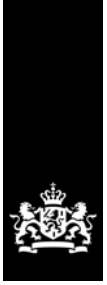


National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Probit function technical support document

Date: 6 June 2017
Document id: 20170606- Methylamine -INTERIM
Status: interim
Author: L. Geraets (RIVM)

substance name	CAS number
Methylamine	**74-89-5**

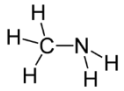
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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 "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 Methylamine



1. Substance identification

CAS-number:	74-89-5
IUPAC name:	monomethylamine
Synonyms:	aminomethane, methanamine, monomethylamine, MMA
Molecular formula:	CH_3NH_2
Molecular weight:	31.1 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	-6°C (at 101.3 kPa)
Vapour pressure:	314 kPa (at 20°C)
Saturated vapor conc:	NA
Conversion factor:	1 mg/m^3 = 0.773 ppm (at 20°C and 101.3 kPa)
	1 ppm = 1.294 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H315-H318-H332-H335

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

Acute effects: The substance is a primary aliphatic amine. Methylamine causes irritation of the eyes, skin and respiratory tract manifested as lacrimation and lesions in the nasal mucosa. At sufficiently high concentrations severe lesions in the nasal area and lungs are reported. Occasionally, also effects in the liver, kidney and brain have been observed at high concentrations. Methylamine also caused neurotoxicity in animals of which the etiology is unclear. The severe lung lesions and related breathing difficulties may be lethal.

Long-term effects: There is no information available concerning the long-term effects after acute exposure. Non-lethal acute toxicity studies reveal that tissue repair occurs. This does not, however, rule out the possibility of irreversible effects. Chronic studies reveal similar toxicity signs as indicated under acute effects. Systemic effects, such as liver and kidney toxicity, are generally observed in chronic studies.

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. AEGL interim TSD (2008), ERPG document (2015) and EU RAR and reference database for methylamine, covering references before and including 1995.
2. The ECHA public dissemination website for methylamine.
3. 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*

[1] AEGL 2008

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

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 7 studies were identified -with 7 datasets for 2 species- with data on lethality following acute inhalation exposure. One dataset was assigned status A for deriving the human probit function, two datasets was assigned status B and four were 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 Methylamine*

Species/strain	RD_{50} (mg/m^3)	Exposure duration (min)	Author/year
OF_1 Swiss Mice, male	182 [NS]	15	Gagnaire *et al.*, 1989

