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

Probit function technical support document

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substance name	CAS number
Tetraethyl lead	**78-00-2**

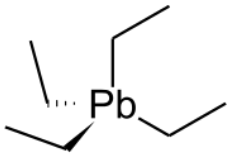
This document describes the derivation of a probit function for application in a quantitative risk analysis (QRA). The probit function has been derived according to the methodology described in RIVM report 2015-0102.

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 "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 Tetraethyl lead



1. Substance identification

CAS-number:	78-00-2
IUPAC name:	Tetraethyl lead
Synonyms:	Tetraethyllead, lead tetraethyl, tetraethylplumbane, TEL
Molecular formula:	$C_8H_{20}Pb$
Molecular weight:	323.4 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	84°C (at 2 kPa)
Vapour pressure:	0.04 kPa (at 20°C)
Saturated vapor conc:	400 ppm = 5381 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.074 ppm (at 20°C and 101.3 kPa)
	1 ppm = 13.453 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	no harmonized H-sentences

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

Acute effects: Information on the exact mechanism of action is not available. The main site of action is the central nervous system. Effects included hyperexcitation, muscular tremors, convulsions, coma and death. Mild manifestations are: insomnia and nervous excitation, nausea, vomiting, associated with tremor, hyperreflexia, muscular contractions, bradycardia, arterial hypertension, and hypothermia. Most severe cases present episodes of complete disorientation, mania, ataxia, hallucinations, exaggerated muscular activity, and violent convulsive seizures, which may terminate in coma and death. In severe cases, muscle, hepatic and renal damage may occur. The clinical picture may persist for days and weeks. A rapid onset of symptoms after exposure indicates a poor prognosis. When the onset of symptoms is delayed for many days recovery is usually complete, but some neurological sequelae have been reported.
The toxic moieties in tetraethyl lead poisoning are the trialkyl metabolites and not the inorganic lead ion.
Long-term effects: No information.

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. No AEGL TSD, ERPG document and EU RAR was available for tetraethyl lead.
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:

[1] WHO (1977, 1994); Cremer and Callaway (1961)

- 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 4 studies were identified -with 4 datasets for 2 species- with data on lethality following acute inhalation exposure. None of the datasets was assigned status A for deriving the human probit function, one dataset was assigned status B1 and 3 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 tetraethyl lead are displayed in Figure 1.

