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

Probit function technical support document

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substance name	CAS number
Formic acid	**64-18-6**

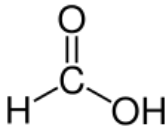
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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

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

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

Technical support document Formic acid



1. Substance identification

CAS-number:	64-18-6
IUPAC name:	formic acid
Synonyms:	aminic acid, formylic acid, hydrogen carboxylic acid, methanoic acid
Molecular formula:	CH_2O_2
Molecular weight:	46.0 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	100°C (at 101.3 kPa)
Vapour pressure:	4.3 kPa (at 20°C)
Saturated vapor conc:	43,000 ppm = 82,280 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.523 ppm (at 20°C and 101.3 kPa)
	1 ppm = 1.913 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H314

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

Acute effects: Inhalation of formic acid produces irritation of the conjunctival mucosa, oropharynx, trachea, and principal bronchi. Formic acid can also induce eye and skin burns, pharyngeal edema, and chronic bronchitis.
Symptoms of high exposure are difficulties in breathing, dyspnoea, burning sensation in upper airways and suffocation due to swelling of the throat. Damage occurs mainly upon contact in the upper airways. Lethality results from pharyngeal edema and suffocation.
Long-term effects: No information.

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. ERPG document for formic 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

[1] ERPG (2008), NTP (1992).

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 7 datasets for 2 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, one dataset was assigned status B1 and 6 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

A total of 2 studies were identified in which sensory irritation was studied. In these studies the following RD_{50} values were observed:

Table 1 *Sensory irritation data for formic acid*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
Mouse, Swiss-Webster	838^{NS}	Not specified	ERPG 2008
Mouse (strain not specified)	1003^{NS}	Not specified	ERPG 2008

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

5. Probit functions from individual studies

All available acute lethality data on formic acid are displayed in Figure 1.

