Recommendation from the Scientific Committee on Occupational Exposure Limits for Phosphoryl trichloride

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Recommendation from the Scientific Committee on Occupational Exposure Limits for Phosphoryl trichloride

<table>
<thead>
<tr>
<th>8-hour TWA:</th>
<th>Not recommended</th>
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<tbody>
<tr>
<td>STEL (15-minute):</td>
<td>0.02 ppm (0.15 mg/m³)</td>
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<tr>
<td>Additional classification:</td>
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<tr>
<td>Biological Limit Value (BLV):</td>
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1. Substance identification, physico-chemical properties

- **Chemical name:** Phosphoryl trichloride
- **Synonyms:** Phosphoric trichloride (PTC); phosphoryl chloride; phosphorus oxychloride; trichlorophosphine oxide; phosphorus oxytrichloride; trichlorophosphorus oxide
- **Molecular formula:** POCl₃
- **Structural formula:**

```
   O
  Cl--P--Cl
   Cl
```

- **EC No.:** 233-046-7
- **Annex I Index No.:** 015-009-00-5
- **CAS No.:** 10025-87-3
- **Molecular weight:** 153.35 g/mol
- **Boiling point (0.039 bar):** 105.8 °C (105.1–108.7) (ECB 2000, ECHA 2012)
- **Melting point:** 1.25 °C
- **Vapour pressure (20 °C):** 40 mm Hg (27.3°C)
- **Specific gravity:** 1.645 (ECHA 2012)
- **Water solubility (25 °C):** reacts violently with water (Majzoobi et al 2009)
- **Vapour density (air=1):** 5.3
- **Conversion factors:**
  - 1 ppm = 6.38 mg/m³
  - 1 mg/m³ = 0.157 ppm

Phosphoryl trichloride is a colourless, fuming liquid with a sharp, penetrating odour. The concentration of saturated vapours is higher than 2 000 mg/m³. In water, phosphoryl trichloride spontaneously degrades by hydrolysis. Vapours of phosphoryl trichloride hydrolyse on contact with moisture in the air. The substance is not flammable.

**EU Classification (EC 2013)**

- **Acute Tox. 2** H330 Fatal if inhaled
- **STOT RE 1** H372 Causes damage to organs through prolonged or repeated exposure (respiratory tract, inhalation)
- **Acute Tox. 4** H302 Harmful if swallowed
- **Skin Corr. 1A** H314 Causes severe skin burns and eye damage
2. Occurrence/use and occupational exposure

Phosphoryl trichloride is used as an intermediate in the production of plasticisers, hydraulic fluids, gasoline additives and fire retardants. It is also used as chlorinating agent and as catalyst (ACGIH 2010). Phosphoryl trichloride is a high volume chemical; global production capacity was estimated to be 200 000 tonnes for about 15 producers in 2002 (OECD 2006).

Background concentrations in a phosphoryl trichloride production plant were mostly below the detection limit but workers were exposed to 10–20 mg/m³ (1.5–3 ppm) of this substance during loading operations (Sassi 1954).

Total shift workplace air measurements of phosphoryl trichloride were performed in a Bayer Chemicals (2004) processing plant: only 3 values (0.03–0.1 mg/m³) of 18 were above the detection limit (0.02–0.1 mg/m³).

Workplace air concentrations were measured in a chemical plant in Switzerland where an organic acid chloride was produced from the free acid by reaction with phosphorus pentachloride. The following concentrations were measured: in the vicinity of a centrifuge during cleaning 0.2 mg/m³, during evacuation 0.9 mg/m³, and after opening 7.9 mg/m³ (Oltramare et al 1975, OECD 2006).

