20230316-ethyl chloroformate
-INHOUDELIJK VASTGESTELD

National Institute for Public Health
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Probit function technical support document

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substance name	CAS number
Ethyl chloroformate	**541-41-3**

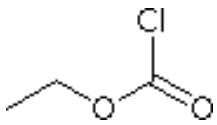
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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 "inhoudelijk vastgesteld" (approved content).

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 ethyl chloroformate

1. Substance identification



CAS-number:	541-41-3
IUPAC name:	Ethyl Chloroformate
Synonyms:	Carbonochloridic acid ethyl ester; Chloroformic acid ethyl ester; ethyl chlorocarbonate; Formic acid, chloro-, ethyl ester;
Molecular formula:	$C_3H_5ClO_2$
Molecular weight:	108.5 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	95°C (at 101.3 kPa)
Vapour pressure:	5.5 kPa (at 20°C)
Saturated vapor conc:	55,000 ppm = 248 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.222 ppm (at 20°C and 101.3 kPa)
	1 ppm = 4.513 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	Human H302-314-330

2. Mechanism of action and toxicological effects following acute exposure

Acute effects: Ethyl chloroformate is corrosive; the health endpoints are all related to this property. The main target organs and tissues for airborne exposure to ethyl chloroformate are the cornea, conjunctiva, skin and respiratory tract. Ethyl chloroformate hydrolyses rapidly in water at room temperature but is not expected to hydrolyse rapidly in ambient air. Symptoms of high exposure are laboured breathing, secretions from nose, mouth and eyes and prostration.
Damage in the upper respiratory system results in mucus secretion and laryngospasm. In addition, pulmonary oedema has been described in animals. The resulting hypoxemia will cause CNS and cardiovascular (myocardial ischemia) effects. Lethality results when the respiratory damage proceeds to inflammation, degeneration and necrosis of affected tissue, atelectasis, emphysema and finally death.
Long-term effects: Chronic exposure produces essentially the same type of health effects. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition, is a possible consequence after single high exposure to ethyl chloroformate. Symptoms occur within minutes to hours after the initial exposure and may persist as non-specific bronchial hyperresponsiveness for months to years.

3. Human toxicity data

No informative reports on human toxicity following acute inhalation exposure were identified in which details about both lethal or non-lethal health effects and the exposure have been documented in sufficient detail.

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 ethyl chloroformate, 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 6 studies were identified -with 6 datasets for 2 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, 1 dataset was assigned status B and 5 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of 1 study was identified in which sensory irritation was studied. In this study the following RD_{50} value was observed:

Table 1 *Sensory irritation data for ethyl chloroformate*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
Swiss-Webster mice	350^{NS}	30	Carpenter 1982

NS: not specified if a plateau in response was reached.

5. Probit functions from individual studies

All available acute lethality data on ethyl chloroformate are displayed in figure 1.

