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
Propylamine	107-10-8

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 Propylamine

1. Substance identification

CAS-number:	107-10-8
IUPAC name:	Propylamine
Synonyms:	1-aminopropane, 1-propane amine, n-propylamine
Molecular formula:	$C_3H_7NH_2$
Molecular weight:	59.1 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	48°C (at 101.3 kPa)
Vapour pressure:	32.9 kPa (at 20°C)
Saturated vapor conc:	320900 ppm = 809 g/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.41 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.46 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H302-311-331-314

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

Acute effects: The substance is a strong basic amine. Propylamine vapour causes irritation of the eyes (corneal oedema), skin and respiratory tract manifested as lacrimation and lesions in the nasal mucosa. Lung oedema may occur at sufficiently high exposure concentrations. This effect may be delayed, and worsened by physical exercise. The substance also affects the central nervous system. Cause of lethality is not exactly known, but likely the result of combined neurotoxicity and severe respiratory difficulties.

Long-term effects: Long-term effects as a result of acute exposure have not been reported in the available literature.

3. Human toxicity data

No informative reports on the 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 the literature search the following technical support documents and databases were consulted:

1. No AEGL or ERPG document was available for this substance.
2. The ECHA public dissemination website and reference database for propylamine, covering references.
3. 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:
   - Substance name and synonyms
   - CAS number
   - lethal*
   - mortal*
   - fatal*
   - LC_{50}, LC
   - probit

[1] Hine et al., 1960.

4. 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 2 studies were identified -with 2 datasets for 1 species- with data on lethality following acute inhalation exposure. One dataset was assigned the status B1 for deriving the human probit function. The other study was assessed to be unfit for probit function derivation (status C). Four LC_{50} values (rat and mouse) were reported in secondary literature, however no experimental details were provided (see appendix 1, section C studies).

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 propylamine*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
Rat	453^{NS}	Unknown	Nielsen and Vinggaard, 1988

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

5. Probit functions from individual studies

All available acute lethality data on propylamine are provided in Figure 1.