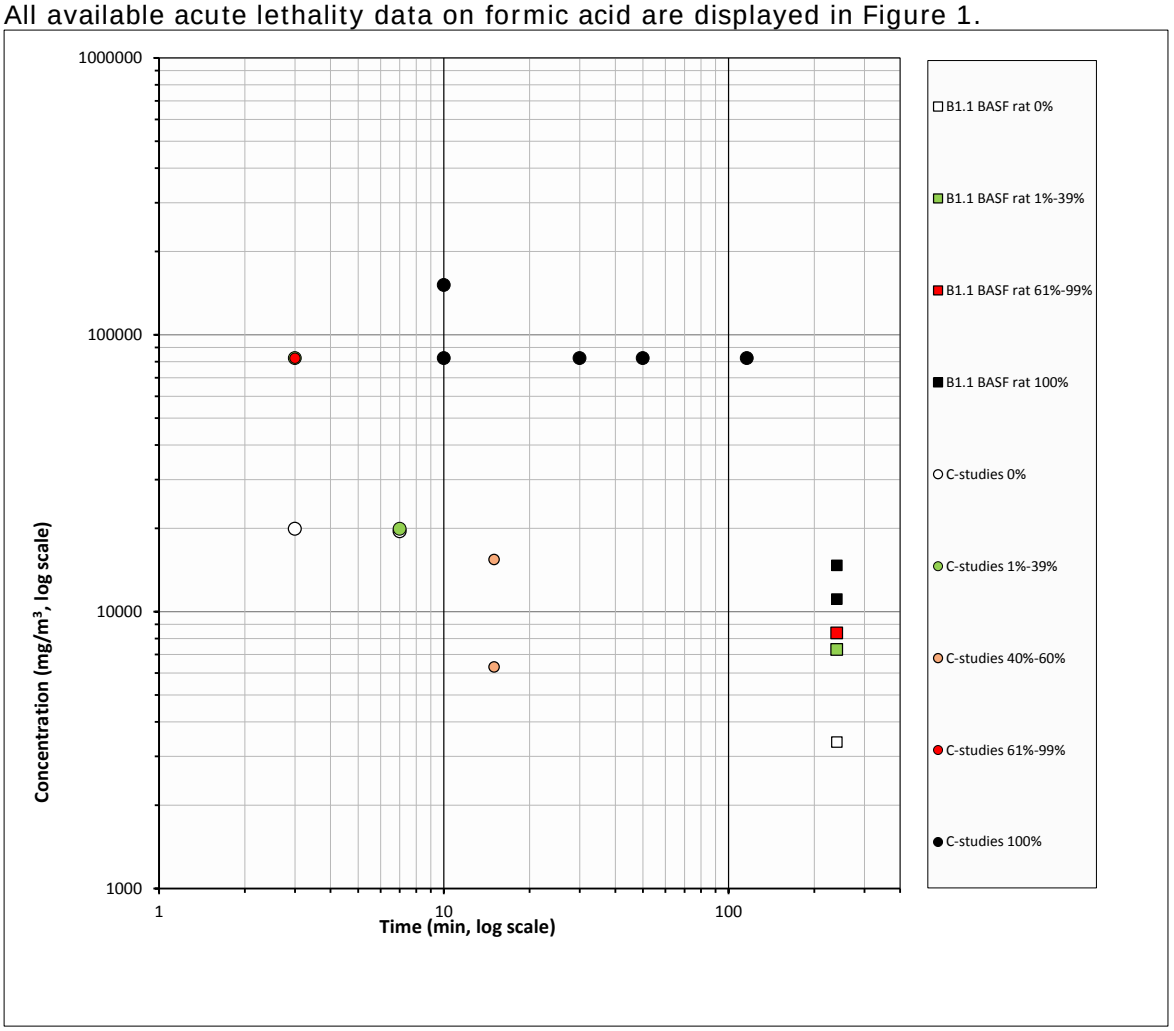


Figure 1 *All available acute lethality data for formic acid.*

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

It was possible to derive a probit function for formic acid based on the available study with B1 quality. Therefore, the probit function was derived using data from this study with B1 quality, which 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 2.

Table 2 *Data selected for initial analysis of the animal probit function of formic acid.*

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	*240-min LC_{50}*	7876 (7593-8173)	N/A