NS: not specified if a plateau in response was reached

5. Probit functions from individual studies

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

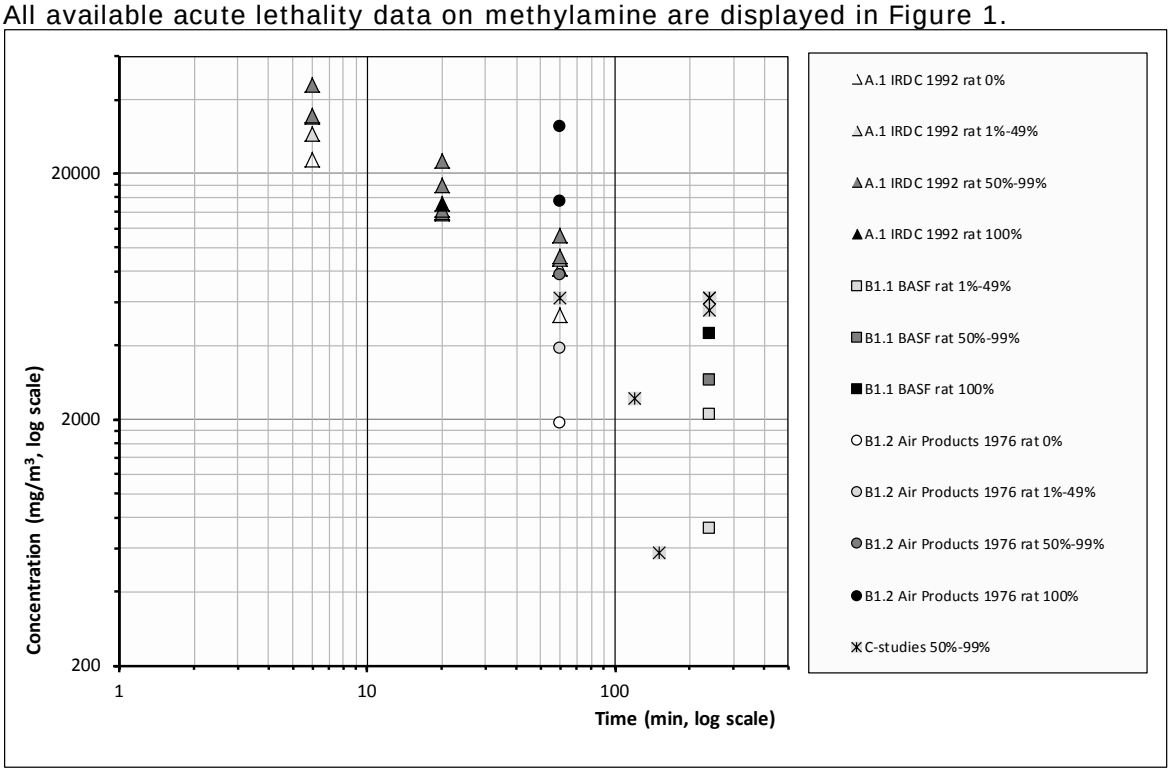


Figure 1 *All available acute lethality data for methylamine.*

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

All A and B1 studies were selected for derivation of the animal probit function for methylamine.

To enable intra-species pooling, LC_{50}-values of B1-studies were scaled using the rat n-value of 1.87 (derived from study A.1 (IRDC 1992)) for methylamine with the following formula (section 6):

$$LC_{50,c} = LC_{50,test}\left(\frac{t_{test}}{t_c}\right)^{(1/n)}$$

With $LC_{50,c}$ = scaled LC_{50} value for common exposure duration t_c
$LC_{50,test}$ = observed LC_{50} value for tested exposure duration
t_c = common exposure duration for intra-species pooling
t_{test} = tested exposure duration
n = species specific (for rat) n-value

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 methylamine.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
A.1	Rat	-38.0 + 3.83xlnC + 2.05xlnt		12270 (11080 - 13380)	1.87 (1.57 – 2.17)
B1.1	Rat	*240-min LC_{50}*	1987 (438.6 - 3293)	*6041*	N/A
B1.2	Rat	*60-min LC_{50}*	6250 (4613 - 8466)	*9054*	N/A

The data of the rat studies A.1 (IRDC, 1992), B1.1 (BASF) and B1.2 (Air Products, 1976) are presented graphically below.

