

Probit function technical support document

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This document has been drafted in accordance with the guidelines described in the document "Evaluation and assessment of probit functions". The document has been checked for completeness by the Netherlands' National Institute of Public Health and the Environment (RIVM).

The document has been assigned the status "proposed" and is up for discussion by the expert panel on probit functions.

substance name	CAS number
phosphorous trichloride	7719-12-2

Technical support document Phosphorous Trichloride

1 Substance identification (based on data from AEGL 2006)

CAS-number:	7719-12-2
IUPAC name:	phosphorous trichloride
Synonyms:	Trichlorophosphine, phosphorous chloride, phosphorous trichloride, (NL : fosfortrichloride)
Molecular formula:	PCl ₃
Molecular weight:	137.33 g/mol
Physical state:	liquid (at 20°C and 1 atm)
Melting point (°C):	-112 (at 1 atm)
Boiling point (°C):	76 (at 1 atm)
Vapour pressure (kPa):	13.3 (at 21°C and 1 atm)
Conversion factor:	1 mg/m ³ = 0.175 ppm (Chemiekaart) 1 ppm = 5.71 mg/m ³
Relative density:	1.5 (at 20°C and 1 atm) (Chemiekaart)
labeling:	R: 14-26/28-35-48/20 (Chemiekaart)

2 Mechanism of action and toxicological effects following acute exposure

Acute effects: The mechanism of action of PCl₃ is not completely understood. The main target organs in inhalation exposure are the cornea, skin and respiratory tract. PCl₃ hydrolyses to HCl, phosphonic acid and pyrophosphonic acids, which may (partly) be responsible for the irritation effects. However, PCl₃ toxicity cannot be fully explained by the hydrolysis products because the substance is more toxic than can be expected from its hydrolysis products. Signs and symptoms that can be expected are: burning eyes, shortness of breath, throat irritation, lacrimation, headache, nausea, burning sensation on the skin, sputum production, chest pains, wheezing, skin rash, blurred vision, vomiting, and abdominal pain. Lethality is caused by tissue damage of the respiratory tract (pulmonary edema) resulting in dyspnoea. Ultimately, hypoxemia will result in CNS depression and cardiovascular effects that may finally lead to deaths.

Long-term effects: Similar effects as for acute exposure are expected after chronic exposure. Asthmatic bronchitis was observed after 1-8 week exposure but resolved upon cessation of exposure.

3 Human toxicity data

No studies have been identified.

4 Animal acute toxicity data

Animal lethal toxicity data considering acute exposure are described in Appendix 2. No studies have been assigned with status A or B for deriving the human probit function, and seven have been assessed to be unfit (status C) for human probit function derivation.

During a literature search the following technical support documents and databases have been consulted:

- 1) AEGL document (interim, 2006), ERPG document (final, 2004), Dutch Intervention Values (2000), Chemiekaart (2008)
- 2) HSDB, RTECS and IUCLID using the following key words:

- a. CAS-number,
 - b. lethal*,
 - c. mortal*,
 - d. LC, LC₅₀,
 - e. probit
- Search time window: 1995-2008.

No studies were identified in which sensory irritation was studied.

5 Probit functions

Animal probit functions could not be derived from available data. The studies that were identified including animal lethality were reported in Appendix 2.

6 Evaluation

All available animal studies that have been identified were assigned the C status. This implies that the available toxicity data for PCl₃ are assessed to be unsuitable for deriving a human probit function.

The study by Weeks et al (1964) did provide LC₅₀ values for the rat and guinea pig as potential point of departure, but these values were considered to be too unreliable for the following reasons. Underlying concentration-response data were not provided by the authors. Despite the fact that up to 40% of PCl₃ was reported to be hydrolysed during exposure, no information was provided about the rate of the hydrolysis and whether the hydrolysis was accounted for in the LC₅₀ calculations. Therefore, it is unknown whether the LC₅₀ calculations were based on nominal, actual or target concentrations and the LC₅₀ values cannot be judged on their merits. Furthermore, data from another study in rats (Monsanto, 1986) using the same time duration of four hours showed contrasting results. No mortality was found by Monsanto (1986) at approximately the calculated LC₅₀ value of Weeks *et al.* (1964). The data of Monsanto suggests an LC₅₀ >2586 mg/m³ (nominal concentration) which is almost five-fold higher, although no information about hydrolysis is provided in this study. The data from the Monsanto study are too limitedly reported to allow the calculation of an LC₅₀ value.

