Probit function technical support document

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substance name	CAS number
Boron trichloride	**10294-34-5**

This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA).

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, have been approved by the scientific expert panel on probit functions on scientific grounds. The status of this document was therefore raised to "interim", pending a decision on its formal implementation.

Subsequently the Ministry of Housing, Spatial Planning and the Environment (VROM) will perform a second tier evaluation to decide whether the probit function will be formally implemented. The decision on actual implementation will primarily be based on the results of a consequence analysis.

Interested parties are invited to submit comments and suggestions concerning this document within 6 weeks after the issue date to the e-mail address mentioned above.

Detailed information on the procedures for derivation, evaluation and formalization of probit functions is available at
http://www.rivm.nl/milieuportaal/bibliotheek/databases/probitrelaties.jsp.

Technical support document Boron Trichloride

1. Substance identification

CAS-number: 10294-34-5
IUPAC name: boron trichloride
Synonyms: boron chloride, trichloroborane, trichloroboron
Molecular formula: $B\text{-}Cl_3$
Molecular weight: 117.2
Physical state: gas (at 20°C and 101.3 kPa)
Boiling point: 12.5°C (at 101,3 kPa)
Vapour pressure: 130 kPa (at 20°C)
Saturated vapour conc: gas (at 20°C and 101.3 kPa)
Conversion factor: 1 mg/m^3 = 0.205 ppm (at 20°C and 101.3 kPa)
1 ppm = 4.875 mg/m^3 (at 20°C and 101.3 kPa)
Labelling: R14-26/28-34

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

Special considerations: BCl_3 hydrolyses very quickly to form hydrogen chloride gas (aerosol) and boric acid (a weak acid). The reaction is claimed to be quick and complete[2]. The toxicity of BCl_3 is thought to result from the HCl hydrolysis product, and is quantitatively and qualitatively similar to that of HCl. In this document the probit function for BCl_3 will be based on the probit relation of HCl.

Acute effects: The main target organs and tissues for inhalation exposure to HCl are the cornea, conjunctiva, skin and respiratory tract. HCl dissolves in the mucous membranes of the respiratory tract and eyes to form hydrochloric acid, a strong acid that produces coagulative necrosis. The health endpoints are all related to the irritative and corrosive properties of HCl. Symptoms of high exposure are laboured breathing, secretions from nose, mouth and eyes and prostration.

Damage occurs in the respiratory system, particularly the upper respiratory tract resulting in mucus secretion, upper airway and/or pulmonary oedema and laryngospasm. The resulting hypoxemia will cause CNS and cardiovascular (myocardial ischemia) effects. Lethality results when the respiratory tissue damage proceeds to inflammation, degeneration and necrosis of affected tissue, atelectasis, emphysema and finally death.

Long-term effects: Chronic exposure produces essentially the same type of health effects. Reactive Airways Dysfunction Syndrome, an acquired asthma-like condition has been described to develop after single exposure to HCl. Symptoms occur within minutes to hours after the initial exposure and may persist as non-specific bronchial hyper-responsiveness for months to years.

[1] National Research Council: AEGL Volume 4 (2004), AHLS Provider manual 3rd ed. (2003), Arts (2000).
[2] Letter from Albemarle Corp to NAC AEGL (2007), verified by 2 RIVM chemical engineers.

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.

4. Animal acute toxicity data

Animal lethal toxicity data considering acute exposure are described in Appendix 1. One study was identified -with 1 relevant datasets for 1 species- with data on lethality following acute inhalation exposure. This study was assessed to be unfit (status C) for human probit function derivation.
No ERPG or AEGL TSDs were available. During a literature search the following databases have been consulted:

1. A search covering data from 1995 - 2008 was performed in HSDB, MEDline/PubMed, Toxcenter, IUCLID, RTECS, with the following search terms:
    - Boron Trichloride and synonyms
    - CAS number
    - lethal*
    - mortal*
    - fatal*
    - LC_{50}, LC
    - probit
2. Unpublished data were sought through networks of toxicological scientists.

