4960		30	3/6
Rat	5740		30	5/6

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

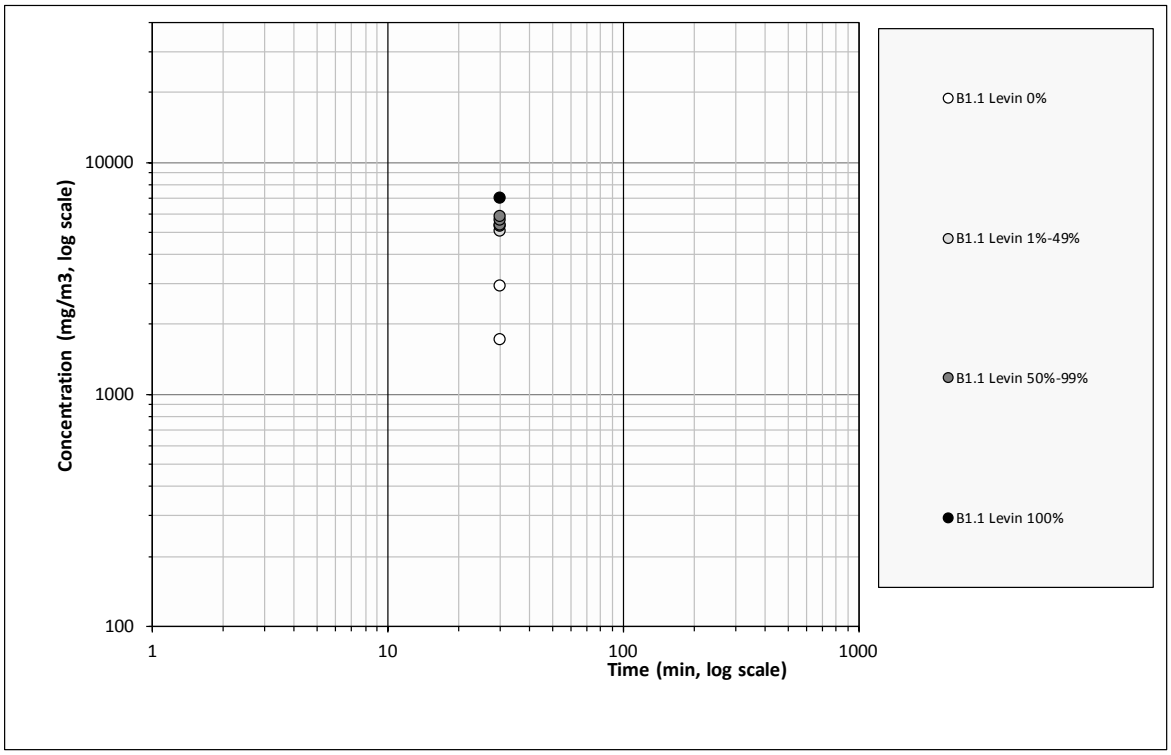
with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
Square-wave exposure	Rat	-73.9	9.20	-
Gradual exposure	Rat	-44.9	5.77	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. *Square-wave exposure*	LC_{50} (mg/m^3) 95%-C.I. *Gradual exposure*	LC_{50} (mg/m^3) 95%-C.I. *Combined analysis*
30	5283 (4133 - 5589)	5785 (5236 - 6863)	5401 (5106 - 5726)

Although the difference in LC_{50} values is minimal, the square-wave exposure resulted in slightly lower 30-min LC_{50} value. As in this exposure scenario the animals were exposed to the desired concentration during the complete exposure period, the results of the analysis of these data were used for human probit derivation.

A graphical overview of the data is presented below. Each concentration-time combination (with 5-6 male animals) represents one point in the plot.



