20230316- chloroacetyl chloride
-VOORGESTELD

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
Chloroacetyl chloride	**79-04-9**

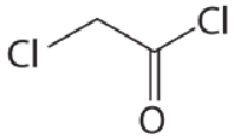
This draft document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

This document has been checked for completeness by the Netherlands' National Institute for Public Health and the Environment (RIVM) and has been assigned the status "voorgesteld" (proposed). The scientific expert panel on probit functions has approved this document for public discussion and comments. Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the email address mentioned above.

If the proposed probit function is approved by the expert panel on scientific grounds, after review and revisions following of public comments, the status of the document and probit function will be 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 chloroacetyl chloride



CAS-number:	79-04-9
IUPAC name:	2-chloroacetyl chloride
Synonyms:	chloroacetic acid chloride, chloroacetic chloride, monochloroacetyl chloride, CAC
Molecular formula:	$C_2H_2Cl_2O$
Molecular weight:	112.9 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	106-110°C (at 101.3 kPa)
Vapour pressure:	2.5 kPa (at 20°C)
Saturated vapor conc:	25000 ppm = 117408 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.213 ppm (at 20°C and 101.3 kPa)
	1 ppm = 4.696 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	Human H301-311-314-331-372

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

Acute effects: Chloroacetyl chloride decomposes exothermally in water or moist air to produce chloroacetic acid and HCl. Chloroacetyl chloride is corrosive to tissues and causes irritation of the eyes, skin, and respiratory system. Pulmonary effects included congestion, alveolar desquamation, pulmonary edema, and bronchopneumonia; seen only after irritation effects of eyes, skin and upper respiratory tract. Lethality results from respiratory damage

Long-term effects: Exposure to high acute exposures may result in permanent lung damage. No specific information available.

3. Human toxicity data

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

AEGL (2007) reported the following:
"Exposure for an undefined period of time (likely few minutes) to an air concentration of 0.011 ppm [0.052 mg/m^3] *CAC was undetectable by odor, 0.023 ppm* [0.108 mg/m^3] *was "barely detectable" and 0.140 ppm* [0.657 mg/m^3] *was "strong" odor to an industrial hygienist (Dow, 1988b). Ocular irritation was not experienced at these concentrations, but 0.910 ppm* [4.274 mg/m^3] *was painful to the eyes and caused lacrimation (Dow 1988b).*

Shift sample CAC air concentrations of 0.05 ppm [0.235 mg/m^3]*, taken over a period of ≥7 hours, were associated with CAC odor that was "readily apparent and objectionable throughout the shift" for workers at two CAC manufacturing sites (Monsanto 1987). The air monitoring method was not specified but had a detection limit of <0.01 ppm* [0.047 mg/m^3]*.*

[1] AEGL 2007

The CAC threshold of irritation (Lim_{ir}) for a group of human volunteers (number, ages, sex not reported) "using subjective indicators" was 0.43 ppm [2.019 mg/m^3] *(Germanova et al. 1988). The nature of the subjective indicators was not stated. The duration of exposure was not reported, but may have been 1 minute, per the definition of Lim_{ir} as stated by Izmerov et al. (1982).*

Dow (2001) reported that CAC vapor can dull the sense of smell and be difficult to detect."

and

"The medical department of a chemical company reported that six workers receiving "mild" inhalation exposures of CAC experienced dyspnea and cough, whereas 19 workers that received "moderate" inhalation exposures had cyanosis and cough (Dow 1988a). CAC air concentrations and exposure durations were not stated."

4. Animal acute toxicity data

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

1. AEGL interim TSD and reference database for chloroacetyl chloride, 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 five studies were identified -with eight datasets for 3 species- with data on lethality following acute inhalation exposure. No dataset was assigned status A for deriving the human probit function, one datasets was assigned status B1 and eight 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 chloroacetyl chloride are displayed in Figure 1.