Sensory irritation
No studies were identified in which sensory irritation of boron trichloride was studied. Since the toxicity is thought to be determined by its hydrolysis product HCl, the RD_{50} values of HCl were used to assess the necessity to make an adjustment for reduced minute volume in animals due to sensory irritation.

5. Probit functions

No probit functions for boron trichloride have been calculated and reported in Appendix 1 due to absence of qualifying studies.

Due to the lack of adequate data (only 1 B-study with a single exposure duration of 1 hour), a graphical representation of the data is not informative.

6. Evaluation

The probit function for BCl_3 is derived with an LC_{50} value based on HCl equivalents, and using the n-value derived for HCl. Since the actual information on the compound's toxicity is very limited, a slightly conservative approach is chosen.

The human probit function for HCl was based on the results from Hartzell 1985. The reason was that the LC_{50} values of the other A study from Arts 2000 were 2-3 times higher than all other reported studies. In absence of a reason to discard the lower LC_{50} values, the lowest of the two A-quality values was selected. In addition, both studies produced roughly equal n-values (1.59 for Arts 2000 and 1.48 for Hartzell 1985). Both HCl A-studies are described in appendix 1.

The 30 minute LC_{50} value of HCl that was used as point of departure for the HCl probit function was 6654 mg/m^3 (Hartzell 1985, calculated excluding the 5 minute data[3]) which equals 4386 ppm. Complete hydrolysis of 1 mole BCl_3 produces 3 moles of HCl. Therefore the LC_{50} value of BCl_3 was estimated with a molar adjustment factor of 3 as 4386 / 3 = 1462 ppm, which equals a **30-min rat LC_{50} =7127 mg/m^3**. The human equivalent LC_{50} was calculated by applying the following assessment factors:

Assessment factor for:	Factor	Rationale
Animal to human extrapolation:	3	
RD_{50}	3	same as used for HCl
Nominal concentration	1	HCl concentrations were determined analytically
Adequacy of database:	2	no adequate studies for BCl_3, uncertainty about the validity of the assumption that the toxicity is completely due to HCl

The estimated human equivalent 30-min LC_{50} value is 7127 / 18 = **396 mg/m^3**.

The experimentally determined n-value for HCl, which is assumed to be equal for BCl_3 was **1.48**. Assuming a regression coefficient (b×n) of 2 for the slope of the curve, the b-value can be calculated as 2 / n = **1.351**.

The human probit function is then calculated on the human equivalent 30 min LC_{50} and using the above parameters to solve the following equation to obtain the a-value (the intercept): $5 = a + 1.370 \times \ln(396^{1.48} \times 30)$ resulting in the a-value of **-11.56**.

$Pr = -11.6 + 1.35 \times \ln(C^{1.48} \times t)$ with C in mg/m^3 and t in min.

The derived human probit function has an acceptable scientific basis. The data on BCl_3 itself are very limited, so that the probit function must be developed assuming that the hydrolysis product HCl determines the inhalation toxicity. This is assessed to be a reasonable assumption. The probit function of HCl is scientifically sound and based on respectively supported by two good studies in the rat with A quality (Hartzell 1985 and Arts 2000).

[3] As a general rule, data from exposure durations less than 10 minutes are excluded because of uncertainties in chamber conditions and the ability of animals to temporarily reduce their minute volume.

The human 60 min LC_1 (Pr = 2.67) calculated with this probit equation is 79 mg/m^3 and the calculated human 60 min $LC_{0.1}$ (Pr = 1.91) is 54 mg/m^3.

Estimated level	**30 min (mg/m^3)**	**60 min (mg/m^3)**
1% lethality, this probit	127	79
0,1% lethality, this probit	87	54
AEGL-3	N/A	N/A
ERPG-3		N/A
LBW		100

No international guideline levels have been established for this chemical. Comparing to LBW levels as presented in the table above the lethal levels derived with this probit function are roughly the same, maybe marginally more conservative. The difference is less than a factor of 2.