Study ID: C.1

Author, year: Kishitani and Nakamura (1978)
Substance: carbon monoxide
Species, strain, sex: mouse, dd strain, males
Number/sex/conc. group: 3-10
Age and weight: age not specified, weight 20 g
Observation period: one week

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*GLP did not exist at the time*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*NA*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*CO in amounts for adjusting their concentrations to the required levels were taken from cylinders by syringes and introduced in the chamber*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Insufficient information to calculate*
Start of exposure relative to equilibration	*After adjusting the concentration of gas in the exposure chamber, animals were placed in the chamber from an entrance provide at the top of the chamber*
Actual concentration measurement	*Gas concentrations inside the exposure chamber were measured by CO_2 infrared gas analyser. However, the concentrations presented are probably target concentrations*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*NA*
Assessment of Reliability	***C*** *Study limited to one exposure duration. No analytical exposure concentrations presented*

In this study two exposure scenarios were applied: I) exposure to constant exposure concentration during 15 minutes and II) exposure to rising exposure concentrations during 15 minutes. Below the results of the first exposure scenario are presented.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Target*	Adjusted		Male
				Dead/tested
Mouse	466	NA	15	0/10

	699	NA	15	1/10
	932	NA	15	1/10
	1165	NA	15	2/10
	1398	NA	15	9/10
	1631	NA	15	6/6
	1864	NA	15	3/3
	2097	NA	15	3/3
	2330	NA	15	3/3

* concentrations as presented by the study authors: 0.4-0.6-0.8-1.0-1.2-1.4-1.6-1.8-2.0%

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2016) as

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3

Probit function	Species	A	b	n-value
	Rat	-24.9	4.23	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.	LC_{50} (mg/m^3) Presented by Kishitani and Nakamura
15	1175 (1040-1318)	1235

No C × t probit function could be calculated from these data alone.

Study ID: other C studies

In this section, studies are described which are classified as C. One of the main reasons for classifying these studies as C is that no post-exposure observation period was included; in most studies animals were sacrificed directly after exposure in order to be able to determine blood HbCO-levels. The data of Lapin (1981) show that mortality occurs during exposure or shortly thereafter (i.e. within one day). Data of Sweeney et al. (2016), though only including a post-exposure observation period of 24 h, support this as 94% of the animals in their study died during exposure and 6% died within one hour after exposure.
Studies without any observation period at all are therefore considered not reliable, as the true mortality incidence could not be ascertained in these studies.

Chang *et al.* (1981) (as cited in ERPG; article written in Chinese) studied the effect of environmental temperature on carbon monoxide induced mortality. The 60-min LC_{50} in mice was reported to be 2295 ppm (2674 mg/m^3) at 25°C and was 60 ppm (70 mg/m^3) at 36°C.

Darmer *et al*. (1972) exposed male Sprague-Dawley rats (whole-body) to carbon monoxide. A post-exposure observation period was not included. The chamber concentration was continuously monitored. An LC_{50} value was reported for exposure duration of 5 minutes (14200 ppm, equivalent to 16543 mg/m^3).

Demaria Pesce *et al.* (1987) investigated in OF_1 mice (male/female) the effect of age on the survival of carbon monoxide induced intoxications. The chamber was flushed with a mixture of 5.0% carbon monoxide, 21% oxygen and 74% nitrogen. Soda lime was used to maintain a low carbon dioxide level (0.05-0.40%). Animals were exposed until it appeared that 50% of all animals had ceased breathing. Two exposure scenarios were applied: 1) male/female mice aged 31 day and 184 day exposed for 76 minutes with a final *p*CO of 5.5 Torr (7200 ppm as cited in AEGL (8388 mg/m^3)) with survival percentages of 36% and 57% for 31-day males and females respectively, and 22 and 63% for 184-day old males and females respectively, 2) male/female mice aged 34 days, 85 days, 230 days and 387 days exposed for 146 minutes with a final *p*CO of 4.4 Torr (5800 ppm as cited in AEGL (6757 mg/m^3)) for 146 minutes, with survival percentages of 40% and 48% for 34-day old males and females, 27% and 67% for 85-day old males and females, 24% for 230-day old males, and 27 and 56% for 387-day old males and females. Except for the about 1-month-old mice, male mice showed a significantly lower survival than females. Survival was not significantly influenced by age.