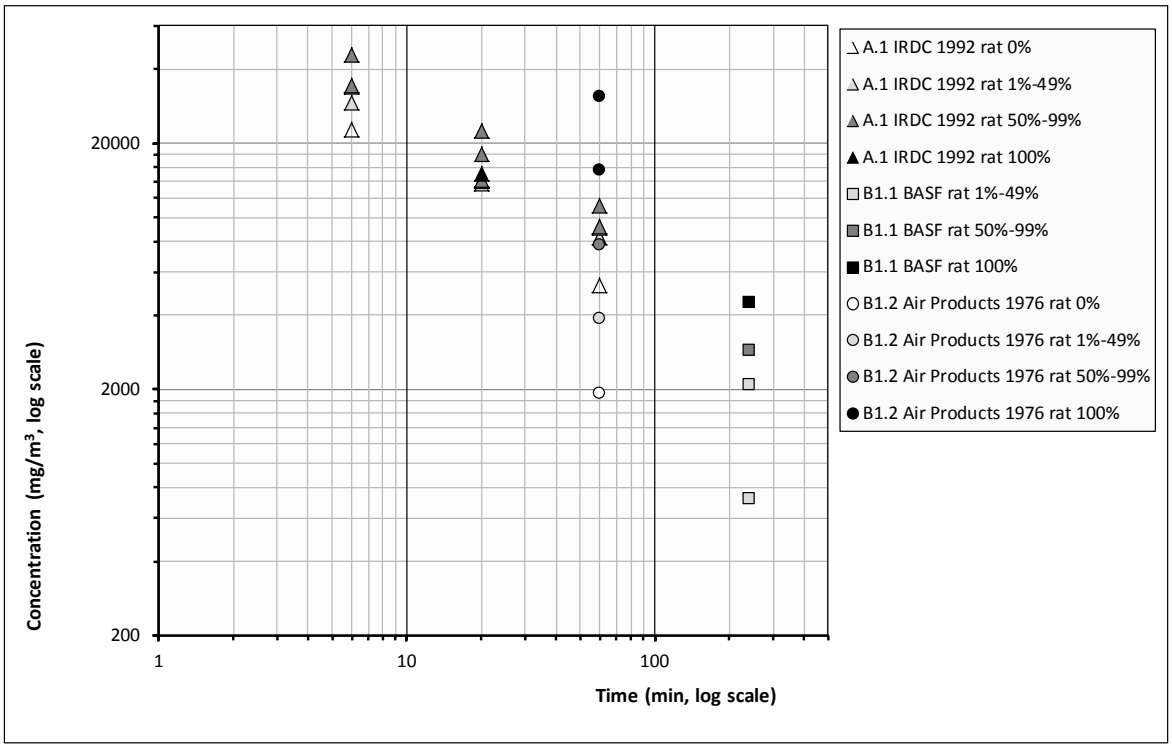


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of methylamine.*

Based on criteria outlined in the guideline the data from studies A.1 and B1.2 were selected for the final dataset for the derivation of the animal probit function.
There appears to be a difference in LC_{50}-values of rat studies A.1, B1.1 and B1.2. Available information on the slope is limited, as only one good-quality rat C x t study is included in the database. Therefore, no conclusion can be drawn whether or not the data of the different datasets (rat studies A.1, B1.1 and B1.2) converge.
Study A.1 included multiple exposure durations ranging from 6-60 min. As a point of departure for the human probit function, a 30-min LC_{50} is preferred. The derivation of a weighted geometric mean LC_{50} value as a point of departure for a probit function requires LC_{50} values for the same exposure duration. Therefore, as the extrapolation from an exposure duration of 60-min to a 30-min value is less uncertain, study B1.2 was included in the final calculations. The 240-min rat study of BASF (1983; study B1.1) was not included for the final dataset for the derivation of the animal probit function because extrapolation to the target exposure duration of 30-60 minutes is believed to be too uncertain. In addition, an exposure duration of 240 min is outside the range of exposure durations included in the A.1 C x t study.

Figure 3 provides an overview of LC_{50} values and LC_{50}-time relationships for all studies in the final analysis. The data that were selected for final analysis of the animal probit function are presented in Table 3 and Figure 4.

The final data eligible for calculating the animal probit function contains two datasets from two studies and includes data from one animal species (*i.e.* rat).

