SCOEL/REC/181
Phosphoryl Trichloride

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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Adopted 23 September 2015

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR PHOSPHORYL TRICHLORIDE

8-hour TWA:	0.01 ppm (0.064 mg/m^3)
STEL:	0.02 ppm (0.13 mg/m^3)
BLV:	-
Additional categorisation:	-
Notation:	-

The present Recommendation was adopted by SCOEL on 2015-09-23

This evaluation is based on the references cited in these reviews and a PubMed search. This Recommendation is based on Greim (2001), Henschler (1984), OECD SIDS (2004) and other sources as referenced.

RECOMMENDATION EXECUTIVE SUMMARY

Outcome Considerations

The critical effect of phosphoryl trichloride is irritation of the upper and lower respiratory tract and the eyes. The chemically related substance phosphorus trichloride exerts similar effects. In addition to its hydrolysis products, hydrochloric acid and phosphoric acid, it is reasonable that the chemical reactivity of phosphoryl trichloride itself contributes to its irritating properties.

Key toxicity data from animal experiments are in agreement with limited human data, although these are not well documented. As the animal and human data support each other in principle, SCOEL considers the available total data set as a sufficient basis for recommending an OEL. As explained in Section 7.3.2, subchronic inhalation of rats (4 months, 4 hours/day, 5 days/week) to 0.08 ppm phosphoryl trichloride resulted in mild and reversible effects (weight loss, respiratory irritation and increased kidney weight). This exposure level was therefore addressed by OECD as a LOAEC.

Derived Limit Values

Taking this LOAEC as value for the critical effect and considering a similar sensitivity of rats and humans, an OEL (8-hour TWA) of 0.01 ppm would provide a sufficient margin of exposure [i.e. factors of 3 for LOAEC instead of NOAEC, 3 for duration (subchronic vs. chronic), rounded to 0.01 ppm].

In addition, a STEL should be provided because of local irritancy. The available limited human data (Section 7.4.1) indicate that a short-term exposure of volunteers to 0.157 ppm phosphoryl trichloride for 1 minute led to "reported discomfort". Along with these data and the animal sub-chronic inhalation data, it appears reasonable that a STEL of 0.02 ppm is protective against short-term irritancy of phosphoryl trichloride for 15 minutes although the data base is limited. This would allow an excursion factor of 2, compared to the recommended OEL.

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 carcinogenic effect should be expected (OECD SIDS 2004). A systemic genotoxic potential of phosphoryl trichloride in somatic or germ cells is unlikely.

There are no data on reproductive toxicity of phosphoryl trichloride. However, it can reasonably be assumed that inhaled phosphoryl trichloride, because of its reactivity and instability in aqueous systems (Section 7.1), will not reach the reproductive organs. The recommended OEL is in an order of magnitude at which the hydrolysis products, hydrochloric acid and phosphoric acid, are easily buffered by the physiological buffering systems. Therefore, no reproductive toxicity is to be expected at the recommended OEL.

Notations

There is no information on the skin sensitising properties of phosphoryl trichloride.No notations are assigned.

Biological Monitoring

Biological monitoring is not relevant for Phosphoryl trichloride as local irritant.

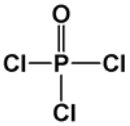
Measurement and measurement systems

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy. Phosphoryl trichloride can be analysed in the workplace air by ion chromatography (Zhao et al. 2011). However, this method is non-specific, because it is based on conversion into hydrochloric acid and quantitation of the latter.

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR PHOSPHORYL TRICHLORIDE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Phosphoryl trichloride
Synonyms:	Phosphoric trichloride (PTC); phosphoryl chloride; phosphorus oxychloride; trichlorophosphine oxide; phosphorus oxytrichloride; trichlorophosphorus oxide
Molecular formula:	$POCl_3$
Structural formula:	
EC No.:	233-046-7
CAS No.:	10025-87-3
Molecular weight:	153.35 g/mol
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 6.36 mg/m^3 1 mg/m^3 = 0.157 ppm

Note:

Phosphoryl trichloride is a colourless, fuming liquid with a sharp, penetrating odour. The concentration of saturated vapours is higher than 2 000 mg/m^3. 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.

