20240312-chlorosulfonic acid-
INHOUDELIJK VASTGESTELD

National Institute for Public Health
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Probit function technical support document

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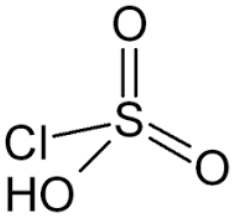
substance name	CAS number
Chlorosulfonic acid	**7790-94-5**

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 Chlorosulfonic acid



1. Substance identification

CAS-number:	7790-94-5
IUPAC name:	sulfurochloridic acid
Synonyms:	chlorosulfuric acid, sulfuric chlorohydrin, chlorosulphuric acid, sulphuric chlorohydrin
Molecular formula:	$ClHO_3S$
Molecular weight:	116.5 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	152°C (at 101.3 kPa)
Vapour pressure:	0.05 kPa (at 20°C)
Saturated vapor conc:	500 ppm = 2423 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.206 ppm (at 20°C and 101.3 kPa)
	1 ppm = 4.85 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H314-335

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

Acute effects: Chlorosulfonic acid is severely irritating to mucous membranes of the eyes, nose and respiratory tract and gives chemical burns to the skin. The substance strongly reacts to moisture in tissues. Chlorosulfonic acid decomposes to one mole of HCl (hydrogen chloride) and one mole of H_2SO_4 (sulfuric acid). The main target organs and tissues for inhalation exposure to chlorosulfonic acid are the upper and lower parts of the respiratory tract. Symptoms are coughing, shortness of breath and burning sensations. Pulmonary oedema is only seen in cases where upper respiratory tract corrosive effects were clearly visible. Neurotoxic effects observed in rodents were only seen at lethal exposure levels. Lethality can occur through suffocation caused by severe swellings in the upper airways blocking air passage or by pulmonary damage.

Long-term effects: Acute exposure can result in long-term damage of the upper (mucous membranes) and lower respiratory tract reducing lung function. The substance can cause erosion of teeth.

Chronic exposure produces similar effects.

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.

4. Animal acute toxicity data

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

[1] References for mechanism of action and toxicological effects following acute exposure.

1. AEGL interim TSD (2008), ERPG document, EU RAR , ECHA database and reference database for chlorosulfonic acid, 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 4 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 B1 and 5 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 chlorosulfonic acid are displayed in Figure 1.