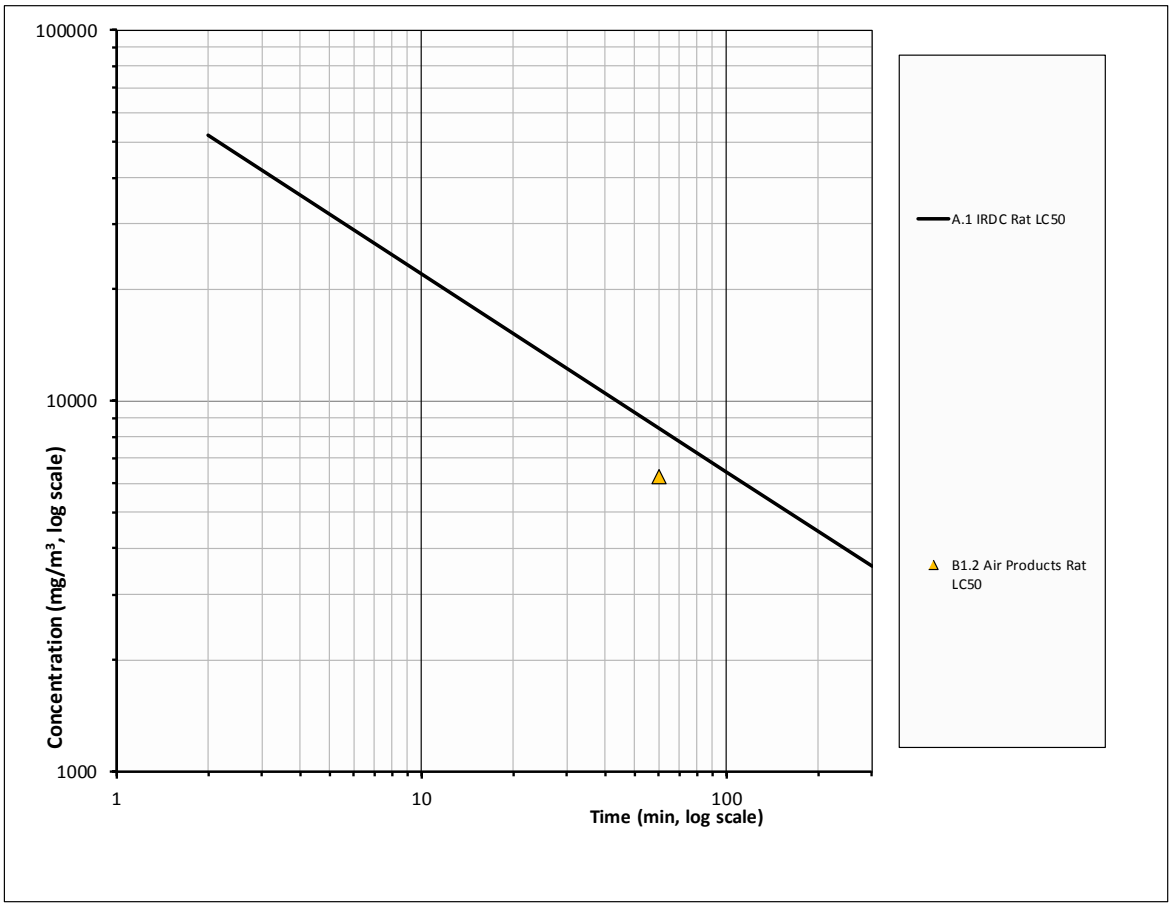


Figure 3 *LC_{50} values of A.1 and B1.2 datasets for methylamine, over time where available.*

Table 3 *Data selected for the derivation of the animal probit function of methylamine.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I. (specify exposure duration)	LC_{50}, 30 minutes (mg/m^3) 95% C.I. *(underline italic for scaled values)*	n-value 95% C.I.
A.1	Rat	-38.0 + 3.83xlnC + 2.05xlnt		12270 (11080 - 13380)	1.87 (1.57 – 2.17)
B1.2	Rat	*60-min LC_{50}*	6250 (4613 - 8466)	*9054*	N/A

The data of the selected datasets are presented graphically below.