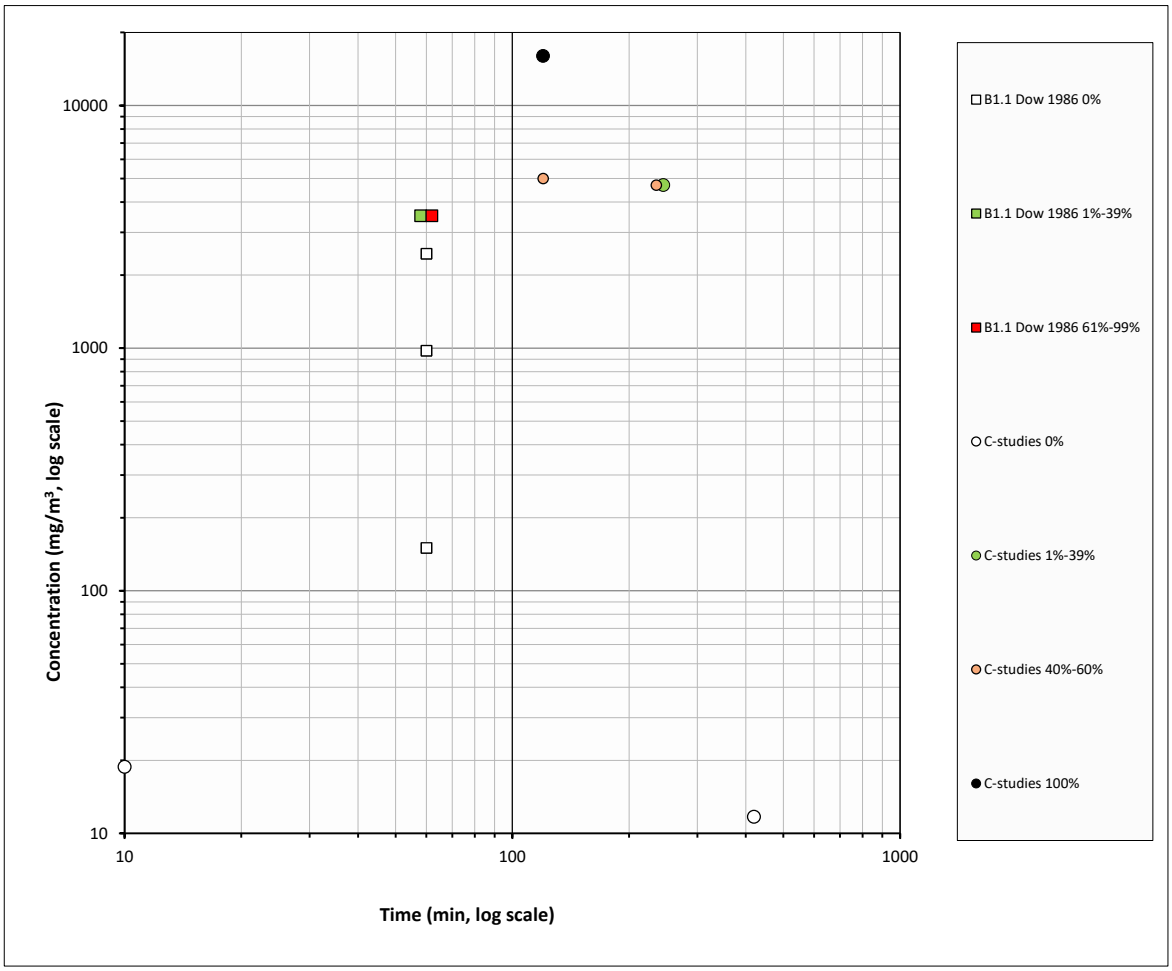


Figure 1 *All available acute lethality data for chloroacetyl chloride.*

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

The only available B1 study was selected for derivation of the animal probit function for chloroacetyl chloride. This study did not enable to produce a concentration-time-lethality relationship.

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 1.

Table 1 *Data selected for initial analysis of the animal probit function of chloroacetyl chloride.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	3508 (Large variances disable estimating 95% confidence-limits)	N/A

The data of study B1.1 with rats are presented graphically below.

