20230316-boron trifluoride
-INHOUDELIJK VASTGESTELD

National Institute for Public Health
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Probit function technical support document

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substance name	CAS number
Boron trifluoride	**7637-07-2**

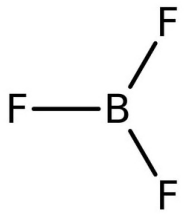
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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 "inhoudelijk vastgesteld" (approved content).

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 Boron trifluoride

1. Substance identification



CAS-number:	7637-07-2
IUPAC name:	Boron trifluoride
Synonyms:	boron fluoride, trifluoroborane, trifluoroboron
Molecular formula:	BF3, structural formula:
Molecular weight:	67.8 g/mol
Physical state:	gas
Boiling point:	-100.4°C (at 101.3 kPa)
Vapour pressure:	>100 kPa (at 20°C)
Saturated vapor conc:	gas
Conversion factor:	1 mg/m^3 = 0.355 ppm (at 20°C and 101.3 kPa)
	1 ppm = 2.820 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	Human H-314-330

2. Mechanism of action and toxicological effects following acute exposure

Special considerations: Unlike other metal fluorides and chlorides, BF_3 does not hydrolyse easily in contact with moisture in air. Instead, in moist air BF_3 forms a mist of the dihydrate ($BF_3 \bullet 2H_2O$). Therefore, the toxicity of BF_3 cannot be easily predicted from HF formation, unlike BCl_3 which hydrolyses very quickly to form HCl mist in moist air.

Acute effects: BF_3 is a primary acidic corrosive chemical. The main consequence of inhalation exposure to BF_3 is irritation of the respiratory tract; irritation of cornea, conjunctiva and skin can also occur. The health endpoints of acute exposure are related to the irritative and corrosive properties of BF_3. Symptoms of high exposure are laboured breathing, secretions from nose, mouth and eyes and prostration. Damage occurs in the respiratory system, primarily in the upper respiratory tract resulting in mucus secretion, upper airway lesions and laryngospasm; some pulmonary oedema has also been reported. The resulting hypoxemia will cause CNS and cardiovascular effects (myocardial ischemia). Lethality results when the respiratory tissue damage proceeds to inflammation, degeneration and necrosis of affected tissue, atelectasis, emphysema and finally death. In addition, renal and liver effects have also been reported.

Long-term effects: In addition, chronic exposure produces irritative effects similar as seen after acute exposure. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition, may well develop after single exposure to high concentrations of BF_3. Symptoms occur within minutes to hours after the initial exposure and may persist as non-specific bronchial hyper-responsiveness for months to years.

3. Human toxicity data

No informative reports on human toxicity following acute inhalation exposure were identified in which details about both lethal or non-lethal 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 final TSD, ERPG document and EU RAR and reference database for boron trifluoride, 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 6 studies were identified -with 9 datasets for 4 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, 1 dataset was assigned status B and 8 were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies on sensory irritation of inhalation exposure to boron trifluoride were found.

5. Probit functions from individual studies

All available acute lethality data on boron trifluoride are displayed in Figure ***1***.