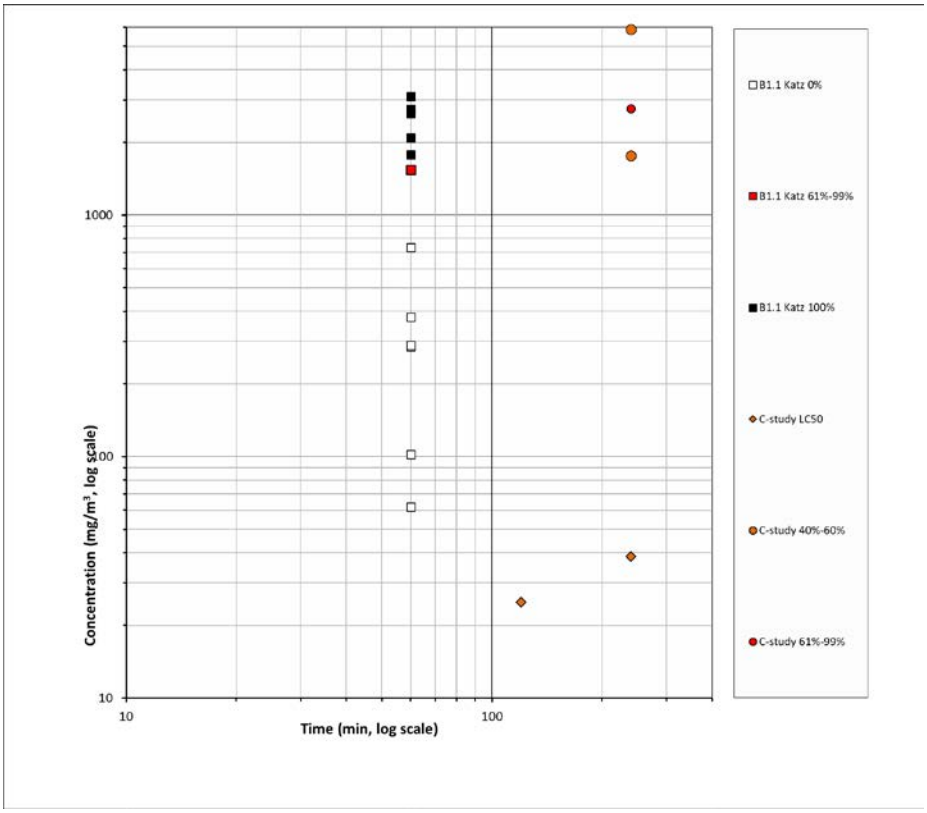


Figure 1 *All available acute lethality data for chlorosulfonic acid.*

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

The B1 study was selected for derivation of the animal probit function for chlorosulfonic acid.

Table 1 *Data selected for initial analysis of the animal probit function of chlorosulfonic acid.*