Appendix 1 Animal experimental research

Study ID: A.1

Author, year: Arts 2000

Substance: Hydrogen Chloride

Species, strain, sex: Male and female rats, unspecified strain

Number/sex/concentration group: 1 / C×T combination / sex, total number of animals was 58

Age and weight: unspecified

Observation period: 14 days

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*Equivalent to OECD 403 (10 animals per concentration); In this study 1 animal/sex/C×T combination was used*
Stability of test compound in test atmosphere	*Some evidence of aerosol formation at 12,300 and 23,400 mg/m^3 concentrations.*
Use of vehicle (other than air)	*Dry air (relative humidity 1%)*
Whole body / nose-only (incl. head/nose-only) exposure	*Head/nose only*
Pressure distribution.	*Positive pressure at the nose of the animals (central cylinder), negative pressure in surrounding hood*
Homogeneity of test atmosphere at breathing zone of animals	*Empty animal location used as sampling point; based on air flow (see below,) homogeneity expected to be present*
Number of air changes per hour	*25ℓ/min for 10 rats, i.e. air flow is sufficient*
Actual concentration measurement	*Acid/base titration based on colour change of titration fluid and amount of air passed through. This method may have produced biased concentration estimates due to interference of CO_2 exhaled by the animals.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*N/A*
Assessment of Reliability	***A***

Results

Each C×T combination consisted of 1 male and 1 female rat. The table provides the numerator of the lethal proportion - the denominator is always 1. The publication provides 2 sets of exposure data (table 4.1 and appendix 1.2; Arts 2000). The exposure data from table 4.1 were used for the calculations below.

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			Male	Female
Rat	4890	45/60/90/120/180	0/0/0/0/1	0/0/0/0/0
Rat	6620	30/45/60/90/120	0/0/0/0/1	0/0/0/0/0
Rat	9020	15/20/30/40/60	0/0/0/0/0	0/0/0/0/0
Rat	9250	60/90/120/150	1/1/1/1	1/1/1/1
Rat	12300	20/30/45/60/90	0/0/1/0/1	0/0/0/1/1
Rat	23400	10/20/30/45/60	0/1/1/1/1	0/1/1/1/1

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, December 2006) as:

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

Where C is concentration in mg/m^3, t is exposure duration in minutes and S is sex (0 = female, 1 = male).

