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

**Probit function technical support document**

Date: 15 February 2017
Document id: 20170215-dimethylamine-interim
Status: interim
Author: Drs. W ter Burg, RIVM

| substance name | CAS number |
|---|---|
| Dimethylamine | 124-40-3 |

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.

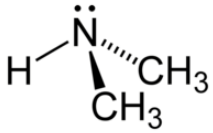
This document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM). The contents of this document, including the probit function, has been approved by the Dutch Expert Panel on Probit Functions on scientific grounds. External parties have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

## 1. Substance identification



| | |
|---|---|
| CAS-number: | 124-40-3 |
| IUPAC name: | Dimethylamine |
| Synonyms: | DMA, *N*-methylmethanamine |
| Molecular formula: | $(CH_3)_2NH$ |
| Molecular weight: | 45.08 g/mol |
| Physical state: | gas (at 20°C and 101.3 kPa) |
| Boiling point: | 7°C (at 101.3 kPa) |
| Vapour pressure: | 170 kPa (at 20°C) |
| Saturated vapour conc: | NA |
| Conversion factor: | 1 mg/m$^3$ = 0.532 ppm (at 20°C and 101.3 kPa) |
| | 1 ppm = 1.88 mg/m$^3$ (at 20°C and 101.3 kPa) |
| Labelling: | H315, 318, 332, 335 (gaseous) |
| | H302, 314, 332, 335 (60% aqueous solution) |

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

**Acute effects**: The substance is a basic secondary aliphatic amine. Dimethylamine 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 lesions in the liver, kidney and testes have been observed at high concentrations. Dimethylamine 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 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 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 a literature search, the following technical support documents and databases were consulted:

1. AEGL interim TSD, ERPG document and EU RAR and reference database for dimethylamine, covering references before and including 1995.
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:
    - Substance name and synonyms

[1] AEGL interim 2008.

- 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 4 datasets for 2 species- with data on lethality following acute inhalation exposure. One dataset was assigned status A for deriving the human probit function, 3 datasets 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 dimethylamine*

| Species/strain | $RD_{50}$ ($mg/m^3$) | Exposure duration (min) | Author/year |
|---|---|---|---|
| Rat / F344 (M) | $1077^{P}$ | 10 | Steinhagen et al., 1982 |
| Mouse / Swiss-Webster (M) | $961^{P}$ | 10 | Steinhagen et al., 1982 |
| Mouse/ Swiss-OF1 (M) | $132^{P}$ | 15 | Gagnaire et al., 1989 |

P: a plateau was reached.

