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

Probit function technical support document

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Author:	L. Geraets (RIVM)
E-mail response to:	safeti-nl@rivm.nl

substance name	CAS number
Methyl bromide	**74-83-9**

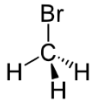
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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/en/Topics/P/Probit_functions.

Technical support document methyl bromide



1. Substance identification

CAS-number:	74-83-9
IUPAC name:	Bromomethane
Synonyms:	Monobromomethane, Bromomethane
Molecular formula:	CH_3Br
Molecular weight:	94.94 g/mol
Physical state:	gas (at 20°C and 101.3 kPa)
Boiling point:	4°C (at 101.3 kPa)
Vapour pressure:	189 kPa (at 20°C)
Saturated vapor conc:	N/A
Conversion factor:	1 mg/m^3 = 0.253 ppm (at 20°C and 101.3 kPa)
	1 ppm = 3.949 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H301, H315, H319, H331, H335, H341, H373

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

Acute effects: The main target organs and tissues for acute inhalation exposure to methyl bromide are the CNS and the lungs. Effects observed in animals include tremors, ataxia, tissue lesions and labored breathing. Symptoms of exposure by inhalation to methyl bromide in humans are headache, visual disturbances, vertigo, GI-effects, irritation of the respiratory system, dyspnea, muscle weakness, hand tremor, convulsions. Methyl bromide also causes pulmonary edema upon exposure to high concentrations. Lethality results from respiratory or circulatory collapse. In animals, a steep concentration-response relationship for mortality is observed.
Long-term effects: Subacute and subchronic inhalation exposure produces CNS effects, degenerative effects in various organs such as brain, adrenals, nasal cavity, testes, kidney, liver, and pulmonary irritation.

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. Although numerous reports of accidental exposure of humans to methyl bromide that resulted in neurotoxicity or deaths are available in the literature, reliable information on exposure concentrations was not available (AEGL, 2012). However, estimates of concentrations leading to human deaths range from 1600-8000 ppm (6318-31592 mg/m^3) for 4-6 hours to 60000 ppm (236940 mg/m^3) for 2 hours (ATSDR, 1992). The health effects upon exposure to methyl bromide were reviewed by Alexeeff and Kilgore (1983). Effects included respiratory effect and effects on the CNS. The onset of symptoms upon inhalation exposure in humans is usually delayed.

Species variability has been reported and summarized by AEGL (2012) as follows: Both in vitro and in vivo comparisons of different species indicate that concentrations of GST enzymes are much lower in human tissues (liver and lung) than in mice or rats (Andersen et al. 1987; Reitz et al. 1989 as cited by AEGL (2012)). The data are consistent with the hypothesis that the rate of activation of mono- and dihalomethanes to toxic metabolites by the GST pathway occurs much more slowly in humans than in rodents. Jager et al. (1988) (as cited by AEGL (2012)) investigated the concentrations of GSH in rodent tissues. Activities of GSH in the liver were 2-3

[1] ERPG (2008), AEGL (2012)

times greater in male B6C3F1 mice than in female mice and F-344 rats of both sexes. Griem et al. (2002) (as cited by AEGL (2012)) compiled ratios of GST activity in rodents to humans in various tissues. The ratios of rat:human and mouse:human GST activity in the liver are 3.95 and 7.64, respectively. On the other hand, nonprotein sulfhydral content (primarily GSH) is similar among human, monkey, and rat tissues on a µmol/mL of tissue basis (Frederick et al. 2002, as cited by AEGL (2012)). This was true for major organs, but not nasal tissue. Rat nasal tissue had more nonprotein sulfhydral content than human tissue.

For the related chemical, methyl chloride, blood concentrations of humans, dogs, and rats exposed to 50 ppm for 6 h reached a plateau during the first hours of exposure; elimination was rapid once the exposures were terminated (Landry et al. 1983; Nolan et al. 1985, as cited by AEGL (2012)). Blood concentrations of methyl chloride in slow human metabolizers plateaued at 60% of those found in the rat and 70% of those found in the dog. Postexposure elimination was most rapid in the rat ($t_{1/2}$ = 15 min). The dog and rapid human metabolizers had the same elimination rate ($t_{1/2}$ = 50 min), and the slow human metabolizers eliminated at the slowest rate ($t_{1/2}$ = 90 min). At 50 ppm, the rat absorbed 10 µg/min/kg whereas the rapid and slow human metabolizers absorbed 3.7 and 1.4 µg/min/kg, respectively. According to Nolan et al. (1985) (as cited by AEGL (2012)), differences in the pharmacokinetics between these three species were adequately explained by the differences in respiratory minute volume and basal metabolic rates (rat > dog > man). Similar comparative studies were not available for methyl bromide, so it should be noted that uptake kinetics of methyl bromide and methyl chloride could be different. Andersen et al. (1980) (as cited by AEGL (2012)) found uptake of methyl chloride to be saturable, being associated with enzymatic metabolism, whereas the rapid, first-order uptake of methyl bromide was considered to be nonenzymatic metabolism.