For these reasons, it was decided to base the human probit function on the LBW (1 hour value) of 50 mg/m³ (Dutch Intervention Values 2008). Using the LBW for human probit function derivation is in accordance with the 'Green book' which holds standard operating procedures for probit function derivations in the field of acute toxicity. The LBW value represents the approximate of the LC₀₁ of humans. Since appropriate data are lacking on PCl₃ toxicity, the human probit function is derived using the default values for the n-value and b-value, respectively n = 2 and b = 1.

Using the above parameters to solve the following equation to obtain the a-value (the intercept): $2.67 = a + 1 \ln *(50^2 \times 60)$ resulting in the a-value of -9.25.

This provides the following probit function: $Pr = -9.25 + 1 * \ln (C^2 \times T)$, where C (concentration) in mg/m³ and T (duration) in minutes.

The derived human probit function for PCl₃ lacks a proper scientific basis. No animal lethality studies were granted the A or B quality, which is desired for deriving a

human probit function. Alternatively, the LBW was used as starting point, which is in accordance with the 'Green book'. The LBW, however, is based on the same animal studies that were given the C-status in this TSD indicating poor quality of the LBW value. In addition, (unknown) uncertainty factors were used to extrapolate from animal to human. Therefore, it might be that the LBW is an overly conservative estimate of the LC_{01} for humans. If new data of sufficient quality may become available it is recommended to revise the TSD immediately and propose an alternate probit function.

Appendix 1 Human lethality

Research

<i>Study ID</i>	<i>Author, year</i>	<i>Number of subjects</i>	<i>Exposure duration (min)</i>	<i>Concentration (mg/m3)</i>	<i>Mortality</i>	<i>Description</i>
A Usable studies						
No data						
B Usable studies under certain conditions						
No data						
C Not usable data						
No data						

Appendix 2 Animal experimental research

Study ID: 2.C.1

Author, year: Weeks et al., 1964 (Wee64)¹

Species, strain: rat, unspecified strain

Number/sex/concentration group: 20 female rats/concentration group; no details are available on the number of groups or the concentrations tested

Age and weight: young-adults, weights not specified

Observation period: 14 days

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No</i>
Study carried out according to guideline(s)	<i>Cannot be determined Concentration groups not specified Number of groups not specified</i>
Stability of test compound in test atmosphere	<i>Hydrolysis occurs to the extent of about 40% during testing</i>
Use of vehicle (other than air)	<i>Mainly air (dried oil-pumped nitrogen to make substance airborne)</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Pressure distribution.	<i>Whole body: negative pressure in test unit: not specified</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolysis.</i>
Number of air changes per hour	<i>15 per hour (100 L/min in 400 L chamber)</i>
Actual concentration measurement	<i>Airborne compounds were estimated by sampling and analyses of the atmosphere. Knowlton filter paper was used to collect particulate matter. Phosphorus was analyzed by the molybdenum blue method, chloride by the Caldwell and Moyer modification of the Volhard method. A cascade impactor was used to determine the particle sizes.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD measured to be about 7.8 µm</i>
Assessment of Reliability	<i>C</i> <i>The results are considered to be of insufficient quality to derive a probit function because:</i>

¹ An unsuccessful attempt was made to retrieve the original dataset from this study by contacting the responsible authority (US Army).

	<ul style="list-style-type: none">• <i>The absence of data on the rate of the hydrolysis and how this is accounted for;</i>• <i>The absence of data on exposure conditions;</i>• <i>It is not known whether the calculated LC₅₀ is based on actual PCl₃ concentrations.</i>
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Results

A 4-hour LC₅₀ of 594 mg/m³ was reported for female rats.

Probit function

An animal probit function and associated LC-values could not be calculated based on data from Weeks et al. (1964).