3. Health significance

3.1. Toxicokinetics

On contact with atmospheric moisture, phosphoryl trichloride degrades to hydrochloric acid and phosphoric acid. The half-life of phosphoryl trichloride in pure water is less than 10 seconds (Riess 2002). Approximately 15 % of the phosphoryl trichloride is hydrolysed in the atmosphere, less in comparison with phosphorus trichloride (40 %, Weeks et al 1964). Additional hydrolysis is expected by reaction of the substance with the humid environment in the respiratory tract and following dissolution in the mucous membranes (Payne et al 1993). However, hydrolysis of phosphoryl trichloride at these sites is delayed by several hours compared to pure water. The velocity and rate of hydrolysis are limiting factors for the distribution of phosphoryl trichloride in the organism. Thus, the damage caused by phosphoryl trichloride is mainly restricted to the respiratory tract including the pulmonary region, if exposure is increased (no quantitative data are available; for further details, see Section 3.2) (OECD 2006).

No data were available on the – very improbable - possibility of penetration of unhydrolysed phosphoryl trichloride into the systemic circulation at realistic exposure concentrations.

3.1.1. Human data

No quantitative data on the toxicokinetics of phosphoryl trichloride in humans were found.

3.1.2. Animal data

No quantitative data were available on uptake, distribution and elimination of phosphoryl trichloride in experimental animals.
3.1.3. Biological monitoring

Biological monitoring is not relevant for this locally acting substance.

3.2. Acute toxicity

3.2.1. Human data

Because of its degradation into hydrochloric acid and phosphoric acid, phosphoryl trichloride has a strong irritating effect on mucous membranes and on the eyes (for details, see Section 3.3).

One study (Payne 1993) describes effects on some people who were exposed to phosphoryl trichloride and its hydrolysis products by an explosion. Three workers who were exposed for from a few seconds up to half a minute or so, and who died within 24 hours, had severe skin burns, ulcerated eyes, inflamed bronchi and pulmonary oedema. Ulcerated eyes, respiratory passages and skin were also seen in one surviving worker who was exposed for several seconds. Concentrations during the first 120 seconds were roughly estimated to have been about 36 800 mg/m³ of phosphoryl trichloride.

Toxic symptoms after acute, accidental inhalation of phosphoryl trichloride are redness and inflammation of the eyes, cough, dyspnoea, vertigo and corrosion of the respiratory tract often accompanied by inflammation of the lung (Vaubel 1903, Buess and Lerner 1956, Rosenthal 1978). A characteristic symptom of acute poisoning with phosphoryl trichloride is severe lung damage (Henschler 1984). In many cases, foamy or sometimes even bloody sputum was observed (Rumpf 1908). Headache, drowsiness and weakness as well as nausea, vomiting and difficulties to swallow were subjectively reported symptoms mainly observed after inhalation of high concentrations of phosphoryl trichloride. In a few cases, enlarged liver, albuminuria and anaemia were also reported, but it is not clear whether these effects resulted from the exposure (Rumpf 1908). The described effects may persist for several weeks or months.

Most toxic symptoms occur after a latency period of some hours (no quantitative data available). Increased sensitivity to infections and to irritants are frequently observed consequences after inhalation exposure to phosphoryl trichloride (Sassi 1954, Herzog and Pletscher 1955).

After oral ingestion, phosphoryl trichloride causes severe damage to the tissues of the gastrointestinal tract by denaturing proteins (Weichardt 1957).

3.2.2. Animal data

Mice showed signs of cholinergic poisoning after ip administration of phosphoryl trichloride (ED₅₀ = 12 mg/kg bw in corn oil). The substance inhibited serum butyrylcholine esterase (BChE) at sublethal doses and muscle acetylcholine esterase (AChE) at lethal doses, but it did not affect brain AChE. The inhibiting effect can be attributed to selective phosphorylation of the esteratic site. The actual phosphorylating agent is phosphorodichloridic acid. Phosphoryl trichloride inhibited brain AChE in house flies (Quistad et al 2000, Segall 2003).

Inhalation

During 4-hour exposures to a concentration of 930–1 070 mg/m³, made to determine the LC₅₀ for phosphoryl trichloride and phosphoryl chloride, experimental animals (rats
and guinea pigs) showed agitation, indications of irritation, porphyrin secretion around the eyes and laboured breathing (Butjagin 1904).