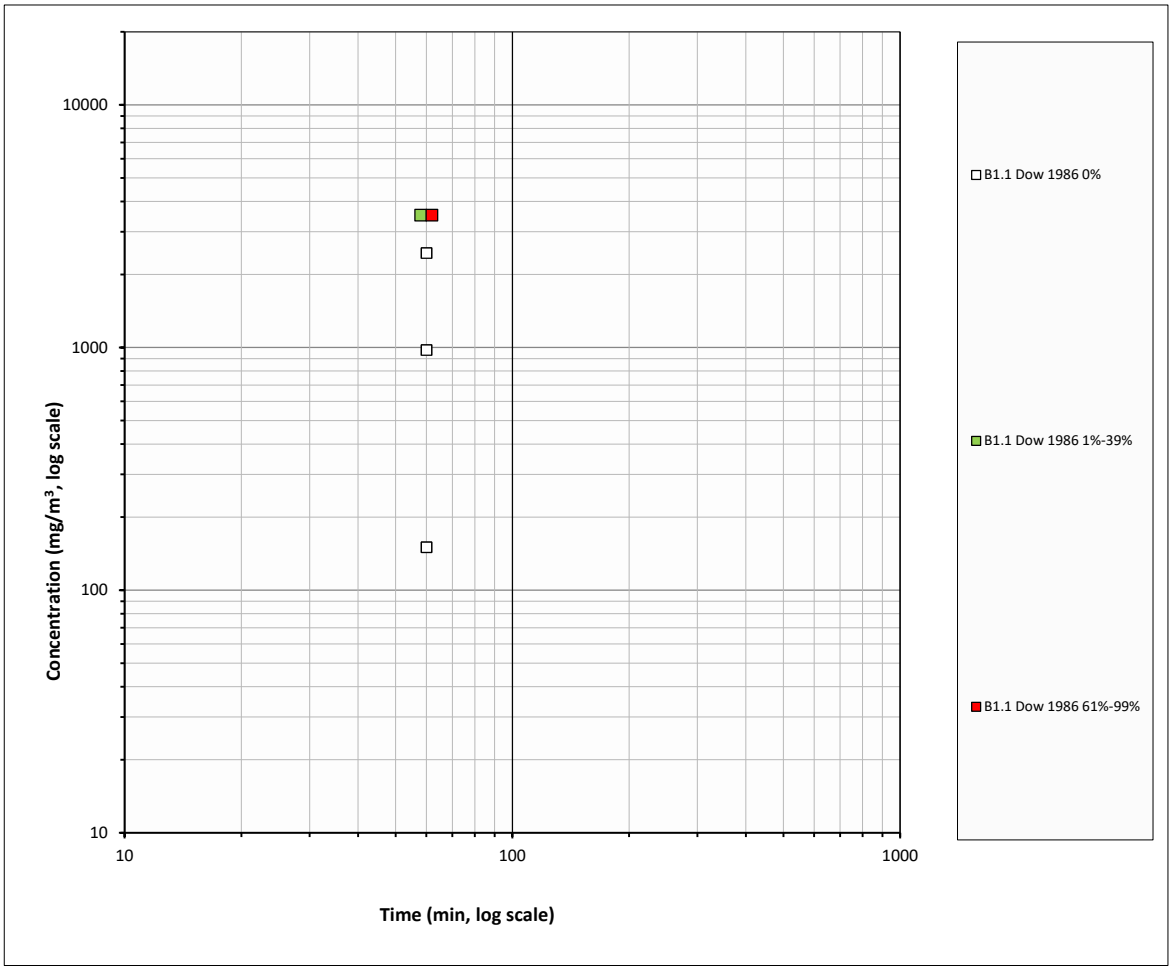


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of chloroacetyl chloride.*

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. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 3.

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

Table 2 *Data selected for the derivation of the animal probit function of chloroacetyl chloride (identical to table 1).*

Study ID	Species	Probit (C in mg/m³, t in min)	LC_{50} at tested exposure duration (mg/m³) 95% C.I.	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	3508 (Large variances disable estimating 95% confidence-limits)	N/A

The data of the selected datasets are presented graphically below.