4. Animal acute toxicity data

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

1. AEGL final TSD, ERPG document and EU RAR and reference database for methyl bromide, 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
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 11 studies were identified -with 14 datasets for 5 species- with data on lethality following acute inhalation exposure. One dataset was assigned status A for deriving the human probit function, two datasets were assigned status B1 and 11 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies on sensory irritation were found.

5. Probit functions from individual studies

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

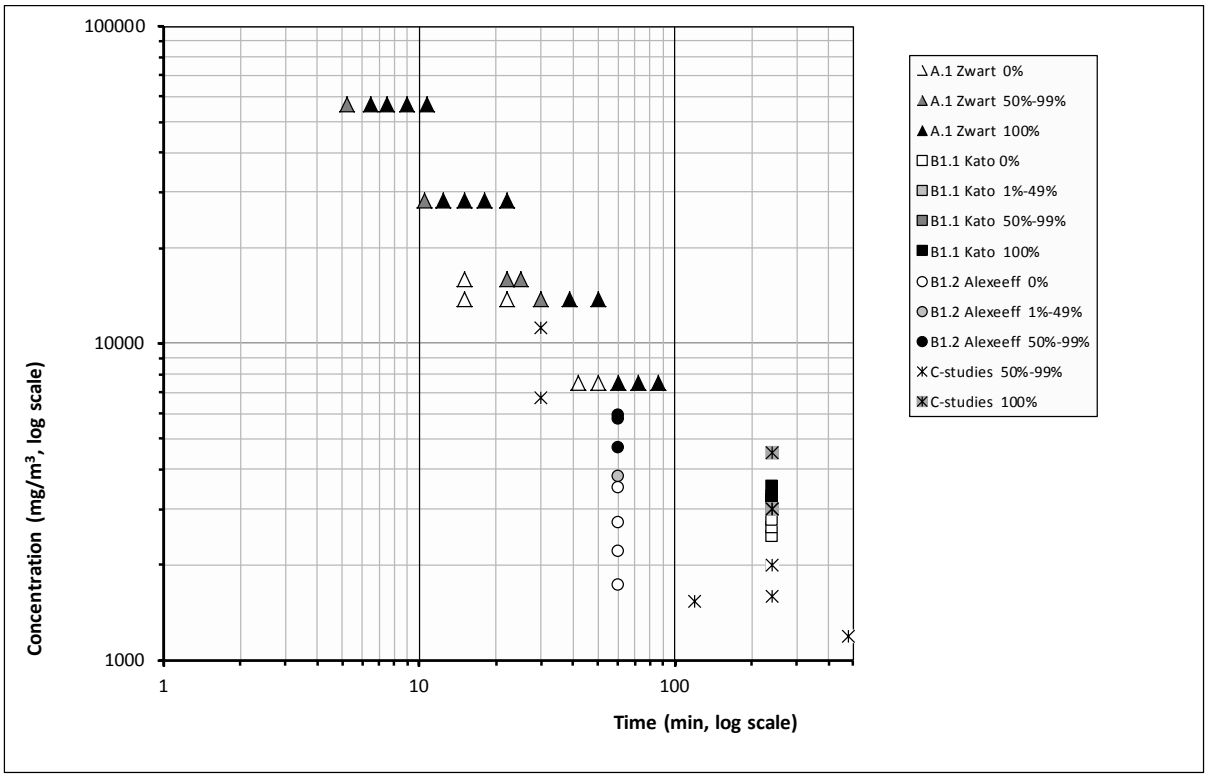


Figure 1 *All available acute lethality data for methyl bromide.*

The data that were selected for initial analysis of the animal probit function are presented in Table 1 and Figure 2.

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

To enable intra-species pooling, LC_{50}-values of B1-studies were scaled using the rat-specific n-value of 1.22 (study A.1) of methyl bromide 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 1.

Table 1 *Data selected for initial analysis of the animal probit function of methyl bromide.*

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	-107 + 9.16×lnC + 7.53×lnt		12930 (11630-13890)	1.22 (1.09-1.34)
B1.1	Rat	*240-min LC_{50}*	3107 (3015-3158)	*17084*	N/A
B1.2	Mouse	*60-min LC_{50}*	4687 (4140-5312)	*8273*	N/A

The data of rat studies A.1 and B1.1 and mouse study B1.2 are presented graphically below.