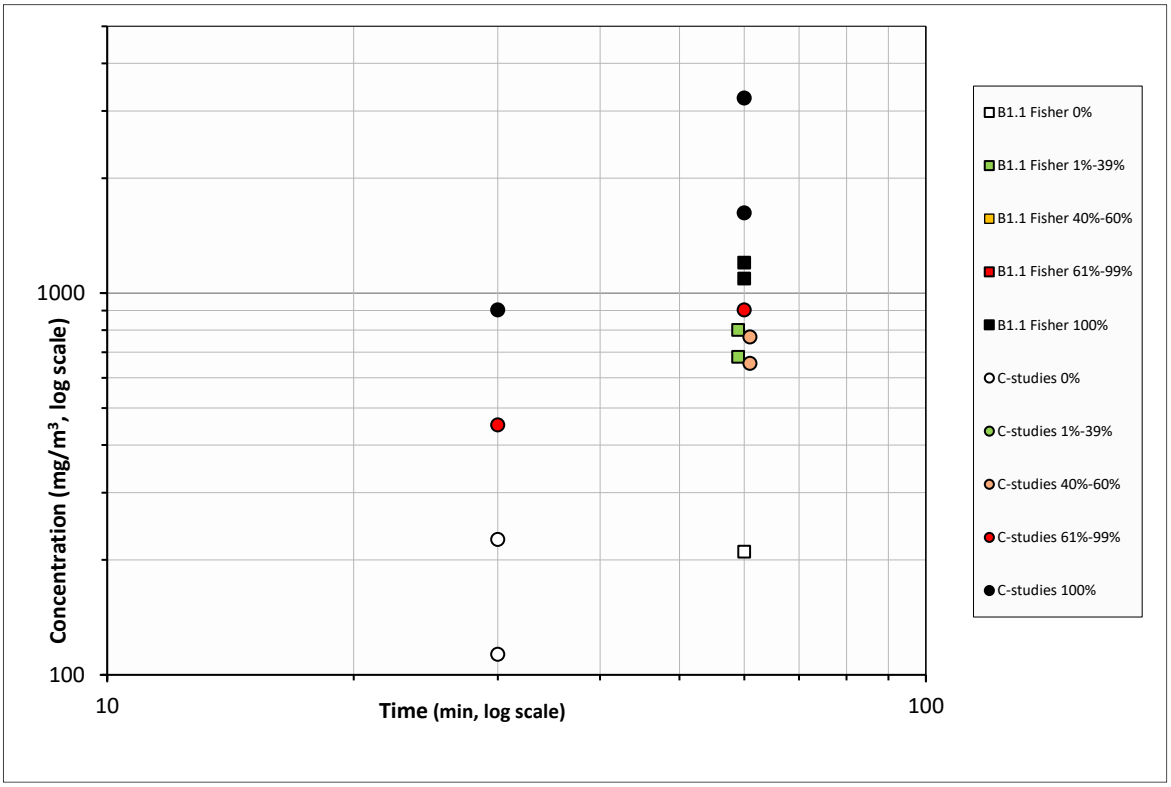


Figure 1 *All available acute lethality data for ethyl chloroformate.*

The data that were selected for initial analysis of the animal probit function are presented in Table 2 and Figure 2. The only B1 study was selected for derivation of the animal probit function for ethyl chloroformate.
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 ethyl chloroformate.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	848 (779 – 949)	*1199*	N/A

The data of the single B1- study with rats is presented graphically below.

