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Probit function technical support document

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substance name	CAS number
1,2-dichloroethane	107-06-2

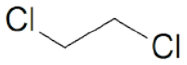
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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/.

Technical support document 1,2-dichloroethane



1. Substance identification

CAS-number:	107-06-2
IUPAC name:	1,2-dichloroethane
Synonyms:	ethylene dichloride, ethylene chloride, glycol dichloride
Molecular formula:	$C_2H_2Cl_2$
Molecular weight:	99.0 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	84°C (at 101.3 kPa)
Vapour pressure:	8.7 kPa (at 20°C)
Saturated vapour conc:	87000 ppm = 358 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.243 ppm (at 20°C and 101.3 kPa)
	1 ppm = 4.118 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H302-315-319-335-350

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

Acute effects: The main target organs and tissues for inhalation exposure to 1,2-dichloroethane are the central nervous system and the lungs. The main health endpoints are related to the CNS depression of the substance resulting in vertigo, ataxia, and narcosis. 1,2-Dichloroethane may also cause irritation in the lungs. Symptoms of high exposure include laboured breathing, narcosis and loss of consciousness. Damage occurs to the lungs, which may become congested or oedematous. Furthermore, liver and kidney damage (degeneration and necrosis) have been reported to occur in animals and humans. Acute lethality results from the damage to the lungs, depression and paralysis of central nervous system function and cardiovascular collapse. Injury to the kidney is considered responsible for the delayed deaths.

Long-term effects: Long-term effects from acute exposure may result from the damage to kidney and liver. After chronic exposure similar effects may occur.

3. Human toxicity data

No informative reports on health effects in humans following acute inhalation exposure were identified. Such reports are considered informative if both health effects as well as the exposure have been documented in sufficient detail.

Sayers *et al*. (1930) reported that two men exposed two minutes to 0.12% of the vapours in air (1200 ppm corresponding to 4942 mg/m^3) experienced no subjective or objective symptoms, except that the odour was very noticeable at this concentration.

4. Animal acute toxicity data

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

[1] ERPG 2014, Heppel et al 1945, Spencer et al 1951

1. ERPG document and EU RAR and reference database for substance, covering references before and including 1995. An AEGL TSD was not available.
2. An additional search covering publications from 1980 onwards was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, 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 focusing on acute exposure are described in Appendix 1. A total of 8 studies was identified -with 14 datasets for 7 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, two datasets were assigned status B1, one dataset was assigned status B2 and five studies (11 datasets) were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies were identified in which sensory irritation was studied.

5. Probit functions from individual studies

All available acute lethality data on 1,2-dichloroethane are provided in Figure 1.