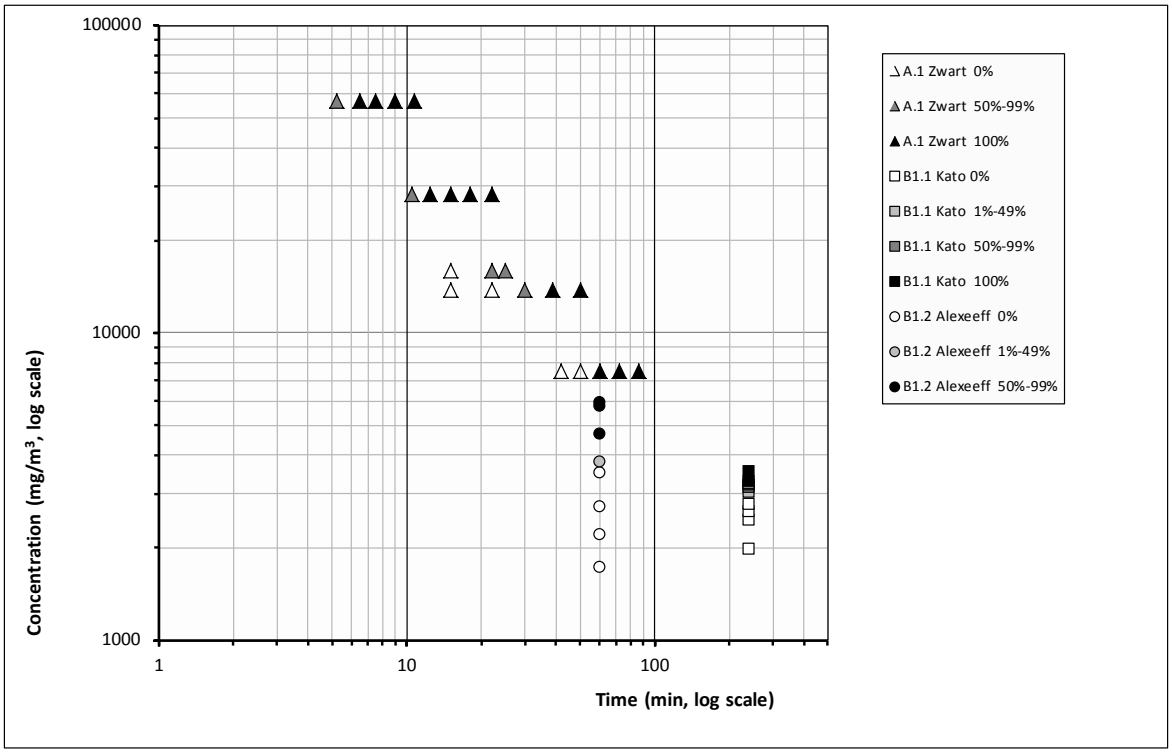


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of methyl bromide.*

Based on criteria outlined in the guideline the data from rat study A.1 and mouse study B1.2 were selected for the final dataset for the derivation of the animal probit function.

The LC_{50}-values of rat studies A.1 and B1.1 and mouse study B1.2 fall within the same order of magnitude. 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 and species (rat studies A.1 and B1.1 and mouse study B1.2) converge.

Rat study A.1 included multiple exposure durations ranging from 5.2-86 min. As a point of departure for the human probit function, a 30-60 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 240-min to a 30-60 min value is believed to be too uncertain, and, in addition, an exposure duration of 240 min is outside the range of exposure durations included in the rat A.1 C x t study, rat study B1.1 (Kato

et al., 1986) was not included in the final dataset for the derivation of the animal probit function.
It is noticed that the inhalation restrainer as applied in study B1.2 (Alexeeff et al., 1985) was a glass tube combined with a neoprene plunger to keep the animals in the appropriate position. This may promote hyperthermia and stress in the exposed animals. A comparison of the 60-min LC_{50} values of this study and of the A.1 study showed a small difference with the B1.2 study having a lower 60-min LC_{50} value (i.e. 4687 mg/m^3 (mouse study B1.2) vs. 7307 mg/m^3 (rat study A.1)). As this difference in LC_{50} value could also be caused by species differences and the applied exposure duration in study B1.2 was limited to one hour, this study can be included in the derivation of the probit.

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 2 and Figure 4.

The final data eligible for calculating the animal probit function contains 2 datasets from 2 studies and includes data from 2 animal species.