LC₅₀ values are 48.4 ppm (380 mg/m³) for rats and 52.5 ppm (335 mg/m³) for guinea pigs (4-hour exposure). Neutralising the pH by simultaneous exposure to ammonia resulted in slightly lower LC₅₀ values (44 ppm = 283 mg/m³ for rats, 41 ppm = 263 mg/m³ for guinea pigs) (Weeks 1964). LC₅₀ values for rats reported in other studies were 11.1 ppm (71 mg/m³) and 17.3 ppm (110 mg/m³) and 31.4 ppm (200 mg/m³) (Roshchin and Molodkina 1977, Mobil Co. 1977a, Marhold and Čížek 1957, Marhold 1972).

The concentration–response regression was very steep for phosphoryl trichloride: LC₁₆ = 56, LC₅₀ = 71 and LC₈₄ = 89 mg/m³ compared to phosphorus trichloride: LC₁₆ = 140, LC₅₀ = 220 and LC₈₄ = 310 mg/m³ (Molodkina 1971).

Rats and guinea pigs exposed to phosphoryl trichloride had dark red lungs with scattered red areas. Phosphoryl trichloride caused desquamation of the epithelium as well as oedemas and haemorrhage (Weeks et al 1964). Inhalation exposure of rats, mice, rabbits and guinea pigs to phosphoryl trichloride at lethal concentrations caused acute irritation of the respiratory tract as well as dystrophic changes in the central nervous system, the liver and the kidney (Molodkina 1971). Besides, weakness, loss of coordination in movements, sweating, laboured breathing, increased lacrimation and opacity of the cornea were observed in rats and guinea pigs after inhalation exposure to phosphoryl trichloride at lethal concentrations. No species-specific differences (mouse, rat, guinea pig) were observed (Molodkina 1971, 1974).

The effects of a single 4-hour low-level inhalation exposure on rodents were also examined (Molodkina 1974, Payne 1993, Weeks 1964). The oxygen consumption was decreased (37.0 ml/kg/min in control animals; 30.5 ml/kg/min in exposed animals) at 6 mg/m³ (1 ppm), while the relative lung weight was increased (0.87 control animals; 0.95 exposed animals). At 1 mg/m³ (0.157 ppm), only a decrease in breathing rate (164 min⁻¹ in control animals; 143 min⁻¹ in exposed animals) was detected (see Addendum).

**Oral**

An oral LD₅₀ has been reported for rats of 380 mg/kg (in vegetable oil, Molodkina 1971). LD₁₆ and LD₈₄ values were 250 and 580 mg/kg bw, respectively. Respective values for phosphorus trichloride were 430, 550 and 675 mg/kg bw (Molodkina 1971).

Decreased locomotor activity, piloerection, ptosis, suspected blood around the eyes and the loss of righting reflex occurred in rats after a single oral dose of phosphoryl trichloride (50, 100, 200, 300 and 400 mg/kg). All rats died at the highest dose and 90 % died at 200 and 300 mg/kg. The surviving animals recovered within 1 week and were necropsied after 2 weeks for further examination. The lungs fused to the rib cage at ≥ 50 mg/kg and at 100 mg/kg, and were filled with a white mass. Besides, irregular thickening of the cardiac mucosa occurred at this dose. Chronic pulmonary disease was observed at 50 mg/kg and above (Mobil Co 1977a).

Clinical and histological changes after ingestion of phosphoryl trichloride are similar to the effects after inhalation exposure. However, the toxicity after oral administration is less, since the gastrointestinal tract is less sensitive towards the irritation effects of acids than the respiratory tract (Roshchin and Molodkina 1977).