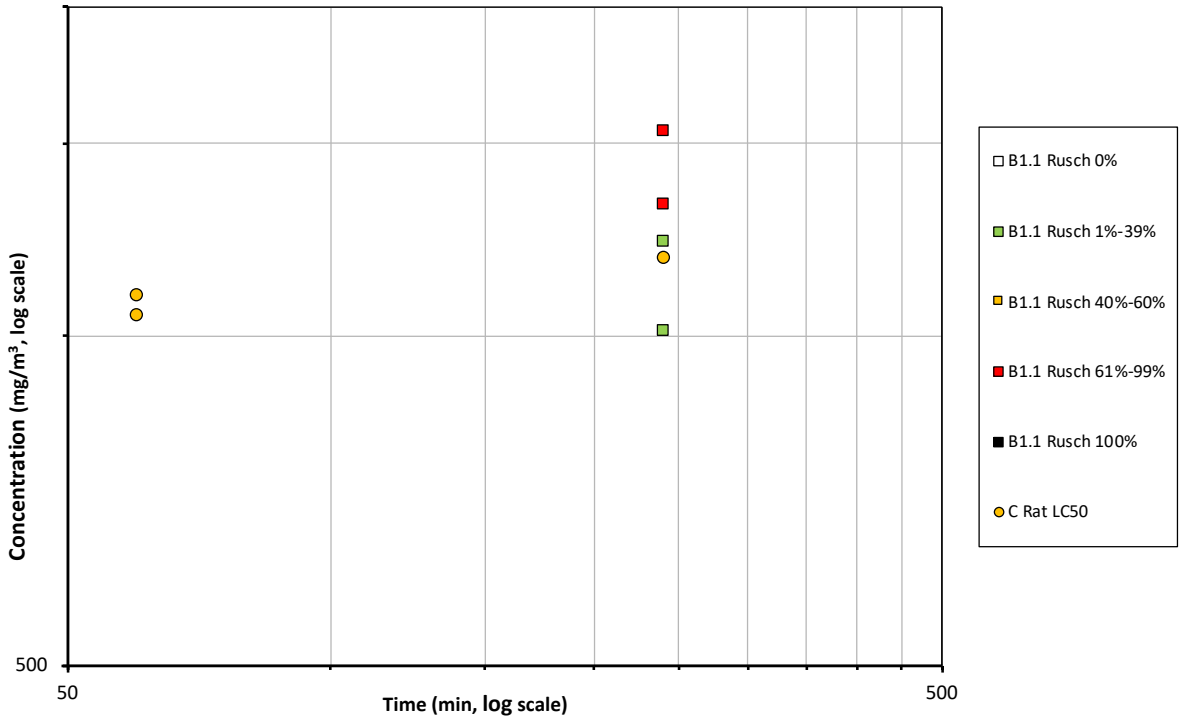


Figure 1 *All available acute lethality data for boron trifluoride.*

The single available B1 study was used for derivation of the animal probit function for boron trifluoride; the data are presented in Table 1 and Figure 2.

The probit function has been calculated and reported in Appendix 1 for study B1.1. The results of the calculations are presented in Table 1.

Table 1 *Data selected for initial analysis of the animal probit function of boron trifluoride.*

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.
B1.1	Rat	*240-min LC_{50}*	1215 (1050 – 1348)	*9720*	N/A

The data of study B1.1 with rats are presented graphically below.