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

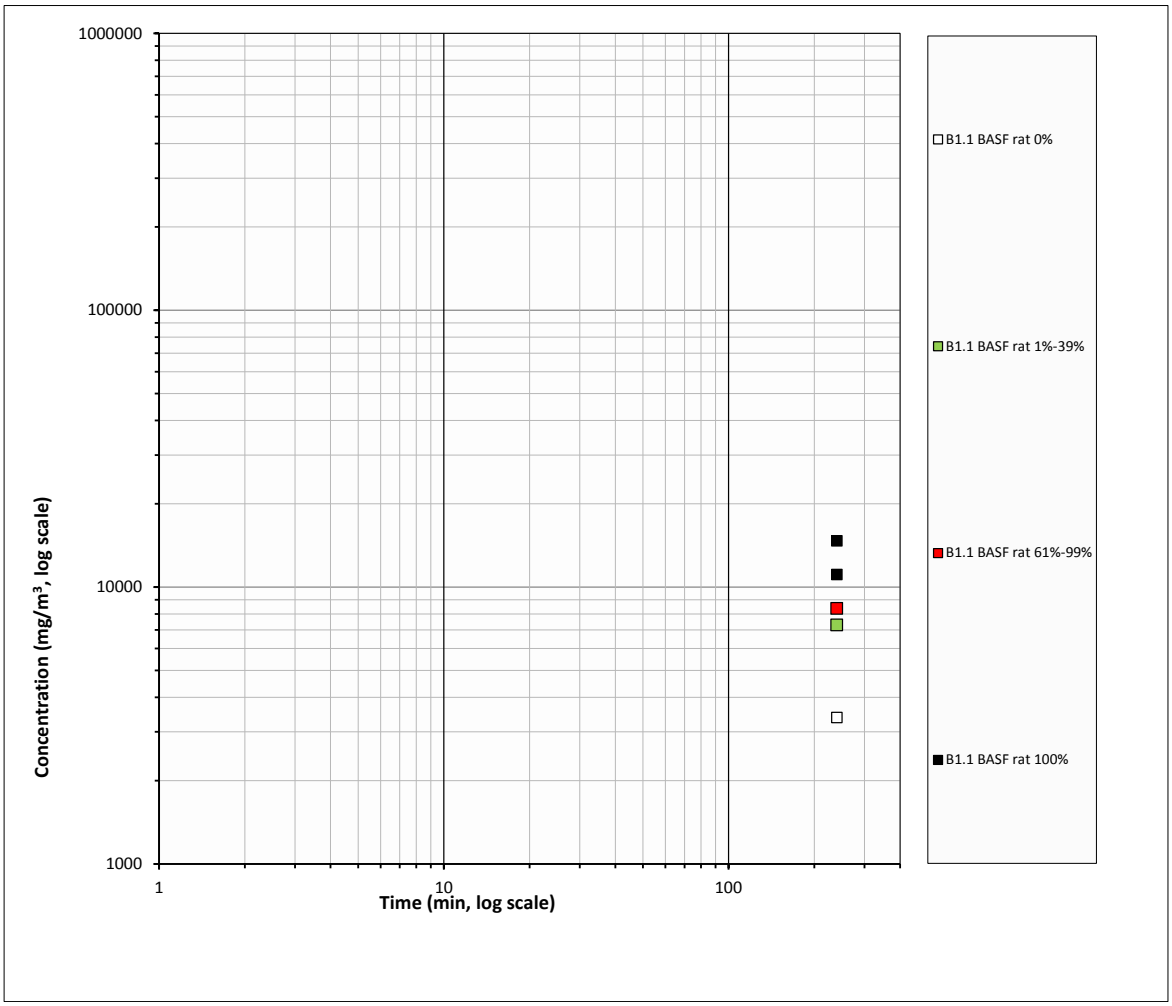


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of formic acid.*

Based on criteria outlined in the guideline the data from rat study B1.1 (BASF 1980) 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 3 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 3 *Data selected for the derivation of the animal probit function of formic 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	rat	*240-min LC_{50}*	7876 (7593-8173)	N/A

The data of the selected dataset are presented graphically below.

