



# Phosgene

## Toxicological Overview

### Key Points

#### Kinetics and metabolism

- most likely routes of exposure are inhalation and ocular
- very rapidly hydrolysed within the respiratory tract to carbon dioxide and hydrochloric acid
- little or no systemic absorption

#### Health effects of acute exposure

- signs of poisoning may be delayed by up to 24 hours post-exposure
- inhalation may lead to eye, nose and throat irritation, wheezing, chest tightness and coughing
- pulmonary oedema, cyanosis, shock and respiratory arrest may also occur
- skin exposure causes irritation, pain, blistering, ulceration and erythema
- ocular exposure results in lacrimation and irritation

#### Health effects of chronic exposure

- there is limited data on effects following chronic exposure
- phosgene is not thought to be carcinogenic, mutagenic or a reproductive toxicant

## Summary of Health Effects

The signs and symptoms of phosgene exposure are often immediate in presentation and include irritation of the eye, nose and throat. However, exposure to low concentrations of phosgene may result in no initial symptoms, allowing inhalation of the vapour for longer periods.

The adverse effects resulting from inhalation exposure to phosgene have been categorised into three distinct phases: initial irritation, followed by a latent phase (up to 24 hours post-exposure) and then a final phase involving the clinical manifestation of pulmonary oedema. The final phase is associated with shortness of breath, production of large quantities of frothy white or yellow sputum, cyanosis, feeling of suffocation, shock and respiratory arrest. Pulmonary oedema may develop rapidly after high level exposure or after a latent period following low level exposure. Cardiovascular effects may follow, secondary to pulmonary oedema.

Dermal exposure to phosgene may cause irritation, pain, blistering, ulceration and erythema.

Delayed effects may occur following an acute exposure to phosgene, including chronic bronchitis, ocular effects, reduced physical fitness and exertional dyspnoea. Rarely, complete recovery has taken years and there is a small chance of permanent lung damage. Long-term effects appear to be more likely in those with existing chronic lung diseases.

There is limited data on the mutagenicity, carcinogenicity and health effects of chronic exposure to phosgene in humans.

Owing to its highly reactive nature, it is not considered likely that phosgene could reach the developing fetus.

## Kinetics and Metabolism

The main routes of exposure to phosgene are inhalation and ocular exposure. Ingestion is not considered a likely route as liquid phosgene vaporises rapidly on release from pressurised containers [1]. Phosgene is highly reactive; its short half-life in aqueous solution ( $t_{1/2}$  around 0.026 s) tends to preclude systemic absorption and distribution [2].

Following inhalation, phosgene is either rapidly hydrolysed to hydrochloric acid and carbon dioxide (and subsequently exhaled) or it penetrates the lower respiratory tract (alveoli) [3, 4]. In the lower respiratory tract phosgene rapidly reacts (acylation) with a range of macromolecules, including enzymes, proteins and phospholipids; this may lead to a depletion of glutathione [3, 4].

## Sources and Route of Human Exposure

Phosgene is an important chemical intermediate, produced in large quantities in the EU (more than 10,000 tonnes a year) [3]. It is required to produce various chemicals, including isocyanates, dyestuffs, polycarbonates, acid chlorides, insecticides and pharmaceutical chemicals [5]. Phosgene is also used in the recovery of metals [5].

There are four potential sources of phosgene in the environment: thermal decomposition of chlorinated hydrocarbons, photo-degradation of organochlorine compounds, fugitive release and deliberate release. When exposed to combustion or intense heat, chlorinated hydrocarbons such as methylene chloride (paint stripper), trichloroethylene and tetrachloroethane may liberate smoke and fumes containing phosgene [2, 3]. Contact of chlorinated solvents with hot metal surfaces may liberate significant quantities of phosgene, eg during the welding of metal that has been prepared by cleaning with chlorinated solvents [6]. Organochlorine pollutants such as chloroform and tetrachloroethylene, and polymers such as polyvinyl chloride, may decompose in the atmosphere (on exposure to solar radiation) to form significant quantities (several hundred thousand tonnes) of phosgene each year [2].