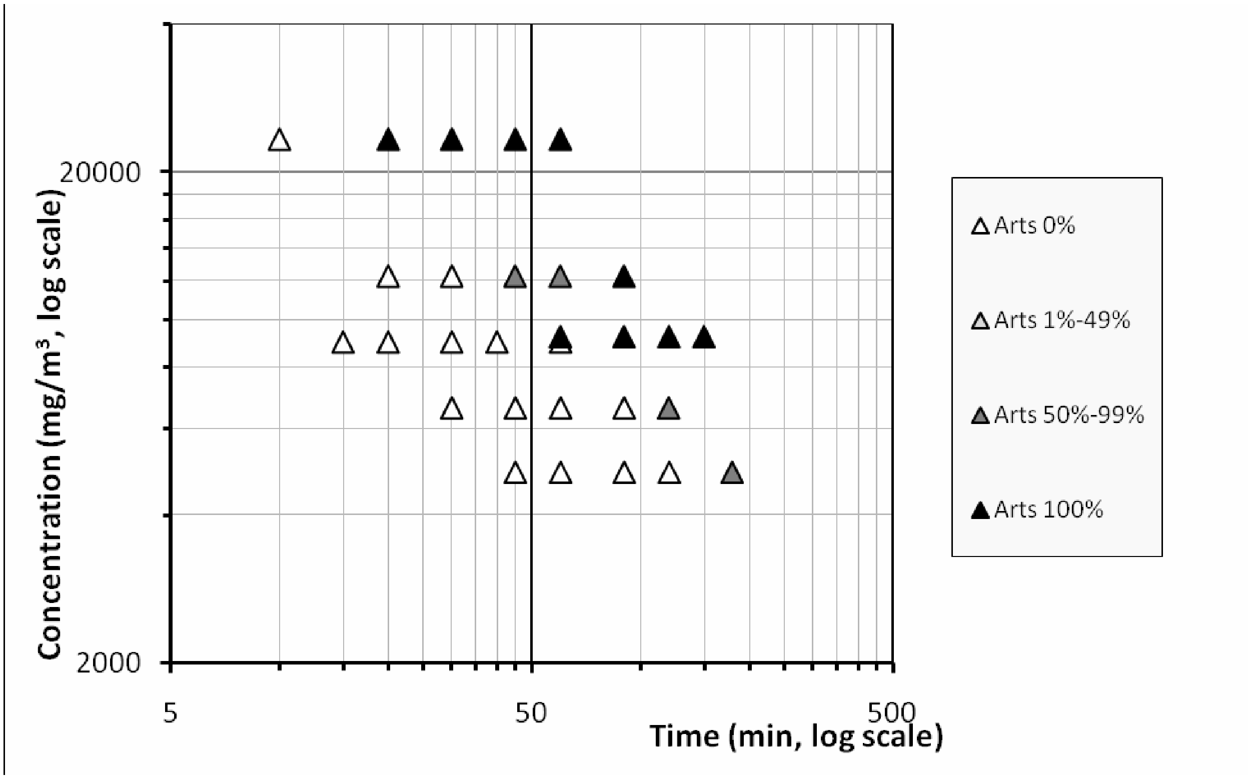
Probit function	*Species*	*a*	*b*	*c*	*d*	*n-value*
Sex as covariate	*Rat*	*-73.9*	*6.67*	*4.19*	*0.53*	*1.59 (1.26 - 1.92)*
Sexes combined	*Rat*	*-73.3*	*6.64*	*4.17*		*1.59 (1.26 - 1.93)*

The 30 minute LC_{50} for both sexes differed by less than a factor 2, nor did analysis with sex as covariate give any indication that sex differences exist. This does not support that sex differences exist in the lethal response. For this reason the data from both sexes were pooled and analyzed to derive the animal probit function (last column in table below). The results for males and females were derived from the analysis with sex as covariate.

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***
10	29930 (21780 - 42990)	32420 (23560 - 47120)	31070 (22970 - 44100)
30	15000 (12460 - 18570)	16250 (13480 - 20360)	15580 (13350 - 18770)
60	9702 (8376 - 11440)	10510 (9066 - 12540)	10070 (9096 - 11420)

If the male and female datasets were analyzed separately, the outcome was slightly different. The 30 minute LC_{50} value (mg/m^3) for males was 15,930 (11,750 - 24,810) and for females 15,130 (12,030 - 24,860).

A graphical overview of the data is presented below. Each C×T combination (with 1 male and 1 female animal) represents one point in the plot.



Study ID: A.2

Author, year: Hartzell 1985

Substance: Hydrogen Chloride
Species, strain, sex: Rat, male Sprague-Dawley
Number/sex/concentration group: 6-8 / group (all male)
Age and weight: adult, weight unspecified
Observation period: 14 days

Criteria	*Comment*
Study carried out according to GLP	*No GLP statement provided*
Study carried out according to guideline(s)	*No mention of guideline OECD 403*
Stability of test compound in test atmosphere	*Aerosol formation*
Use of vehicle (other than air)	*Air*
Whole body / nose-only (incl. head/nose-only) exposure	*Head-only (in restrainer tubes), placed in small clean air space during chamber equilibration*
Pressure distribution.	*Not specified*
Homogeneity of test atmosphere at breathing zone of animals	*Not specified*
Number of air changes per hour	*Not specified*
Actual concentration measurement	*Batch sampling with soda lime near breathing zone to determine analytical concentration.* *Intermittent sampling of small aliquots analyzed with Ion Specific Electrode and continuous sampling (conductivity detector) to maintain stable HCl level during the test.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*Not available*
Assessment of Reliability	***A***

