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

Probit function technical support document

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Status: interim
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substance name	CAS number
Allylamine	107-11-9

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.

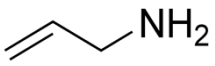
This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have 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 Allylamine

1. Substance identification



CAS-number:	107-11-9
IUPAC name:	Allylamine
Synonyms:	2-propeen-1-amine, 2-propenylamine
Molecular formula:	$CH_2=CHCH_2NH_2$
Molecular weight:	57.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	53°C (at 101.3 kPa)
Vapour pressure:	26.2 kPa (at 20°C)
Saturated vapour conc:	262000 ppm = 624 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.421 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.38 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H301-311-331

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

Acute effects: Allylamine is a severe respiratory, eye and skin irritant due to its alkaline character. The substance is known for its ability to cause cardiotoxicity. It has been used in several animal studies to induce cardiac and vascular lesions to model human cardiovascular disease. The toxicological mode of action is hypothesized to include the metabolic formation of acrolein and hydrogen peroxide. Exposed humans display eye, skin and respiratory irritation, headache, and nausea. Higher concentrations induced pulmonary oedema, haemorrhage in the alveolar space and cardiotoxicity (heart lesions) in animals. Mortality is likely the result of heart failure, lung failure or a combination thereof.

Long-term effects: Long-term effects after acute exposure have not been reported in the available literature. Chronic studies indicate the same effects after chronic exposure as seen after acute exposure.

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.

4. Animal acute toxicity data

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

1. AEGL document (final 2005) covering references before 1995. No ERPG document was 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:
   - allylamine and synonyms
   - CAS number
   - lethal*

[1] AEGL final 2005

- mortal*
- fatal*
- LC_{50}, LC
- probit

3. Unpublished data were sought through networks of toxicological scientists.

Animal lethal toxicity data considering acute exposure are described in Appendix 1. Two studies were identified with two datasets for one species with data on lethality following acute inhalation exposure. No datasets have been assigned status A for deriving the human probit function, one dataset was assigned status B2 and one has been assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

One 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 allylamine*

Species/strain	*RD_{50} (mg/m^3)*	*Exposure duration (min)*	*Author/year*
Mouse / male OF_1 Swiss	21^P	15	Gagnaire *et al.* 1989

[P] plateau was reached after 10 to 15 minutes.

5. Probit functions from individual studies

All available acute lethality data on allylamine are provided in Figure 1. Since it concerns data from one study, the data are used for animal and human probit function derivation.

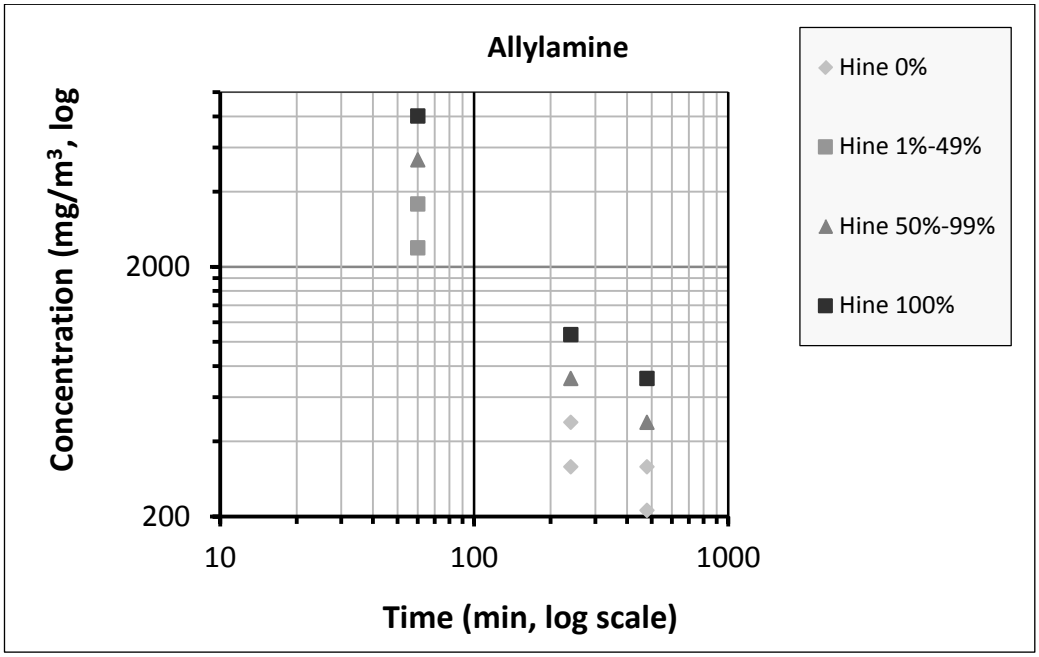


Figure 1 *All available acute lethality data for allylamine*

It was not possible to derive a probit function for allylamine based on studies with A quality. Therefore, the probit function was derived using data from the B2.1 study listed in the table below.