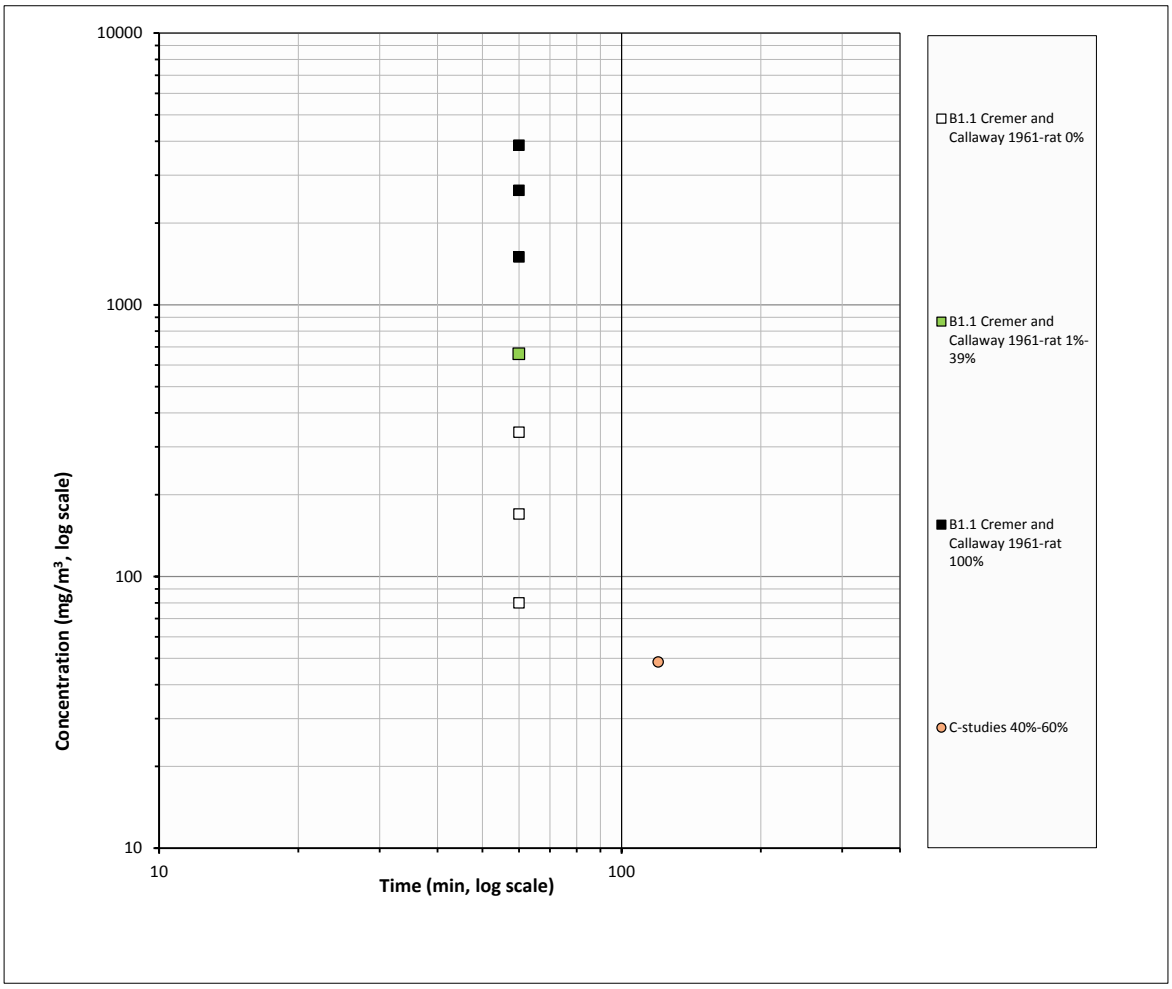


Figure 1 *All available acute lethality data for tetraethyl lead.*

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

It was possible to derive a probit function for tetraethyl lead based on the only available study with B1 quality. However, this B1 study did not enable to produce a concentration-time-lethality relationship.

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 tetraethyl lead.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	n-value 95% C.I.
B1.1	Rat	*60-min LC_{50}*	709 (C.I. could not be calculated)	N/A

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

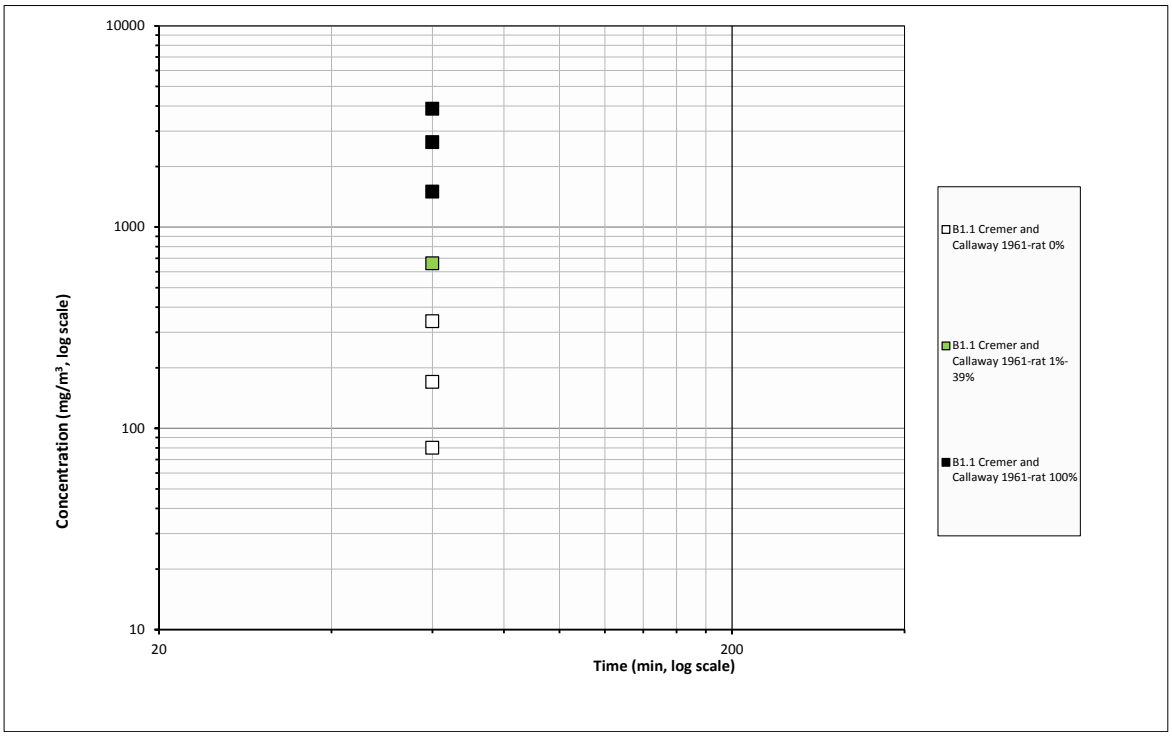


Figure 2 *Data selected for the initial analysis for the derivation of the animal probit function of tetraethyl lead.*

Based on criteria outlined in the guideline the data from rat study B1.1 (Cremer and Callaway, 1961) 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 one dataset from one study and includes data from one animal species.