Results

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality	
			Exposed	responded
rat	13984	5	6	0
rat	16530	5	6	3
rat	19128	5	6	2
rat	21747	5	6	0
rat	23498	5	6	3
rat	30856	5	6	6
rat	8275	10	6	0
rat	11596	10	6	1
rat	12333	10	8	5
rat	12806	10	8	1
rat	13938	10	6	6
rat	6627	15	6	0
rat	9380	15	6	3
rat	12130	15	6	4
rat	13619	15	6	4
rat	15185	15	6	6
rat	7393	22.5	6	2
rat	9749	22.5	6	4
rat	11380	22.5	6	6
rat	12317	22.5	6	2
rat	13142	22.5	8	4
rat	15408	22.5	6	6
rat	3967	30	6	2
rat	5644	30	6	4
rat	6217	30	6	1
rat	8780	30	8	8
rat	9834	30	6	4
rat	12586	30	6	6

Species	Concentration (mg/m^3)	Exposure duration (min)	Lethality Exposed	responded
rat	2725	60	6	0
rat	3467	60	6	3
rat	3952	60	6	1
rat	6501	60	8	7
rat	6779	60	6	6
rat	7378	60	6	6

Probit function

The probit function and associated LC-values have been calculated using the DoseResp program (Wil ten Berge, December 2006) as:

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

Where C is concentration in mg/m^3 and t is exposure duration in minutes.

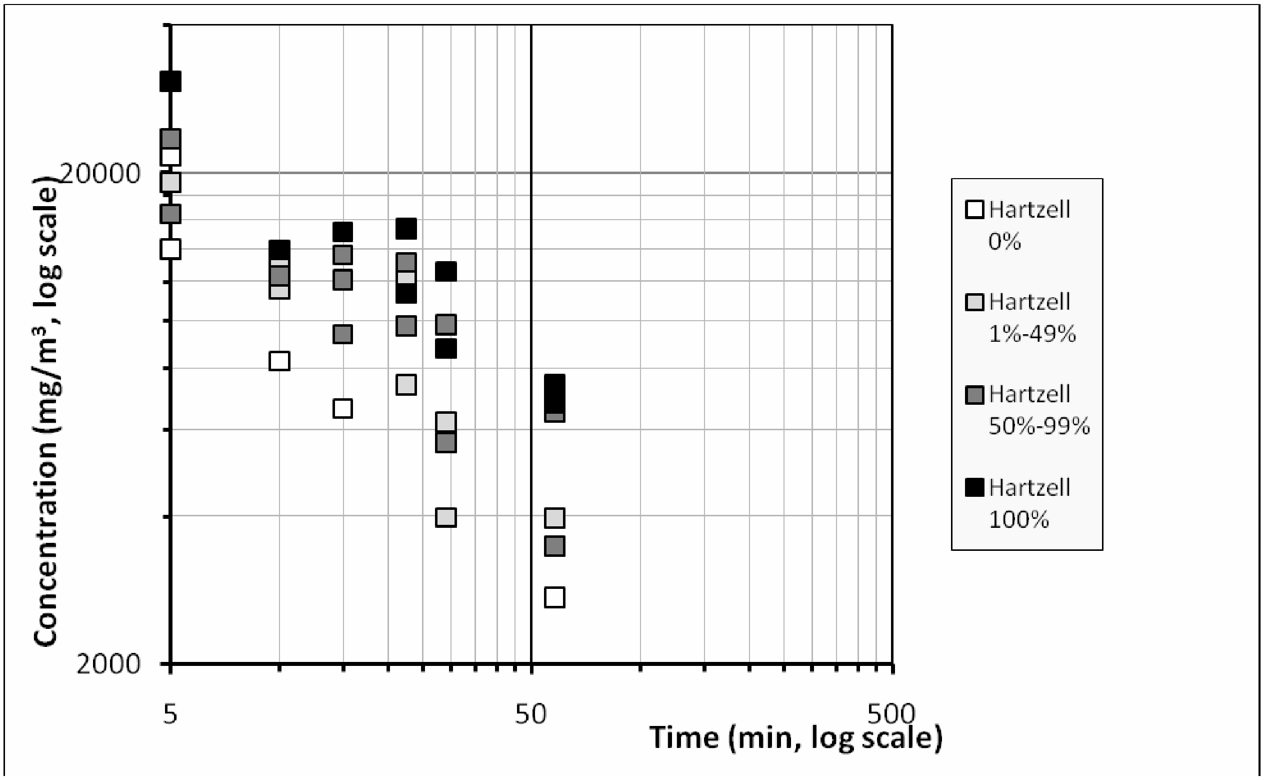
Usually 5 minute data are excluded from the calculation; to assess the influence of including the 5 minute data, the calculations were performed with and without the 5 minute data.