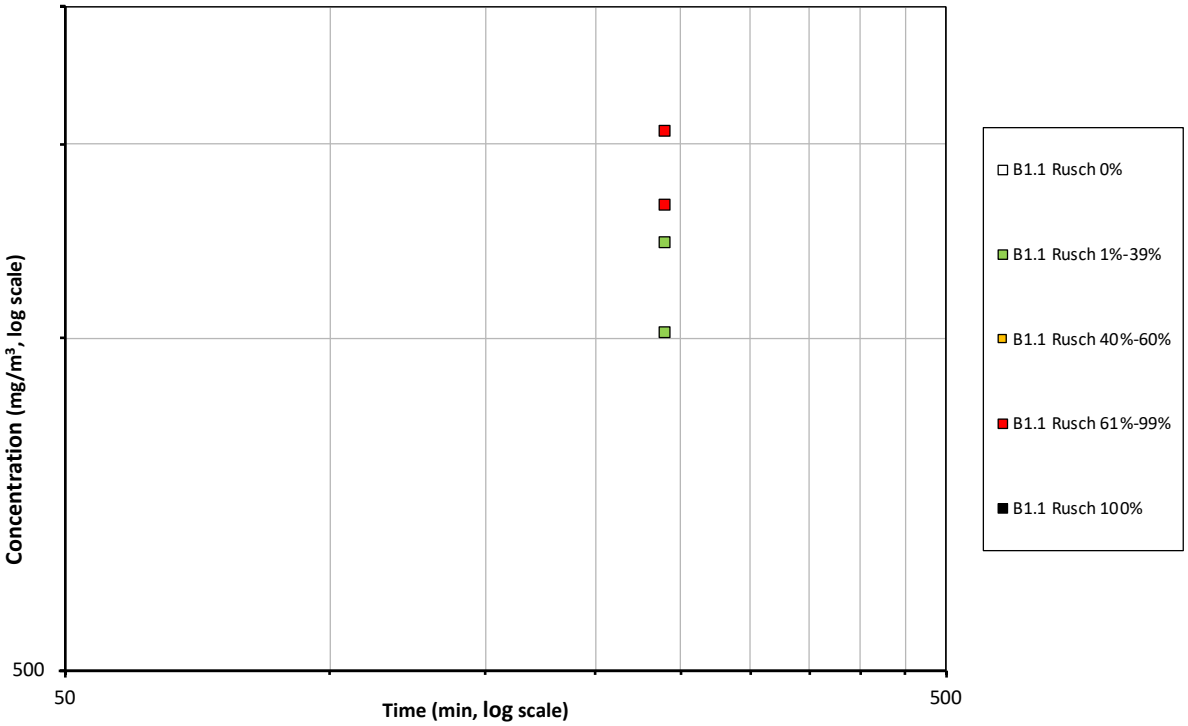


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of boron trifluoride.*

Based on criteria outlined in the guideline the data from studies B1.1 were selected for the final dataset for the derivation of the animal probit function. The data that were selected for final analysis of the animal probit function are presented in Table 2 and Figure 3.

The final data eligible for calculating the animal probit function contains 1 dataset from 1 study and includes data from 1 animal species.

Table 2 *Data selected for the derivation of the animal probit function of boron trifluoride (identical to table 1).*

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.
B1.1	Rat	*240-min LC_{50}*	1215 (1050 – 1348)	*9720*	N/A

The data of the selected datasets are presented graphically below.