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonized classification and labelling for Phosphoryl trichloride is provided by ECHA (2015), as summarized in Tables 1 and 2.

Table 1: Phosphoryl trichloride: Classification according to part 3 of Annex VI, table 3.1 (list of harmonised classification and labelling of hazardous substances of Regulation (EC) No 1272/2008 (ECHA 2015).

Index no.	Internat. Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)		
015-009-00-5	Phosphoryl trichloride	233-046-7	10025-87-3	Acute Tox 4 Skin Corr. 1A Acute Tox. 2 STOT RE 1	H302 H314 H330 H372	GHS06 GHS05 GHS08 Dgr	H302 H314 H330 H372	EUH014 EUH029		

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

Table 2: Phosphoryl trichloride. Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No 1272/2008; DSD classification (table 3.2) (ECHA 2015).

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
R14 **T+; R26** **T; R48/23** **Xn; R22** **C; R35** **R29**	14 22 26 35 48/23	(1/2) 7/8 26 36/37/39 45	 T+ C	-	-

3. Chemical Agent and Scope of Legislation

Phosphoryl trichloride is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Phosphoryl trichloride is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. Existing Occupational Exposure Limits

Occupational exposure limits for Phosphoryl trichloride exist in a number of countries, as shown in Table 3. An IOELV (indicative occupational exposure limit value) has been adopted at EU level, and national limit values will exist in all Member States. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries. In addition to the OELs, there are no biological threshold limit values established.

Table 3: Existing OELs for phosphoryl trichloride; adapted from the GESTIS database (GESTIS 2015).

EU-countries	TWA (8 hrs)		STEL (15 min)		
	ppm	mg/m³	ppm	mg/m³	References
Austria	0.2	1	0.8	4	GKV (2011)
Belgium	0.1	0.64			RD (2014)
Denmark	0.1	0.6	0.2	1.2	BEK (2011)
European Union	0.01	0.064	0.02	0.13	SCOEL (2016)
Finland			0.5	2.4	MoSH (2012)
France	0.1	0.6			INRS (2012)
Germany (AGS)	0.2	1.3	0.2	1.3	BAUA (2006)
Germany (DFG)	0.2	1.3	0.2	1.3	DFG (2014)
Ireland	0.2	1.2	0.6	3.6	HSA (2011)
Latvia		0.05			GESTIS (2015)
Spain	0.1	0.64			INSHT (2011)
Sweden	0.1	0.6	0.2	1.2	SWEA (2011)
United Kingdom	0.2	1.3	0.6	3.8	HSE (2011)

Non EU-countries	ppm	mg/m³	ppm	mg/ m³	
Australia	0.1	0.63			Safe Work Australia (2011)
Canada (Ontario)	0.1	0.6	0.5	3	Ontario Ministry of Labour (2013)
Canada (Québec)	0.1	0.63			IRSST (2010)
China		0.3		0.6	GESTIS (2015)
New Zealand	0.1	0.63			HS (2013)
Singapore	0.1	0.63			GESTIS (2015)
South Korea	0.1	0.6	0.5	3	GESTIS (2015)
Switzerland	0.1	0.6	0.1	0.6	SUVA (2015)
USA (NIOSH)	0.1	0.6	0.5	3.0	NIOSH (2007)

5. Occurrence, Use and Occupational Exposure

5.1. Occurrence and use

Phosphoryl trichloride does not occur naturally and is not found in the environment, because it is completely hydrolyzed in water within less than 10 s at 20 °C (via the hydrolysation intermediate phosphorodichloric acid), forming phosphoric acid and hydrochloric acid (WHO 1989). Consequently, it is not considered a persistent chemical. When it is released from anthropogenic sources, it readily dissociates. Any emission into water, air, or the terrestrial compartment results in the formation of the hydrolysis products causing a pH shift, which determines the impact of phosphoryl trichloride on aquatic life (OECD SIDS 2004).