Workplace exposure limits (WEL) have been set in the UK to protect workers from the harmful effects of phosgene. The long-term exposure limit (LTEL) is 0.08 mg/m<sup>3</sup> (8-hour time weighted average exposure (TWA) reference period). The short-term exposure limit (STEL) is 0.25 mg/m<sup>3</sup> (15-minute reference period) [7].

## Health Effects of Acute/Single Exposure

### Human data

#### Inhalation

The adverse health effects of phosgene exposure are primarily related to the pathological responses of the pulmonary system, the critical effect being pulmonary oedema [4]. Pulmonary oedema may develop rapidly after high level exposure or after a latent period following low level exposure [1]. The threshold toxicity levels for phosgene are summarised in the table below.

#### Estimated threshold toxicity values for inhalation exposure to phosgene

Dose		Effect
ppm min	mg/m <sup>3</sup> min	
>30	>120	Onset of lung damage
>150	>600	Pulmonary oedema
~300	~1,200	LCt <sub>1</sub>
~500	~2,000	LCt <sub>50</sub>
~1,300	~5,200	LCt <sub>100</sub>

LCt: dose that would result in 1, 50 or 100% fatalities in an exposed population. Dose expressed as Ct; the product of concentration (C) and time (t) of exposure

**Reference**  
International Programme on Chemical Safety (IPCS). Phosgene. Environmental Health Criteria 193, 1997. World Health Organization: Geneva.

Phosgene generally conforms to Haber's rule in that certain physiological effects of exposure (eg lung damage or death) are proportional to the product of concentration and duration of exposure (Ct). There is limited evidence to suggest that on repeated dosing or chronic exposure an adaptation response to phosgene may develop, which could cause some deviation from Haber's rule (see the section on animal data under health effects of chronic/repeated exposure, below) [8].

Three distinct phases (initial, latent and final phase) have been described for health effects following the inhalation of phosgene [2].

Immediately following exposure (ie the initial phase) an individual may experience eye, nose and throat irritation, pain and coughing, wheezing and chest tightness [9].

The latent phase is a period defined by a lack of overt symptoms following the initial effects detailed above. During this phase, histology may reveal progressive detrimental changes; also non-specific symptoms (eg headache, nausea and vomiting) may be observed [1, 10, 11].

The duration of the latent phase is inversely proportional to the dose, it typically lasts from 30 minutes to 24 hours [1, 10]. The latent phase may be absent following exposure to a supra-lethal concentration of phosgene.

The final phase involves the clinical manifestation of pulmonary oedema, associated with shortness of breath, productive cough (white or yellow frothy fluid sometimes with haemoptysis), cyanosis, shock and respiratory arrest. Pulmonary oedema may rarely be delayed for up to 72 hours [1]. Hypervolaemia and hypoxia caused by pulmonary oedema may lead to cardiovascular effects, including hypotension and tachycardia [10]. Death may follow pulmonary oedema as a result of anoxia [10].

Massive exposures may cause pulmonary intravascular haemorrhage, leading to immediate death by pulmonary vasculature occlusion [10]. Infectious pneumonitis may develop 24–48 hours after exposure and has a high mortality rate [11]. In most fatal cases, death is within 48 hours of exposure [1].

### Dermal/ocular exposure

Exposure of (moist) skin to phosgene may cause skin irritation, pain, blistering, ulceration and erythema [1, 2]. Ocular effects may also occur, such as excessive lacrimation and irritation. Splashes of liquefied phosgene may cause irritation, corrosive burns, frost-bite, complete corneal opacification and perforation [1, 2].

### Delayed effects following acute exposure

Chronic bronchitis and emphysema have been reported following acute exposure [8]. Reduced physical fitness and exertional dyspnoea may occur months after exposure [1]. Case studies suggest normal levels of lung function are typically recovered within weeks; however, complete recovery may take years and there is a small chance of permanent lung damage [10]. Long-term effects on exposure to phosgene appear to be more likely in those with existing chronic lung diseases (such as chronic obstructive pulmonary disease and chronic bronchitis) [1, 5]. In one study, the extent of chronic detriment to lung function correlated more closely with smoking habits than with the severity of intoxication [5].

There is some evidence that prolonged respiratory effects on exposure to phosgene do not tend to occur at doses of less than 150 ppm min [9].