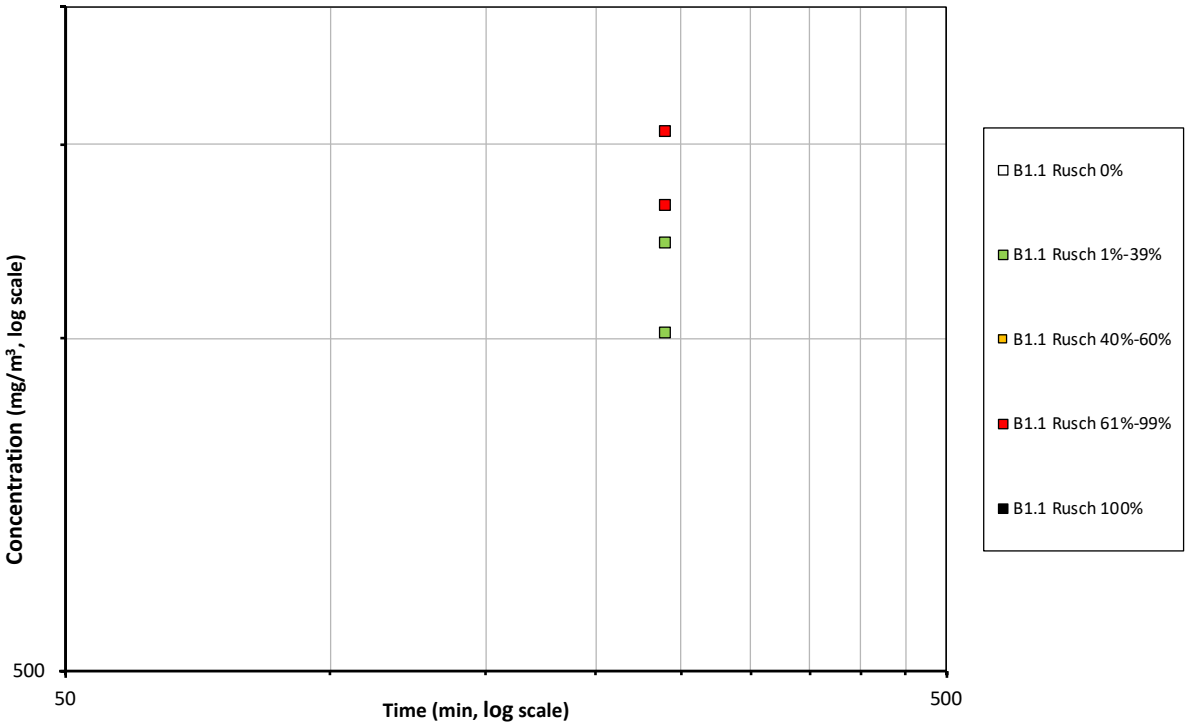


Figure 3 *Final data selected for derivation of the animal probit function of boron trifluoride (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from study B1.1 have been used to derive a point of departure as outlined above. This was the only available study that met the required quality criteria.
Since no A- or B2-studies were available to derive a chemical-specific n-value, the default n-value of 2 was used.

The Point of Departure for the human probit function is a 240-minute geometric mean animal LC_{50} value of 1215 mg/m^3 and the default n-value of 2.

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	3	No rationale to deviate from default assessment factor.
Nominal concentration	1	Well performed actual concentration assessment.
Adequacy of database	2	Only a single B1-study; large extrapolation needed to short exposure durations due to 4-hour exposure duration.

The estimated human equivalent 240-minute LC_{50} value is 1215 / 6 = **203 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): $5 = a + 1 \times \ln (203^2 \times 240)$ resulting in the a-value of **-11.10**.

$Pr = -11.1 + 1 \times \ln (C^2 \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has a scientifically weak basis. The probit function is based on a single study in the rat with B quality, exposing a total of 40 rats to concentrations between 1010 and 1540 mg/m^3.

The human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 86 mg/m^3 and the calculated human 60 min LC_1 (Pr = 2.67) is 126 mg/m^3.

Table 4 *LC-values 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	122	86
1% lethality, this probit	178	126
AEGL-3[1] (2013, final)	110	88
ERPG-3[1] (2009)		100
LBW (2015)	110	88

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

[1] 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: B1.1

Author, year: ***Rusch et al 1986***
Substance: Boron Trifluoride
Species, strain, sex: Male and female F344 Rats
Number/sex/conc. group: 5/sex/concentration
Age and weight: 9 weeks old, weight unspecified
Observation period: 14 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	*Exposure was to the stable dihydrate, (a fuming liquid) thus avoiding hydrolysis in air. The BF_3 content of the test material was 63.87%. The $BF_3 \bullet 2H_2O$ atmosphere was generated with a nebulizer.*
Use of vehicle (other than air)	*Filtered conditioned air, relative humidity 44-53%.*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body.*
Type of restrainer	*N/A*
Pressure distribution	*Chambers operated under negative pressure, not further specified.*
Homogeneity of test atmosphere in breathing zone of animals	*Not specified; no drawing of experimental setup and sampling location.*
Number of air changes per hour	*Air flow was 50 ℓ/min in a 225 ℓ chamber (13.3 air changes / h).*
Equilibration time (t95)	*Equilibration time T_{99}: 21 min according to author. Calculated T_{95}: 13.5 min.*
Start of exposure relative to equilibration	*At start of concentration build-up, removal of the animals following exposure > 30 min after termination of exposure.*
Actual concentration measurement	*One sample/hr in an impinger, followed by analysis using an ion-selective electrode.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*Reported particle size (Anderson particle size sampler): MMAD 1.8 µm (GSD 1.9).*
Assessment of Reliability	***B1*** This study received B1 status because only 1 exposure duration was studied. Otherwise well performed.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality, sexes combined	
	Measured	Adjusted		lethal	exposed
Rat	1010		240	3	10
Rat	1220		240	2	10
Rat	1320		240	8	10
Rat	1540		240	9	10