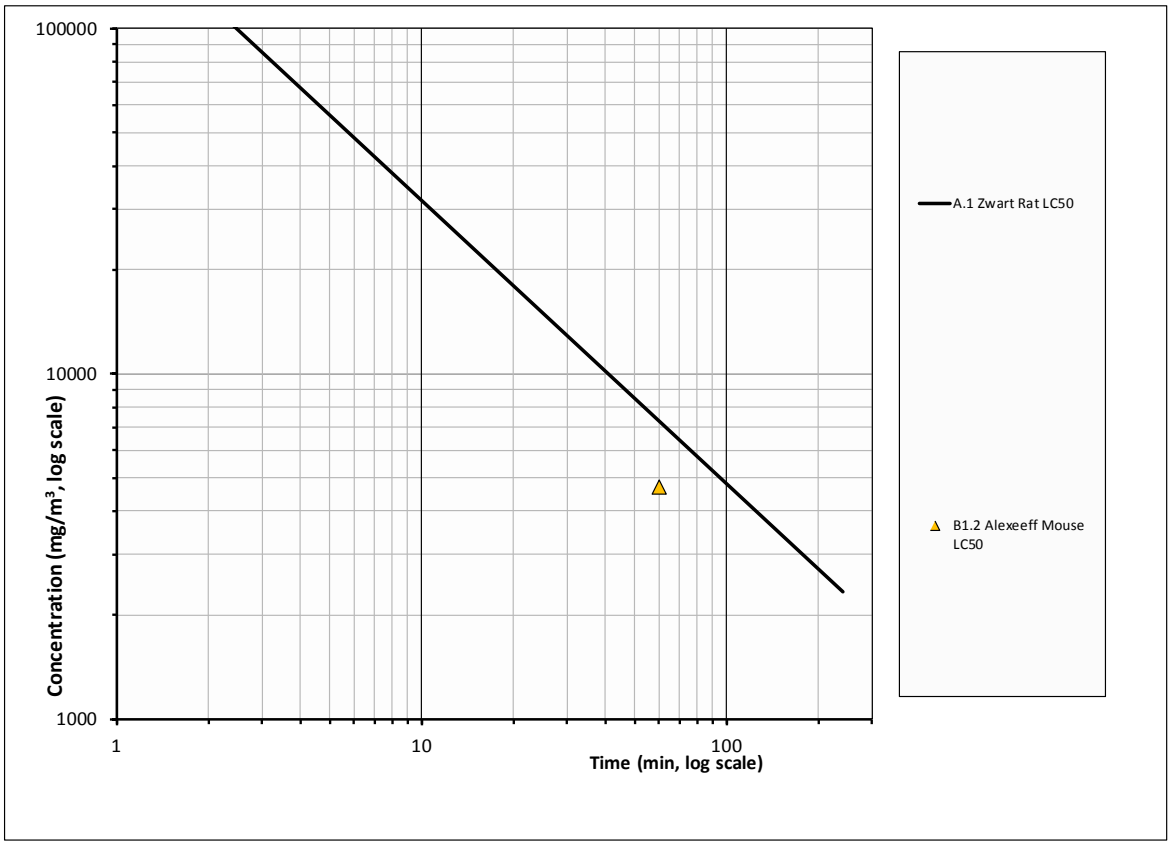


Figure 3 *LC_{50} values of A.1 and B1.2 datasets for methyl bromide, over time where available.*

Table 2 *Data selected for the derivation of the animal probit function of methyl bromide.*

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	-107 + 9.16×lnC + 7.53×lnt		12930 (11630-13890)	1.22 (1.09-1.34)
B1.2	Mouse	*60-min LC_{50}*	4687 (4140-5312)	*8273*	N/A

The data of the selected datasets are presented graphically below.

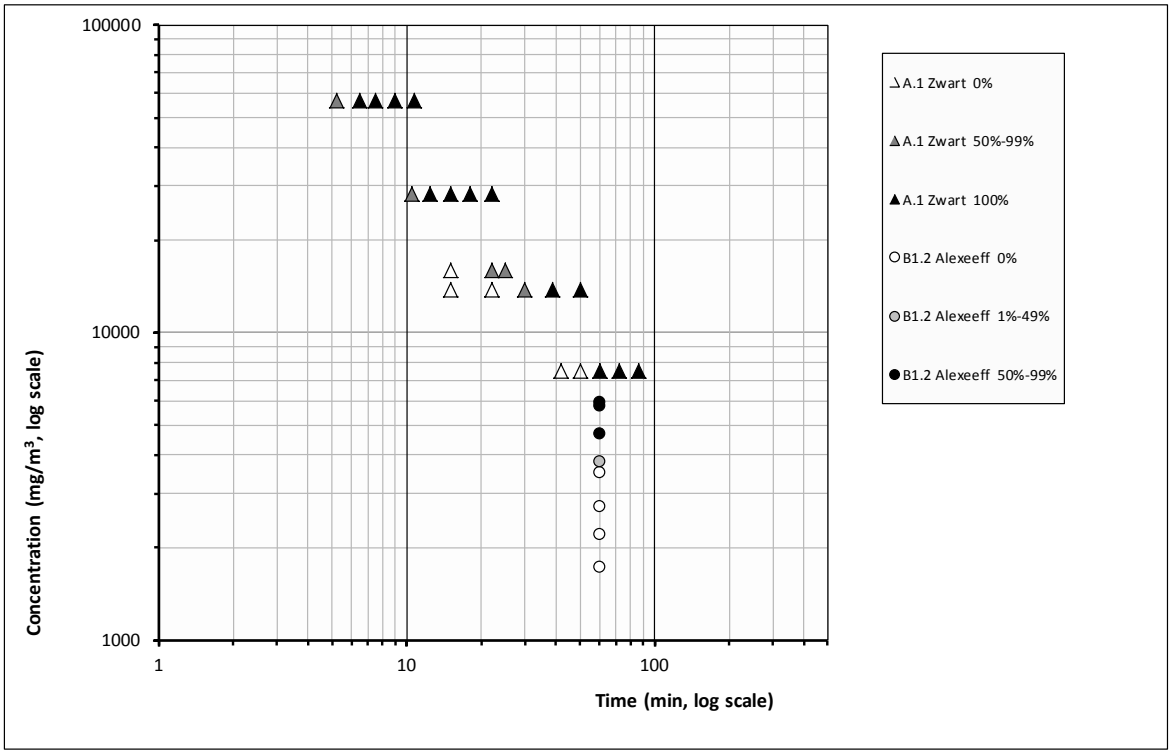


Figure 4 Final data selected for derivation of the animal probit function of methyl bromide.