## 5. Probit functions from individual studies

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

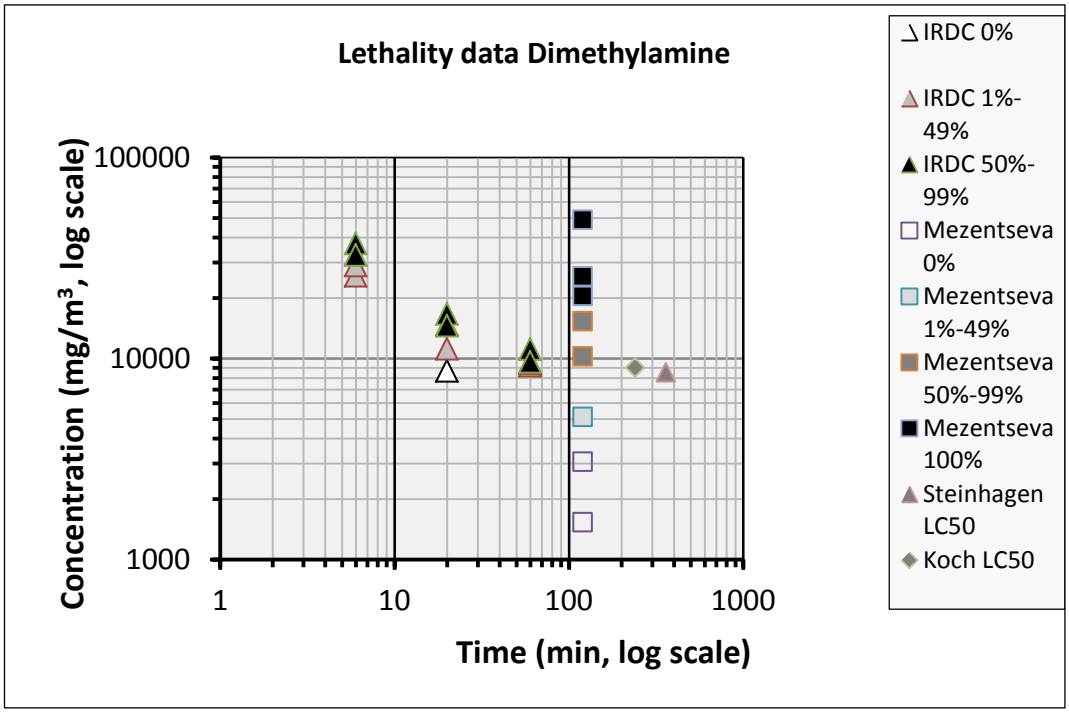



***Figure 1*** *All available acute lethality data for dimethylamine*

The data that were selected for primary analysis of the animal probit function are presented in Table 2 and Figure 3.

Only one study with A-quality allowed the derivation of an animal probit function for dimethylamine.

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 dimethylamine*

| Study ID | Species | Probit (C in mg/m$^3$, t in min) | $LC_{50}$, 30 minutes (mg/m$^3$) 95% C.I. |
|---|---|---|---|
| *A.1* | *Rat* | *-18.6 + 2.10 ×ln C + 1.07 × ln t* | *13,730 (11,140-23,630)* |

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

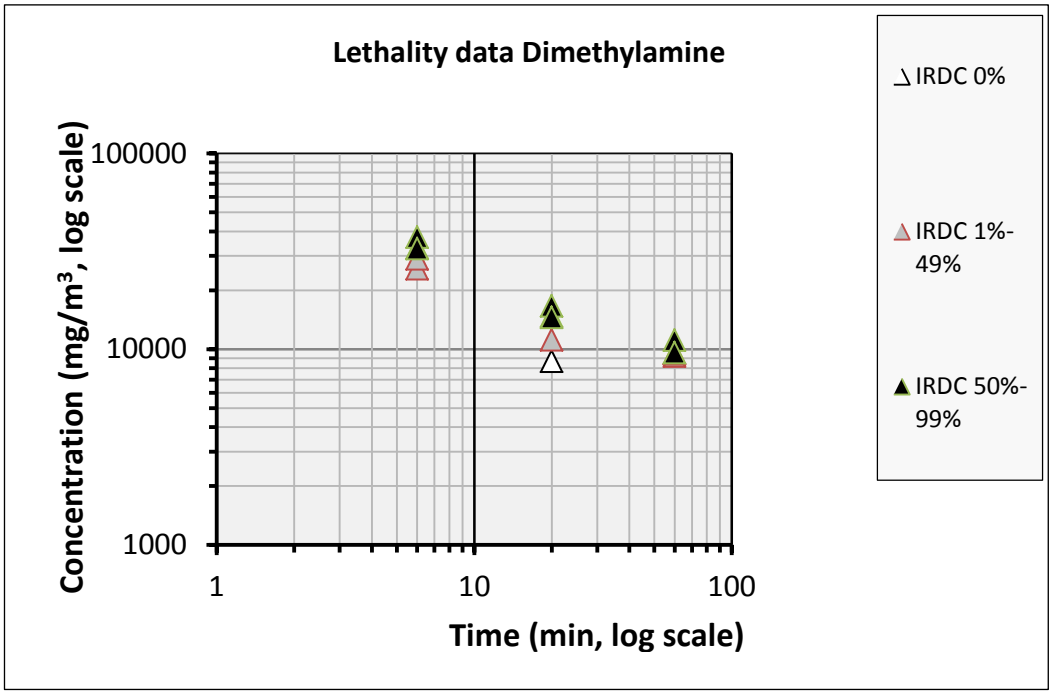



***Figure 2*** *Data selected for the initial and final analysis for the derivation of the animal probit function of dimethylamine.*