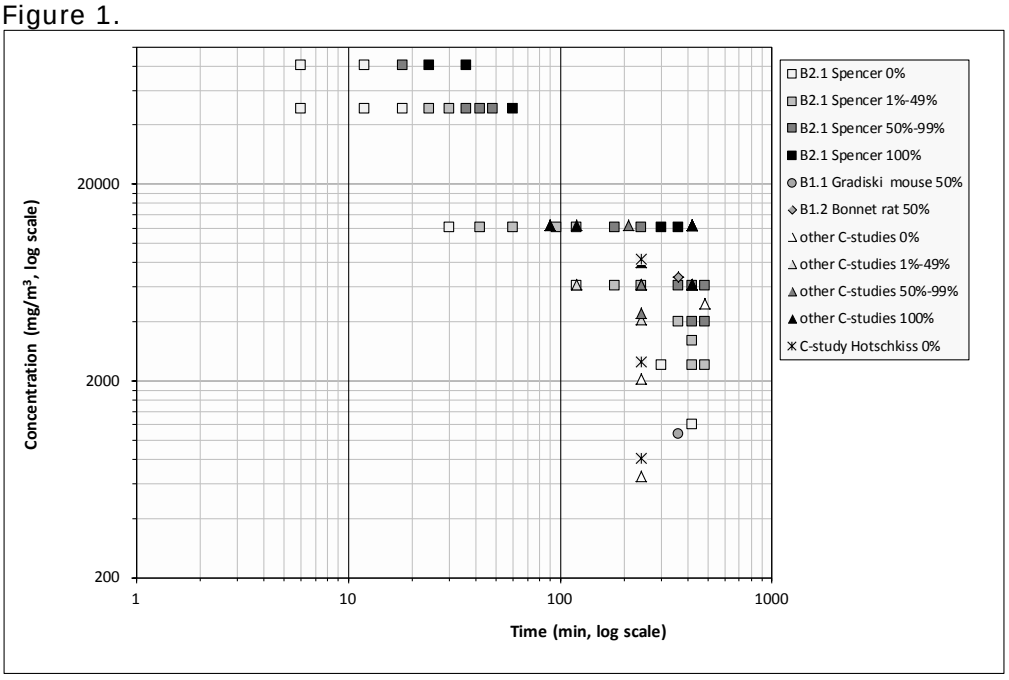


Figure 1 *All available acute lethality data for 1,2-dichloroethane*

The data that were selected for primary analysis of the animal probit function are presented in Table 1 and Figure 2.

It was not possible to derive a probit function for 1,2-dichloroethane based on studies with A quality. Therefore, the probit function was derived using data from studies with B quality listed in the table below.

A probit function has been calculated and reported in Appendix 1 for each of the reported studies. The results of the calculations are presented in the table below.

Table 1 *Data selected for derivation of the animal probit function of 1,2-dichloroethane*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 30 minutes (mg/m^3) 95% C.I.	LC_{50}, 360 minutes (mg/m^3) 95% C.I.
B1.1	Mouse	-	-	1079 (1034 - 1124)
B1.2	Rat	-	-	6778 (6494 - 7281)
B2.1	Rat	-41.1 + 3.30×lnC + 3.06×lnt	51260 (44150 - 60320) n-value: 1.08 (0.98 – 1.18)	5116 (4377 - 6048)

The data of the mouse study B1.1 and rat studies B1.1 and B2.1 are presented graphically below.

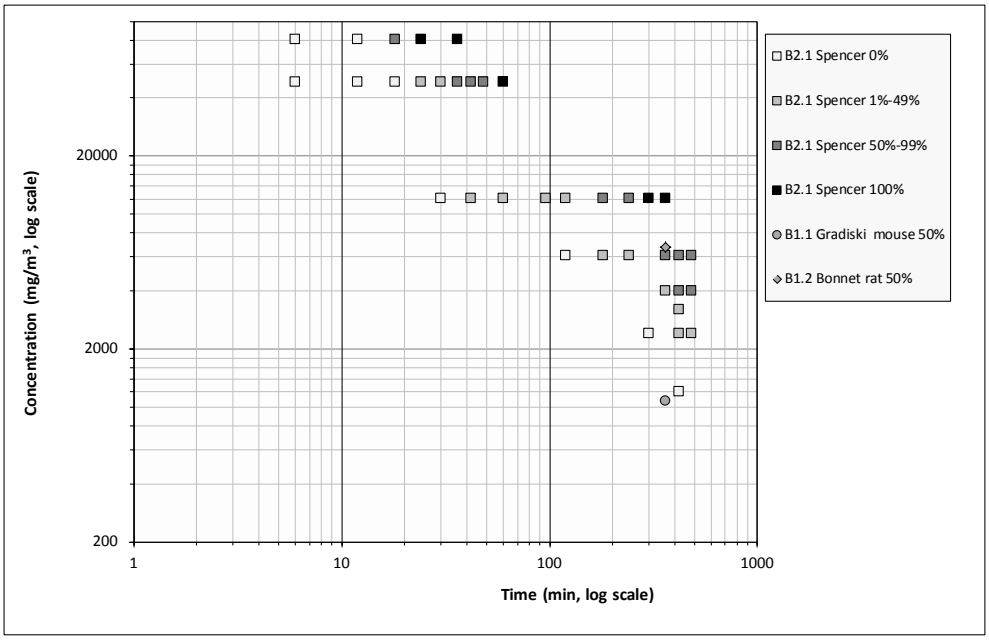


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of 1,2-dichloroethane*

Mice appear to be more susceptible to the acute effects of 1,2-dichloroethane exposure than rats.

The studies B1.1 (Gradiski *et al*., 1978) and B1.2 (Bonnet *et al*., 1980) were limited to an exposure duration of 6h. Study B2.1 (Spencer *et al*., 1951) included exposure durations of between 6 to 480 minutes. According to the methodology (RIVM-report 2015-0102), preference is given to animal LC_{50} value for an exposure duration of between 10 and 240 minutes.
The B2.1 rat-study of Spencer *et al*. (1951) was therefore given preference over the two available B1 studies (B1.1: Gradiski *et al*., 1978; B1.2: Bonnet *et al*., 1980). Moreover, this B2.1 study included multiple concentration-time combinations.