6. Derivation of the human probit function

To derive the human probit function the results from rat study A.1 and mouse study B1.2 have been used to derive a point of departure as outlined above.

The species-specific n-value was 1.22 for the rat (study A.1).

The species-specific LC_{50}-values, calculated for a common exposure duration of 60 minutes, were 7307 mg/m^3 for the rat (study A.1) and 4687 mg/m^3 for the mouse (study B1.2). From these, a geometric mean overall LC_{50}-value of 5852 mg/m^3 was calculated according to the general formula for the geometric mean of time-scaled LC_{50}-values below:

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

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).

Hence, the Point of Departure for the human probit function is a 60-minute geometric mean animal LC_{50} value of 5852 mg/m^3 and an n-value of 1.22 (study A.1).

The human equivalent LC_{50} was calculated by applying the following assessment factors:

Table 3 *Rationale for the applied assessment factors.*

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	1	Uptake of methyl bromide is higher in rodents than in humans (based on comparative respiratory rates and comparisons with methyl chloride) and because GST levels in rodents are higher than in humans, resulting in more rapid production of toxic metabolites (see section 3).
Nominal concentration	1	Analytically determined concentrations
Adequacy of database:	1	Database consists of well conducted A and B1 studies

The estimated human equivalent 60-minute LC_{50} value is 5852 / 1 = **5852 mg/m^3**.

The experimentally determined n-value was **1.22** (study A.1). Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.64**.

The human probit function is then calculated on the human equivalent 60 min LC_{50} using the above parameters to solve the following equation to obtain the a-value (the intercept): 5 = a + 1.64 × ln ($5852^{1.22}$× 60) resulting in the a-value of **–19.06**.

Pr = -19.1 + 1.64 × ln (C $^{1.22}$ × 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 and one study in the mouse with B1 quality, including total 32 Cxt combinations, with 5.2 up to 86 min exposure duration 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 1242 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 1816 mg/m^3.

Table 4 *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	2193	1242
1% lethality, this probit	3206	1816
AEGL-3[2] (2012, final)	5134	2922
ERPG-3[2] (2008)	-	790
LBW (2015)	5200	2900

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

[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: Zwart, 1988
Substance: methyl bromide
Species, strain, sex: Rat, Wistar-derived (Bor:WISW), males
Number/sex/conc. group: 2 (except for one group which has 6 animals/group)

Age and weight: No information available on age, bodyweight 202 g
Observation period: 14 days

Evaluation of study quality

Criteria	***Comment***
Study carried out according to GLP	*Yes, GLP statement provided*
Study carried out according to OECD 403 guideline(s)	*Yes*
Stability of test compound in test atmosphere	*No information*
Use of vehicle (other than air)	-
Whole body / nose-only (incl. head/nose-only) exposure	*Nose-only*
Type of restrainer	*Animals were exposed in modified Batelle polycarbonate animal holders which were inserted into a nose-only inhalation equipment of the institute's design.*
Pressure distribution	*A positive pressure difference of about 1 cm H_2O was generated between the inhalation equipment and the environment of the holders.*
Homogeneity of test atmosphere in breathing zone of animals	*Methyl bromide test atmospheres were generated by mixing an adjustable flow of the test material with the airflow before entering the inhalation equipment.*
Number of air changes per hour	*The inhalation equipment was ventilated with 0.6 m^3/h (10 L/min)*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*The actual concentration was determined continuously by total carbon analysis by way of a flame ionisation detector.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***A*** *Well-performed study, including multiple exposure concentrations and exposure durations. Concentrations were determined analytically*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	7.5×10^3		42	0/2
Rat	7.5×10^3		50	0/2
Rat	7.5×10^3		60	2/2
Rat	7.5×10^3		72	2/2
Rat	7.5×10^3		86	2/2
Rat	13.8×10^3		15	0/2
Rat	13.8×10^3		22	0/2
Rat	13.8×10^3		30	1/2
Rat	13.8×10^3		39	2/2
Rat	13.8×10^3		50	2/2
Rat	16.0×10^3		15	0/2
Rat	16.0×10^3		22	1/2
Rat	16.0×10^3		25	3/6
Rat	28.3×10^3		10.5	1/2
Rat	28.3×10^3		12.5	2/2
Rat	28.3×10^3		15	2/2
Rat	28.3×10^3		18	2/2
Rat	28.3×10^3		22	2/2
Rat	57.0×10^3		5.2	1/2
Rat	57.0×10^3		6.5	2/2
Rat	57.0×10^3		7.5	2/2
Rat	57.0×10^3		9	2/2
Rat	57.0×10^3		10.8	2/2