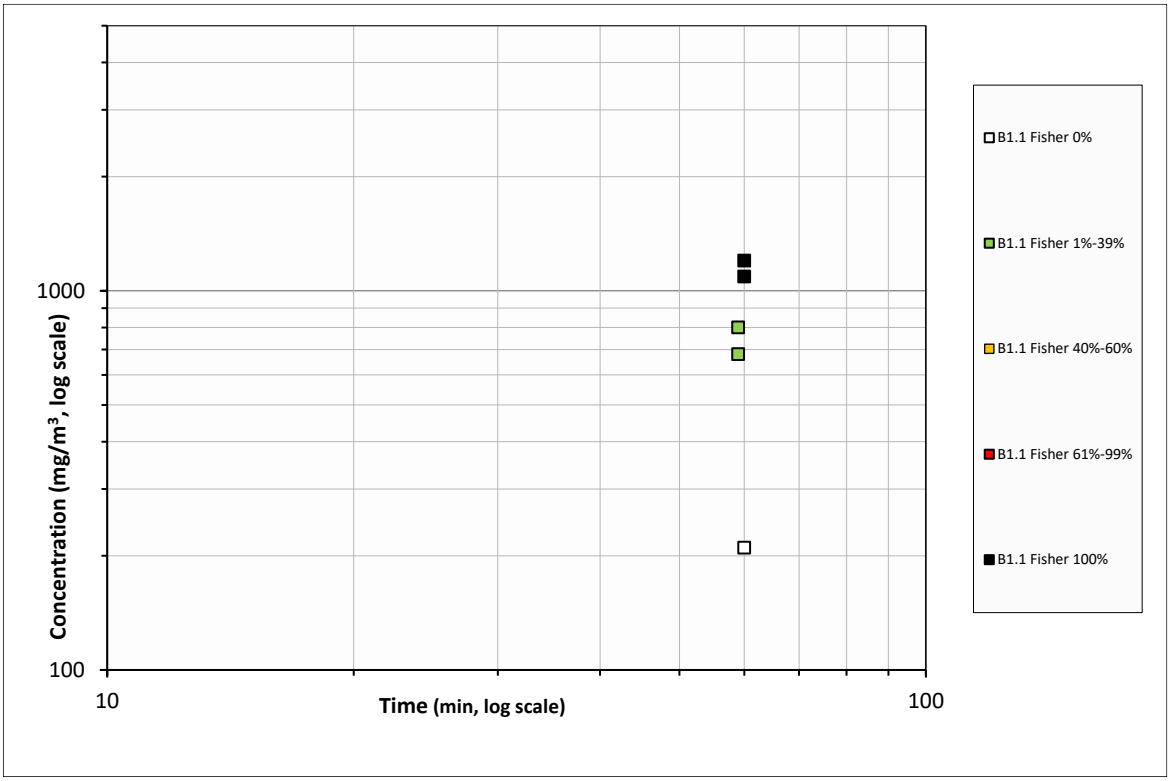


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of ethyl chloroformate.*

Based on criteria outlined in the guideline the data from study B1.1 were selected for the final dataset for the derivation of the animal probit function because this was the only eligible study. The data selected for final analysis of the animal probit function is presented in Table 3 and Figure 3.

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

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	848 (779 – 949)	*1199*	N/A

The data of the selected dataset are presented graphically below.