The final data for calculating the animal probit function contains 1 dataset from 1 study and includes data from 1 animal species.

Table 2 *Data selected for the final analysis for the derivation of the animal probit function of 1,2-dichloroethane*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 30 minutes (mg/m^3) 95% C.I.
B2.1	Rat	-41.1 + 3.30×lnC + 3.06×lnt	51260 (44150 - 60320) n-value: 1.08 (0.98 – 1.18)

The data of the selected dataset is presented graphically below.

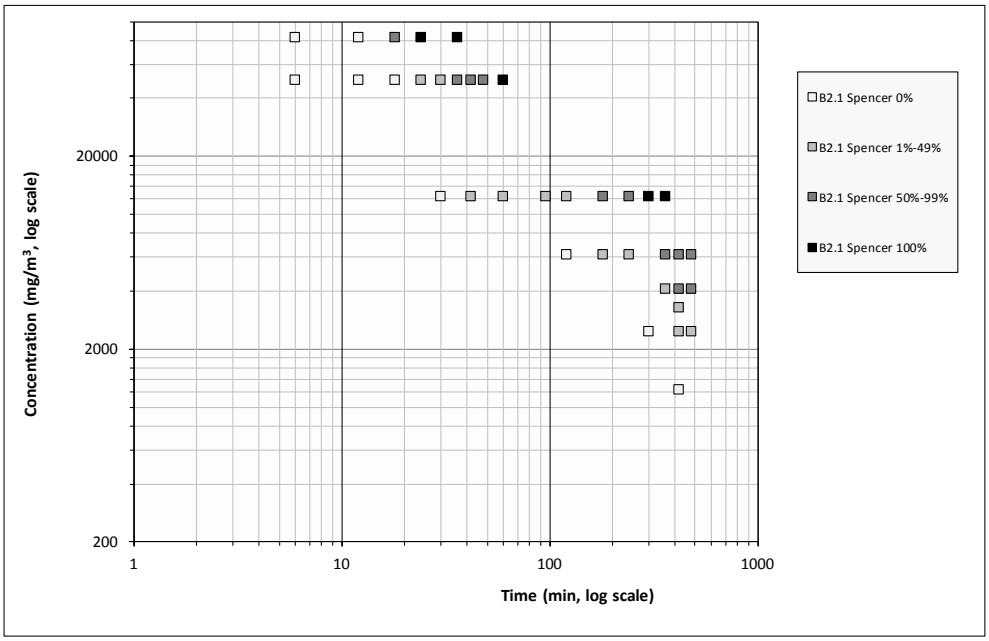


Figure 3 *Final data selected for the derivation of the animal probit function of 1,2-dichloroethane*

6. Derivation of the human probit function

To derive the human probit function, the results from study B2.1 (Spencer *et al*., 1951) have been used to derive a point of departure. The reason was that the study was well-performed, included several concentration-time combinations, and observed mortality in the range from 0 to 100% mortality. Further, it was noted that the results of this

study were supported by the rat study of Bonnet *et al*. (1980) with reported 6h LC_{50} of 6778 (6494 – 7281) mg/m^3. Especially when focussing solely on the 6h time-point, it is noticed that the rat data of Bonnet et al. (1980) fit very well in the 6h rat data of Spencer et al. (1951).
Further, when focusing solely on the 4h time-point, it is noticed that the data of Hotschkiss et al. (2010) fit very well in the 4h data of Spencer et al. (1951). The table below presents the lethality data for an exposure period of 4h derived from Spencer et al. (1951) and Hotschkiss et al. (2010). Also the data of Heppel et al. (1945; C-study) are incuded:

Concentration (mg/m^3)	**Lethality (%)**	**Reference**
6100	5	Spencer et al. (1951)
6177	0	Heppel et al. (1945)
8355	0	Hotchkiss et al. (2010)
12100	95	Spencer et al. (1951)
12354*	94	Heppel et al. (1945)

*: 3.5-hour exposure

Based on these 4h data, the following is considered:

- The range in concentration between approximately 0% and 100% lethality is small.
- Based on the Spencer *et al*. and Heppel *et al*. data the 4h LC_{50} will be somewhere between 6000 and 12000 mg/m^3. Considering the small range between 0% and 100% lethality, this is not refuted by the Hotschkiss *et al*. observations: it cannot be ruled out that lethality might have started to occur at slightly higher concentrations in the Hotschkiss *et al*. study, if these have been tested.
- Therefore, the Hotschkiss *et al*. datapoint is in line with 4h observations from Spencer *et al*. and Heppel *et al*. and does not disprove these data.
- The fact that the probit function from the Spencer *et al*. study results in a 4h LC_{50} closer to 6100 than to 12100 mg/m^3 is also determined by data points for other durations; Hotschkiss *et al*. does not provide information for other exposure durations.

Based on this, it is considered that using the data of Spencer *et al*. (1951) will not result in an overestimation of the acute toxicity of 1,2-dichloroethane.

As a point of departure for deriving the human probit function, the 30 min LC_{50} value of 52100 mg/m^3 for the rat from the study B2.1 (Spencer *et al*., 1951) was taken. The human equivalent LC_{50} was calculated by applying the following assessment factors:

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	Default.

Nominal concentration	1	Target concentrations presented. However, evidence available that the target concentrations are likely to reflect the actual concentrations accurately: - the method of test atmosphere generation is not expected to result in large differences between target and nominal concentrations - the substance has a high vapour pressure, and target concentrations are <25% of the saturated vapour concentration - > 90% of nominal concentration was found during combustion analysis Therefore, a factor of 1 was justified.
Adequacy of database:	1	One B2 study available, with multiple concentration-time combinations, supported by a B1-study.

The estimated human equivalent 30-minute LC_{50} value is 52100 / 3 = **17367 mg/m^3**.

The experimentally determined n-value was **1.08** (study B2.1, Spencer *et al.* (1951)). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.85**.

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): $5 = a + 1.85 \times \ln (17367^{1.08} \times 30)$ resulting in the a-value of **–20.8**.

$Pr = -20.8 + 1.85 \times \ln (C^{1.08} \times t)$ 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 one rat study with B2 quality, including 37 concentration-time combinations, exposure durations varying from 6 to 480 minutes, and response rates in the range from 0 to 100% mortality.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 2852 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 1949 mg/m^3.

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
1% lethality, this probit	5418	2852
0.1% lethality, this probit	3704	1949
AEGL-3	-	-
ERPG-3 (2014)	-	1235
LBW (2015)	-	2000

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

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: Gradiski *et al*., 1978
Substance: 1,2-dichloroethane
Species, strain, sex: Mouse, OF1, female
Number/sex/conc. group: 20/group
Age and weight: age not specified, 20±1 g weight
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	Whole body
Type of restrainer	NA
Pressure distribution.	Negative pressure
Homogeneity of test atmosphere in breathing zone of animals	The test substance is mixed with clean air before entering the inhalation chamber
Number of air changes per hour	An air flow of 10 m^3/h was applied. The volume of the inhalation chamber was 170 L. The number of air changes per hour was 60.
Equilibration time (t95)	0.05 min
Start of exposure relative to equilibration	Probably after complete equilibration. The authors stated that the animals were placed in the inhalation chamber not before attaining the desired concentration.
Actual concentration measurement	Actual concentration was analysed continuously using gas chromatography.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	NA
Assessment of Reliability	**B1** Well performed study. Limited to one exposure duration.

Results

Lethality data were presented by the Gradiski *et al*. in a graph as presented below. In addition to 1,2-dichloroethane, other chlorinated aliphatic hydrocarbons were tested.

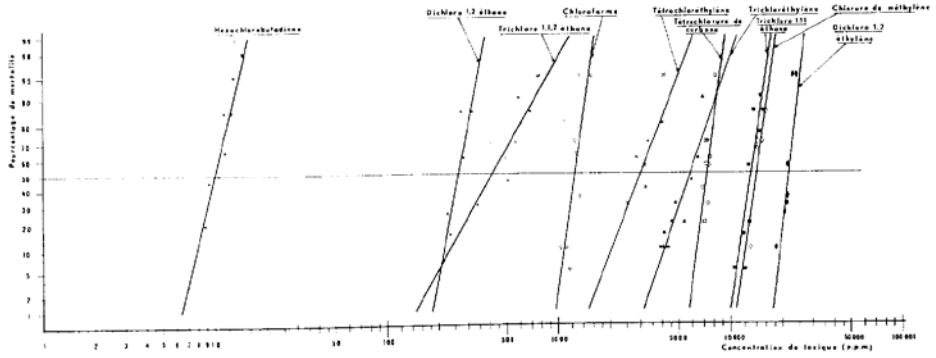


Fig. 3. — Détermination des concentrations létales 50 (p.p.m.) chez la souris des solvants aliphatiques chlorés.