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

Table 2 *Data selected for derivation of the animal probit function of allylamine*

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	*-36.8 + 3.22 ×ln C + 3.68 × ln t*	8932 (6284-12690)

6. Derivation of the human probit function

The lethality data of allylamine is scarce. The study by Hine et al. (1960) was the only acute lethal toxicity study found for allylamine. The AEGL TSD mentions one additional study showing mortality after acute exposure; this study was aimed to determine the cardiotoxicity of allylamine after acute exposures. In this study, animals were sacrificed at various points in time after cessation of the exposure ranging from 8 hours to 14 days. As one animal died at day 5 after cessation of exposure, it is concluded that the observation periods were too short. For this reason, the data by Guzman et al. (1961) were not considered suitable for human probit function derivation.

To derive the human probit function the results from the study by Hine et al., 1960 (B2.1) have been used to derive a point of departure. As the point of departure for deriving the human probit function the calculated 30-min LC_{50} value (8932 mg/m^3) for the rat 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	Toxicity of allylamine is a combination of respiratory irritation and cardiotoxicity, hence not only caused by a portal of entry effect. In addition, sensory irritation as defined by the RD_{50} value is well below the calculated LC_{50} values, indicating an additional protection mechanism in the test species in comparison to humans.
Nominal concentration	1	Animals were exposed to vapour generated by evaporation, due to the high vapour pressure the actual exposure concentration is not expected to deviate much from the nominal concentration.
Adequacy of database:	1	One B2-study available including data for three exposure durations and information on sensory irritation.

The estimated human equivalent 30-minute LC_{50} value is 8930 / 3 = **2977 mg/m^3**.

The experimentally determined n-value was **0.87** (Hine et al., 1960). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **2.30**.

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): $5 = a + 2.30 \times \ln (2977^{0.87} \times 30)$ resulting in the a-value of **-18.82.**

$Pr = -18.8 + 2.30 \times \ln (C^{0.87} \times t)$ 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 a study in the rat with B quality, where 5 male animals per group were exposed to concentrations at three different exposure durations resulting in mortality rates ranging from 0%-100%.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 413 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 283 mg/m^3.

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
1% lethality, this probit	916	413
0.1% lethality, this probit	627	283
AEGL-3 (2005, final)	93	42
ERPG-3	N/A	N/A
LBW (2015)	430	200

Comparing these values with equivalent (inter)national guideline levels, amongst which the Dutch LBW (2015) and the AEGL-3, the derived probit function provides values are approximately a factor 1.5 to ten higher.

Appendix 1 Animal experimental research

Study ID: B2.1

Author, year: Hine et al., 1960

Compound: allylamine
Species, strain, sex: Rat, Long-Evans, male
Number/sex/concentration group: 5/group, 12 groups
Age and weight: Age not specified, weights ranged from 120-160 grams.
Observation period: 10 days

Criteria	*Comment*
Study carried out according to GLP	GLP did not exist at that time
Study carried out according to OECD guideline(s)	OECD guideline 403 did not exist at that time
Stability of test compound in test atmosphere	No information
Use of vehicle (other than air)	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 at breathing zone of animals	The metered fluid was delivered using a 10 ml Luer-Lok syringe into an evaporator through which metered air moved at a uniform rate.
Number of air changes per hour	Whole body: 7.0-9.5 L per minute in a 19.5-L chamber resulting in 21.5 to 29 air changes per h.
Equilibration time (t95)	t95 in minutes: 6.2 - 8.4 min
Start of exposure relative to equilibration	No information is provided about the start of exposure to the animals relative to equilibration time. If animals were present during the built up of the exposure, the animals were exposed at least 51 minutes of the 60 minutes at levels at t95 (95% of nominal concentration) or higher.
Actual concentration measurement	Concentration measurements were not performed, nominal concentrations were calculated.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	B2
	The study is assigned the B2-status, because it lacks analytically measured concentrations.

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			Exposed	Responded
Rat	2380	60	5	1
	3570	60	5	1
	5355	60	5	3
	8044	60	5	5
	317	240	5	0
	476	240	5	0
	714	240	5	3
	1071	240	5	5
	212	480	5	0
	317	480	5	0
	476	480	5	4
	714	480	5	5

Animals that died, died within 24-hr post-exposure.