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}*	1424	N/A

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

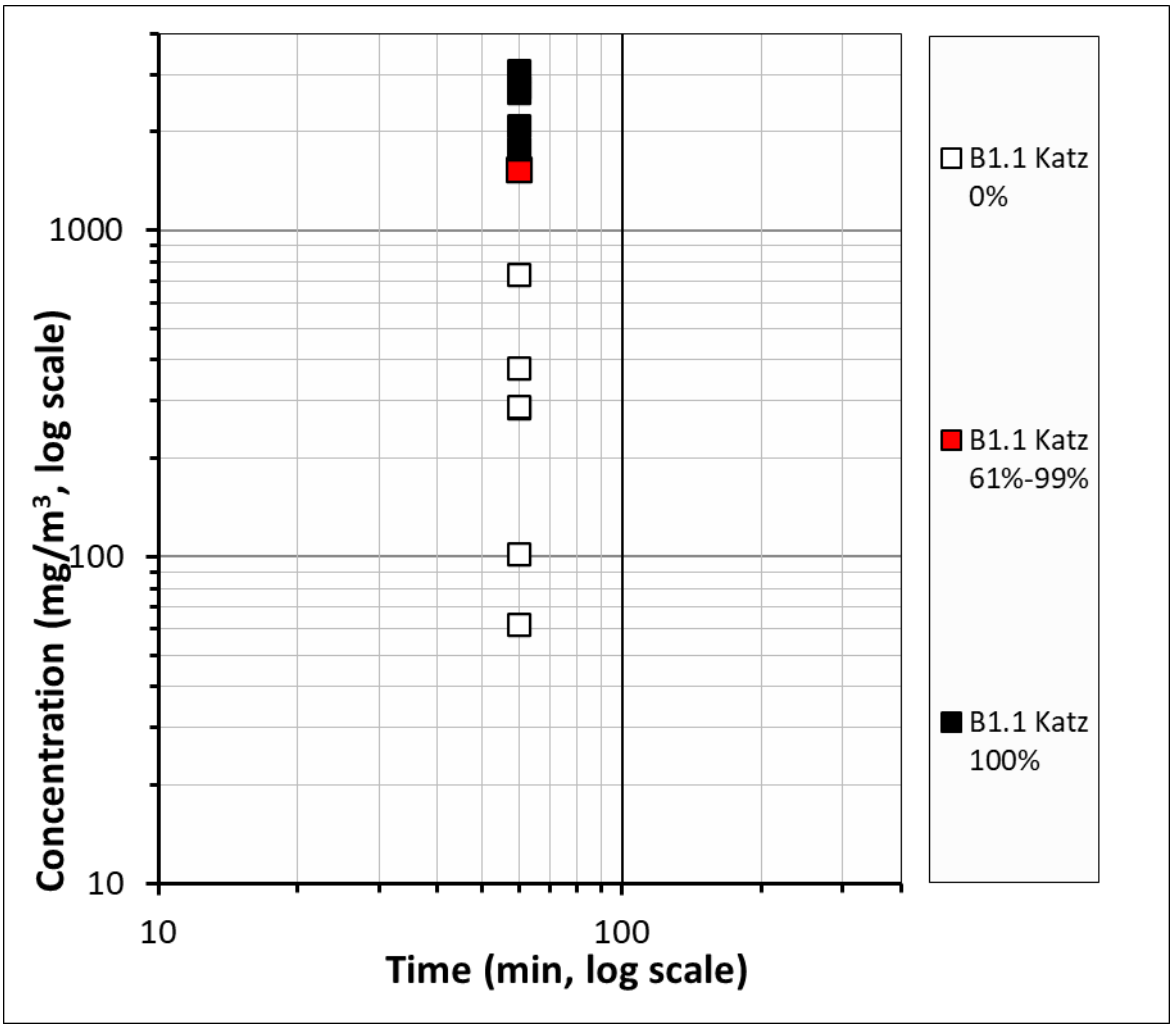


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of chlorosulfonic acid.*

Based on criteria outlined in the guideline the data from the B1 study was selected for the final dataset for the derivation of the animal probit function. It is the only available B1 study and seems to be well performed taking into account the difficulties that the substance presents to create a test atmosphere. 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 chlorosulfonic acid (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.	n-value 95% C.I.
B1.1		*60-min LC_{50}*	1424	N/A

The data of the selected datasets are presented graphically below.

