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

Probit function technical support document

Date: 16 March 2023
Document id: 20230316-phosporous oxychloride-INHOUDELIJK VASTGESTELD
Status: inhoudelijk vastgesteld (approved content)
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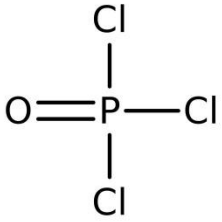
substance name	CAS number
Phosphorous oxychloride	**10025-87-3**

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 phosphorous oxychloride



1. Substance identification

CAS-number:	10025-87-3
IUPAC name:	phosphorous oxychloride
Synonyms:	phosphoric trichloride, phosphoryl trichloride
Molecular formula:	$POCl_3$
Molecular weight:	153.3 g/mol
Physical state:	liquid (at 20°C and 101.3 kPa)
Boiling point:	106°C (at 101.3 kPa)
Vapour pressure:	3.6 kPa (at 20°C)
Saturated vapor conc:	36000 ppm = 229567 mg/m^3 (at 20°C)
Conversion factor:	1 mg/m^3 = 0.16 ppm (at 20°C and 101.3 kPa)
	1 ppm = 6.4 mg/m^3 (at 20°C and 101.3 kPa)
Labelling:	H302-H314-H330-H372

2. Mechanism of action and toxicological effects following acute exposure

Special considerations: sAccording to Weeks et al. 15% of total $POCl_3$ will be hydrolysed. Irritation may be (partially) caused by HCl and phosphoric acid, to which phosphorous oxychloride ($POCl_3$) mainly hydrolyses. However, the mechanism of action of $POCl_3$ is not completely understood, and the rate and completeness of the hydrolysis are unknown.

Acute effects: The main target organs following airborne exposure are the cornea, skin and respiratory tract. Signs and symptoms that might occur 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 oedema) resulting in dyspnoea. Ultimately, hypoxemia will result in CNS depression and cardiovascular effects that may finally lead to death.

Long-term effects: Similar effects as for acute exposure are expected after chronic exposure. For structurally related PCl_3, asthmatic bronchitis was observed in workers after 1-8 week exposures to 14-27 ppm (80-154 mg/m^3), but this resolved upon cessation of exposure. The development of asthmatic bronchitis after repeated exposure might also be expected for $POCl_3$.

3. Human toxicity data

No informative reports on health effects in humans following acute inhalation exposure to $POCl_3$ were identified. Such reports are considered informative if both health effects as well as the exposure conditions 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 phosphorous oxychloride, 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 two studies were identified -with datasets for 2 species- with data on lethality following acute inhalation exposure. No datasets were assigned status A for deriving the human probit function, no datasets were assigned status B and two were assessed to be unfit (status C) for human probit function derivation.

Sensory irritation

No studies were identified in which sensory irritation was studied.

5. Probit functions from individual studies

All available acute lethality data on phosphorous oxychloride are displayed in Figure 1. Because all these studies were classified as C, it was not possible to derive a probit function for phosphorous oxychloride.