5.2. Production and use information

Phosphoryl trichloride is a large-volume chemical produced and used worldwide (OECD SIDS 2004). It can be manufactured using different methods:

1. by a radical reaction of phosphorus trichloride with oxygen while cooling (Buechel et al., 2000). The reaction is accelerated by carrying it out under pressure and can be performed either continuously or batchwise. Air can be used instead of oxygen (Riess 2002). The presence of orthophosphoric acid has a catalytic effect, while traces of sulfur, sulfur compounds, and heavy metals (e.g. iron, copper, cobalt) decrease the reaction rate (Buechel et al. 2000, Riess 2002);

2. by heating a mixture of anhydrous phosphorus pentoxide and phosphorus pentachloride (Buechel et al. 2000). The use of the expensive phosphorus pentachloride can be avoided by using a mixture of the trichloride and chlorine with the pentoxide. Raw phosphoryl trichloride is purified by fractional distillation. It is not known, whether phosphoryl trichloride is still industrially produced using this method (OECD SIDS 2004).

In the chemical industry phosphoryl trichloride is also formed as a by-product of the industrial synthesis of organic acid chlorides by reaction of free acid with phosphorus pentachloride (Oltramare et al. 1975).

The global production capacity of phosphoryl trichloride was estimated to be 200 000 tonnes for about 15 producers in 2002 (OECD SIDS 2004). Approximately 150 000 tonnes/year of the manufacturing capacity are in the OECD countries and 50 000 tonnes/year in non-member countries. In 1995 the phosphoryl trichloride manufacturing capacities were about 39 900 tonnes in the USA, 100 000 tonnes in Western Europe, and 30 000 tonnes in Japan. In Western Europe in 2004 there were 4 producers of phosphoryl trichloride. Three of them had production plants in Germany.

As far as the uses of phosphoryl trichloride are concerned, because of its high reactivity, it has a large number of applications in chemical processes, mainly as an intermediate in the manufacturing of the following products (OECD SIDS 2004, ACGIH 2010, HJDH 2001, WHO 1989):

- plastics and elastomers additives (55 % of the total amount produced)
- lubricant oil additives (4 %)
- surfactants and sequesterants (2 %)
- organophosphorous compound such as pesticides (7 %)
- functional fluids, e.g. phosphate ester hydraulic fluids (22 %)

The miscellaneous uses account for 10% and may include the following:

- chlorinating agent,
- catalyst,
- semiconductors,
- phosphorus oxychloride, surfactants and stabilizers,
- production of special metallic deposits,
- manufacture of organophosphines,
- solvent in cryoscopy (anhydrous solvent; O'Neil 2006).

Phosphoryl trichloride can be converted by multistage–chemical synthesis to nerve gases. Therefore, the production and export is stringently controlled under the International Chemical Weapons Convention (OECD SIDS 2004).

5.3. Occupational exposure

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/m^3) of 18 were above the detection limit (0.02–0.1 mg/m^3).

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/m^3, during evacuation 0.9 mg/m^3, and after opening 7.9 mg/m^3 (OECD SIDS 2004, Oltramare et al. 1975).

5.4. Routes of exposure and uptake

The dermal contact and inhalation are the primary routes of exposure. Contact with the skin and eye can cause severe chemical burns and corrosive injuries.

Since phosphoryl trichloride hydrolyzes rapidly in the environment, bioaccumulation is negligible.

During manufacturing and processing of phosphoryl trichloride, it is assumed that workers may be exposed only to some minor levels because releases into the workplace are controlled by the closed manufacturing systems applied (OECD SIDS 2004). On the other hand, the pattern of exposure in the workplace is usually difficult to define because phosphoryl trichloride, when released, it volatilizes and hydrolyses rapidly and accurate estimates of workers exposure levels are difficult to obtain.

Furthermore, exposure the general population may occur only as a consequence of accidental releases. However, due to the short half-life of phosphoryl trichloride in the environment, its impact is expected to be negligible (WHO 1989).