**Dermal**

The dermal LD₁₀ for rabbits was 1 000 mg/kg in males and 631 mg/kg in females; an LD₅₀ could not be determined (Mobil Co 1977a).
Acute toxicity of related compounds and metabolites

The LD$_{50}$ for the related compound phosphorus trichloride was 550 mg/kg in rats after oral application (Roshchin and Molodkina 1977) and the inhalation LC$_{50}$ was 104 ppm (662 mg/m$^3$) for rats and 50.1 ppm (319 mg/m$^3$) for guinea pigs (Weeks et al 1964). The irritative effect of phosphorus trichloride was reported to be more pronounced (Roshchin and Molodkina 1977), which is probably due to the higher hydrolysis rate of about 40% in the atmosphere (Weeks et al 1964).

The inhalation LC$_{50}$ of the hydrolysis product hydrochloric acid is 1 110 ppm (1 665 mg/m$^3$) for rats and the oral LD$_{50}$ value for rats is 220–237 mg/kg. The other metabolite, phosphoric acid, has an oral LD$_{50}$ value of 1 530 mg/kg in rats (Greim 2001, Butjagin 1904).

3.3. Irritation and corrosivity

The degradation products hydrochloric acid and phosphoric acid are responsible for the strong irritating and corrosive effects of phosphoryl trichloride.

3.3.1. Human data

Redness, inflammation and corrosion were observed after accidental dermal exposure to phosphoryl trichloride. The intensity of the described effects was dependent on the concentration and on the degree of humidity (of the air and the skin) (Weichardt 1957).

Inhalation of phosphoryl trichloride causes severe irritation of the mucous membranes and of the eyes. Besides, corrosion of the dental enamel was reported (Roshchin and Molodkina 1977, Henschler 1984, Mclaughlin 1946). Severe irritation and corrosion of the respiratory tract followed by inflammation processes in the lung and the bronchial tubes in particular were reported, even leading to pulmonary oedemas (Henschler 1984).

An irritation threshold (concentration inducing subjective discomfort) of 1.0 mg/m$^3$ (0.157 ppm) was determined after a 1-minute exposure of human volunteers to phosphoryl trichloride (Molodkina 1971 and 1974, Roshchin and Molodkina 1977, Radionova and Ivanov 1979).

Incidental observations that simultaneous exposure to phosphoryl trichloride caused abatement of warning sensory effects were confirmed in animals (Weeks et al 1964).

3.3.2. Animal data

Skin

Application of undiluted phosphoryl trichloride on the shaved skin of rabbits caused swelling of the skin folds, formation of haemorrhagic fissures and poorly curing ulcers. Hyperaemia and punctiform haemorrhage occurred after brushing mouse-tails with phosphoryl trichloride (Molodkina 1971, Radinova and Ivanov 1979).

Eyes

Irreversible, necrotic changes and total blindness were caused by instillation of concentrated phosphoryl trichloride into the rabbit eye (Molodkina 1974).
Respiratory tract

In the study by Weeks et al (1964), rats and guinea pigs were exposed for 4 hours to phosphoryl trichloride and its hydrolysis products; hydrolysis in the inhaled air was calculated to be 15%. Phosphoryl trichloride caused irritating and corrosive effects on the mucosa of the respiratory tract (and of the eyes) of animals exposed to sublethal and lethal concentrations. Ammonia neutralisation of hydrolysis products appeared to lessen the sensory effects (judging from behavioural response of animals to irritation of airways) but did not decrease the toxicity. Desquamation of the tracheal and bronchial epithelia led to plugging of the respiratory lumen.

Inhalation exposure at lethal and sublethal concentrations caused acute irritation of the respiratory tract as well as necroses of mucous membranes of the trachea, bronchi and bronchioles. Oedemas of the walls of the alveoli did also occur (Molodkina 1971). An “irritation threshold” of 1 mg/m³ was determined for rats by measuring the decrease in the breathing rate of the animals (for further details, see Section 3.2; Molodkina 1971 and 1974, Roshchin and Molodkina 1977).