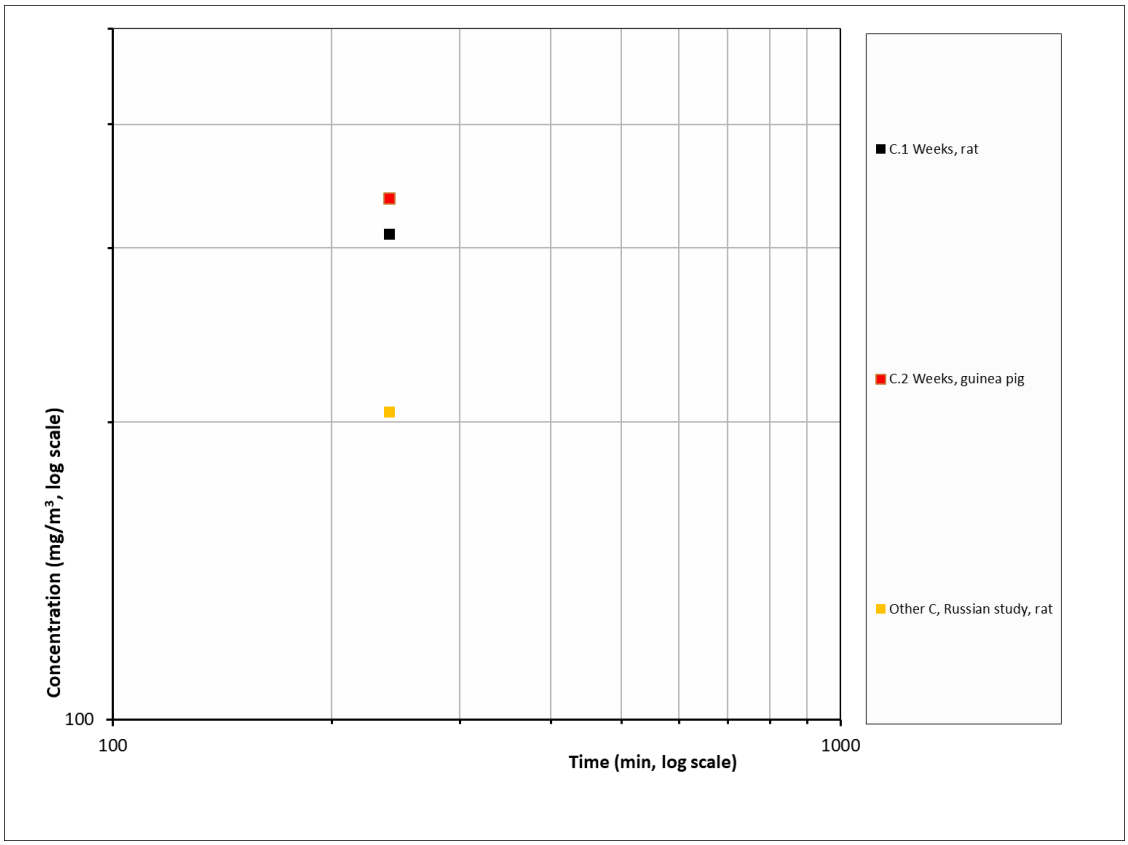


Figure 1 *All available acute lethality data (LC_{50}) for phosphorous oxychloride.*

6. Derivation of the human probit function

The study by Weeks *et al.* (1964) provides 4h-LC_{50} values for the rat and guinea pig. However, these values could not be used because underlying concentration-response

data were not provided by the authors. In their paper the LC_{50} for the rat was characterized by 48.4 µmol/mol $POCl_3$, 61.8 µg P/L and 30 µg/L particulate matter. With atomic weight 30.9 for phosphor and 24.2 L/mol, 48.4 ppm results from 61.8 µg P/L. Hence these values are not independent. The 15% hydrolysis mentioned in the paper was calculated from by assuming that the particulate matter consisted of phosphoric acid.

According to the NAC/AEGL Committee (NAC/AEGL, 2011) human- and animal data indicate some variability in the toxic response to $POCl_3$ but that the data are insufficient to reliably describe species variability in the toxic response to inhaled $POCl_3$. The Committee further concluded that, based on the study by Weeks et al. (1964) and on the basis of an unverified LC_{50} in rats (RTECS, 2009), rats and guinea pigs appeared to respond similarly.

Exposure to $POCl_3$ might allow the formation of larger concentrations of phosphoric acid (H_3PO_4) and hydrochloric acid (HCl) in the lungs than would be possible from exposures to each of the individual chemicals (at the same levels) which would possibly be acting more anterior in the respiratory tract and cause greater damage.

Due to a lack of underlying data, it is concluded that no human probit function for $POCl_3$ can be derived with sufficient reliability.

Appendix 1 Animal experimental research

Study ID: C.1

Author, year: ***Weeks et al., 1964[(1)]***
Substance: $POCl_3$
Species, strain, sex: rat, unspecified strain
Number/sex/conc. group: 20 female rats/concentration group
Age and weight: young adults, weight not specified
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	*Hydrolysis occurred to about 15% during testing*
Use of vehicle (other than air)	*Nitrogen/air: vapors were generated by passing dried, oil-pumped nitrogen through the liquid contained in a glass dispersion bubbler. The vapors so formed were mixed with air in a mixing bowl before entering the exposure chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution	*Unknown*
Homogeneity of test atmosphere in breathing zone of animals	*Not specified*
Number of air changes per hour	*15 per hour (100 L/min in 400L chamber)*
Equilibration time (t95)	*T95 = 3*(400/100) = 12 minutes*
Start of exposure relative to equilibration	*Unknown*