The author reported that males and females were 'equally affected', without providing the actual sex specific response data. Clinical signs elicited by the exposures included dry and moist rales, gasping, excessive oral and nasal discharge, and lacrimation, indicative of respiratory distress and irritation. Recovery was apparent for the rats surviving beyond 6 days postexposure. Body weight gain depression, and increases in kidney and liver weights, were also noted.
The nominal-to-actual ratio of the air concentration was 4-5, which the authors attributed to losses associated with high concentration aerosol generation.

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
Sexes combined	Rat	-28.0	4.64

No C × t probit function could be calculated from these data alone. The authors concluded that males and females were equally affected, and they provided only the pooled data. An LC_{50} value for sexes combined has been calculated.

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
240			1215 (1050 - 1348)

The authors report a 240-minute LC_{50} of 1210 mg/m^3 (1080-1350 mg/m^3) for sexes combined, our analysis estimated a 240-minute LC_{50} of 1215 (1050-1348) mg/m^3.

Study ID: C studies

Kasparov and Kiry (1972) reported a 4-hour LC_{50} of 1180 mg/m^3 following exposure of 50 albino rats to boron trifluoride[2]. It was not stated if animals were exposed to nominal or measured concentrations (4-h value was however comparable to the value found in the Rusch et al. 1986 study). Necropsy of exposed animals revealed cyanosis of mucous membranes and haemorrhage of internal organs including the lungs. Lung weights were increased, and histopathological pulmonary examination of the lungs revealed oedema, alveolar duct destruction, and vascular dilation. Hyperaemia and oedema were observed in the kidneys, spleen, and brain. The mucous membranes of the eyes showed evidence of irritation.

Stokinger and Spiegel (1953) exposed groups of 10 rats, 10 mice, and 10 guinea pigs to nominal concentrations of boron trifluoride. Exposure was to 2115 mg/m^3 for 5.5 hrs and 381 mg/m^3 for 10.9 hours (all species) and 987 mg/m^3 for 1.4 hrs (guinea pigs). Every species was exposed to 2-3 concentration levels, with different exposure durations and 3 species simultaneously in a dynamically operated exposure chamber. The actual exposure may have been much less (in the Rusch 1986 study, the nominal-to actual ratio was 4-5). The purity of the chemical and the age, sex, and strain of the animals were not reported. The data did not allow calculation of an LC_{50} value for any of the species.

Zapp (1948) performed a range-finding study with rats, guinea pigs and dogs, all of unknown sex, strain or age. The author reported nominal or target concentrations between 700 and 4000 mg/m^3. Some animals died during exposure, all others were sacrificed well before a 14-day post-exposure period. A marked species difference was noted: all guinea pigs died within minutes after initiation of exposure that hardly affected dogs and rats within the same time period. The mode of action in guinea pigs was suggestive of acute bronchospasm. This study was reported elsewhere as DuPont (1948).

Rusch et al (2008) exposed male and female rats 4 hours to actual concentrations up to 74.4 mg/m^3. No lethality occurred. The nominal-to-analytical ratio was 13-37, due to considerable wall loss of the compound.

Vernot at al (1977) reported a 1-hour inhalation LC_{50} value for boron trifluoride in male rats of 1091 mg/m^3 (902-1317) and in female rats of 1046 mg/m^3 (826-1323). The exposures may have been static with a bell-jar as inhalation chamber. Hardly any information was provided on the generation, administration, sampling and analysis of the test atmosphere.

[2] Taken from Final AEGL document, based on translation of Russian study that was unavailable to the probit TSD author.

Appendix 2 Reference list

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