Table 2 *Data selected for the derivation of the animal probit function of tetraethyl lead.*

Study ID	Species	Probit (C in mg/m^3, t in min)	LC_{50} at tested exposure duration (mg/m^3) 95% C.I.	n-value 95% C.I.
B1.1		*60-min LC_{50}*	709 (C.I. could not be calculated)	N/A

The data of the selected datasets are presented graphically below.

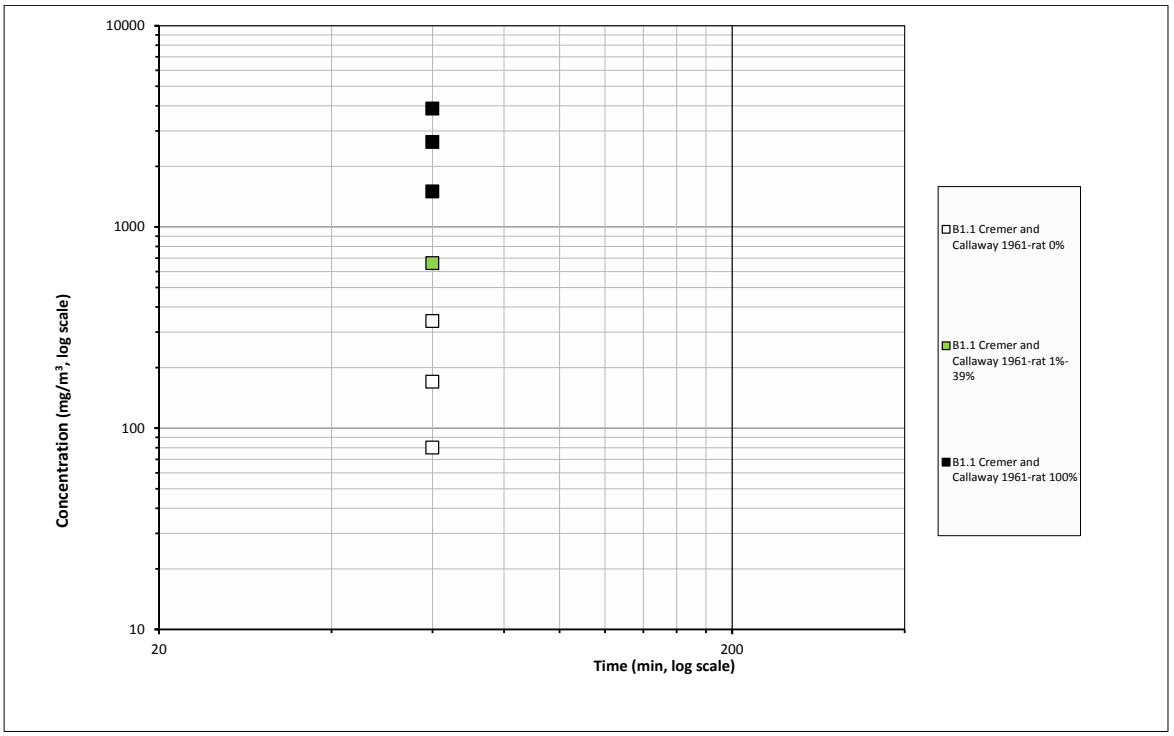


Figure 3 *Final data selected for derivation of the animal probit function of tetraethyl lead (identical to figure 2).*

6. Derivation of the human probit function

To derive the human probit function the results from study B1.1 (Cremer and Callaway, 1961) have been used to derive a point of departure as outlined above.

The Point of Departure for the human probit function is a 60-minute animal LC_{50} value of 709 mg/m^3 and a 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	default

Nominal concentration	1	B1-study with analytically determined concentrations. There may be some issues with respect to the reliability of the applied analytical method used at that time. It is however noted that the difference between the nominal and analytical concentration is quite limited. Further, the nominal concentration is, except for the two highest test concentrations (with 100% lethality), <25% of the saturated vapour concentration.
Adequacy of database:	2	Only one B1-dataset was found. The study was performed using only one exposure duration.

The estimated human equivalent 60-minute LC_{50} value is 709 / 6 = **118 mg/m³**.

No reliable experimentally determined n-value was available, so the default n-value of **2** 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**.

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): $5 = a + 1 \times \ln(118^2 \times 60)$ resulting in the a-value of **-8.64**.

$Pr = -8.64 + 1 \times \ln(C^2 \times t)$ with C in mg/m³ 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 B1 quality, including 116 animals, an exposure duration of 60 minutes and response rates between 0 and 100%.

The calculated human 60 min $LC_{0.1}$ (Pr = 1.91) calculated with this probit equation is 25 mg/m³ and the calculated human 60 min LC_1 (Pr = 2.67) is 37 mg/m³.