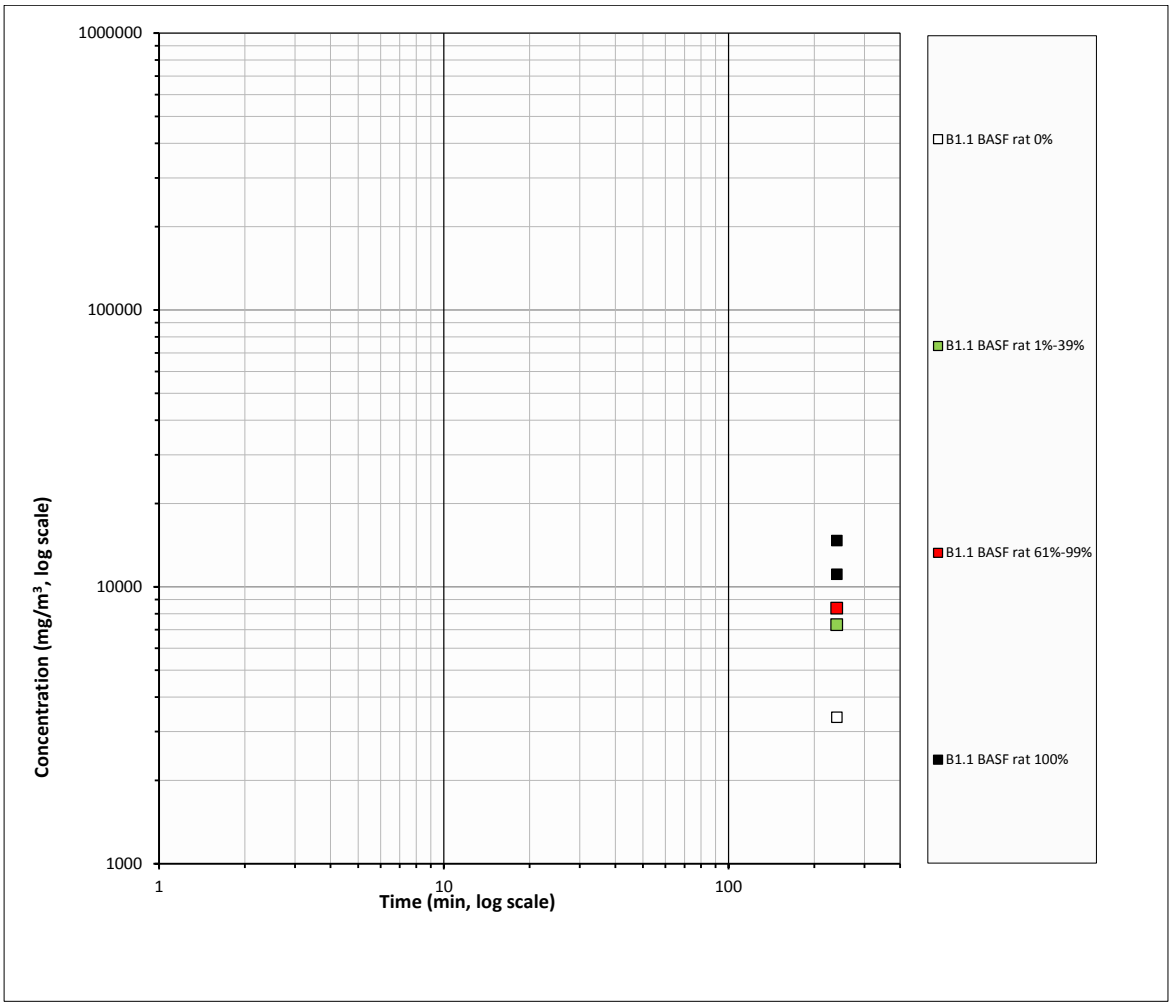


Figure 3 *Final data selected for derivation of the animal probit function of formic acid (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from study B1.1 (BASF 1980) have been used to derive a point of departure as outlined above.

The Point of Departure for the human probit function is a 240-minute animal LC_{50} value of 7876 mg/m^3 and a 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	default
Nominal concentration	1	B1-study with analytically determined concentrations
Adequacy of database:	2	Only one B1-dataset was found. The study was performed using only one exposure duration well outside the exposure duration target range of 30-60 min. This creates a relative large uncertainty because of extrapolation over a large range of exposure duration.

The estimated human equivalent 240-minute LC_{50} value is 7876 / 6 = **1313 mg/m^3**.

No reliable experimentally determined n-value was available, so the default n-value of **2** 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**.

The human probit function is then calculated on the human equivalent 240 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1 \times \ln(1313^2 \times 240)$ resulting in the a-value of **–14.80**.

$Pr = -14.8 + 1 \times \ln(C^2 \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically acceptable basis. The probit function is based on one study in the rat with B1 quality, including 100 animals, an exposure duration of 240 min and response rates between 0 and 100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 549 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 803 mg/m^3.

Table 5 *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	776	549
1% lethality, this probit	1135	803

AEGL-3	-	-
ERPG-3[2] (2008)	-	478
LBW (2017)	1300	1100

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

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

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: ***BASF 1980+2014***
Substance: formic acid
Species, strain, sex: Rat, Sprague-Dawley, male+female
Number/sex/conc. group: 10
Age and weight: age not specified; weight 185 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; however it was stated that study was in accordance with OECD 403*
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	*Negative pressure of 15-20 Pa*
Homogeneity of test atmosphere in breathing zone of animals	*A pump delivered the test substance at constant rates to a glass evaporator heated to 40-70°C. The vapor was diluted with fresh air before it entered the exposure chamber.*
Number of air changes per hour	*Number of air changes not specified; 200 L steel glass inhalation chamber*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Samples taken from breathing zone. Air was abstracted with a tube at a rate of 5.4 L/min from the exposure chamber and guided through an IR photometer and then back to the inhalation chamber.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***B1*** *Well-performed study. Limited to one exposure duration.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	

Rat	3.38×10^3		240	0/10	0/10
Rat	7.29×10^3		240	2/10	1/10
Rat	8.37×10^3		240	8/10	8/10
Rat	11.1×10^3		240	10/10	10/10
Rat	14.7×10^3		240	10/10	10/10

Probit function

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

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

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

Probit function	Species	a	b	d	n-value
Sex as variable	Rat	-109	12.7	-0.19	-
Sexes combined	Rat	-109	12.7		-

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
240	7819 (7419-8229)	7935 (7541-8369)	7876 (7593-8173)

The study authors calculated a combined LC_{50} of 7.85×10^3 mg/m^3.

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.

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

Study ID: C studies

As part of an interlaboratory trial, BASF (1979) exposed rats to an atmosphere enriched or saturated with formic acid (SVC= 82,280 mg/m^3, see section 1). Mortality was as follows: 2/12, 5/6, 6/6 and 6/6 at an exposure duration of 3, 10, 30 and 50 minutes, respectively.