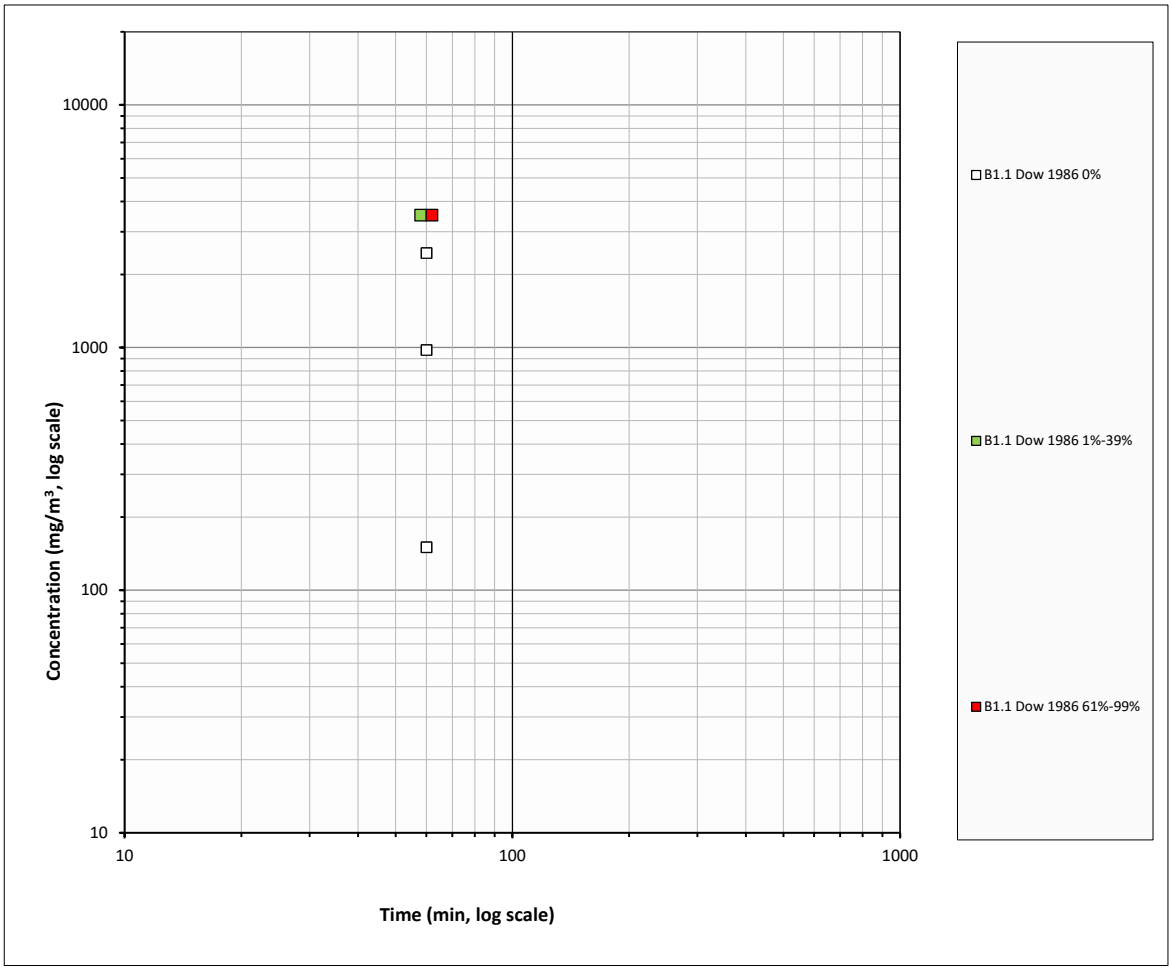


Figure 3 *Final data selected for derivation of the animal probit function of chloroacetyl chloride (identical to figure 2).*

6. Derivation of the human probit function

The evaluation of the individual animal studies resulted in one dataset being eligible for calculating the animal probit function for chloroacetyl chloride (see section 5). This study (B1.1; Dow, 1986) resulted in a 60-min LC_{50} value (sexes combined) of 3508 mg/m^3 (i.e. similar to the highest test concentration; large variances disable estimating 95% confidence-limits). In this study, mortality was observed at the highest concentration of 3508 mg/m^3 (males: 5/6, females: 1/6), with no mortality at the lower concentrations.

It is noted that nominal concentrations of chloroacetyl chloride in the study of Dow (1986) were calculated to be a factor 2-3 higher than the analytical concentrations. The study authors considered that substantial decomposition of chloroacetyl chloride to monochloroacetic acid and hydrogen chloride gas occurs in the presence of humid air. It was considered by the study authors that these may have contributed to the observed effects, however these degradation products were not measured during exposure.

Considering the decomposition process of chloroacetyl chloride it indicates that chloroacetyl chloride is initially insoluble in water, but at the water-chloracetyl chloride interface, a slow (but not specified) reaction produces monochloroacetic acid at first. When sufficient acid is formed to solubilize the two phases, a violent reaction forming monochloroacetic acid and HCl occurs (Morris and Bost 2002).