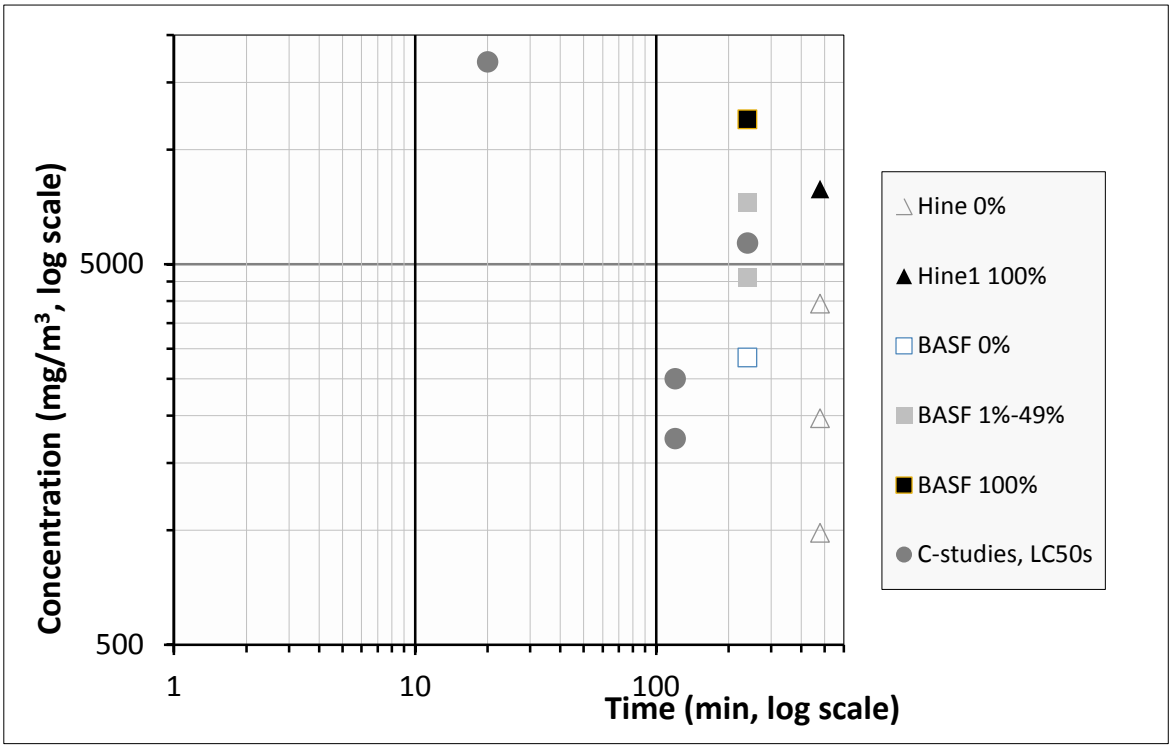

Figure 1 *All available acute lethality data for propylamine*

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

It was possible to derive a probit function for propylamine based on the available study with B1 quality (study B1.1; BASF, 1978). 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 the table below.

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

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50}, 240 minutes (mg/m^3) 95% C.I.
B1.1	Rat	-20.4 + 2.87×lnC	7057 (6130-8188)

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

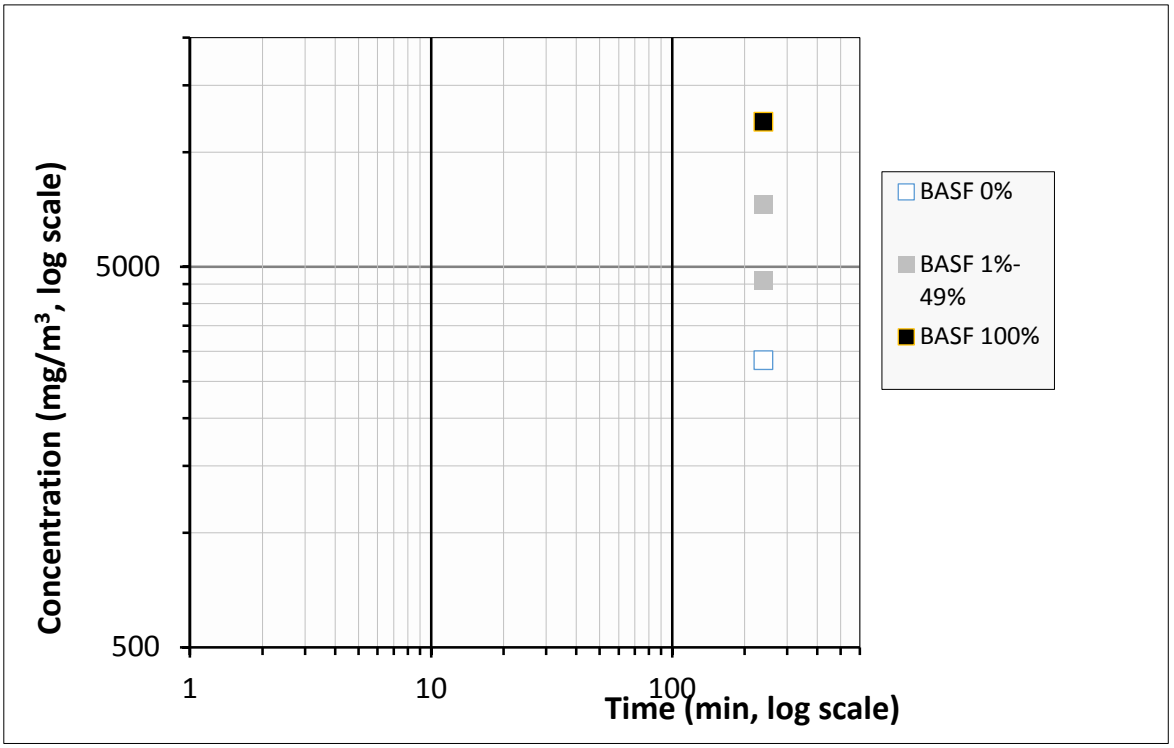

Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of propylamine.*

The final data eligible for calculating the animal probit function contains one dataset from one study and includes data from one animal species (see Table 2).

The data of the selected dataset is presented graphically below.