Duration (minutes)	LC_{50} (mg/m^3) 95%-C.I. Reported by Gradiski *et al*. (1978)
360	1079 (1034 - 1124)

The individual animal lethality data were not available.
No C × t probit function could be calculated from these data alone.

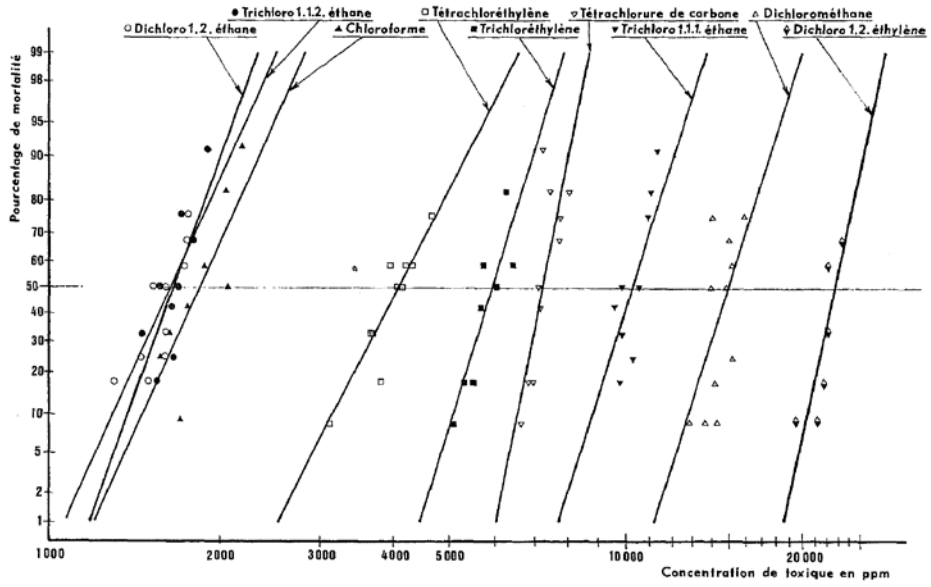
Study ID: B1.2
Author, year: Bonnet *et al*., 1980
Substance: 1,2-dichloroethane
Species, strain, sex: rat, Sprague-Dawley, male
Number/sex/conc. group: 12/group
Age and weight: age not specified, 130-200 g
Observation period: 14 days

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	Whole body
Type of restrainer	NA
Pressure distribution.	Negative pressure
Homogeneity of test atmosphere in breathing zone of animals	The test substance is mixed with clean air before entering the inhalation chamber
Number of air changes per hour	An air flow of 12 m^3/h was applied. No information on the volume of the inhalation chamber and air changes per hour
Equilibration time (t95)	Insufficient information to calculate t95
Start of exposure relative to equilibration	Probably after complete equilibration. The authors stated that the animals were placed in the inhalation chamber not before attaining the desired concentration.
Actual concentration measurement	Actual concentration was analysed continuously using gas chromatography.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	NA
Assessment of Reliability	**B1** Well performed study. Limited to one exposure duration.

Results

Lethality data were presented by Bonnet *et al*. in a graph as presented below. In addition to 1,2-dichloroethane, other chlorinated aliphatic hydrocarbons were tested.



Duration (minutes)	LC_{50} (mg/m^3) 95%-C.I. Reported by Bonnet *et al.* (1980)
360	6778 (6494 - 7281)

The individual animal lethality data were not available.
No C × t probit function could be calculated from these data alone.

Study ID: B2.1
Author, year: Spencer et al., 1951
Substance: 1,2-dichloroethane
Species, strain, sex: Albino rats, Wistar-derived, males and females
Number/sex/concentration group: 10-54 animals/group
Age and weight: not specified
Observation period: 14 to 21 days, or, until it was certain that they had fully recovered from the effects of the exposure as judged by appearance, behaviour, and recovery of body weight.