The related substance phosphorus trichloride exerts effects similar to phosphoryl trichloride and is also hydrolysed to hydrochloric acid (and phosphoric acid). The irritant potency of phosphorus trichloride is 5–6 times higher than that of hydrochloric acid (Henschler 1984, NRC 2011). In the study by Weeks et al (1964), hydrolysis in the inhaled air was calculated to be 40%. Ammonia neutralisation of hydrolysis products decreased the toxicity, significantly in guinea pigs.

Due to the delayed hydrolysis, the severity of the irritant effects on deep airways caused by phosphoryl trichloride is higher compared to that of phosphorus trichloride.

3.4. Sensitisation

3.4.1. Human data

No data were available.

3.4.2. Animal data

No data on phosphoryl trichloride were available.

Its metabolite hydrochloric acid produced no sensitisation in a guinea pig maximisation test at a concentration of 1% dissolved in 70% ethanol. Besides, a 5% solution of hydrochloric acid, applied to the mouse ear 7 days after uncovered application of a 1% solution on 4 consecutive days to the abdominal skin did not induce sensitisation (Gad et al 1986).

3.5. Repeated dose toxicity

3.5.1. Human data

In a phosphoryl trichloride production plant, workers were exposed to 10–20 mg/m³ (1.5–3 ppm) of this substance during loading operations. In some areas, the concentration of phosphoryl trichloride frequently increased to 70 mg/m³ (11 ppm) as a result of leaks (Sassi 1954). Effects of peak exposures occurred about 1–3 hours after inhalation, while symptoms after chronic poisoning at 10–20 mg/m³ became manifest after 1–7 weeks. Reported symptoms were ocular and respiratory irritations, cough, acute dyspnoea and asthmatic bronchitis. Pulmonary emphysema as well as slight leukocytosis and neutrophilia developed subsequently. In many cases, recovery
was not complete within the time of follow-up and irreversible damage developed in some severe cases.

Tharr and Singal (1980) examined the effects of phosphoryl trichloride exposure at unstated levels on 37 workers. Sixty-five per cent of the exposed workers (24/37) but only 5% of unexposed control persons (1/22) suffered from intermittent respiratory distress, such as laboured breathing, chest tightness and wheezing. Bronchitis and cough occurred in 30% of the exposed and in 14% of the unexposed workers. However, lung function tests did not reveal differences between exposed and unexposed persons. Also, the duration of exposure did not significantly influence lung function.

Two years later, 26 of the previously exposed and 11 of the unexposed workers participated in a follow-up study to determine possible long-term consequences (Moody 1981). Half of the subjects (13/26) in the exposed group still suffered from breathing difficulties, while the unexposed persons did not show any symptoms. Five of these 13 workers exposed to phosphoryl trichloride considered the symptoms to be work-related. Because of the small sample size and poor information on exposure concentrations, no reliable conclusion can be drawn from these data (Henschler 1984, Payne et al 1993).

### 3.5.2. Animal data

**Inhalation**

Rats and guinea pigs were exposed to phosphoryl trichloride at concentrations of 1.34 mg/m³ (0.2 ppm) and 0.48 mg/m³ (0.08 ppm), 4 hours per day, 5 days per week over a period of 4 months with a 4-month post-exposure observation period (Molodkina 1971, Roshchin and Molodkina 1977). Body weight loss, changes in breathing rate and oxygen consumption as well as irritation of the respiratory tract were observed. Exposure to phosphoryl trichloride at 1.34 mg/m³ (0.2 ppm) caused severe irritation of the respiratory tract followed by chronic rhinitis, tracheitis, bronchial catarrh with desquamation of the epithelia and hyperplasia of the mucous glands. Dystrophic changes of liver, brain tissue and kidney were also observed at this concentration. In addition, signs of enterocolitis occurred after 4 months of inhalation exposure. Besides, dose dependent cytogenetic damages in the bone marrow, changes in bone tissue, calcification of the renal tubuli and of the testis as well as decreased sperm motility occurred. The recovery of rats and guinea pigs was still incomplete 4 months after terminating the exposure. Especially the respiratory passages remained affected (no further details given; Roshchin and Molodkina 1977). At the lower concentration (0.48 mg/m³, 0.08 ppm), the observed effects were less pronounced. Only irritation of the mucous membranes of the respiratory tract occurred, indicated by rhinitis and catarrhal bronchitis. The relative kidney weights were increased in rats, probably due to the irritating effects of the acidic metabolites of phosphoryl trichloride excreted in the urine. The recovery of the low-dosed animals was complete 4 months post-exposure (Roshchin and Molodkina 1977).