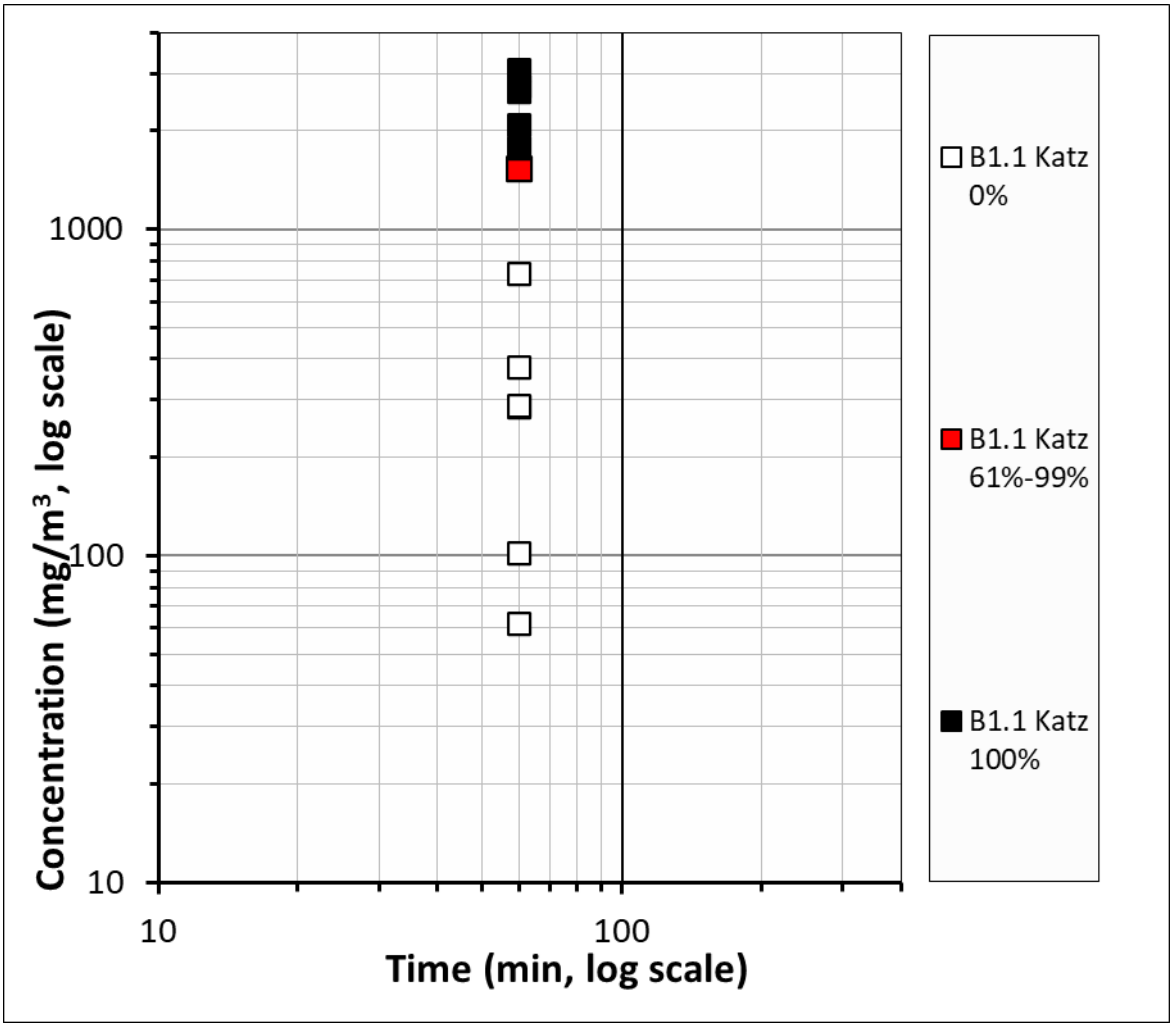


Figure 3 *Final data selected for derivation of the animal probit function of chlorosulfonic acid (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from study B1.1 (Katz, 1987) have been used to derive a point of departure as outlined above. It is the only eligible study available for probit function derivation.

This B1 study included one exposure duration and provided a 60-min LC_{50} value of 1424 mg/m^3. It is not possible to derive a substance specific n-value for chlorosulfonic acid based on the available animal data. However, the Expert panel on the Dutch intervention values for emergency response concluded that since the mechanism of action and health effects reported for sulfuric acid (one of the hydrolysis products) and chlorosulfonic acid are the same it is justified to apply the n-value of sulfuric acid to chlorosulfonic acid (RIVM, 2016). The Expert panel on the Dutch intervention values for emergency response stated the following: "Chlorosulfonic acid is a strong corrosive acid and hydrolyzes exothermically in situ upon contact with moist mucous membranes to form equimolar amounts of the strong corrosive acids HCl and H_2SO_4. Animal studies indicated that chlorosulfonic acid is more acutely toxic than HCl or H_2SO_4, or a mixture of HCl + H_2SO_4, but do not allow determination of the relative toxicities of these chemicals. Because no human or animal studies were available for derivation of the VRW and AGW, the values are based on the structural analogy to H_2SO_4. This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, chlorosulfonic acid, and the two compounds have a similar mode of toxicity (eye and respiratory irritants)".
In the derivation of the human probit function it is therefore decided to follow the approach by the Expert panel on Dutch intervention values for emergency and apply the n-value of sulfuric acid here. The probit technical support document of sulfuric acid (RIVM 2019) describes a n-value of 2.14 (arithmetic mean of rat and mouse n-value), which will be adopted to derive the human probit function for chlorosulfonic acid.

The Point of Departure for the human probit function is a 60-minute animal LC_{50} value of 1424 mg/m^3 and an arithmetic mean n-value of 2.14.

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 value
Nominal concentration	1	Actual concentrations were measured.
Adequacy of database:	2	Only one B1-study

The estimated human equivalent 60-minute LC_{50} value is 1424 / 6 = **237 mg/m³**.

The experimentally determined n-value was **2.14** (based on sulfuric acid; see explanation above). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **0.935**.