6. MONITORING EXPOSURE

For phosphoryl trichloride there are no standardised air monitoring methods available neither from OSHA, NIOSH or DFG-MAK (NIOSH 2015; Parlar and Hartwig 2015). It is difficult to measure phosphoryl trichloride levels in the air because of their reactivity with atmospheric moisture. Existing analytical methods do not distinguish between phosphoryl trichloride and its hydrolysis products (WHO 1989).

A possible method to consider is described by Zhao et al. (2011) according to which phosphoryl trichloride is analysed in the workplace air by ion chromatography. The phosphoryl trichloride is collected and turned into hydrochloric acid, then separated and detected with a conductivity detector, qualified by elution time and quantified by peak height or peak area. The detecting limit of the method was 0.12 µg/ml and the recovery was 97.8% - 103.8%. All parameters of the method meet the requirements of GBZ/T 210.4-2008 "Guide for establishing occupational health standards - Part 4: Determination methods of air chemicals in workplace (Chinese Edition)". However, this method is non-specific, because it is based on conversion into hydrochloric acid and quantitation of the latter.

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

On contact with atmospheric moisture, phosphoryl trichloride degrades to hydrochloric acid and phosphoric acid (Majzoobi et al. 2009). The half-life of phosphoryl trichloride in pure water is less than 10 seconds (Riess 2002). Approximately 15 % of the substance is hydrolysed in the atmosphere (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). 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 7.2) (OECD SIDS 2004).

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

7.1.1. Human data

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

7.1.2. Animal data

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

7.1.3. In vitro data

There are no in vitro data on toxicokinetics.

7.1.4. Toxicokinetic modelling

There are no data on toxicokinetic modelling (short living compound with local action).

7.1.5. Biological monitoring

Biological monitoring is not relevant for this locally acting substance (local irritant).

7.2. Acute toxicity

7.2.1. Human data

Phosphoryl trichloride has a strong irritating effect on mucous membranes and on the eyes (for details, see Section 7.4).

One study (Payne et al. 1993) describes effects on some people who were exposed to phosphoryl trichloride and its hydrolysis products by an explosion. Three workers who were exposed from a few seconds up to ca. half a minute, 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/m^3 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 (Buess and Lerner 1956, Rosenthal et al. 1978, Vaubel 1903). 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 (Herzog and Pletscher 1955, Sassi 1954).

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

7.2.2. Animal data

Mice showed signs of cholinergic poisoning after intraperitoneal administration of phosphoryl trichloride (ED_{50} = 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 et al. 2003).

Inhalation

Some of the older studies are not well documented. Specifically, the time of inhalation is not always given together with LC50 data.

During 4-hour exposures to a concentration of 930–1 070 mg/m³, made to determine the LC_{50} for phosphoryl trichloride and phosphoryl chloride, experimental animals (rats and guinea pigs) showed agitation, indications of irritation, chromodakryorhea around the eyes and laboured breathing (Butjagin 1904).

LC50 values are 48.4 ppm (308 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 or 283 mg/m³ for rats, 41 ppm or 263 mg/m³ for guinea pigs) (Weeks 1964). LC50 values for rats reported in other studies were 11.1 ppm (71 mg/m³), 17.3 ppm (110 mg/m³) and 31.4 ppm (200 mg/m³) (Marhold 1972, Marhold and Čížek 1957, Mobil Co 1977a, Roshchin and Molodkina 1977).

The concentration–response regression was very steep for phosphoryl trichloride: LC_{16} = 56, LC_{50} = 71 and LC_{84} = 89 mg/m^3. [Comparison to phosphorus trichloride: LC_{16} = 140, LC_{50} = 220 and LC_{84}= 310 mg/m^3 (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 and 1974).

The effects of a single 4-hour low-level inhalation exposure on rodents were also examined (Molodkina 1974, Payne et al. 1993, Weeks et al. 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), whereas 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.

Oral exposure

An oral LD_{50} has been reported for rats of 380 mg/kg (in vegetable oil, Molodkina 1971). LD_{16} and LD_{84} values were 250 and 580 mg/kg bw, respectively. Corresponding 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 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).