The data from study A.1 were selected for the final dataset for the derivation of the animal probit function. The data from the other studies was judged to be unreliable since essential information on study details was not provided.
The final data for calculating the animal probit function contains one dataset from one study and includes data from one animal species (see Figure 2 and Table 2).

## 6. Derivation of the human probit function

To derive the human probit function the results from IRDC (1992; A.1) have been used to derive a point of departure. The reason was that the IRDC 1992 study was well described and included three exposure durations (6, 20 and 60 minutes). Three additional studies (Steinhagen et al. 1982; Koch et al., 1980 and Mezentseva, 1956) only tested at one exposure duration. Furthermore, the available study descriptions are too poor to judge the quality of these studies. Therefore, the data of these additional studies cannot be used for derivation of a probit function.

As the point of departure for deriving the human probit function the calculated 30 min $LC_{50}$ value of 13,730 mg/m$^3$ for the rat from the IRDC 1992 (A.1) 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 | Default value. 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 | Concentrations were analytically determined. |
| Adequacy of database: | 1 | A well performed A study is available. |

The estimated human equivalent 30-minute $LC_{50}$ value is 13730 / 3 = 4577 **mg/m$^3$**.

The experimentally determined n-value was **1.96** (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 = 1.02.

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): $5 = a + 1.02 \times \ln (4577^{1.96} \times 30)$ resulting in the a-value of **-15.33**.

$Pr = -15.3 + 1.02 \times \ln (C^{1.96} \times t)$ with C in mg/m$^3$ and t in min.

The derived human probit function has a scientifically sound basis. The probit function is based on one study in the rat with A quality, including 15 C x t combinations.

The human 60 min $LC_1$ (Pr = 2.67) calculated with this probit equation is 992 mg/m$^3$ and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 678 mg/m$^3$.

| Estimated level | 30 min (mg/m$^3$) | 60 min (mg/m$^3$) |
|---|---|---|
| 1% lethality, this probit | 1413 | 992 |
| 0.1% lethality, this probit | 966 | 678 |
| AEGL-3 (2008, interim) | 590 | 460 |
| ERPG-3 (2015) | | 658 |
| LBW (2015) | 610 | 480 |

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

## Appendix 1 Animal experimental research

**Study ID: A.1**
Author, year: IRDC, 1992
Substance: Dimethylamine
Species, strain, sex: Rat, CD Sprague-Dawley, male and female
Number/sex/concentration group: 5/sex/concentration with a total of 15 groups
Age and weight: 49-63 days old, weights 208-292 g (males) and 158-220 g (females)
Observation period: 14d

***Evaluation of study quality***

| ***Criteria*** | ***Comment*** |
|---|---|
| Study carried out according to GLP | Author states that the test was performed in accordance with US EPA GLP standards effective 1989 |
| Study carried out according to guideline(s) | No statement of compliance with OECD guideline 403 provided |
| Stability of test compound in test atmosphere | Stable |
| Use of vehicle (other than air) | Air |
| 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 introducing a metered amount of test material and air into chamber inlet |
| Number of air changes per hour | 50 l/min in a 150 l glass chamber results in 20 air changes per hour |
| Equilibration time (t95) | 9 minutes |
| Start of exposure relative to equilibration | No information is available to determine the start of exposure relative to equilibrium. A transfer chamber is used to rapidly put in and out the test animals in the larger glass chamber of 150 l and thus is seems that exposure started after equilibration. Actual concentrations have been determined every 2 minutes. |
| Actual concentration measurement | Actual concentrations were measured every two minutes, which did not deviate much from target concentration. 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. |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure; | NA |