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): $5 = a + 0.94 \times \ln (237^{2.14} \times 60)$ resulting in the a-value of **-9.77**.

$Pr = -9.77 + 0.94 \times \ln (C^{2.14} \times t)$ 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 60 animals, one exposure duration and except for one datapoint all either 0% or 100% mortality.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 51 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 74 mg/m^3.

Table 4 *LC-values 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	70	51
1% lethality, this probit	102	74
AEGL-3[2] (2008, interim)	31	25
ERPG-3[8] (1991)		30
LBW (2016)	89	74

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are similar to the LBW and higher compared to the AEGL and ERPG.

[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.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: Katz, 1987 (Eastman Kodak Company)
Substance: chlorosulfonic acid
Species, strain, sex: rat, CRL:CD (SD)BR, male and female
Number/sex/conc. group: 5/sex/group
Age and weight: eight weeks old, 189 g (male) and six weeks old, 184 g (female) for higher three concentrations.
eight weeks old, 189 g (male) and six weeks old, 189 g (female) for lower three concentrations
Observation period: 14 days

Note that males and females were exposed separately (different concentrations) and there was approximately a two week period between the experiment with the higher concentrations, which was conducted first, and the experiment with the lower concentrations.

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*yes*
Study carried out according to OECD 403 guideline(s)	*yes*
Stability of test compound in test atmosphere	*Hydrolysis leading to aerosol formation*
Use of vehicle (other than air)	*Dried oil-free air*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole-body*
Type of restrainer	*N/A*
Pressure distribution	*Chambers were kept at negative pressure.*
Homogeneity of test atmosphere in breathing zone of animals	*The aerosol and vapour atmosphere was generated by passing dried compressed oil-free air over liquid chlorosulfonic acid dropped on a heated glass bead-packed column. The substance hydrolyzed upon entering the chamber showing visible aerosol droplets.*
Number of air changes per hour	*10 L/min in 20 L glass bell jar chamber*
Equilibration time (t95)	*6 min.*
Start of exposure relative to equilibration	*No information.*
Actual concentration measurement	*Samples were collected twice during each 1h exposure using midget impingers containing distilled water ensuring both vapour and aerosol collection; at a flow rate of 2.4-4.4 L/min for 10-min. The samples were analysed for chloride ion using ion chromatography.*

Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*A total of 6 measurements were taken (2 in each of the three lowest concentrations tested) by using a Anderson Mini Impactor. Greater than 91% of the aerosol particles were equal or less than 4.7 µm in 5/6 measurements. In the sixth measurement this was 76.9%. No measurements were performed in the higher concentration groups*
Assessment of Reliability	***B1*** *Technically well performed study. Included only one exposure duration and therefore deprived of A quality. It is noted that the concentration ranges within the lower and higher concentration groups have minimal spacing between concentrations*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Target		Male	Female
Rat				Dead/tested	
	102	70	60	0/5	
	285	282	60	0/5	
	379	563	60	0/5	
	1777	1500	60	5/5	
	2638	2250	60	5/5	
	3096	3400	60	5/5	
	61	70	60		0/5
	289	282	60		0/5
	735	563	60		0/5
	1539	1500	60		4/5
	2091	2250	60		5/5
	2743	3400	60		5/5

The author calculated a LC_{10} value of 630, 1066, and 926 mg/m^3 for males, females and sexes combined respectively.