Dermal exposure

The dermal LD_{10} for rabbits was 1 000 mg/kg in males and 631 mg/kg in females; an LD_{50} 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/m³) for rats and 50.1 ppm (319 mg/m³) for guinea pigs (Weeks et al. 1964).

The inhalation LC_{50} of the hydrolysis product hydrochloric acid is 1110 ppm (1665 mg/m³) 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 (Butjagin 1904, Greim 2001).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. 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).

7.3.2. Animal data

7.3.2.1. 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 on body weight, increased relative kidney weight and the respiratory tract effects were less pronounced. 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" (Henschler 1984, Molodkina 1971, Roshchin and Molodkina 1977). Accordingly, OECD SIDS (2004) 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 (hydrolysis product), were studied after 90 days of inhalation exposure in rats and mice (CIIT 1984). The animals were exposed to 0 (control), 10, 20 and 50 ppm (0, 15, 30 and 75 mg/m³). In the high dose group, both rats and mice had decreased body weight gain. Hydrochloric acid produced dose- and time-dependent inflammatory changes of the nasal cavity in rats in all dose groups. Exposed mice developed cheilitis (at 50 ppm) and eosinophilic globules in the nasal turbinates (all concentrations). There was no effect on haematology, clinical chemistry and urinalysis in any of the groups. No sign of systemic toxicity was reported, 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).

7.3.2.2. Oral exposure

No data were available.

7.3.2.3. Dermal exposure

No data were available.

7.3.3. In vitro data

No data are reported.

7.4. Irritancy and corrosivity

It has been discussed in the past that the degradation products hydrochloric acid and phosphoric acid contribute to the strong irritating and corrosive effects of phosphoryl trichloride.

7.4.1. 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 (Henschler 1984, McLaughlin 1946, Roshchin and Molodkina 1977). 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/m³ (0.157 ppm) was determined after a 1-minute exposure of human volunteers to phosphoryl trichloride (Molodkina 1971 and 1974, Radionova and Ivanov 1979, Roshchin and Molodkina 1977). However, these studies are not well documented.

7.4.2. Animal data

7.4.2.1. 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).

7.4.2.2. Eyes

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

7.4.2.3. 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. The irritative effect of the related compound phosphorus trichloride was reported to be more pronounced (Roshchin and Molodkina 1977), which is probably due to a higher hydrolysis rate (Weeks et al 1964).

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 7.2.2; 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.

7.4.3. In vitro data

No data are reported.

7.5. Sensitisation

7.5.1. Human data

No data were available.

7.5.2. 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).

7.5.3. In vitro data

No data are reported.

7.6. Genotoxicity

7.6.1. Human data

No data were available.

7.6.2. 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. were 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 SIDS 2004).

7.6.3. 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 and 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.

7.7. Carcinogenicity

7.7.1. Human data

No data were available.

7.7.2. Animal data

No data on phosphoryl trichloride were available.

The carcinogenic potential of the hydrolysis product 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 preneoplatic 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 (exposed), 25/99 (air control) and 24/99 (colony control)]. Hydrochloric acid did not cause histopathological changes in lung, liver, kidney and testes and did not produce gross lesions (Sellakumar et al. 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).

7.8. Reproductive toxicity

7.8.1. Human data

No data were available.

7.8.2. Animal data

7.7.2.1. 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/m_3 (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 therefore inadequate for risk assessment.

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

7.7.2.2. Developmental toxicity

No data were available.

7.8.3. In vitro data

No data were available.

7.9. Mode of action and adverse outcome pathway considerations

Due to its high chemical reactivity, phosphoryl trichloride is considered a portal-of-entry toxicant and it is not considered to reach internal organs. However secondary effects, including hypoxia due to lung damage (OECD SIDS 2004), may occur. Thus, preventing portal-of-entry toxicity should prevent internal organ effects.

7.10. Lack of specific scientific information

There is a specific lack of human epidemiological studies and of experimental data upon long-term inhalation exposure.

8. GROUPS AT EXTRA RISK

No data are available.

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