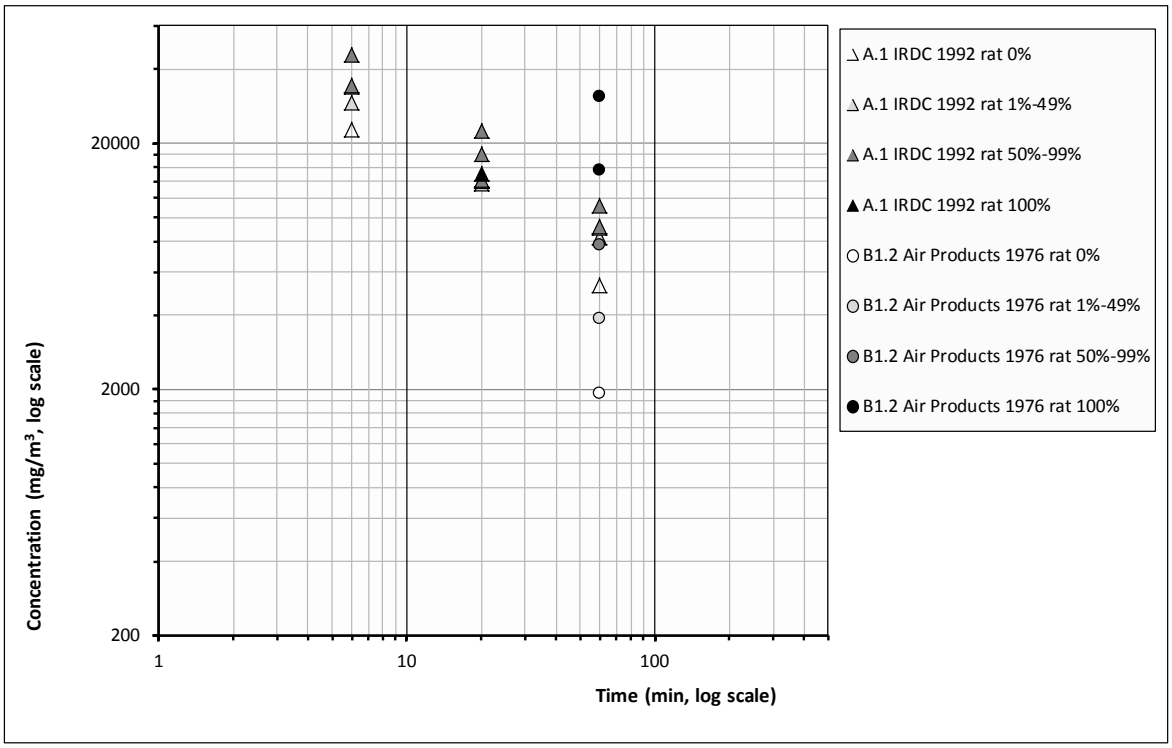


Figure 4 Final data selected for derivation of the animal probit function of methylamine.

6. Derivation of the human probit function

To derive the human probit function the results from the rat studies of IRDC (1992; study A.1) and Air Products (1976; study B1.2) have been used for derivation of a point of departure as outlined above.

An n-value of 1.87 was derived from rat study A.1 (IRDC, 1992).

The LC_{50}-values of all applicable A- and B1-studies were calculated for a common exposure duration of 30 minutes. To enable this intra-species pooling, LC_{50}-values of B1-studies were scaled using the species specific (for rat) n-value of 1.87 with the following formula:

$$LC_{50,c} = LC_{50,test}\left(\frac{t_{test}}{t_c}\right)^{(1/n)}$$

With $LC_{50,c}$ = scaled LC_{50} value for common exposure duration t_c
$LC_{50,test}$ = observed LC_{50} value for tested exposure duration
t_c = common exposure duration for intra-species pooling
t_{test} = tested exposure duration
n = species specific (for rat) n-value

Finally, the species-specific geometric mean LC_{50}-values were calculated from all available (time-scaled) LC_{50} values of studies A.1 and B1.2. The 30-min species-specific LC_{50}-value was 10540 mg/m^3 for the rat. The overall formula for the geometric mean of time-scaled LC_{50}-values is as follows:

$$\overline{LC_{50}} = \left[\prod_{j=1}^{s}\left(\prod_{i=1}^{m} LC_{50,i}\right)^{1/m}\right]^{(1/s)}$$

With $\overline{LC_{50}}$ = geometric mean LC_{50}-value across species
$LC_{50,i}$ = LC_{50}-value of study i.
m = number of observations on LC_{50}-values within a species (i=1…m).
s = number of species for which LC_{50}-values are pooled (j= 1…s).

The Point of Departure for the human probit function is a 30-minute geometric mean animal LC_{50} value of 10540 mg/m^3 and n-value of 1.87.

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. In addition, sensory irritation as defined by the RD_{50} value is well below calculated LC_{50} values, indicating an additional protection mechanism in the test species in comparison to humans.
Nominal concentration	1	Analytically determined concentrations
Adequacy of database:	1	Database consists of well conducted A and B1 studies

The estimated human equivalent 30-minute LC_{50} value is 10540 / 3 = **3513 mg/m^3**.

The experimentally determined n-value was **1.87** (A.1; IRDC (1992)). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.07**.

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): $5 = a + 1.07 \times \ln(3513^{1.87} \times 30)$ resulting in the a-value of **–15.00**.