Probit function

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

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

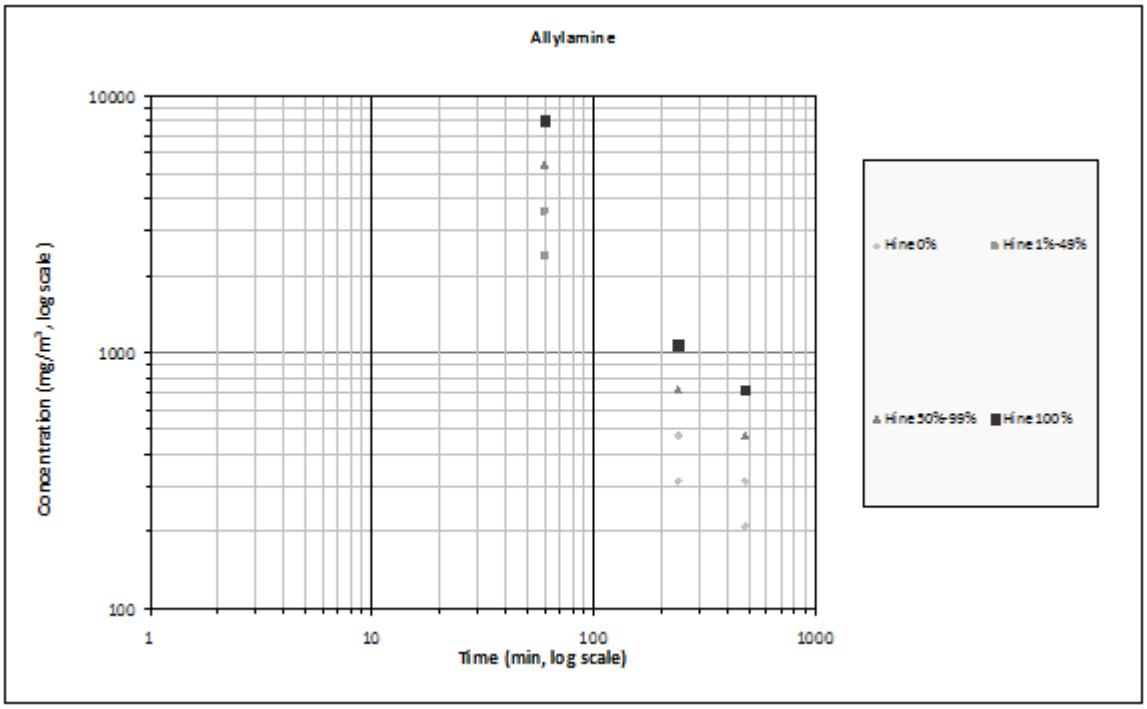
with C for concentration in mg/m^3, t for time in minutes and S for sex (0 = female, 1 = male).

Probit function	*Species*	*a*	*b*	*c*	*n-value*
	rat	*-36.8*	*3.22*	*3.68*	*0.874 (0.755-0.993)*

The probit function is based on male data.

The derived probit function provides the following LC_{50} values for the 10, 30 and 60 minute exposure duration.

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I. combined*
10	31380 (18460-53152)
30	8930 (6284-12690)
60	4041 (3155-5188)


Allylamine
10000
1000
100
Concentration (mg/m³, log scale)
1
10
100
1000
Time (min, log scale)
Hine 0%
Hine 1%-49%
Hine 50%-99%
Hine 100%

1
2

Study ID: C studies

The AEGL reported a study by Guzman et al. (1961) where cardiotoxicity was tested in the Long-Evans rat after allylamine exposure. The concentrations tested ranged from 20-100 ppm (48-238 mg/m^3) for durations ranging from 4 to 48 hours. The number of animals per group ranged from 1 to 20 rats. The animals were sacrificed periodically to examine the heart after 8 hours to 14 days after cessation of the exposure. Two rats died spontaneously (prior to sacrifice). One died 5 days after 4 hr exposure to 238 mg/m^3 and another died immediately after 8 hr exposure to 95 mg/m^3. Because this study included short observation periods; the study was given the C status.

Appendix 2 Reference list

AEGL 2005, NAS/COT subcommittee for Acute Exposure Guideline Levels, Allylamine (CAS Reg. No. 107-11-9), Final 2005.

Chemiekaarten. Allylamine (drukhouder), 31e editie. 2016

Dutch Intervention Values (2015) Allylamine

Gagnaire, F., S. Azim, P. Bonnet, P. Simon, J.P. Guenier, and J. De Ceaurriz. 1989. Nasal irritation and pulmonary toxicity of aliphatic amines in mice. J. Appl. Toxicol. 9:301-304.

Hine, C.H., J.K. Kodama, R.J. Guzman, and G.S. Loquvam. 1960. The toxicity of allylamines. Arch. Environ. Health 1:343-352.