Hartzell *et al*. (1985) exposed rats head-only to carbon monoxide. Limited details on the experimental set-up were provided. Animals were probably exposed until incapacitation and death occurred, and a post-exposure observation period was not included. The exposure period in order to induce death was reported for various exposure concentrations (3000 – 10000 ppm, i.e. 3495 – 11650 mg/m^3). LC_{50} values of 8636 and 5207 ppm (10061 and 6066 mg/m^3) were reported for 15 and 30 minutes exposure durations, respectively.

Herpol *et al*. (2007) exposed male/female Wistar rats to various concentrations of carbon monoxide (ranging from 750 to 9750 ppm (874-11359 mg/m^3)) for 30 minutes. A post-exposure observation period was not included. An LC_{50} value of 5607 ppm (6532 mg/m^3) was reported (as cited in AEGL). Concentrations were grouped and the mortality was only presented for these groups (and not for the individual exposure concentrations).

Hilado *et al*. (1978) exposed mice (Swiss-Webster and ICR) whole-body to carbon monoxide for 30 minutes. A post-exposure observation period was not included. The authors reported 30-min LC_{50} values of 3570 ppm (4159 mg/m^3) for Swiss-Webster mice and 8000 ppm (9320 mg/m^3) for ICR mice.

Kimmerle (1973) reported LC_{50} values of 8800, 6100, 5500, 4670 ppm (10252, 7107, 6408, 5441 mg/m^3) for rats exposed for 10, 20, 30, 60 minutes respectively. No details were available on the experimental setup. A reference was made to unpublished results (1972-1973) of Bayer AG. The original report was not available to the Probit Panel, therefore the quality of the study and the reported LC_{50}-values could not be evaluated.

Rose et al. (1970) exposed male Sprague-Dawley rats, male Hartley guinea pigs and male Swiss mouse for 4 hour to carbon monoxide via whole body exposure. A post-exposure observation period was not included. The study comprised of inhalation experiments under normobaric and hyperbaric conditions. Below the lethality data under normobaric conditions are presented. It is noted that the difference in lethality between normobaric and hyperbaric conditions is limited.

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality
			Male
			Dead/tested
Rat	1864	240	1/4
Rat	2097	240	2/4
Rat	2330	240	4/8
Rat	2563	240	11/12
Guinea pig	4660	240	0/8
Guinea pig	5872	240	2/8
Guinea pig	7398	240	5/8
Guinea pig	9297	240	7/8
Mice	2313	240	0/16
Mice	2598	240	1/16
Mice	2744	240	7/32
Mice	3088	240	14/16
Mice	3495	240	15/16

The study authors presented the following 4h-LC_{50} values (95% confidence interval) for normobaric conditions:
Rat: 2070 (1831-2341) mg/m^3
Guinea pig: 6550 (5509-7788) mg/m^3
Mouse: 2800 (2679-2926) mg/m^3

Winston and Roberts (1978) investigated the influence of increasing age on acute lethality induced by carbon monoxide (or hypoxic hypoxia). Mice of various ages (ranging from 2 days to 150 days) were exposed (whole body) to 2000 ppm (2330 mg/m^3) for exposure periods up to 6 hours. It is stated that exposure was terminated when 100% lethality in one age group was achieved. A post-exposure observation period was probably not included.
Mortality occurred in 3 of 37 2-day-old mice, 21 of 32 17-day-old mice, 16 of 20 30-day-old mice, 11 of 17 54-day-old mice, 10 of 20 108-day-old mice, and 6 of 18 150-day-old mice. The animals of the youngest and that of the oldest age group were found to be more resistant to CO. These two groups were also found less susceptible to lethal effects from hypoxic hypoxia when mice were exposed to a reduced oxygen concentration of 7.5%.

Appendix 2 Reference list

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