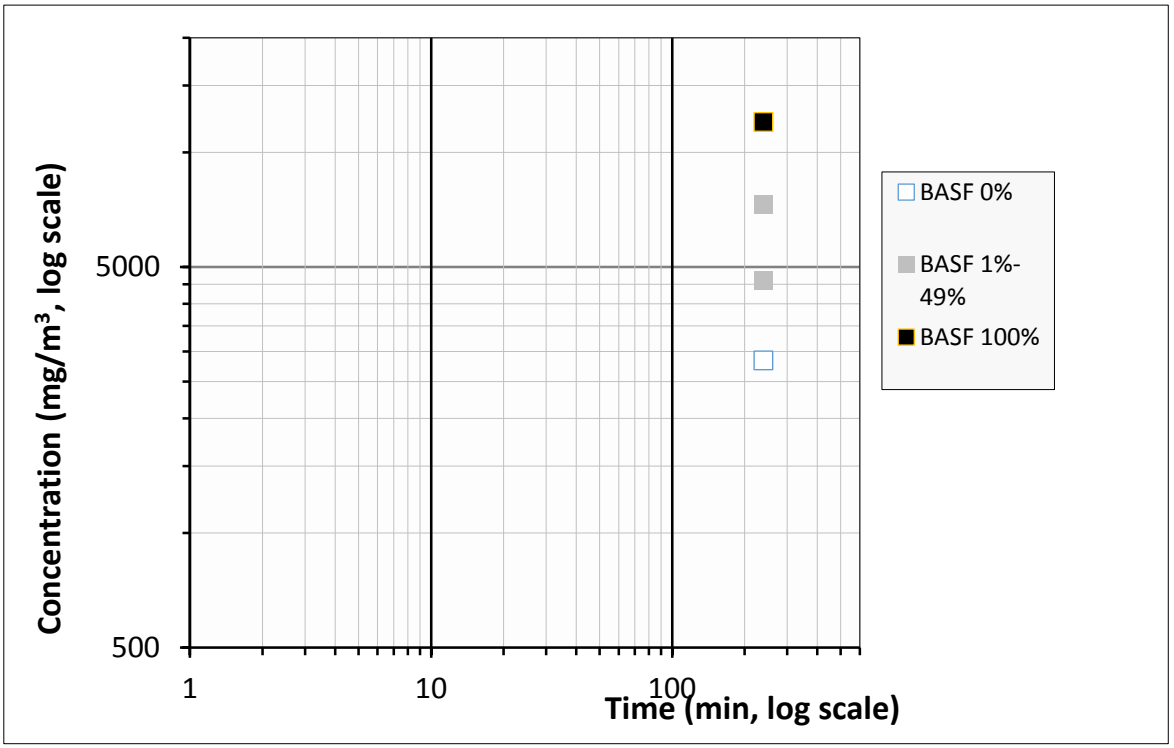

Figure 3 *Final data selected for derivation of the animal probit function of propylamine (identical to figure 2)*

6. Derivation of the human probit function

To derive the human probit function, the results from study report by BASF (1978) have been used to derive a point of departure. The reason was that it was the only study from which a reliable LC_{50} value could be obtained. The Hine et al. (1960) study only showed 0% or 100% mortality where all animals died during exposure, leading to an unreliable LC_{50} value. Other reported LC_{50} values could not be evaluated (see other C studies in appendix).

As a point of departure for deriving the human probit function, the 240 min LC_{50} value of 7057 mg/m^3 for the rat from the study report by BASF (B1 quality study) 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 propylamine 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	Analytical concentrations.
Adequacy of database:	2	One B1 study is available, where only one duration was tested thus providing no information on the n-value. Remaining information are inadequate to support a lower factor.

The estimated human equivalent 240-minute LC_{50} value is 7057 / 6 = 1176 **mg/m^3**.

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 240 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1 \times \ln(1176^2 \times 240)$ resulting in the a-value of **-14.62**.

$Pr = -14.6 + 1 \times \ln(C^2 \times t)$ 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 1 study in the rat with B1 quality, where 20 animals per group were exposed.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 726 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 497 mg/m^3.