$ClCH_2COCl + H_2O \rightarrow ClCH_2COOH + HCl$

The decomposition in water to form hydrochloric acid and monochloroacetic acid has a $t_{1/2}$ of <30 minutes, although in the gas phase, the hydrolysis of chloroacetyl chloride in water vapor is slow ($t_{1/2}$ not stated) (Dow 2001, as cited in AEGL).

For the degradation product HCl, a 30-min weighted geometric LC_{50} value of 5198 mg/m^3 (3431 ppm) and the arithmetic mean n-value was 1.367 were available as PoD for the human probit function of HCl (RIVM, 2017). Converting this 30-min LC_{50} to a 60-min value results in a 60-min LC_{50} value for HCl of 3131 mg/m^3 (2064 ppm). It is noted that a 3-fold difference with the 60-min LC_{50} of 3508 mg/m^3 (747 ppm) for chloroacetyl chloride was observed. Based on the presumption that 1 ppm of chloroacetyl chloride results in 1 ppm of HCl and the LC_{50} values expressed in ppm differ three-fold, it is considered that the contribution of HCl to the observed lethality of chloroacetyl chloride exposure may be limited.
For the degradation product monochloroacetic acid, a human probit function has not been derived due to lack of suitable lethality data and the fast crystallization of the chemical in air (Probit TSD not published). The technical support document for the Dutch intervention values of monochloroacetic acid points towards the absence of lethality in an acute 4-hour rat study of TNO up to the highest concentration of 1268 mg/m^3 (322 ppm) tested (RIVM, 2021).
Non-lethal effects for chloroacetyl chloride observed in the specific study of Dow (1986; B1.1) included squinting, lacrimation, gasping, laboured breathing, and stress related clinical signs (lethargy, salivation, stained eyes and face, urine stained perineum). Further it was stated that “Gross pathological examination of rats that died during the post-observation period revealed lung and nasal tissue congestion that could not be definitively ascribed to upper respiratory irritation during exposure or general circulatory collapse (shock). Facial and perineal soiling seen in these animals were secondary to exposure-induced stress. One male that died prior to termination and five females that survived to termination had bilaterally enlarged adrenals. While it was unclear whether this effect was stress-related or a direct effect of exposure, the most likely explanation was that it was a response to stress.”

It can be argued that also in the humid environment of the respiratory tract chloroacetyl chloride can react to form its decomposition products monochloroacetic acid and hydrochloric acid. Based on the study description of Dow (1986; study B1.1), the consideration of the decomposition in water and moist environments and the relative toxicity of the decomposition products, the Expert Panel on Probit Functions considers this B1.1. study (Dow, 1986) and its results valid for the purpose of human probit function derivation for chloroacetyl chloride.

To derive the human probit function the results from rat study B1.1 (Dow, 1986) have been used to derive a point of departure as outlined above.

First, the default n-value of 2 was selected as no experimentally derived value for n was available.
Second, the LC_{50}-value of B1.1 was calculated to be 3508 mg/m^3 for 60 minutes.

The Point of Departure for the human probit function is a 60-minute animal LC_{50} value of 3508 mg/m^3 and the default n-value of 2.

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

Table 3 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale

Animal to human extrapolation:	3	Default
Nominal concentration	1	The concentrations were measured analytically in the B1.1 study.
Adequacy of database:	2	Only one B1 study available. Decomposition of chloroacetyl chloride into hydrochloric acid and monochloroacetic acid may have occurred in this study; however, the contribution of the decomposition products to the observed lethality is considered limited.

The estimated human equivalent 60-minute LC_{50} value is 3508 / 6 = **585 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): $5 = a + 1.0 \times \ln (585^{2.0} \times 60)$ resulting in the a-value of **-11.80**.

$Pr = -11.8 + 1 \times \ln (C^2 \times t)$ 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 one study in the rat with B1 quality, including 48 animals, a single exposure duration of 60 minutes. Observed response rates were either 0% or 50% (when sexes combined), 0% and 83% (males only) and 0% and 17% (females only).

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 122 mg/m³ and the calculated human 60 min LC_1 (Pr = 2.67) is 179 mg/m³.