Because only mild and reversible subchronic effects and no obvious mutagenic activities were detected at 0.48 mg/m³ (0.08 ppm) the authors characterised this concentration as “near to chronic threshold” (Molodkina 1971, Roshchin and Molodkina 1977, Henschler 1984). Accordingly, OECD (2006) considered this concentration to be the LOAEC for weight loss, respiratory irritation and increased kidney weights.

The effects of hydrochloric acid, one of the metabolites of phosphoryl trichloride, were studied after 90 days of inhalation exposure in rats and mice (CIIT 1984). The animals were exposed to 10, 20 and 50 ppm (15, 30 and 75 mg/m³). Hydrochloric acid
produced dose- and time-dependent inflammatory changes of the nasal cavity in rats at all dose groups. Exposed mice developed cheilitis (at 50 ppm) and eosinophilic globules in the nasal turbinate (all concentrations). No histopathological changes were observed in either rats or mice at any concentration tested. No signs of systemic toxicity occurred, but the authors considered systemic effects as a possible result of irritation/corrosion. The NOAEC for local effects caused by hydrochloric acid was < 10 ppm (15 mg/m³) in rats and mice (CIIT 1984).

**Oral**

No data were available.

**Dermal**

No data were available.

### 3.6. Genotoxicity

#### 3.6.1. In vitro

Phosphoryl trichloride gave negative results (with and without metabolic activation) in an Ames test with *Salmonella typhimurium* and in *Saccharomyces cervisiae* at concentrations of 0.001–5 µl/plate (Mobil Co 1977b).

The hydrolysis product hydrochloric acid also gave negative results at 0.001–5 µl/plate in an Ames test with and without S9 mix (Isquith et al 1988). Hydrochloric acid was not mutagenic in a DNA repair assay with *Bacillus subtilis*, but showed ambiguous results in another DNA repair test with *Escherichia coli* (McCarroll et al 1981a/b).

A cytogenetic assay performed with Chinese hamster ovary (CHO) cells was positive for hydrochloric acid at 10 or 14 mM (pH 5.8 or 5.5) with and without metabolic activation (Morita et al 1989). In another cytogenetic assay, hydrochloric acid did not cause genotoxic effects in mouse lymphoma cells incubated with 0.1–0.8 µl/ml (Isquith et al 1988).

No data on phosphoric acid were available.

#### 3.6.2 In vivo – Human data

No data were available.

#### 3.6.3. In vivo – Animal data

Cytogenetic damage (chromosomal aberrations) in the bone marrow of rats was observed after 4 months of inhalation exposure to phosphoryl trichloride at a concentration of 1.34 mg/m³ (0.2 ppm). No significant changes were detected at 0.48 mg/m³ (0.08 ppm) (Roshchin and Molodkina 1977). However, since no details of the experimental design, controls etc. are given, this information cannot be adequately assessed (NIWL 1999). Due to the chemical properties of phosphoryl trichloride, a transfer of the compound to the bone marrow following inhalation exposure is considered unlikely (OECD 2006).

### 3.7. Carcinogenicity

#### 3.7.1. Human data

No data were available.
3.7.2. Animal data

No data on phosphoryl trichloride were available.