Hoechst (1981) exposed male/female Wistar rats (n=18/sex/conc) to saturated vapour concentration of formic acid via nose-only inhalation for 3, 10 and 116 minutes. The test atmosphere concentration was not analytically verified. Mortality was 75% after a 3 min exposure and 100% after a 10 min exposure period. Most deaths occurred within 24 hours after the treatment. At extended exposure period, all animals died after 21 to 116 minutes of exposure. Closed lids, unkempt fur, snout swiping, discharge from nose and eye, salivation, blood in urine, dyspnea, respiration sounds, unsteady gait, trembling, loss of pain reflex, corrosion of nose and corneal opacity. Following initial weight loss the four surviving animals were free of symptoms from day 3 post treatment and gained weight, but the 2 females did not reach the initial pre-treatment body weights within the 14-d observation period. There were findings in survivors. Animals that died: lungs showed dark red to black areas, contained bloody, frothy liquid. Trachea was brown coloured in 3 animals. Stomach was severely distended in rats exposed 10 or minutes or longer. Urinary bladder content was bloody in 2 females. Intestinal tract was markedly reddened.

Kuznetsova (1975, in Russian) exposed mice and rats to various concentrations of formic acid. Mice died within 40-50 hours after inhalation of >3×10^3 mg/m^3 (>1590 ppm) (duration probably 15 min). Histological examination of animals dying 1-3 days post-exposure revealed hyperemia, and haemorrhage of the lungs, proliferation of parenchymal tissue, and dystrophy of kidneys, liver, spleen and cardiac muscle. The presented LC_{50} values for rat and mouse were 15.2 × 10^3 mg/m^3 and 6.2 × 10^3 mg/m^3), respectively.

Shell (1982) exposed Wistar rats (n=3/sex/conc) for 10 minutes to a concentration of 79,000 ppm (151,165 mg/m^3) formic acid. Animals were exposed whole body in a 10 L inhalation chamber. The exposure concentration was estimated from the weight loss of material from the reservoir, the air flow rate through the generator and the duration of exposure. All animals died at the first post-exposure observation day.

In the REACH registration dossier of formic acid, an acute inhalation study with Sprague-Dawley rats is presented (Unnamed Study Report, 1980/1981). Formic acid solutions with 10, 25 and 50% were used. Animals were exposed nose-only for 0.5-7h. Concentrations were not analytically determined. Also, it was stated that the calculated concentrations were not reliable as the weight of consumed water would falsify the result of such calculations. Mortality increased with the concentration of the formic acid solutions. Clinical signs indicate irritation/corrosion of the eyes and of the respiratory system.

		Exposure period (h)			
% formic acid solution	**Calculated concentration test substance (mg/l)**	**0.5**	**1**	**3**	**7**
10	19.5	-	-	-	0/12
25	19.9/21.5	-	-	0/12	1/6
50	No data	0/12	1/12	2/12	5/6

Appendix 2 Reference list

BASF (2014). Bestimmung der akuten Inhalationtoxizität LC_{50} von Ameisensäure als Dampf. Ergänzung Nr. 1 zum Bericht. Studienummer 78/651. Experimentelle Toxikologie und Okologie, BASF SE, Ludwigshafen, Germany.

BASF (1980). Bestimmung der akuten Inhalationtoxizität LC_{50} von Ameisensäure als Dampf bei 4stündiger Exposition an Sprague-Dawley Ratten. Studienummer 78/651

BASF AG (1979). Dept. of Toxicology, unpublished study (78/651), Dec. 3, 1979. As cited from ERPG (2008).

Chemiekaarten. Ed 33. Den Haag. TNO/SDU uitgevers, 2018.

ERPG. Emergency Response Planning Guideline; Formic acid. American Industrial Hygiene Association. 2008.

Hoechst (1981). As cited from ERPG (2008) and REACH registration dossier (accessed online 05-03-218)

Kuznetsova EE (1975). Data for establishment of a maximum permissible concentration of formic acid vapors in the air of a work zone. Gog. Trud. Prof. Zabol. 12:49-51. As cited in ERPG 2008. Article in Russian.

NTP (1992). NTP Technical Report on toxicity studies of Formic acid. Adminstered by inhalation to F344/N rats and B6C3F1 mice. NIH publication 92-3342.

RIVM 2017. Interventiewaarden gevaarlijke stoffen. http://www.rivm.nl/rvs/Normen/Rampen_en_incidenten/Interventiewaarden.

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

Shell (1982). Experiment RTB 2220. Test standardization: inhalation toxicity testing of 8 chemicals according to the OECD inhalation hazard test, TSCA Fiche OTS0205969.

Unnamed Study Report (1980/1981). As cited from REACH registration dossier (accessed online 05-03-218)