Table 4 *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	173	122
1% lethality, this probit	253	179
AEGL-3[2] (2007, interim)	310	244
ERPG-3[2]	-	-
LBW (2021)	310	240

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

[2] AEGL and ERPG values were converted from ppm to mg/m³ with the conversion factor calculated in section 1. Therefore, the AEGL and ERPG values in mg/m³ can deviate slightly from those reported in the AEGL and ERPG TSDs.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: ***Dow 1986***
Substance: Chloroacetyl chloride
Species, strain, sex: Rat, Fischer 344, male and female
Number/sex/conc. group: 6
Age and weight: 6-8 weeks, weights on test day ranged 220-295 g for males and 140-168g for females
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes*
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	*See below**
Use of vehicle (other than air)	*-*
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 material was vaporized into stainless steel and glass 112 liter Rochester-type chambers using a glass J-tube apparatus. The air supplied to the chambers was controlled by a system designed to maintain temperature and relative humidity of 22ºC and 50%, respectively.*
Number of air changes per hour	*An airflow of 30 liter/min, corresponding to 16 air changes/hour based on a 112 liter inhalation chamber.*
Equilibration time (t95)	*11.2 min*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*During each exposure, a known volume of the chamber atmosphere was pulled through a bubbler which contained reagent solution known to simultaneously collect and derivatize chloroacetyl chloride.* *Following collection, the samples were analysed for chloroacetyl chloride content by high performance thin layer chromatography.**
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*

Assessment of Reliability	***B1*** *Relatively well-performed study, though using a single exposure concentration*

** nominal concentrations of chloroacetyl chloride during exposure were calculated based on the amount of test material used and the total air passed through the chamber during each exposure period. Nominal concentrations of chloroacetyl chloride (102, 598, 956 and 1366 ppm, corresponding to 479, 2808, 4489, 6415 mg/m³) were calculated to be a factor 2-3 higher than the analytical concentrations. The study authors considered that substantial decomposition of chloroacetyl chloride to monochloroacetic acid and hydrogen chloride gas occurs in the presence of humid air. These degradation products were not measured during exposure and may have contributed to the observed effects.*

Results

Species	Concentration (mg/m³)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
Rat	150	N/A	60	0/6	0/6
Rat	977	N/A	60	0/6	0/6
Rat	2451	N/A	60	0/6	0/6
Rat	3508	N/A	60	5/6	1/6

The authors of the study derived one-hour LC_{50} values of 660 ppm (3099 mg/m³) for males and > 747 ppm (>3508 mg/m³) for females.

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/m³, and S for sex (0 = female, 1 = male).

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-78.7	10.1	1.93	-
Sexes combined	Rat	-82.2	10.7	-	-

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/m³) 95%-C.I. Male	LC_{50} (mg/m³) 95%-C.I. Female	LC_{50} (mg/m³) 95%-C.I. Combined
60	3189 (2222-3644)	3859 (3425-7255)#	3508 (Large variances disable estimating 95% confidence-limits)

It is noted that the estimated 60-min LC_{50} value for females falls outside the range of tested concentrations.

The results for males and females were derived from the analysis with sex as covariate.

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

Study ID: C studies

Carpenter *et al*. (1949) reported acute inhalation studies with several chemicals in male and female Sherman rats including a 14-day post-exposure period. For several of these chemicals tested the target concentration was 1000 ppm (range of 700-1390 ppm) *[4696 mg/m³ (range 3287 – 6528 mg/m³)]*. In one of these studies chloroacetyl chloride was used as test item with an exposure period of 4 hour. However, no precise lethality data were presented; for the groups of substances tested at 1000 ppm (700-1390 ppm) mortality was between 33% (2/6) and 67% (4/6) (mean ca. 50%).
No further experimental results were provided. The atmosphere was generated by delivering the liquid into an evaporator through which metered air was forced into the 9-liter glass exposure chamber. Analytical concentrations were not measured.

Herzog (1959; cited from AEGL) treated 80 rats for 2 hours with 0.5-30 mg/L chloroacetyl chloride concurrently with mice and guinea pigs (see below) in 72.7 or 74.1 L glass bottles using a static exposure method (sex, strain, number of animals/concentration not specified). It was not specified whether the air concentrations were analytical or nominal (probably nominal). Animals were observed during exposure and for the following five days. Results were not given other than that all animals inhaling ≥16 mg/L died on study, and that 5 rats inhaling 2381-6480 ppm *[11182-30432 mg/m³]* died within the first 2-3 minutes of exposure.