$Pr = -15.0 + 1.07 \times \ln(C^{1.87} \times t)$ 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 one study in the rat with A quality and one study in the rat with B1 quality. Further, these data included in total 21 C x t combinations, including durations from six minute to 60 minutes and lethality in the range of 0-100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 524 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 766 mg/m^3.

Table 5 *LC-vales 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	759	524
1% lethality, this probit	1110	766
AEGL-3[2] (2008, interim)	660	453
ERPG-3[2] (2015)	-	647
LBW (2015)	660	450

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

[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: A.1

Author, year: IRDC, 1992
Substance: methylamine
Species, strain, sex: rat, albino, male and female
Number/sex/conc. group: 5/sex/group
Age and weight: 48-76 days; 205-298 g (males) and 162-222 g (females)
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes, according to US EPPA TSCA GLP*
Study carried out according to OECD 403 guideline(s)	*No statement of compliance with OECD guideline 403 provided; however, study seems to be according to OECD TG 403.*
Stability of test compound in test atmosphere	*Stable*
Use of vehicle (other than air)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*NA*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*A metered amount of gas was mixed with compressed air and introduced in the test chamber.*
Number of air changes per hour	*Air flow of approximately 51 L/min (range: 50.19 - 51.9 L/min) in a 150 L chamber. This approximates 20 air changes per hour.*
Equilibration time (t95)	*8.8 min*
Start of exposure relative to equilibration	*Probably after complete equilibration. It is stated that exposures were conducted in a specially designed chamber which permitted stable exposure concentrations to be established prior to animal entry. A transfer chamber was used to move the animals rapidly (within 10 sec) into and out of the exposure atmosphere.*
Actual concentration measurement	*Gas-phase IR spectrometry, with 20 meter variable-pathlength gas cell, which was calibrated prior to exposure. Measurements were continuous and reported every two minutes. Actual concentrations did not deviate much from target concentration.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*NA*
Assessment of Reliability	***A*** *Well-performed study including multiple exposure duration and concentration combinations.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality	
	Measured	Adjusted		Male	Female
				Dead/tested	Dead/tested
Rat	22774	NA	6	0/5	0/5
Rat	29115	NA	6	2/5	1/5
Rat	33903	NA	6	5/5	4/5
Rat	34291	NA	6	3/5	3/5
Rat	45678	NA	6	4/5	5/5
Rat	13716	NA	20	2/5	1/5
Rat	13975	NA	20	4/5	2/5
Rat	14234	NA	20	4/5	2/5
Rat	15010	NA	20	5/5	5/5
Rat	17987	NA	20	3/5	5/5
Rat	22516	NA	20	5/5	4/5
Rat	5305	NA	60	0/5	0/5
Rat	8243	NA	60	1/5	1/5
Rat	9058	NA	60	4/5	0/5
Rat	9187	NA	60	3/5	3/5
Rat	11219	NA	60	5/5	4/5

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).