| | |
|---|---|
| Assessment of Reliability | A; Well conducted study. |

**Results**

| Species | Concentration ($mg/m^3$) | Exposure duration (min) | Lethality | |
|---|---|---|---|---|
| | | | Exposed | Responded |
| Rat | 25756 | 6 | 10 | 2 |
| | 28952 | 6 | 10 | 4 |
| | 32900 | 6 | 10 | 5 |
| | 37412 | 6 | 10 | 6 |
| | 32712 | 6 | 10 | 5 |
| | 8686 | 20 | 10 | 0 |
| | 14777 | 20 | 10 | 5 |
| | 11167 | 20 | 10 | 4 |
| | 16657 | 20 | 10 | 8 |
| | 14551 | 20 | 10 | 5 |
| | 9212 | 60 | 10 | 2 |
| | 11130 | 60 | 10 | 8 |
| | 9626 | 60 | 10 | 7 |
| | 9475 | 60 | 10 | 1 |
| | 9550 | 60 | 10 | 4 |

The calculated $LC_{50}$ values (using the DoseResp program) for the separate exposure durations of 6, 20 and 60 minutes are 33180, 13380 (12110-16020) and 9936 (9494-10860) $mg/m^3$, respectively.

**Probit function**

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

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

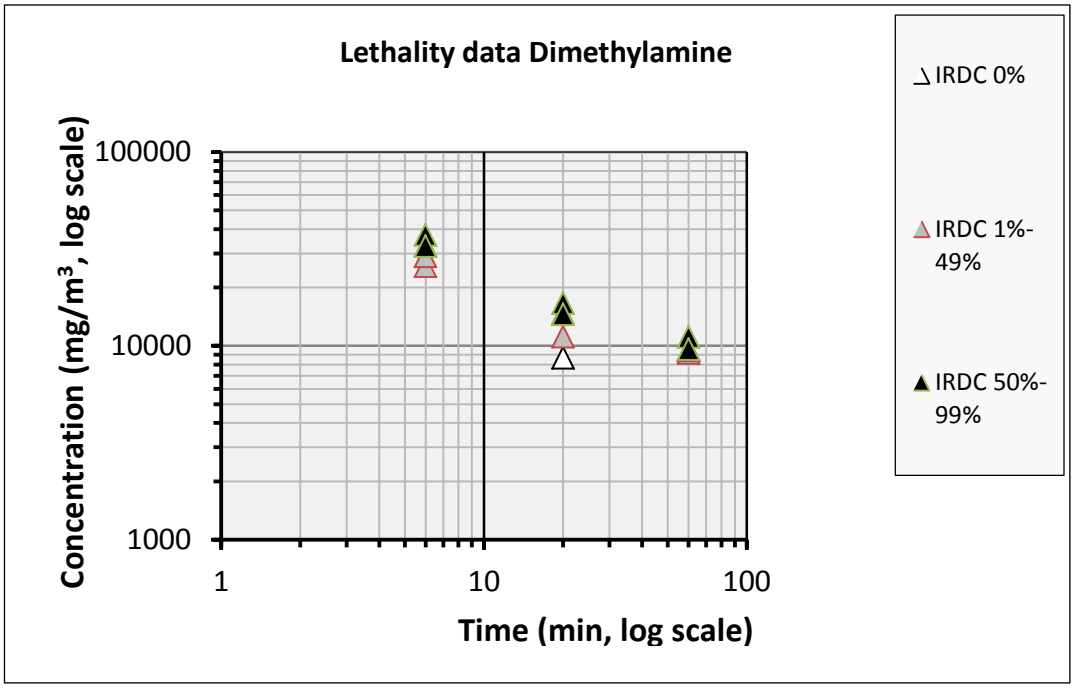
with C for concentration in $mg/m^3$, t for time in minutes and S for sex (0 = female, 1 = male).