Herzog (1959; cited from AEGL) exposed 220 white mice (sex not specified) for 2 hours to 0.5-30 mg/L chloroacetyl chloride concurrently with rats and guinea pigs (see above and below, respectively). The number of mice/concentration were 10 or 20 at 3-14 mg/L; 30 concentrations and/or the number of mice/group were not stated at < 3 mg/L and >14 mg/L. Animals were observed during exposure and for the following 5 days. No mice died at ≤649 ppm *[3048 mg/m³]*, all mice inhaling ≥3030 ppm *[14230 mg/m³]* died during the 2-hour exposure, and 18 mice inhaling 2381-6480 ppm *[11182-30432 mg/m³]* died within the first 2-3 minutes of exposure. Over the 5-day period, all mice died at ≥10 mg/L. Herzog (1959) calculated the mean lethal concentration, i.e., the 2-h LC_{50}, over the 5-day period as 5.2 mg/L using the statistical integration method of Behrens (1929). A 2-h LC_{50} of 1066 ppm *[5006 mg/m³]* was obtained by probit analysis (using the Number Cruncher Statistical System). Symptoms of irritation of the upper respiratory passages were seen at ≥0.5 mg/L. The animals initially appeared agitated and had signs of eye and respiratory irritation (rubbed mouth with paws, scratched themselves, had half-open and watery eyes), profound dyspnea, foamy pink liquid at the mouth, and eventually cyanosis of the extremities, spastic convulsions, apnea, and death. Mice that died between days 2-5 in some cases no longer had dyspnea, but remained in a state of prostration, refused to eat, and did not groom themselves. Symptom severity was related to the exposure concentration, with severe effects occurring within 2-5 minutes at ≥10 mg/L, whereas at 2-5 mg/L, symptoms had a “slower evolution” and only mild dyspnea was seen at the end of the exposure period. Necropsy and histopathology revealed that the majority of the lesions were in the trachea and lungs. Lesions in the trachea included lumen blocked with blood-soaked necrotic tissue, mucosal necrosis, hyperemia, edema, atrophy, detachment of mucosa. The lungs were enlarged and congested, and had lesions including dilated interalveolar capillaries, hemorrhagic alveolitis, bronchopneumonia, emphysema, and atelectasis. Lung congestion and pulmonary edema caused the death of most of the animals. Other less commonly seen lesions included mild hyperemia of the heart and liver, glomerular edema and glomerulonephritis, and mild brain hemorrhage. The incidence and severity of the lesions increased with concentration, although it was not specified which effects occurred at a given test concentration. Based on the fact that upper respiratory irritation was seen in mice at 0.5 mg/L, Herzog (1959) suggested that the maximum workplace air concentration should remain below 0.01 mg/L.

Herzog (1959; cited from AEGL) also exposed 120 white mice (sex, strain, number/concentration not specified) for 5 minutes to 10-65 mg/L chloroacetyl chloride similarly to the 2-hour exposure study. Details of the results were not stated other than that death occurred even within this (5-minute) period. Herzog (1959) theorized that deaths during exposure were due to inhibition of the respiratory center reflex, and those occurring post-exposure were due to pulmonary lesions (congestion and edema).

Herzog (1959; cited from AEGL) exposed 50 guinea pigs (sex, strain, number/concentration not specified) for 2 hours to 0.5-30 mg/L chloroacetyl chloride, concurrently with the rats and mice (see above). The only results given were that all animals inhaling ≥3462-3895 ppm *[16259-18292 mg/m^3]* died during the 5-day observation period, and that 3 animals inhaling 2381-6480 ppm *[11182-30432 mg/m^3]* died within the first 2-3 minutes of exposure.

Four male rats exposed to “concentrated” chloroacetyl chloride all died within two hours (Younger Labs 1969; cited from AEGL). The exposure concentration was not specified, although it was stated that 27.9 g liquid chloroacetyl chloride was vaporized or left in the equipment, and that air was supplied at 4 L/min to a 35 L metal chamber. Immediately upon exposure, the rats showed signs of irritation including pawing at the face and mouth, and tightly shut eyes. Within 10 minutes, rats had reddened eyes with nasal and salivary excretion and gasping, and within 30 minutes they had opaque corneas, and death occurred after 90 (3/4 rats) or 120 (1/4) minutes. Severely hemorrhaging lungs were seen at necropsy.

The REACH registration dossier on chloroacetyl chloride (ECHA, 2022) presents a 4h LC_{50} of 1000 ppm *[4696 mg/m^3]*. No details presented. It is assumed this study is similar to Carpenter (1949).

Appendix 2 Reference list

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