Actual concentration measurement	*Measured test atmosphere samples were passed through Knowlton filter paper (to first collect particulate matter) and next through Edgewood collection bubblers containing water. The filter paper was weighed and its particulate content removed by dissolving in a measured volume of water. Aliquots from the aqueous solutions of the collection bubblers and of the dissolved particulate matter were analysed for Cl, P and N content. P was analysed by the molybdenum blue method, Cl by the Caldwell and Moyer modification of the Volhard method, and N by the Foler-Nessler reagent. Total particulate concentration of the chamber atmosphere was determined from the increase in weight of the Knowlton filter paper*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*A cascade impactor was used to determine the particle size distribution of the droplets. MMAD estimated to be about 0.5 µm*
Assessment of Reliability	***C*** *Data not usable for probit derivation as underlying data are not available*

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

Results

A 4-hour LC_{50} of 48.4 ppm was reported for female rats which corresponds to 309 mg/m^3.

Probit function

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

Study ID: C.2

Author, year: ***Weeks et al., 1964***
Substance: $POCl_3$
Species, strain, sex: guinea pig, unspecified strain
Number/sex/conc. group: 10 male guinea pigs/concentration group
Age and weight: not specified
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	*Hydrolysis occurred to about 15% during testing*
Use of vehicle (other than air)	*Nitrogen/air: vapors were generated by passing dried, oil-pumped nitrogen through the liquid contained in a glass dispersion bubbler. The vapors so formed were mixed with air in a mixing bowl before entering the exposure chamber*
Whole body / nose-only (incl. head/nose-only) exposure	*Whole body*
Type of restrainer	*N/A*
Pressure distribution	*Unknown*
Homogeneity of test atmosphere in breathing zone of animals	*Not specified*
Number of air changes per hour	*15 per hour (100 L/min in 400L chamber)*
Equilibration time (t95)	*T95 = 3*(400/100) = 12 minutes*
Start of exposure relative to equilibration	*Unknown*

Actual concentration measurement	*Measured test atmosphere samples were passed through Knowlton filter paper (to first collect particulate matter) and next through Edgewood collection bubblers containing water. The filter paper was weighed and its particulate content removed by dissolving in a measured volume of water. Aliquots from the aqueous solutions of the collection bubblers and of the dissolved particulate matter were analysed for Cl, P and N content. P was analysed by the molybdenum blue method, Cl by the Caldwell and Moyer modification of the Volhard method, and N by the Foler-Nessler reagent. Total particulate concentration of the chamber atmosphere was determined from the increase in weight of the Knowlton filter paper*
Particle size distribution measurement in breathing zone of the animals in case of aerosol exposure	*A cascade impactor was used to determine the particle size distribution of the droplets. MMAD estimated to be about 0.5 µm*
Assessment of Reliability	***C*** *Data not usable for probit derivation as underlying data are not available*

Results

A 4-hour LC_{50} of 52.5 ppm was reported for male guinea pigs which corresponds to 335 mg/m^3.

Probit function

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

Study ID: Other C studies

Molodkina, (1974, as cited in AEGL 2011), exposed rats to lethal or near-lethal concentrations of phosphorous oxychloride. At 5-15 minutes of exposure, the rats exhibited inactivity and decreased respiration, followed by convulsions. Rats that survived showed continued lacrimation and corneal opacities, and ulcers around the mouth several days after cessation of exposure. The report provided a threshold concentration of 0.96 ppm (6.1 mg/m^3) based upon integrated characteristics. It is unclear as to what effect this threshold pertains or the precise nature of the integrated characteristics. Molodkina also examined the response of guinea pigs to acute inhalation of phosphorus oxychloride. Lacrimation and corneal opacities were reported for animals after acute exposure to lethal or near lethal concentrations. No other details were reported.

Monsanto (1991, as cited in AEGL 2011) exposed groups of male Sprague-Dawley rats (number not provided) for 18 minutes to 159.7 mg phosphorus oxychloride/L (approximately 160,000 mg/m^3) in a 35-L chamber. The concentration of the test material was such that there was a fog in the chamber. Within two minutes the rats were having difficulty breathing and their eyes were closed. At 10 minutes, weakness, convulsions, and collapse were observed, and one rat died. At 18 minutes all rats were dead. Necropsy revealed lung congestion. No further details were provided.

RTECS reported (as cited in AEGL 2011) a 4-hr LC50 of 32 ppm (205 mg/m^3) for rats in a 1972 Russian study. No further details were provided.

Appendix 2 Reference list

AEGL, National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 10. Washington, DC. The National Academies Press, 2011.

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