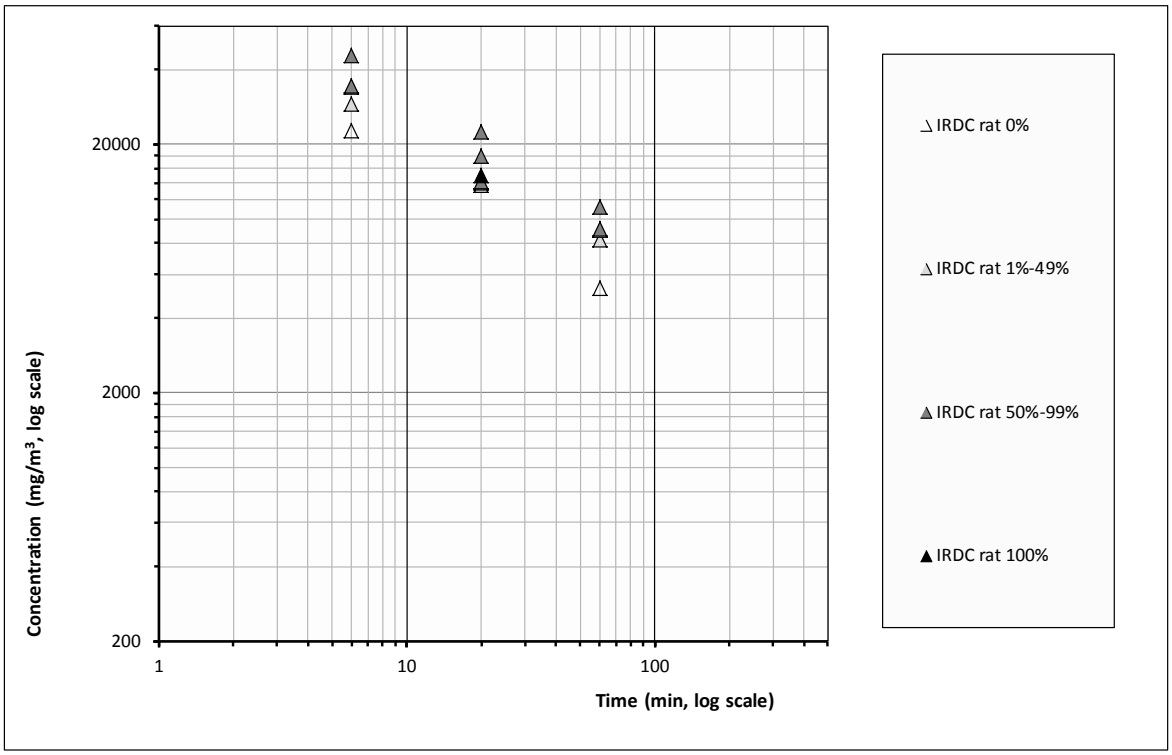
Probit function	Species	a	b	c	d	n-value
Sex as covariate	Rat	-38.4	3.88	2.08	-0.40	1.87 (1.57 – 2.16)
Sexes combined	Rat	-38.0	3.83	2.05	-	1.87 (1.57 – 2.17)

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
10	20990 (17880 - 23750)	23270 (20330 - 26530)	22080 (19620 - 24320)
30	11650 (10050 - 13070)	12910 (11410 - 14630)	12270 (11080 - 13380)
60	8033 (6730 - 9317)	8903 (7618 – 10450)	8467 (7353 - 9636)

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.

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

A graphical overview of the data is presented below. Each concentration-time combination (with 5 male and 5 female animals) represents one point in the plot.


20000
2000
200
1
10
100
Concentration (mg/m³, log scale)
Time (min, log scale)
IRDC rat 0%
IRDC rat 1%-49%
IRDC rat 50%-99%
IRDC rat 100%

1
2

Study ID: B1.1

Author, year: Study report 1983 by BASF
Substance: Methylamine
Species, strain, sex: Rat, Wistar, male and female
Number/sex/conc. group: 10/sex/group, 5 animals per cage
Age and weight: 8 weeks, males: 248 ± 35 g, females: 175 ± 15 g
Observation period: 14-15 days

Evaluation of study quality

Criteria	Comment
Study carried out according to GLP	*No GLP statement provided*
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	*No information*
Use of vehicle (other than air)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*NA*
Pressure distribution.	*Negative pressure of 1.7%.*
Homogeneity of test atmosphere in breathing zone of animals	*Metered test substance was mixed with air and introduced in a 200 L inhalation chamber.*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Concentrations were determined by gas chromatography by drawing test atmosphere once per hour from the breathing zone of the animal*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*NA*
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	0.72×10^3	NA	240	0/10	2/10
Rat	2.1×10^3	NA	240	2/10	3/10
Rat	2.9×10^3	NA	240	8/10	9/10
Rat	4.5×10^3	NA	240	10/10	10/10

Probit function

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

$Pr = a + b \times \ln C + d \times S$

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

Probit function	Species	a	b	d	n-value
Sex as covariate	Rat	-9.66	1.89	0.52	-
Sexes combined	Rat	-8.70	1.80	-	-

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	2297 (311.3 - 5795)	1749 (113.7 – 3972)	1987 (438.6 - 3293)