As short term exposures in acute inhalation studies may sometimes give deviating results due to difficulties in achieving the targeted test atmosphere and breath-holding of the test animals, the data were analysed with and without the six minute data. As the study has been well performed there is no reason the exclude the 6 minute data. The analyses also do not support exclusion of the data.

| Probit function | Species | a | b | C | n-value |
|---|---|---|---|---|---|
| Sexes combined, Excl. 6 minutes | *Rat* | *-36.9* | *4.05* | *1.12* | *3.60 (2.03 – 5.17)* |
| Sexes combined, All data | | *-18.6* | *2.10* | *1.07* | *1.96 (1.36- 2.56)* |

| Duration (minutes) | $LC_{50}$ ($mg/m^3$) 95%-C.I. Combined, excl 6 min data | $LC_{50}$ ($mg/m^3$) 95%-C.I. Combined, all data |
|---|---|---|

| | | |
|---|---|---|
| 10 | 16,710 (13,610-20,200) | 24,040 (18,960-42,860) |
| 30 | 12,310 (11,400-13,430) | 13,730 (11,140-23,620) |
| 60 | 10,150 (9,66-11,410) | 9,649 (6,961-18,550) |



**Study ID: C.1**
Author, year: Steinhagen et al., 1982
Substance: Dimethylamine
Species, strain, sex: Rats, F344, males
Number/sex/concentration group: Total of 90 animals divided over 7 groups, number of animals per group unknown.
Age and weight: Age not specified, weights varied between 158 to 218 grams
Observation period: 48 hours

| *Criteria* | *Comment* |
|---|---|
| Study carried out according to GLP | *No GLP statement provided.* |
| Study carried out according to guideline(s) | *No statement of compliance with OECD guideline 403* |
| Stability of test compound in test atmosphere | *No information* |
| Use of vehicle (other than air) | *Pure dimethylamine gas or mixed with nitrogen* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *NA* |
| Pressure distribution. | *No information* |
| Homogeneity of test atmosphere at breathing zone of animals | *No information* |
| 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 analyzed continuously by IR spectrophotometry. Calibration by injecting measured volumes of pure dimethylamine gas into 5.64-l closed-loop system* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure; | *N.A.* |
| | |
| Assessment of Reliability | *C* |
| | *The study was assigned quality C, because exact exposure data were lacking from this study. Only one figure was given from which the exposure-response data can be estimated. In addition, the observation period only lasted 48 hours* |
| | |

## Results

| Species | Concentration ($mg/m^3$) | Exposure duration (min) | Lethality | |
|---|---|---|---|---|
| | | | Male (%) | |
| Rat | 1128 | 360 | 0 | |
| | 1880 | 360 | 0 | |
| | 4700 | 360 | 0 | |
| | 7500[a] | 360 | 20[a] | |
| | 8900[a] | 360 | 40[a] | |
| | 9500[a] | 360 | 83[a] | |
| | 11500[a] | 360 | 80[a] | |
| | 8535 | 360 | $LC_{50}$ | Calculated by Steinhagen *et al*. 1982 |

[a] These values were estimated from a graph

## Probit function

A probit function could not be calculated.

**Study ID: C.2**
Author, year: Koch et al., 1980
Substance: Dimethylamine
Species, strain, sex: Rats, Wistar, female
Number/sex/concentration group:10/group, number of groups not specified.
Age and weight: 8 weeks old, weights not specified.
Observation period: 14 days

| *Criteria* | *Comment* |
|---|---|
| Study carried out according to GLP | *No GLP statement provided* |
| Study carried out according to 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 information* |
| Whole body / nose-only (incl. head/nose-only) exposure | *Not specified, likely whole body* |
| Type of restrainer | *No information* |
| Pressure distribution. | *No information* |
| Homogeneity of test atmosphere at breathing zone of animals | *No information* |
| Number of air changes per hour | *No information* |
| Equilibration time (t95) | *No information* |
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *Gas chromatography* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure; | *N.A.* |
| Assessment of Reliability | *C* |
| | *The reliability of the calculated $LC_{50}$ cannot be evaluated, because individual exposure and response data were not provided* |