Probit function

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

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

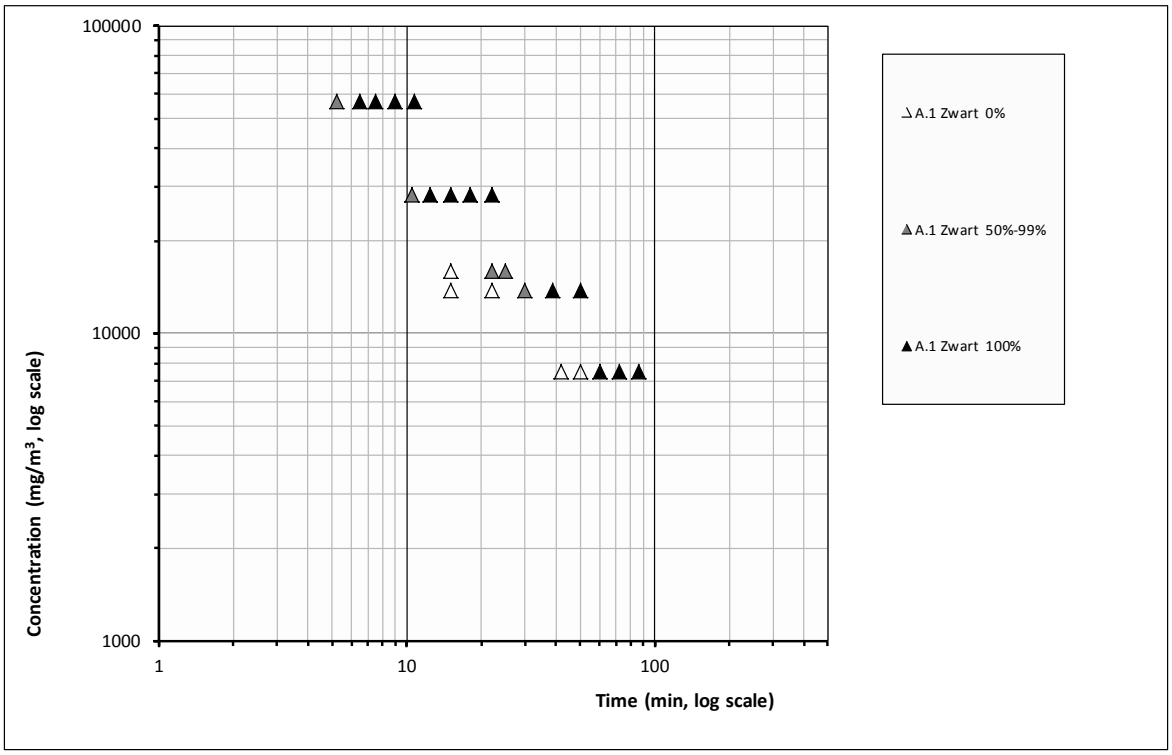
with C for concentration in mg/m^3, t for time in minutes.

Probit function	Species	a	b	c	n-value
	Rat	-107	9.16	7.53	1.22 (1.09-1.34)

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I. Male	LC_{50} (mg/m^3) 95%-C.I. (presented by study author)
10	31920 (27790-35200)	*
30	12930 (11630-13890)	12.9×10^3 (11.6×10^3 - 13.9×10^3)
60	7307 (6286-8251)	7.3×10^3 (6.3×10^3 – 8.3×10^3)

* Zwart (1988) only reported LC_{50} values for exposure durations of 3.5, 7.5, 15, 30, 60, 240 and 480 min

A graphical overview of the data is presented below. Each concentration-time combination (with 2 male animals, except for one group with 6 animals) represents one point in the plot.


100000
10000
1000
1
10
100
Concentration (mg/m³, log scale)
Time (min, log scale)
A.1 Zwart 0%
A.1 Zwart 50%-99%
A.1 Zwart 100%

1
2
3

Study ID: B1.1

Author, year: Kato et al., 1986
Substance: methyl bromide
Species, strain, sex: Rats, Sprague-Dawley, male
Number/sex/conc. group: 5 or 10
Age and weight: 6 weeks, no information available on body weight
Observation period: one week

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	*N/A*
Pressure distribution	*No information available*
Homogeneity of test atmosphere in breathing zone of animals	*Gas was distributed evenly throughout the gas chamber.* *The flow rate was adjusted from the mixing chamber by observing a flow meter so that an appropriate concentration could be maintained at all times.*
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	*During exposure, methylbromide concentration inside the gas chamber was analysed every 10 minutes using gas chromatography.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*
Assessment of Reliability	***B1*** *Reasonably-performed study, limited to one exposure duration*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Rat	1982	N/A	240	0/5
Rat	2456	N/A	240	0/5
Rat	2634	N/A	240	0/5