The carcinogenic potential of hydrochloric acid was tested in an inhalation study with SD rats. One hundred rats per group were exposed to air or to 10 ppm (14.9 mg/m³) hydrochloric acid or were kept unexposed for lifetime (128 weeks). No differences in body weight or mortality rate and no neoplastic or preneoplastic nasal lesions occurred in any of the animals. However, an increased number of hyperplasia of the larynx (26/99) and trachea (22/99) was detected in the exposed rats compared to the air control rats (2/99 and 6/99). The total tumour incidences in various organs were similar in all groups (19/99, 25/99 and 24/99). Hydrochloric acid did not cause histopathological changes in lung, liver, kidney and testes and it did not produce gross lesions (Sellakumar 1985).

Oral administration of hydrochloric acid (5–10 times per week) at concentrations of 90–360 mg/kg over a period of 11 months did not increase the tumour incidence in mice. Besides, it did not act as a tumour promoter after pre-treatment of the mice with a known carcinogen. However, only the gastrointestinal tract of the mice was probably examined (Dyer et al 1946).

3.8. Reproductive toxicity

3.8.1. Human data

No data were available.

3.8.2. Animal data

Fertility

Decreased sperm motility was observed in rats and guinea pigs after inhalation exposure to phosphoryl trichloride at 1.34 mg/m³ (0.2 ppm) over a period of 4 months. No specific effects were reported for the lower exposure level of 0.48 mg/m³ (0.08 ppm) in that study (no further details given; Roshchin and Molodkina 1977). Inhalation exposure of female rats to phosphoryl trichloride at concentrations of 0.4 and 1.0 mg/m³ (0.06 and 0.16 ppm) over a period of 4 months decreased the number of primary follicles and intensified the process of atresia. Besides, phosphoryl trichloride induced changes in the oestrous and ovarian cycle. The author considered these effects as secondary to general toxicity, since they were always accompanied by signs of poisoning (Pashkova 1973).

Both studies are only poorly documented and inadequate for risk assessment.

No data were available on the effects of hydrochloric acid or phosphoric acid on fertility.

Developmental toxicity

No data were available.

4. Recommendations

The critical effect of phosphoryl trichloride is irritation of the upper and lower respiratory tract and eyes. The chemically related substance phosphorus trichloride exerts similar effects. However, owing to a more delayed hydrolysis to hydrochloric
and phosphoric acid, the severity of respiratory injury by phosphoryl trichloride appears more protracted and significantly higher, compared to phosphorus trichloride.

Key data from animal experiments are in agreement with limited human data. After exposure of volunteers to 1.0 mg/m³ (0.157 ppm) phosphoryl trichloride for 1 minute, signs of irritancy were noted as “reported discomfort” (Molodkina 1971 and 1974, Roshchin and Molodkina 1977, Radionova, Ivanov 1979). Such a short-term effect is avoided by setting a STEL. However, the STEL is derived for a peak concentration of 15 minutes, which requires a time adjustment (from 1 min to 15 min). Acute irritation thresholds in human subjects may be extrapolated to longer exposures using Haber’s law that describes a linear influence of both peak concentration and peak duration (Doull and Rozman 2000, Miller et al 2000, Shusterman et al 2006). Shusterman et al (2006) have conducted a systematic literature review that included a semiquantitative comparison of psychophysical data on irritation effects extracted from controlled human exposure studies. With the exception of dust exposure, peak exposure concentration had a proportionally greater effect on sensory irritation than exposure duration. Along with these data, it is reasonable that a STEL of 0.02 ppm is protective against short-term irritancy of phosphoryl trichloride for 15 minutes. This derivation is also in compliance with time adjustment procedures for acute lethality (Berge et al 1986, NIOSH 1995, US EPA 2002). A STEL of 0.02 ppm is therefore recommended.