**Results**

| Species | Concentration 95% C.I.(mg/m$^3$) | Exposure duration (min) | Lethality | |
|---|---|---|---|---|
| | | | Female | |
| Rat | 8990 (8186-9872) | 240 (T = 21.9°C) | $LC_{50}$ | Calculated |
| | 8595 (7746-9539) | 240 (T = 22°C) | $LC_{50}$ | Calculated |
| | 9214 (8353-10163) | 240 (T = 29°C) | $LC_{50}$ | Calculated |

Values are based on calculations by Koch *et al.*

**Probit function**
A probit function could not be calculated.

**Study ID: C.3**
Author, year: Mezentseva., 1956
*Original study in Russian, only summary in AEGL TSD available.*
Substance: Dimethylamine
Species, strain, sex: Mouse, strain and sex not specified.
Number/sex/concentration group: 10-16/group
Age and weight: not specified
Observation period: 20 days

| *Criteria* | *Comment* |
|---|---|
| Study carried out according to GLP | *GLP did not exist at the time* |
| Study carried out according to 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) | |
| Whole body / nose-only (incl. head/nose-only) exposure | *Whole body* |
| Type of restrainer | *NA* |
| Pressure distribution. | *No information* |
| Homogeneity of test atmosphere at breathing zone of animals | *Dimethylamine vapour was generated by air flow over predetermined volume of 20% dimethylamine liquid* |
| Number of air changes per hour | *No information* |
| Equilibration time (t95) | *No information* |
| Start of exposure relative to equilibration | *No information* |
| Actual concentration measurement | *Not known whether analytical measurements were performed* |
| Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure; | *No information* |
| Assessment of Reliability | *C* |
| | *The study was too limitedly reported. Unknown whether analytical measurements were performed.* |

## Results

| Species | Concentration ($mg/m^3$) | Exposure duration (min) | Lethality | |
|---|---|---|---|---|
| | | | Exposed | Responded |
| Mouse | 49,068 | 120 | 16 | 16 |
| | 25,568 | 120 | 16 | 16 |
| | 20,492 | 120 | 16 | 16 |
| | 15,322 | 120 | 16 | 15 |
| | 10,227 | 120 | 16 | 11 |
| | 5,114 | 120 | 16 | 1 |
| | 3,064 | 120 | 16 | 0 |
| | 1,532 | 120 | 10 | 0 |

The 2-hour $LC_{50}$ calculated using the DoseResp program (Wil ten Berge, 2015) is 8703 $mg/m^3$ (95% CI: 7170 – 10200 $mg/m^3$).

## Probit function

Because only one exposure duration was tested it was not possible to derive an animal probit function that also includes the exposure time.

## Appendix 2 Reference list

AEGL 2008, NAS/COT subcommittee for Acute Exposure Guideline Levels, Dimethylamine (CAS Reg. No. 124-40-3), Interim 06/2008.

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

Dutch Intervention Values (2015) Dimethylamine

ERPG 2015, Emergency Response Planning Guidelines, Dimethylamine, American Industrial Hygiene Association, 2015.

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.

IRDC (International Research and Development Corporation). 1992. Acute inhalation toxicity evaluation on dimethylamine in rats. Study sponsored by Air Products and Chemicals, Inc., Allentown, PA.

Koch F., G. Mehlhorn, R.Kliche, and R. Lang. 1980. [Untersuchungen zur aerogenen Intoxication bei Ratten durch Methylamine]. Wiss Z. Karl-Marx-Univ. Leipzig. Naturwiiss. R. 29: 463-474.

Mezentseva, N.V. 1956. Data on the Toxicity of Dimethylamine. Gigiyena i Sanitariya (Hygiene and Sanitary) 21: 47-49.

Steinhagen, V.H., J.A. Swenberg, and S.S. Barrow. 1982. Acute inhalation toxicity and sensory irritation of methylamine. Amer. J. Industr. Hyg. Assoc. 43: 411-417.