Probit function	*Species*	*a*	*b*	*c*	*n-value*
Including 5 min exposure	*Rat*	*-21.58*	*2.39*	*1.64*	*1.46 (1.12 - 1.79)*
Excluding 5 min exposure	*Rat*	*-20.68*	*2.31*	*1.56*	*1.48 (0.97 - 1.99)*

The analysis with and without the 5 minute exposure essentially gave the same result, and are both presented below.

Duration (minutes)	*LC_{50} (mg/m^3) 95%-C.I.* ***With 5 min data***	*LC_{50} (mg/m^3) 95%-C.I.* ***Without 5 min data***
10	14190 (12170 - 16730)	13990 (10870 - 18320)
30	6671 (5527 - 7730)	6654 (5390 - 7770)
60	4144 (3081 - 5176)	4163 (2891 - 5415)

A graphical overview of the data is presented below. Each concentration-time combination (with 6-8 animals) represents one point in the plot.


20000
2000
Concentration (mg/m³, log scale)
5
50
500
Time (min, log scale)
Hartzell 0%
Hartzell 1%-49%
Hartzell 50%-99%
Hartzell 100%

Study ID: C.1

Author, year: Vernot 1977

Substance: Boron trichloride
Species, strain, sex: Male and female Sprague-Dawley rats
Number/sex/concentration group: 5 / concentration
Age and weight: adult, 200-300 grams
Observation period: unspecified

Criteria	*Comment*
Study carried out according to GLP	*GLP idd 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)	*No information*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Pressure distribution.	*In bell jar, static atmosphere*
Homogeneity of test atmosphere at breathing zone of animals	*No forced mixing of chamber air*
Number of air changes per hour	*No (static atmosphere)*
Actual concentration measurement	*'Standard techniques', SD of 5% or less*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	*No information*
Assessment of Reliability	***C*** Only the LC_{50} value was reported, and the testing conditions and detail of reporting do not meet current standards

Results

Boron trichloride was one of the chemicals reported as part of a range finding toxicity program in 110 organic and inorganic compounds.

Species	Exposure duration (min)	LC_{50} (mg/m^3). 95% cfd-i	
		Male	Female
Rat	60	12387 (10935 - 14030)	21538 (19208 - 24146)

Appendix 2 Reference list

Arts, J.H.E., C. Mommers, and H. Muijser: Toxic Effects from Accidental Releases of Hazardous Substances (TEARHS) – Lethal and non-lethal effects in rats upon exposure during short periods of time. TNO Nutrition and Food Research, report V99.1136. Zeist (2000).

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