Study ID: 2.C.2**Author, year: Weeks et al., 1964; (Wee64)²**

Species, strain: guinea pig, strain not specified

Number/sex/concentration group: 10 male guinea pigs/concentration group

Age and weight: not specified

Observation period: 14 days

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No</i>
Study carried out according to guideline(s)	<i>Cannot be determined Concentration groups not specified Number of groups not specified</i>
Stability of test compound in test atmosphere	<i>Hydrolysis occurs to the extent of about 40% during testing</i>
Use of vehicle (other than air)	<i>Mainly air (dried oil-pumped nitrogen to make substance airborne)</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Pressure distribution.	<i>Whole body: negative pressure in test unit: not specified</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolysis.</i>
Number of air changes per hour	<i>15 per hour (100 L/min in 400 L chamber)</i>
Actual concentration measurement	<i>Airborne compounds were estimated by sampling and analyses of the atmosphere. Knowlton filter paper was used to collect particulate matter. Phosphorus was analyzed by the molybdenum blue method, chloride by the Caldwell and Moyer modification of the Volhard method. A cascade impactor was used to determine the particle sizes.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD measured to be about 7.8 µm</i>
Assessment of Reliability	C <i>The results are considered to be of insufficient quality to derive a probit function because:</i> <ul style="list-style-type: none"> • <i>The absence of data on the rate of the hydrolysis and how this is accounted for;</i> • <i>The absence of data on exposure</i>

² An unsuccessful attempt was made to retrieve the original dataset from this study by contacting the responsible authority (US Army).

	<i>conditions;</i> <ul style="list-style-type: none">• <i>It is not known whether the calculated LC₅₀ is based on actual PCl₃ concentrations.</i>
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Results

A 4-hour LC₅₀ of 286 mg/m³ was reported for male guinea pigs.

Probit function

An animal probit function and associated LC-values could not be calculated based on data from Weeks et al.

Study ID: 2.C.3**Author, year: Monsanto, 1986 (MSDS); Mon86**

Species, strain: Rat, strain not specified

Number/sex/concentration group: 10 rats/concentration; unspecified sex

Age and weight: not specified

Observation period: not specified

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No information</i>
Study carried out according to guideline(s)	<i>No information</i>
Stability of test compound in test atmosphere	<i>Hydrolysis occurs</i>
Use of vehicle (other than air)	<i>No information</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body and nose-only</i>
Pressure distribution.	<i>No information</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolysis.</i>
Number of air changes per hour	<i>Not specified</i>
Actual concentration measurement	<i>Not specified</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD: not specified</i>
Assessment of Reliability	C <i>Actual concentrations are insufficiently reported; some mortality was reported at the highest concentration tested; an LC₅₀ value cannot be calculated.</i>

Results

The authors observed a large difference between the nominal concentration and the analytical concentration, which might be explained by hydrolysis of PCl₃. However, no information is available on the rate and extent of the hydrolysis. In the table below the nominal concentrations are given.

Species	Concentration (mg/m ³)			Exposure duration (min)	Lethality	
	Nominal	Analytical based on Cl content	Analytical based on P content		Nose only	Whole body
Rats	162	91	-	240	0/10	0/10
	577	577	468	240	0/10	0/10
	1587	908	674	240	0/10	0/10
	2586	1256	857	240	2/10	3/10

Probit function

An animal probit function and associated LC-values could not be calculated, since only one exposure duration is tested and (some) mortality was only observed at the highest concentration tested. Based on this study the 4-hour LC₅₀ is supposedly higher than 2586 mg/m³ (nominal concentration).

Study ID: 2.C.4**Author, year: Butjagin, 1904; (But04)**

Species, strain: Cat, strain not specified

Number/sex/concentration group: 1 cat/concentration

Age and weight: weights varied from 2100-3540g

Observation period: varied from none to 7 days

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No</i>
Study carried out according to guideline(s)	<i>No</i>
Stability of test compound in test atmosphere	<i>The substance hydrolyses in test atmosphere by an unknown percentage</i>
Use of vehicle (other than air)	<i>unknown</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Pressure distribution.	<i>Whole body: negative pressure in test unit: not specified</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolysis.</i>
Number of air changes per hour	<i>No data available</i>
Actual concentration measurement	<i>Mohr, Volhard and weight analyses were performed.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD: not specified</i>
Assessment of Reliability	<i>C</i>
	<i>Outdated study is not considered very reliable. Data not usable for probit derivation. Animals were not handled according to one protocol. Uncertain to what levels the animals were exposed.</i>

Results

Species	Concentration backcalculated (mg/m ³)	Exposure duration (min)	Lethality
Cats	4.45	180	0/1
	16.3	360	0/1
	19.8	360	0/1
	29.6	360	0/1
	64	420	0/1
	64	600	0/1
	324	360	0/1
	326	360	0/1

	551	360	0/1
	753	390	1/1
	784	306	1/1
	988	240	1/1
	3536	181	1/1

Probit function

An animal probit function and associated LC-values could not be calculated based on data from Butjagin (1904).