Rat	2768	N/A	240	0/10
Rat	3029	N/A	240	3/10
Rat	3155	N/A	240	3/5
Rat	3191	N/A	240	7/10
Rat	3226	N/A	240	8/10
Rat	3286	N/A	240	10/10
Rat	3538	N/A	240	5/5

Probit function

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

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

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Rat	-209	26.6	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.	LC_{50} (mg/m^3) 95%-C.I. (presented by study author)
240	3107 (3015-3158)	3080 (3001-3199)

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

Study ID: B1.2

Author, year: Alexeeff et al., 1985
Substance: methyl bromide
Species, strain, sex: Mice, Swiss-Webster, male
Number/sex/conc. group: 6
Age and weight: no information available on ages, body weight 25-30 g
Observation period: one week

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	*Nose-only exposure*
Type of restrainer	*Animals were restrained in glass tubes (2.6 cm diameter), with a 0.8-cm opening for nose exposure. They were contained in the anterior portion of the tube by an adjustable neoprene plunger.*
Pressure distribution	*The chamber pressure was maintained at 1.00±0.08 inches H_20. The chamber pressure was negative with respect to the glove-box pressure. The exposure chamber was within a glove box located in a fume hood. The system was operated under slightly negative pressure for safety considerations and to prevent rebreathing by the animals.*
Homogeneity of test atmosphere in breathing zone of animals	*The methyl bromide concentration was adjusted with a microflow regulator on the methyl bromide cylinder and diluted with 3.28±0.02 L/min of compressed air.*
Number of air changes per hour	*The total system air flow was 3.33±0.4 L/min; an inhalation chamber of 0.8L was used.*
Equilibration time (t95)	*0.7 min*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*The exposure chamber concentrations of methyl bromide were continually sampled through a septum using a gas-tight syringe and immediately injected in a gas chromatograph.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*N/A*

Assessment of Reliability	***B1*** *Reasonably performed study, limited to one exposure duration.* *It is noticed that the inhalation restrainer was a glass tube with a neoprene plunger to keep the animals in the appropriate position. This may promote hyperthermia and stress in the exposed animals. As the exposure duration was limited to one hour, this is considered acceptable.*

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		Male
				Dead/tested
Mice	870	N/A	60	0/6
Mice	1720	N/A	60	0/6
Mice	2200	N/A	60	0/6
Mice	2720	N/A	60	0/6
Mice	3500	N/A	60	0/6
Mice	3820	N/A	60	1/6
Mice	4700	N/A	60	4/6
Mice	5770	N/A	60	5/6
Mice	5930	N/A	60	5/6

Probit function

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

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

with C for concentration in mg/m^3.

Probit function	Species	a	b	n-value
	Mouse	-38.9	5.20	-

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.	LC_{50} (mg/m^3) 95%-C.I. (as presented by study author)
60	4687 (4130-5312)	4680 (4110-5320)

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

Study ID: C studies

Bakhishev (1973) (as cited in NAC/AEGL, 2012) exposed rats and mice (number and strains not reported) to methyl bromide for 30 min. The 30-min LC_{50} for rats was reported to be 2,830 ppm (11176 mg/m^3) and a 30-min LC_{50} of 1,700 ppm (6713 mg/m^3) was reported for mice. No full information on the study was available, therefore the study quality and the calculated LC_{50}-values could not be evaluated.

Balander and Polyak (1962) (as cited in NAC/AEGL, 2012) reported a 2h LC_{50} in mice of 397 ppm (1538 mg/m^3).

Honma *et al*. (1985) exposed male Sprague-Dawley rats (5/concentration) whole-body) to methyl bromide for 8 hours (268, 335, 402, 469, 536 ppm, corresponding to 1058, 1323, 1587, 1852, 2117 mg/m^3). All rats survived at 1058 mg/m^3. Death occurred in all rats (100% mortality) at 1587 mg/m^3. The number of deaths did not increase beyond 6h after the cessation of exposure at all concentrations. The authors reported an 8h LC_{50} of 302 ppm (1193 mg/m^3). As no full information on the mortality (at each applied exposure concentration) was available, this calculated LC_{50} could not be evaluated.

Irish *et al*. (1940) exposed rats and rabbits to single exposures of methyl bromide at a series of concentrations, in order to determine, for each concentration, the shortest exposure to which all succumbed and the longest exposure from which all survived. A post-exposure period of 4 weeks was included. Limited information on study details such as test atmosphere generation or actual concentration measurement was available. Exposure of rats to methyl bromide at 13,000, 5,200, 2,600, 520, 260, 220, or 100 ppm (51337, 20535, 10267, 2053, 1027, 869, 395 mg/m^3) resulted in 100% mortality in 6, 24, and 42 min and 6, 22, 26, and >26 h, respectively. Survival was 100% when exposures at the respective concentrations were 3, 6, and 24 min and 2, 8, 12, and 22 h. Survival times for rabbits exposed at the same concentrations were longer by a factor of 2-3.