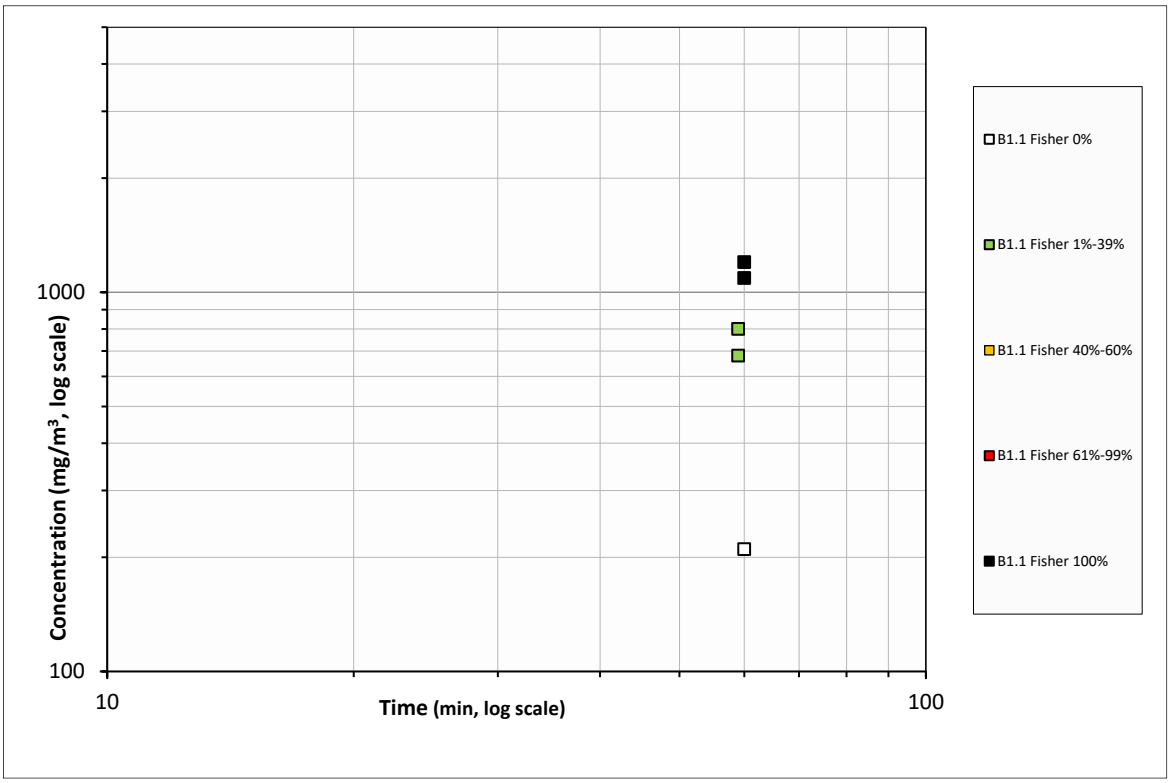


Figure 3 *Final data selected for derivation of the animal probit function of ethyl chloroformate (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from Study B1.1 have been used to derive a point of departure as outlined above, since this was the only eligible study.

The Point of Departure for the human probit function is a 60-minute rat LC_{50} value of 848 mg/m^3 and the default n-value of 2. 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:	3	No reason to deviate from default AF of 3
Nominal concentration	1	In the study, probably analytical concentrations were reported. Tested concentrations are well below 25% SVC.

Adequacy of database:	1	Despite the availability of only one B1-study, the probit is supported by a study with the structurally related compound methyl chloroformate.

The estimated human equivalent 60-minute LC_{50} value is 848 / 3 = **283 mg/m³**.

No reliable experimentally determined n-value was available, so the default n-value of **2.0** was used. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.0**.

The human probit function is then calculated on the human equivalent 60 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1 \times \ln (283^2 \times 60)$ resulting in the a-value of **-10.383**.

Pr = -10.4 + 1 × ln (C^2 × t) with C in mg/m³ and t in min.

The derived human probit function has a scientifically weak basis. The probit function is based on 1 study in the rat with B quality, with 6 groups of 10 animals and lethality ranging from 0-100% (but supported by a study with the structurally related compound methyl chloroformate).

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 61 mg/m³ and the calculated human 60 min LC_1 (Pr = 2.67) is 89 mg/m³.

Table 5 *LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m³)	60 min (mg/m³)
0.1% lethality, this probit	86	61
1% lethality, this probit	126	89
AEGL-3 (2017, final)	27	21
ERPG-3 (2015)		45
LBW (2015)	36	28

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

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: **Fisher 1981**
Substance: ethyl chloroformate
Species, strain, sex: Male and female Fischer 344 (Charles River) rats
Number/sex/conc. group: 5 rats/sex/concentration
Age and weight: 'young adult'; in methyl chloroformate study: 50-60 days at exposure, males 156-204 gr., females 114-149 gr.
Observation period: 10 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*No GLP statement provided. Laboratory quality statement provided*
Study carried out according to OECD 403 guideline(s)	*OECD guideline 403 did not exist at the time. Most OECD 403 criteria appear to be met*
Stability of test compound in test atmosphere	*No mention of aerosol formation / condensation, but unlikely given the atmosphere generation method and concentration range*
Use of vehicle (other than air)	*HEPA filtered air*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body in a 1.3 m^3 Hinner-style chamber*
Type of restrainer	*Whole body exposure, no restrainers*
Pressure distribution	*Not provided in this study's summary, but 1 mm H_2O negative pressure in the methyl chloroformate (MCF) study by the same author*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by evaporation and diluted with air before introduction into the chamber*
Number of air changes per hour	*Not provided in this study's summary, but in excess of 12 air changes/h, typically 21 air changes/h in the MCF study*
Equilibration time (t95)	*t95 estimated to be 9 minutes in the MCF study*
Start of exposure relative to equilibration	*At start of concentration build-up, animals remained inside the chamber until the concentration had returned to zero*
Actual concentration measurement	*Concentrations were monitored using real-time variable pathlength infrared photo-spectrometry. Sampling in the centre of the exposure chamber, after verifying an even (<4% variability) concentration distribution*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*Presence or absence of aerosol not reported*