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: B1.2

Author, year: Air Products 1976
Substance: Methylamine
Species, strain, sex: Rat, albino, male
Number/sex/conc. group: 10 males/group
Age and weight: age and body weight not 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 403 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)	*No*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*NA*
Pressure distribution.	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*The test atmosphere was obtained by mixing the methylamine gas with air.*
Number of air changes per hour	*Air flow of 16.7 L/min applied in a 70 L exposure chamber; resulting in approximately 14 air changes per hour*
Equilibration time (t95)	*12.6 min*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Exposure was probably based on nominal concentrations and exposure concentrations were not analytically determined.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*NA*
Assessment of Reliability	***B1*** *Study limited to one exposure duration. Although exposure was based on nominal concentrations, this is considered acceptable:* - *For gases, efficiency for dynamic test atmosphere generation is expected to be near 100%, hence it is assumed that the actual concentration will be close to the nominal concentration if the gas and the dilution airflow have been measured correctly.* - *Based on the available data, the airflow measurements were considered acceptable.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	1941	NA	60	0/10
Rat	3882	NA	60	2/10
Rat	7764	NA	60	6/10
Rat	15528	NA	60	10/10
Rat	31056	NA	60	10/10

Probit function

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

$Pr = a + b \times \ln C$

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
Sex as covariate	Rat	-14.0	2.17	-

Duration (minutes)	LC_{50} (mg/m^3) 95%-C.I. Male
60	6250 (4613 - 8466)

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

Study ID: C.1

Author, year: Koch *et al*., 1980
Substance: Methylamine
Species, strain, sex: rats, Wistar, female
Number/sex/conc. group: 10/group, 27 groups divided into three series. The series were defined as having a certain exposure concentration range and temperature.
Age and weight: 8 weeks old, 180-203 g (average weight per series)
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*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	*Filtered air, adjusted to achieve a certain level of humidity during exposure*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*NA*
Pressure distribution.	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*Test atmosphere was generated by passing air through filters before mixing with the test substance. The mixed air stream was then introduced into the chamber.*
Number of air changes per hour	*No information*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Test atmosphere was analysed during exposure by gas chromatography*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*NA*
Assessment of Reliability	***C*** *No individual animal data presented. Experiment limited to one exposure duration. Few study details are available. LC_{50} values and confidence intervals are provided. The method of probit-analysis was used for LC_{50} calculation.*

Results

Individual animal lethality data were not provided. The authors calculated LC_{50} values using probit analysis.

Species	Concentration range tested (mg/m3)	Exposure duration (min)	Temperature (°C)	LC_{50} (mg/m^3) 95%-C.I. female
Rat	2406 - 13505	240	22.3	6222 (4680 - 8271)
Rat	3584 - 8916	240	22.2	6272 (5248 - 7495)
Rat	3584 - 8916	240	29.1	5690 (5097 - 6352)

1

Study ID: other C studies

Sarkar and Sastry (1992) reported a rat 2.5h LC_{50} of 578 mg/m^3 with a 95 % confidence interval of 510 – 655 mg/m^3. Female albino rats (age: 2 months, bw: 80-100g) were exposed for 2.5h via whole-body inhalation to methylamine vapour. The test atmosphere was prepared from a 40% aqueous methylamine solution, in a glass bell jar of 12.5 L capacity. Methylamine solution was kept in the bell jar for 3h prior to the exposure of the animals. A post-exposure observation period of 24h was included, which is considered not sufficient to cover for possible delayed deaths.

In the report of DuPont Company (1985) of the 2-week rat inhalation study, a 4-hour rat approximate lethal concentration of 4300 ppm (5564 mg/m^3) was reported based upon a preliminary range-finding study. The study report of the preliminary range-finding study is not available to the Probit Panel.

Gorbachev (1957; as presented in AEGL 2008) determined an LC_{50} of 1890 ppm (2446 mg/m^3) for mice exposed for 2 hours to methylamine. No further method details, including the test concentrations, were available. Methylamine intoxication was characterized by agitation, nasal blood discharge, labored breathing, cyanosis, head tremors, shaky gait, heightened reflexes, clonic spasms, and death from respiratory standstill. Pathomorphological study of dead animals revealed pulmonary hemorrhage, necrotic tracheobronchitis, and hyperemia in blood vessels of internal organs and of the brain. Animals that died later had dystrophic changes in the liver and kidneys.

Appendix 2 Reference list

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