Groups of 10 male and 10 female F344 rats inhaled methyl bromide at 150, 225, 338, 506, 760, or 1,140 ppm (592, 889, 1335, 1998, 3001, 4502 mg/m^3) for 4 h (Japanese Ministry of Labour 1992, (as cited in NAC/AEGL 2012 and IPCS 1995)). At concentrations of 338 ppm (1335 mg/m^3) or greater, there was decreased locomotor activity, ataxia, nasal discharge, lacrimation, diarrhea, irregular breathing, and bradycardia. All rats exposed at 760 and 1,140 ppm (3001 and 4502 mg/m^3) died. Necropsy revealed pulmonary congestion, hepatic degeneration, renal necrosis, myocardial hemorrhages, hemorrhage and necrosis of the adrenal glands, and congestion of the thymus. Rats in the 225, 338, and 506 ppm (889, 1335 and 1998 mg/m^3) groups exhibited metaplasia of the olfactory epithelium, and rats exposed at 760 and 1,140 ppm (3001 and 4502 mg/m^3) (no deaths) exhibited necrosis of the olfactory epithelium.
Groups of 10 male and 10 female BDF1 mice inhaled methyl bromide at 100, 150, 225, 338, 506, or 760 ppm (395, 592, 889, 1335, 1998, 3001 mg/m^3) for 4 h (Japanese Ministry of Labour 1992, (as cited in NAC/AEGL 2012 and IPCS 1995)). All mice in the 760 ppm (3001 mg/m^3) group died, and all but two male mice died in the 506 ppm (1998 mg/m^3) group. Mice in these groups exhibited decreased locomotor activity, tremor, convulsions, diarrhea, irregular breathing, and bradypnoea. Mice in the 100, 150, 225, and 338 ppm (395, 592, 889, 1335 mg/m^3) groups did not exhibit any clinical signs. Necropsy of the two highest dose groups revealed pulmonary congestion, hepatic degeneration and necrosis, renal tubular necrosis, karyorrhexis of the thymus and lymph nodes, and necrosis of the olfactory epithelium. A single female mouse exposed at 338 ppm (1335 mg/m^3) exhibited metaplasia of the olfactory epithelium.

No full information on the study was available, therefore the study quality and the calculated LC_{50}-values could not be evaluated.

Newton (1994) exposed Beagle dogs (1/concentration) whole body for 7h to 233, 314, 345, 350 or 394 ppm (920, 1240, 1362, 1382, 1556 mg/m^3). Exposure resulted in a hunched posture and labored breathing during the last 3 hour at 1240 mg/m^3 or above. Mortality was not observed. However, the exposure to 1556 mg/m^3 was terminated at the sixth hour due to abnormal clinical signs.

Sayers et al. (1929) exposed guinea pigs (6/group) to methyl bromide via whole body inhalation with exposure durations of 5 to 800 minutes and exposure concentrations of 390 to 370300 mg/m^3. A 1.5 h exposure to 2290 ppm (9043 mg/m^3), 4.5 h to 590 ppm (2330 mg/m^3), 13.5h to 490 ppm (1935 mg/m^3) resulted in 100% mortality. A 1.5 h exposure to 590 ppm (2330 mg/m^3), 4.5h to 310 ppm (1224 mg/m^3), and 13.5h to 150 ppm (592 mg/m^3) resulted in 0% mortality (as presented by ERPG, 2008). Most deaths were observed during the experiment, but a single animal was found death 6h after cessation of exposure. Two animals/group were killed directly after cessation of the exposure, two were killed after 4 days, and two were killed after 8 days. As part of the animals were killed directly after cessation of exposure, the true mortality incidence cannot be ascertained.

Groups of 6 or 10 ICR-SPF male mice inhaled methyl bromide at 312, 357, 377, 449, or 464 ppm (1232, 1410, 1489, 1773, 1832 mg/m^3) for 4 h (Yamano 1991 as cited in NAC/AEGL 2012). No deaths occurred at 312 ppm (1232 mg/m^3). Mortality was 10% at 357 and 377 ppm (1410, 1489 mg/m^3), 90% at 449 ppm (1773 mg/m^3), and 100% at 464 ppm (1832 mg/m^3). The 4-h LC_{50} was 405 ppm (95% confidence limits of 386-425 ppm). The mortality rates of mice exposed at 500 ppm for 105, 120, 130, 140, 150, and 180 min were 0, 0, 11, 15, 85, and 90%, respectively. The post-exposure observation period was not specified. Mortality in mice exposed at 500 ppm for 150 min that had been injected with GSH (500 mg/kg) previously was only 5.3% compared with 85% in mice that were not injected with GSH.

No full information on the study was available, therefore the study quality and the calculated LC_{50}-values could not be evaluated.

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