Study ID: 2.C.5**Author, year: Butjagin, 1904; (But04)**

Species, strain: Rabbit, strain not specified

Number/sex/concentration group: 1 rabbit/concentration

Age and weight: weights varied from 1050-1710g

Observation period: varied from none to 7 days

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No</i>
Study carried out according to guideline(s)	<i>No</i>
Stability of test compound in test atmosphere	<i>The substance hydrolyses in test atmosphere by an unknown percentage</i>
Use of vehicle (other than air)	<i>unknown</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Whole body</i>
Pressure distribution.	<i>No data available</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolyzes.</i>
Number of air changes per hour	<i>No data available</i>
Actual concentration measurement	<i>Mohr, Volhard and weight analyses were performed.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD: not specified</i>
Assessment of Reliability	<i>C</i>
	<i>Outdated study is not considered very reliable. Data not usable for probit derivation. Animals were not handled according to one protocol. Uncertain to what concentrations animals were exposed.</i>

Results

Species	Concentration (mg/m ³)	Exposure duration (min)	Lethality	
Rabbit	16.3	360	0/1	
	19.8	360	0/1	
	29.6	360	0/1	
	64	420	0/1	
	64	600	0/1	
	326	360	0/1	
	988	240	0/1	
	3536	181	1/1	

Probit function

An animal probit function and associated LC-values could not be calculated based on data from Butjagin (1904).

Study ID: 2.C.6

Author, year: Molodkina, 1973; (Mol73) – in Russian, obtained from ERPG-document, original reference not available.

Species, strain: Rat, strain not specified

Number/sex/concentration group: not specified

Age and weight: not specified

Observation period: not specified

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>Not specified</i>
Study carried out according to guideline(s)	<i>Not specified</i>
Stability of test compound in test atmosphere	<i>The substance hydrolyses in test atmosphere by an unknown percentage</i>
Use of vehicle (other than air)	<i>unknown</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Not specified</i>
Pressure distribution.	<i>No data available</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified</i>
Number of air changes per hour	<i>No data available</i>
Actual concentration measurement	<i>Not specified</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD: not specified</i>
Assessment of Reliability	<i>C</i>
	<i>Only LC₅₀ reported, no exposure time given.</i>

Results

An LC₅₀ value of 223 mg/m³ (unknown exposure time)

Study ID: 2.C.7**Author, year: Roshchin, 1977; Ros77**

Species, strain: not specified

Number/sex/concentration group: 646 white rats, 57 guinea pigs, 102 white mice, 12 rabbits in total for entire study (includes also other compounds and subacute studies.

Age and weight: not specified

Observation period: not specified

<i>Criteria</i>	<i>Comment</i>
Study carried out according to GLP	<i>No</i>
Study carried out according to guideline(s)	<i>No</i>
Stability of test compound in test atmosphere	<i>The substance hydrolyses in test atmosphere by an unknown percentage</i>
Use of vehicle (other than air)	<i>unknown</i>
Whole body / nose-only (incl. head/nose-only) exposure	<i>Not specified</i>
Pressure distribution.	<i>Not specified</i>
Homogeneity of test atmosphere at breathing zone of animals	<i>Not specified, mother compound unlikely to be homogenous due to hydrolysis.</i>
Number of air changes per hour	<i>Not specified</i>
Actual concentration measurement	<i>Mohr, Volhard and weight analyses were performed.</i>
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure;	<i>MMAD: not specified</i>
Assessment of Reliability	<i>C</i>
	<i>No study details were provided. An LC₅₀ of 226 mg/m³ was reported without information about the species or the exposure conditions.</i>

Results

No relevant results reported.

Appendix 3 Reference list

- But04 Butjagin PW. Experimentelle studien uber den Einflufs Technisch und Hygienisch Wichtiger Gase und Dampfe auf den Organisms. Archiv f Hyg. (1904), Vol 49. 307-335
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