In animal experiments, subchronic exposure (4 months, 5 days/week, 4 hours/day) of rats to phosphoryl trichloride vapours at a concentration of 1.34 mg/m³ (0.21 ppm) caused clear-cut toxic effects, persisting for 1–4 months after exposure. Similar subchronic exposures (4 hours/day, 5 days/week for 4 months, with recovery for 4 months) of guinea pigs and rats to 0.48 mg/m³ (0.075 ppm) phosphoryl trichloride resulted in mild and reversible irritation of the upper parts of the respiratory tract that disappeared 1 month after cessation of exposure. This concentration was characterised by the authors as being “near to chronic threshold”; OECD (2006) considered this concentration as the LOAEC (Section 3.5.2). Based on these data, a long-term irritation effect is prevented if the proposed STEL of 0.02 ppm is not exceeded at any time. It is therefore not necessary to establish a separate 8-hour TWA in this case.

Phosphoryl trichloride was not mutagenic in an Ames test, with and without metabolic activation. In general, because of its rapid decomposition to hydrochloric and phosphoric acid after absorption, no specific systemic effects are to be expected (OECD 2006). Thus, a systemic genotoxic potential of phosphoryl trichloride in somatic or germ cells is unlikely.

There is no information on the skin sensitising properties of phosphoryl trichloride and on its metabolite phosphoric acid.

Analytically, phosphoryl trichloride can be detected by ion chromatography. However, so far no validated method for the analysis has been described in literature.

The present Recommendation was adopted by SCOEL on xxx.
5. References


Miller FJ, Schlosser PM, Janszen DB (2000). Haber’s rule: a special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint. Toxicology 149:21-34.


http://www.epa.gov/oppt/aegi/pubs/humanhealth.htm


### Addendum

Compilation of effects in experimental animals exposed to phosphoryl trichloride by inhalation (NIWL 1999).

<table>
<thead>
<tr>
<th>Exposure, level (mg/m³) and duration</th>
<th>Species</th>
<th>Effects</th>
<th>Reference</th>
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<tbody>
<tr>
<td>930–1070 4 hours Cat, rabbit (one of each)</td>
<td>Cat: agitation, salivation, red noses, dyspnoea, corneal and nasal ulceration, pleurisy, reddened trachea, death after 36 hours. Rabbit: sneezing, agitation, conjunctivitis, secretions from eyes and nose.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>530–1090 6.5 hours Cat (one animal)</td>
<td>Salivation, dyspnoea, death after 390 minutes, corneal ulceration, emphysema, swollen epiglottis.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>586 4 hours Rat</td>
<td>LC₅₀</td>
<td>Weeks et al 1964</td>
<td></td>
</tr>
<tr>
<td>330 6 hours Cat, rabbit (one of each)</td>
<td>Cat: agitation, coughing, sneezing, salivation, conjunctivitis, rhinitis, dyspnoea, red nose, ulcerated cornea and nose, emphysema, swollen epiglottis. Rabbit: agitation, nasal secretion, rhinitis, reduced respiratory rate, dyspnoea, red nose, ulcerated cornea.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>282 4 hours Guinea pig</td>
<td>LC₅₀</td>
<td>Weeks et al 1964</td>
<td></td>
</tr>
<tr>
<td>226 Rodents</td>
<td>LC₅₀</td>
<td>Roshchin &amp; Molidkina 1977</td>
<td></td>
</tr>
<tr>
<td>40–90 7 hours Cat, rabbit (one of each)</td>
<td>Cat: sneezing, secretion, cough, dyspnoea, conjunctivitis, red nose. Rabbit: marked decline in respiratory rate, but few other symptoms</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>13–27 6 hours Cat, rabbit (one of each)</td>
<td>Cat: salivation, dyspnoea. Rabbit: slight irritation, nasal secretion, reduced respiratory rate.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>13–20 6 hours Cat, rabbit (one of each)</td>
<td>Cat: salivation, nasal secretion, cough, dyspnoea, conjunctivitis, liquid accumulation in lungs. Rabbit: slight restlessness, marked drop in respiratory rate.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
<tr>
<td>4–5 3 hours Cat (one animal)</td>
<td>Sneezing, coughing, salivation, nasal secretion, reduced respiratory rate.</td>
<td>Payne et al 1993</td>
<td></td>
</tr>
</tbody>
</table>