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 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	N/A
Pressure distribution.	No information
Homogeneity of test atmosphere in breathing zone of animals	The test atmosphere was generated by introducing a metered amount of 1,2-dichloroethane liquid into a tube through which air entered the 160-L inhalation chamber. Heat was applied at the point of vaporization as needed to complete volatilization.
Number of air changes per hour	Air flow of 15-30 L/min in a 160 L chamber. Approximately 5.6 to 11.3 air changes per hour.
Equilibration time (t95)	16-32 min
Start of exposure relative to equilibration	Information in publication is unclear. However the exposure probably started after concentration build-up based on the following: “The rats were introduced in groups of 5 to 12 within a period of 15 seconds and were removed through the chamber door within a similar interval of time at the end of exposure. It was shown by a continuously recording analyser that the animals were introduced without appreciable alteration of the vapour concentration.”

Actual concentration measurement	All vapour concentrations were repeatedly checked by combustion analysis. The authors stated that results were better than 90% of the calculated theoretical (i.e. nominal) concentrations. Actual and nominal concentrations were not presented by the authors. Based on type of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the nominal concentrations are quite similar to the target concentrations.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A

Assessment of Reliability	**B2** The study included many C × t combinations. However, only target concentrations were reported and therefore the study was not given the A-status. Although only target concentrations were reported, evidence is available that the target concentrations are likely to reflect the actual concentrations accurately: - Based on the method of test atmosphere generation (evaporation, introduction of a metered amount of the substance; see above), it is assumed that the nominal concentrations are quite similar to the target concentrations. - Further, the authors state that the analytical concentrations were better than 90% of the nominal concentration. - 1,2-Dichloroethane has a high vapour pressure. For a vapour, it is expected that the nominal concentration will be close to the actual concentration unless condensation has occurred. Calculations of the ratio of the highest target concentration vs. saturated vapour concentration (SVC), which is below 0.25 (i.e. $81.0 \times 10^3/360000 = 0.23$), further confirms the statement of the authors. Based on all this, the confidence in the results of the study is high, however an A status could not be assigned since actual concentrations were not reported, consequently the study is assigned the B2-status.

Additional remark: The authors presented information on the time of death as follows: “Death of rats tended to occur at three different time intervals and in such as manner as to suggest three separate toxic actions of fatal degree. At 20000 ppm (81.0×10^3 mg/m^3) deaths occurred in deep anesthesia during the period of exposure, undoubtedly due to depression and paralysis of function of the central nervous system. At all vapour concentrations a large proportion of the rats died rather suddenly and quietly a few hours after being removed from the chamber, showing marked cyanosis, reduced body temperature, stupor or coma, and failing respiration. The character of this response and its sudden development often after apparent full recovery suggest “shock” or cardiovascular

collapse. All other deaths occurred over a period of two to seven days with progressive loss of weight and other evidence of toxic effects. These deaths appeared to be the result of injury to the kidney."

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Target	Adjusted		Male+female*
				Dead/tested
Rat	81.0×10^3	NA	6	0/10
	81.0×10^3	NA	12	0/20
	81.0×10^3	NA	18	16/20
	81.0×10^3	NA	24	20/20
	81.0×10^3	NA	36	10/10
	48.6×10^3	NA	6	0/10
	48.6×10^3	NA	12	0/41
	48.6×10^3	NA	18	0/52
	48.6×10^3	NA	24	4/41
	48.6×10^3	NA	30	22/54
	48.6×10^3	NA	36	30/42
	48.6×10^3	NA	42	38/43
	48.6×10^3	NA	48	30/31
	48.6×10^3	NA	60	22/22
	12.1×10^3	NA	30	0/22
	12.1×10^3	NA	42	1/44
	12.1×10^3	NA	60	1/32
	12.1×10^3	NA	96	1/44
	12.1×10^3	NA	120	6/51
	12.1×10^3	NA	180	24/40
	12.1×10^3	NA	240	38/40
	12.1×10^3	NA	300	22/22
	12.1×10^3	NA	360	20/20
	6.1×10^3	NA	120	0/10
	6.1×10^3	NA	180	1/24
	6.1×10^3	NA	240	2/41
	6.1×10^3	NA	360	7/10
	6.1×10^3	NA	420	24/30
	6.1×10^3	NA	480	7/10
	4.0×10^3	NA	360	5/32
	4.0×10^3	NA	420	17/31
	4.0×10^3	NA	480	20/32
	3.2×10^3	NA	420	10/30
	2.4×10^3	NA	300	0/20
	2.4×10^3	NA	420	3/33
	2.4×10^3	NA	480	4/20
	1.2×10^3	NA	420	0/20