Estimated level	30 min (mg/m^3)	60 min (mg/m^3)
1% lethality, this probit	1027	726
0.1% lethality, this probit	702	497
AEGL-3	-	-
ERPG-3		-
LBW (2007)		500

Compared with equivalent (inter)national guideline levels as presented in the table above, the lethal levels derived with this probit function are similar to a factor 2 higher than the LBW.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: Study report 1978 by BASF
Substance: propylamine
Species, strain, sex: Rat, Sprague-Dawley, males and females
Number/sex/concentration group: 10
Age and weight: 185 ± 15 g, no age specified.
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 guideline(s)	OECD guideline 403 did not exist at the time (prior to 1981), but indicated that it was conducted similarly
Stability of test compound in test atmosphere	stable
Use of vehicle (other than air)	N/A
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	Test substance was administered by known concentration and flow to an evaporator at 24 °C where it is mixed with air and introduced in a 200 L inhalation chamber.
Number of air changes per hour	No information
Equilibration time (t95)	No information
Start of exposure relative to equilibration	No information
Actual concentration measurement	Concentrations were determined by gas chromatography by drawing 1 L/min test atmosphere from breathing zone of the animal.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	**B1** Study included one exposure duration and was therefore not given the A status.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	
	12.0×10^3	-	240	10/10	10/10
	7.27×10^3	-	240	5/10	2/10
	4.6×10^3	-	240	3/10	1/10

	2.84 x 10^3	-	240	0/10	0/10

Probit function

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

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

with C for concentration in mg/m^3 and S as covariate for sex,

Probit function	Species	a	b	C	d	n-value
Sexes combined	Rat	-20.4	2.87	-	-	-
Sex as covariate	Rat	-22.2	3.02	-	0.70	-

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 (minutes)	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	6305 (5184-7698) 6320 (by study author)	7946 (6529-9779) 7870 (by study author)	7057 (6130-8188)

C studies

Author, year: Hine et al., 1960
Substance: Propylamine
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

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 guideline(s)	OECD guideline 403 did not exist at the time.
Stability of test compound in test atmosphere	No information.
Use of vehicle (other than air)	N/A
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	No information
Number of air changes per hour	Whole body: 7.0-9.5 L/minute in a 19.5 L chamber.
Equilibration time (t95)	6.16 to 8.36 minutes
Start of exposure relative to equilibration	No information
Actual concentration measurement	The metered fluid was delivered using a 10 mL Luer-Lok syringe into a evaporator through which metered air moved at a uniform rate. Concentration measurements were not performed, nominal values calculated.
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	N/A
Assessment of Reliability	C This study by Hine et al. either showed no mortality or 100% mortality and therefore did not allow probit function derivation. Further, the information as to the exact time of death is unknown.

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			Exposed	Responded
Rat	984	480	5	0
	1,968	480	5	0
	3,936	480	5	0

	7,872	480	5	5

The data from this study do not allow probit function derivation. The reported 8-hour LC_{50} value of 5,683 mg/m^3 is considered to be unreliable, because only 0% and 100% mortality was observed, and all animals that died, died after 4 to 6 hours exposure. Therefore, the 8-hour LC_{50} value of 5,683 mg/m^3 is highly uncertain.

Other C studies.

Additional LC_{50} values were reported in secondary sources of which the original studies could not be retrieved. A 4-hour LC_{50} in rats of 5,683 mg/m^3 was reported which refers to the debatable 8-hour LC_{50} reported by Hine et al. (1960; see above). A 2-hour LC_{50} in mice of 2,500 mg/m^3 was reported by Izmerov et al. (1982, in Russian). The Dutch Interventions Values Substance Document for propylamine (2007) further makes mention of a 2-hour LC_{50} in rats of 1,740 mg/m^3. Because these LC_{50} values are not in agreement with Hine et al. (1960) or BASF (1978) and experimental details are not available for evaluation, none of these LC_{50} values were used for probit function derivation.

Additionally, in a MSDS one other LC_{50} was found, that could not be traced back to a source: a 20-min LC_{50} of 6920 ppm (17000 mg/m^3). This value however does not seem to be contradictive with BASF (1978) and Hine et al. (1960).

Appendix 2 Reference list

BASF, 1978. Bericht über die Bestimmung der akuten Inhalationstoxizität LC_{50} von n-Propylamin bei 4stündiger Exposition an Sprague-Dawley-Ratten (confidential data; full study report evaluated).

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

Izmerov et al., 1982. “Toxicometric parameters of industrial toxic chemicals under single exposure”. Moscow, Centre of International Projects. (in Russian).

Nielsen G.D., Vinggaard A.M. 1988. Sensory irritation and pulmonary irritation of C3-C7 n-alkylamines: mechanisms of receptor activation. Pharmacol. Toxicol. 63(4) : 293-304

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