Probit function

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

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

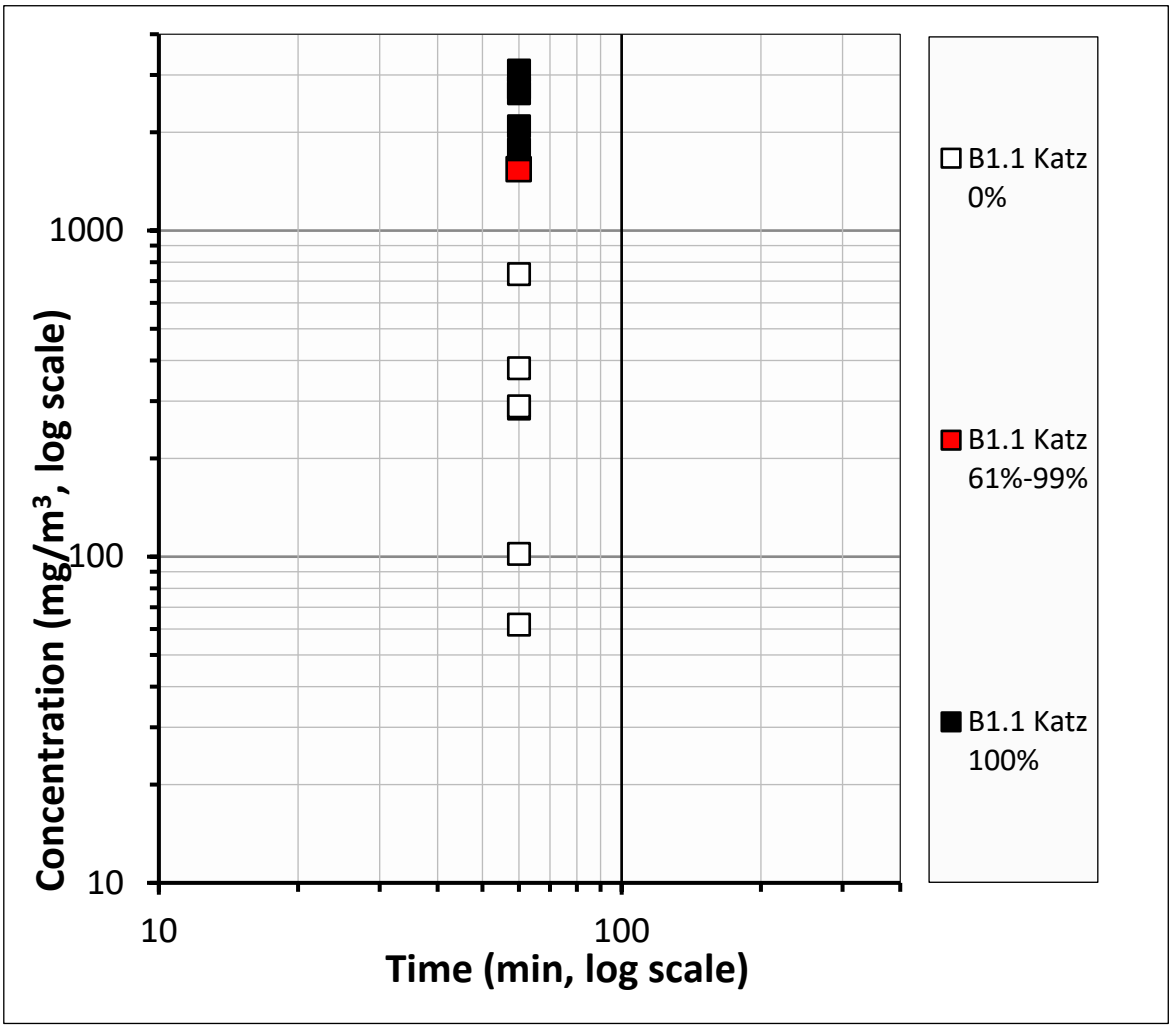
with C for concentration in mg/m^3 and S for sex (1 = female, 0 = male).

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-65.6	1.04	-4.95	N/A
Sexes combined	Rat	-73.9	1.09	N/A	N/A

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	883 (C.I. could not be calculated)	1419 (C.I. could not be calculated)	1424 (C.I. could not be calculated)

A graphical overview of the data is presented below. Each concentration-time combination represents one point in the plot.