* no information on the number of animals per sex available

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, 2015) as

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

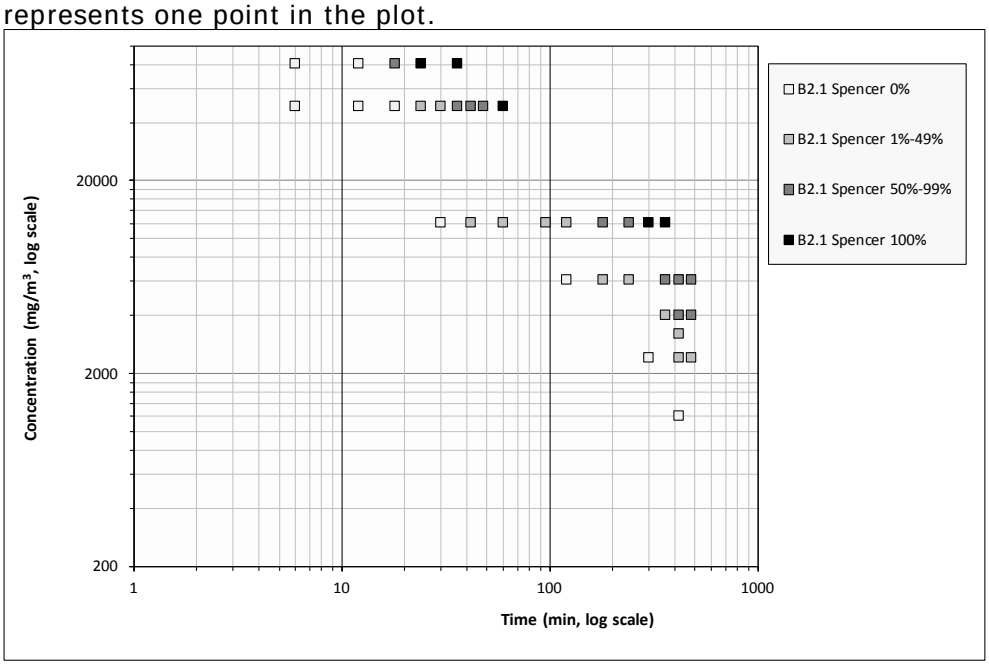
with C for concentration in mg/m^3, t for time in minutes and S for sex (0 = female, 1 = male).

Probit function	Species	a	b	c	d	n-value
	Rat	-41.1	3.30	3.06	-	1.08 (0.98-1.18)

Duration (minutes)	LC_{50} (mg/m^3) 95%-C.I. Male and female*
10	142000 (112600 - 181600)
30	51260 (44150 - 60320)
60	26950 (24070 – 30570)

* no information on the number of animals per sex available

A graphical overview of the data is presented below. Each concentration-time combination (with 10-52 animals (males and females combined)) represents one point in the plot.



Study ID: 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 the short post-exposure observation periods. Based on information on time of deaths for study B2.1 (Spencer et al., 1951), deaths are expected to still occur on day 7 post-exposure.

Francovitch *et al.* (1986) exposed male CD-1 Swiss mice to 1,2-dichloroethane (1000, 1250 and 1500 ppm, corresponding to 4118, 5148 and 6177 mg/m^3) via head-only inhalation exposure for 4 hours following a 10 min equilibration period. Exposure to 1,2-dichloroethane was preceded by SKF 525A, phenobarbital, or 3-methylcholanthrene. A maximum post-exposure observation period of maximal 48h was included, which is considered not sufficient to cover for possible delayed deaths. Control mice received i.p. injection with the appropriate vehicle (0.9% saline or corn oil) in a volume of 10 ml/kg. Individual animal lethality was not presented, and results were mainly read from the graphs. Exposure to 4118 mg/m^3 for 4h resulted in 17% (2/12) mortality and 27% (3/11) mortality at 24h and 48h after exposure. Exposure for 4h to 6177 mg/m^3 resulted in 60% (9/15) mortality at a post-exposure period of 24h.