Delayed ocular effects on exposure to phosgene have also been reported, including photophobia and excessive lacrimation [1].

It has been suggested that anoxia (resulting from pulmonary oedema) may be responsible for other chronic effects that have been tentatively (not conclusively) associated with phosgene intoxication. These include neurasthenia, epilepsy, peripheral Raynaud-like syndrome and dysfunction of the peroneal nerve (resulting in 'foot drop') [2].

## Animal and in-vitro data

The acute effects of phosgene observed in animal models are consistent with those described for humans. The lung is the primary target organ in all species with the characteristic pathological feature being the delayed clinical manifestation of pulmonary oedema. In most experimental animal species, the lethal dose (LC<sub>t50</sub>) for phosgene is 1,000–2,000 mg/m<sup>3</sup> min [2].

The pulmonary effects of sub-lethal phosgene exposure in animals include oedema, petechial haemorrhage, bronchial epithelial necrosis, increase in lung weight, changes in blood gas chemistry (consistent with hypoxia) and increased protein, collagen and leukocytes in bronchoalveolar lavage (BAL) [12, 13]. Immunotoxic effects (ie net deficiencies in respiratory tract immunological response) have also been seen after acute exposure to phosgene in experimental animals [14].

## Health Effects of Chronic/Repeated Exposure

### Human data

#### General toxicity

There is a paucity of data concerning the effects of chronic phosgene exposure in humans.

In one study of workers at a phosgene factory, no instances of long-term illness or death were attributable to phosgene exposure [15]. The average concentration of phosgene measured in the factory was  $0.01 \text{ mg/m}^3$ , equating to a Ct of  $4.8 \text{ mg/m}^3 \text{ min}$  ( $1.2 \text{ ppm min}$ ) for an 8-hour working day [15].

No excess deaths or deaths from respiratory disease were demonstrable in workers in a uranium processing plant routinely exposed to 'low' or occasionally 'high' levels of phosgene [16, 17].

#### Genotoxicity

There is insufficient evidence with which to assess the mutagenicity of phosgene in humans.

#### Carcinogenicity

The limited available evidence does not suggest that phosgene is carcinogenic to humans. Two studies on the same cohort of chemical workers exposed for approximately 35 years to phosgene (and to peak exposures above 1 ppm) showed no increase in mortality from cancer [5].

#### Reproductive and developmental toxicity

Owing to its highly reactive nature, it is considered unlikely that phosgene could reach the developing fetus [3].

### Animal and in-vitro data

#### Inhalation

Rats exposed whole body to 0.1 or 0.2 ppm five times a week, 0.5 ppm twice a week or 1 ppm once a week for up to 12 weeks showed no mortality. At and above 0.2 ppm, relative lung weights were increased, histological effects were more pronounced and collagen deposition was observed. For the two highest doses (0.5 and 1 ppm), body weights were decreased, and collagen and elastin were found at significantly higher levels in the lung homogenate. The study appears to conform to Haber's rule as similar effects were observed in the 0.2 and 1 ppm groups and these were greater than those in the 0.1 ppm exposed group [3].

In one study, dogs were exposed one to three times a week to  $96\text{--}160 \text{ mg/m}^3$ , for 30 minutes for up to 12 weeks. The main effects were chronic bronchiolitis and emphysema [2].

An 'adaptation' response to chronic/repeated phosgene exposure has been observed, where the dose was not overwhelming and repeated daily. The adaptation response was shown to decrease over the period of a month [18]. Such data indicates the need for care when attempting to use Ct to predict the response in cases of chronic/repeated exposure [8].

Given that the pulmonary system is the target organ for phosgene, studies have investigated the effect of exposure on susceptibility to respired pathogens. Such studies have observed a decrease in host resistance to various pathogens [2].

### Genotoxicity

Phosgene has tested negative in the Ames test (TA100 and TA98) in the presence and absence of metabolic activation [3].

### Carcinogenicity

No adequate studies are available for the assessment of the carcinogenicity of phosgene in animals [2].

### Reproductive and developmental toxicity

There is insufficient data available on the reproductive effects of phosgene.



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