Assessment of Reliability	***B1*** *Only one exposure duration. Probably well conducted study, only parts of report available*

The full study report was not available. Some assumptions have been made regarding the quality of the study based on the study with methyl chloroformate conducted by the same study director almost at the same time at the same institute.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
Rat	0		60	0/5	0/5
	210		60	0/5	0/5
	680		60	1/5	0/5
	800		60	1/5	1/5
	1090		60	5/5	5/5
	1200		60	5/5	5/5

Probit function

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

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

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	d
Sex as variable	Rat	-50.6	8.21	0.51
Sexes combined	Rat	-48.2	7.89	

The LC_{50} values for both sexes did not differ by more than a factor of 2. This does not support the proposition that sex differences exist in the lethal response. For this reason, the data from both sexes were pooled and analysed to derive the animal probit function.

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. Female	LC_{50} (mg/m^3) 95%-C.I. Combined
60	823 (733 – 957)	858 (771 – 1020)	848 (779 – 949)

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

Study ID: C.1

Author, year: Carpenter 1982

Substance: ethyl chloroformate
Species, strain, sex: male Swiss-Webster mice,
Number/sex/concentration group: 4 / concentration
Age and weight: unspecified
Observation period: unspecified, but at least 20 hours

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*Study was designed as an RD_{50} study, and therefore not compliant with OECD guideline 403*
Stability of test compound in test atmosphere	*Probably aerosol present from the test atmosphere generation system*
Use of vehicle (other than air)	*Air*
Whole body / nose-only (incl. head/nose-only) exposure	*Head-only*
Type of restrainer	*Body plethysmopgraph*
Pressure distribution.	*No information on pressure distribution provided*
Homogeneity of test atmosphere in breathing zone of animals	*Test material was delivered at a known rate to an aerosol generator and directed into a 9 ℓ steel chamber with probably 4 mice exposed simultaneously*
Number of air changes per hour	*Flow was 20 ℓ/min minute for (most likely) 4 animals*
Equilibration time (t95)	*t95 = 1.35 minutes*
Start of exposure relative to equilibration	*Probably at start of concentration build-up, after a 10-minute fresh air control period*
Actual concentration measurement	*Nominal concentration assessment*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Not reported*
Assessment of Reliability	***C*** *Only one exposure duration, unknown but probably short observation period, insufficient exposure generation and characterization*

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	% decrease respiratory rate	Lethality
Mouse	113	30	11%	
	226	30	52%	
	451	30	54%	3 / 4
	903	30	74%	4 / 4

Probit function

Due to the nature of the data no probit function and LC_{50} value have been calculated for this study. The derived RD_{50} value was reported to be 350 mg/m^3. This concentration is around the threshold for lethality. A review of the breathing pattern suggested that at the 903 mg/m^3 exposure level 1 animal certainly and 1 had questionable pulmonary irritation breathing pattern. No information was provided on the breathing pattern at the lower concentrations, but pulmonary irritation may also have played a role at concentrations below 903 mg/m^3.

Study ID: other C studies

Death occurred in 9/10 rats exposed to 903 mg/m^3 methyl chloroformate vapour at 20°C for 60 minutes (BASF 1970a).

Death occurred in 11/12 rats exposed to an atmosphere 'enriched or saturated' at 20°C for 3 minutes (BASF 1970b).

In a publication with toxicological data on many chemicals Vernot (1977) reported 1-hour LC_{50} values in rats for ethyl chloroformate of 654 mg/m^3 for males and 767 mg/m^3 for females. Many relevant details of the study design were not provided.

At the WARF institute (1972) 10 rats per group were exposed for 1 hour at nominal concentrations of 3240 or 1620 mg/m^3 ethyl chloroformate. All test animals in the high dose group died within 2 hours, and in the low dose group all died overnight.

Appendix 2 Reference list

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