Study ID: C studies

Mamleeva and Bakhtizina (1976; as cited in AEGL, 2008) exposed white rats (rat strain, number and sex not specified) by inhalation for 4 hours to chlorosulfonic acid (CSA). How the CSA atmosphere was generated, the concentrations tested, and the study observation period were not specified. The stainless steel exposure chamber air was noted to contain a light mist during exposure. The CSA exposure concentration was measured analytically, although the sample collection method and frequency were not stated. A 4 hour LC_{50} of 38.5 mg/m^3 was determined, but neither individual nor group animal toxicity or mortality data were provided.

Mamleeva and Bakhtizina (1976; as cited in AEGL 2008) exposed mice (strain, number, and sex not stated) by inhalation for 2 hours to CSA. The report did not specify how the CSA atmosphere was generated, the concentrations tested, or the observation period. The stainless steel exposure chamber air was noted to contain a light mist during exposure. The CSA exposure concentration was measured analytically, although the sample collection method and frequency were not stated. An LC_{50} of 25 mg/m^3 was obtained. It is noted that in the REACH registration dossier of chlorosulfonic acid (ECHA, 2021) a 2-hour LC_{50} of 52.5 mg/m^3 is mentioned for this study.

Groups of Crl:CD BR rats (10/sex/group) were exposed for 4 hours nose-only to dynamically generated CSA aerosol concentrations (analytical) of 0, 1765, 2768, or 5864 mg/m^3 (Hagan and Fisher 1987; as cited in AEGL 2008). The 1765 and 2768 mg/m^3 groups were exposed 6 days before the 5864 mg/m^3 group. The test chamber (stainless steel and glass) was 240 L, the air flow was 150 L/minute, and CSA aerosol was generated by blowing dry compressed air over the test fluid in a nebulizer. The aerosol particle size was not determined in this study. Test concentrations were measured hourly by sorbent tube sampling and HPLC analysis, and were lower than the nominal concentrations (0, 4100, 3800, and 10,000 mg/m^3, respectively) due to reaction of the aerosol with the chamber walls. No sex related differences were seen in the animal responses. During exposure, one animal died at 1765 mg/m^3, 5 died at 2768 mg/m^3, and 5 at 5864 mg/m^3. The 14-day mortality was not proportional to the measured CSA levels, being 0/20, 8/20, 13/20, and 9/20 at 0, 1765, 2768, and 5864 mg/m^3, respectively.

In a pulmonary function study, male ~8-week-old Crl:CD BR rats (4/concentration) were exposed for 1 hour to target concentrations of 563, 750, or 1125 mg/m^3 CSA aerosol (Gordon 1987; as cited in AEGL 2008). The test atmospheres were generated as by Katz (1987). The calculated nominal concentrations were 700, 1002, and 1266 mg/m^3. The analytical concentrations and particle size were not reported. Animals were weighed prior to exposure and on post-test day 6, and were observed for mortality for 13 days but were not necropsied. On the day before and after exposure, the rats were anesthetized and intubated and subjected to pulmonary function analysis. Each rat served as its own control. Parameters tested included lung volume and capacity, ventilation force and pressure, dynamic compliance, and airway resistance. One low-concentration rat survived to day 13; the others died on days 7-11 except one mid-concentration rat died just after the pulmonary testing. The reliability of these lethality results is confounded by the fact that the animals were additionally stressed by the anaesthesia and intubation in the pulmonary function studies.

The REACH registration dossier of chlorosulfonic acid presents a 4-hour LC_{50} value of 40 mg/m^3 in rats. No further details are mentioned (ECHA, 2021).

Appendix 2 Reference list

Chemiekaarten. Ed 32. Den Haag. TNO/SDU uitgevers, 2017.

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Katz GV, 1987. Acute inhalation toxicity and one-hour LC_{10} value of chlorosulfonic acid in the rat. Accession No. 900669. HAEL No. 86-0128. 236025T TK-87-58.

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Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard *et al*. Methods for the derivation of probit functions to predict acute lethality following inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.