Table 4 *LC-values calculated with the derived probit function compared with existing acute inhalation exposure guidelines.*

Estimated level	30 min (mg/m³)	60 min (mg/m³)
0.1% lethality, this probit	36	25
1% lethality, this probit	52	37
AEGL-3	-	-
ERPG-3	-	-
LBW	-	-

A comparison with equivalent (inter)national guideline levels cannot be made.

Appendix 1 Animal experimental research

Study ID: B1.1

Author, year: ***Cremer and Callaway (1961)***
Substance: Tetraethyl lead
Species, strain, sex: Rat, albino, sex not specified
Number/sex/conc. group: 12-20 animals/conc. group
Age and weight: age not specified; 175-230 g
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	*Head-only.* *The inhalation exposures were carried out in an all-glass chamber. The apparatus was designed so that only the heads of the rats were in contact with the vapour. No further details were provided.*
Type of restrainer	*No information*
Pressure distribution	*No information*
Homogeneity of test atmosphere in breathing zone of animals	*Pure solutions of tetraethyl lead were injected into the chamber by a mechanically driven syringe. No further details were provided.*
Number of air changes per hour	*Air flow of 50 L/min*
Equilibration time (t95)	*Insufficient information to calculate t95*
Start of exposure relative to equilibration	*No information*
Actual concentration measurement	*Samples of air were taken at intervals during the 60-minute exposure period into Neal bubblers at approximately 1 litre/min through accurately calibrated critical orifices. The bubblers contained 5 ml of 100-200 petroleum ether. Tetraethyl lead was analysed polarographically.*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*No*

Assessment of Reliability	***B1*** *Study seems to meet the standards, though some details on study characteristics are missing. Limited to one exposure duration.* *There may be some issues with respect to the reliability of the analytical method used at that time.* It is however noted that the difference between the nominal and analytical concentration is quite limited. Further, the nominal concentration is, except for the two highest test concentrations (with 100% lethality), < 25% of the saturated vapour concentration.*

* IDLH states that the tetraethyl lead analytical methods prior to 1968 were not reliable. However, the basis for their statement is not clear.

Results

Species	Concentration (mg/m^3)		Exposure duration (min)	Lethality
	Measured	Adjusted		
				Dead/tested
Rat	0.08×10^3	NA	60	0/16
Rat	0.17×10^3	NA	60	0/16
Rat	0.34×10^3	NA	60	0/20
Rat	0.66×10^3	NA	60	3/16
Rat	1.50×10^3	NA	60	16/16
Rat	2.64×10^3	NA	60	20/20
Rat	3.87×10^3	NA	60	12/12

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	-76.8	12.5	N/A

Duration (min.)	LC_{50} (mg/m^3) 95%-C.I.
60	709 (C.I. could not be calculated)

The study authors reported a 60-min LC_{50} of 0.85×10^3 mg/m^3.

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

Study ID: C studies

Akatsuka (1973) reports a 7-hour LC_{Lo} of 650 mg/m^3 for mouse. Further details are not provided.

IDLH mentions a rat LC_{50} of 6 ppm (81 mg/m^3). However no details on the exposure duration and other study characteristics are provided. The original publication could not be retrieved.

RTECS presents 2 hour inhalation LC_{50} value for mouse of 48.52 mg/m^3. Further details are not provided. The original publication is in Russian language.

Appendix 2 Reference list

Akatsuka K (1973). Tetraalkyl lead poisoning. Sangyo Igaku (Japanese Journal of Industrial Health) 15:3-66. Article written in Japanese. As cited in IDLH.

Chemiekaarten. Ed 33. Den Haag. TNO/SDU uitgevers, 2018.

Cremer J.E. and Callaway S. (1961). Further studies on the toxicity of some tetra and trialkyl lead compounds. Br J Ind Med. 1961 Oct;18:277-82.

IDLH. Immediately dangerous to life or health. Tetraethyl lead. https://www.cdc.gov/niosh/idlh/78002.html accessed online d.d. 07-03-2018.

RIVM 2017. Interventiewaarden gevaarlijke stoffen. http://www.rivm.nl/rvs/Normen/Rampen_en_incidenten/Interventiewaarden.

Ruijten M.W.M.M., J.H.E. Arts, P.J. Boogaard, P.M.J. Bos, H. Muijser, A. Wijbenga. Methods for the derivation of probit functions to predict acute lethality following inhalation of toxic substances. RIVM report 2015-0102. Bilthoven, RIVM, 2015.

WHO (1977). World Health Organization (WHO), Environmental Health Criteria (EHC) no. 3. Lead.

WHO (1994). World Health Organization (WHO), International Programme on Chemical safety (IPCS). Lead, organic.