Heppel *et al.* (1945) exposed rats, mice, and guinea pigs to 6,177 and 12,354 mg/m^3 and rabbits, hogs, cats and raccoons to 6,177 mg/m^3 1,2-dichloroethane for varying time durations (1.5 to 7 hours). A maximum of two different concentrations were tested per animal species. 1,2-Dichloroethane was volatilized at a constant rate by passing a steady flow of air through the liquid; the vapours joined the main air stream entering the chamber. The study was given the C status because only target concentrations were given (although analytical concentration measurements were performed) and, more importantly, a post-exposure observation period of only five days was applied. This period is considered not sufficient to cover for possible delayed deaths. Therefore the true mortality incidence could not be ascertained
The results are shown in the table below.

Species	Target concentration (mg/m^3)	Exposure duration (min)	Lethality
			Responded/exposed
Rat	6,177	240	0/13
	6,177	420	4/20
	12,354	90	0/15
	12,354	210	15/16
	12,354	420	20/20
Mouse	6,177	120	1/23
	6,177	420	20/20
	12,354	120	19/19
	12,354	420	22/22
Guinea pig	6,177	420	6/12
	12,354	420	14/14
Rabbit	12,354	420	12/16

Species	Target concentration (mg/m^3)	Exposure duration (min)	Lethality
			Responded/exposed
Hog	12,354	420	2/2
Cat	12,354	420	0/3
Raccoon	12,354	420	0/2

Hotchkiss *et al.* (2010) exposed Fischer 344 rats via inhalation exposure to 1,2-dichloroethane. The study included three experiments, *i.e.* two acute inhalation toxicity experiments and one acute neurotoxicity experiment. Exposure concentrations were analytically determined and were for the first acute inhalation toxicity experiment 0, 196.4, 607.8 or 2029.0 ppm (corresponding to 0, 809, 2503, 8355 mg/m^3) for an exposure duration of 4h (5 animal/sex/concentration). A second acute inhalation toxicity experiment was performed to assess possible tissue-specific toxicity at lower exposure concentrations and longer exposure duration. In the second experiment exposure concentrations were 0, 52.8, 107.5 or 155.8 ppm (corresponding to 0, 217, 443 or 642 mg/m^3) for an exposure duration of 8h or 52.4 ppm (217 mg/m^3) for an exposure duration of 4h (5 animals/sex/concentration). There was no mortality observed at any exposure concentration. A post-exposure observation period of 24h was included in the acute inhalation toxicity experiments which is considered not sufficient to cover for possible delayed deaths. An acute neurotoxicity experiment was included as well in this study. In this experiment, rats (10 animals/sex/concentration) were exposed to 0, 196.4, 607.8, 2029 ppm, corresponding to 0, 809, 2503, 8355 mg/m^3) for 4h (i.e. similar exposure concentrations and duration as in the first acute inhalation toxicity experiment). Rats were sacrificed 2-weeks following exposure. Mortality was also not observed in this experiment and no probit or LC_{50} could be derived.

Sayers *et al*. (1930) exposed guinea pigs to 1,2-dichloroethane at various concentrations ranging from 2471 to 288260 mg/m^3 for exposure periods up to 8h. A post-exposure observation period of maximum 8 days was included, which is considered not sufficient to cover for possible delayed deaths. One-third of the animals were killed almost immediately (if they did not die before removal), one-third was killed at the end of day 4 of the observation period, and one-third was killed at the end of day 8 of the observation period. Lethality data were semi-quantitatively presented in a graph. Animals exposed to 1200 ppm (4942 mg/m^3) for 8h showed neither signs of toxicity nor deaths. No pathological changes were observed at this level either (as reported in ERPG 2014).

Storer *et al.* (1984) exposed male B6C3F1 mice for 4h via whole body exposure to 0, 158, 499, 1072 and 1946 ppm (corresponding to 651, 2055, 4414, 8014 mg/m^3). A 24h post-exposure observation period was included which is considered not sufficient to cover for possible delayed deaths. The resulting mortality was 0/5, 0/5, 0/5, 4/5 and 5/5.

Appendix 2 Reference list

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