

Phosgene

Toxicological overview

Key Points

Kinetics and metabolism

- Main route of entry is inhalation
- Very rapidly hydrolysed within respiratory tract to carbon dioxide and hydrochloric acid
- Little or no systemic absorption

Health effects of acute exposure

- Extremely poisonous by inhalation
- Signs of poisoning may be delayed by up to 24 hours post exposure
- Inhalation may lead to eyes, nose and throat irritation, dyspnoea and coughing.
- Pulmonary oedema, cyanosis, shock and respiratory arrest may also occur
- Skin exposure causes irritation and erythema
- Ocular exposure results in lacrimation and inflammation

Health effects of chronic exposure

- Limited data, but effect of acute exposure expected to be similar to acute exposure
- Phosgene is not thought to be carcinogenic or mutagenic

Toxicological Overview

Summary of Health Effects

The clinical manifestations 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.

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) subsequent to the onset of chest pain, discomfort, thirst, headache, nausea, increased cough (with haemoptysis), production of large quantities of frothy white or yellow sputum, cyanosis, feeling of suffocation and non-cardiogenic pulmonary oedema (occurring up to 48 hours post exposure).

All individuals known to have been exposed to phosgene should be assessed at hospital irrespective of the presence or severity of early signs and symptoms as these are not reliable prognostic indicators.

Kinetics and metabolism

The primary route of exposure is by inhalation. Phosgene is highly reactive; its short half-life in aqueous solution ($t_{1/2} \sim 0.026$ s) tends to preclude systemic absorption and distribution. Hydrolysis of phosgene within the moist environment of the pulmonary system may cause the liberation of hydrochloric acid and carbon dioxide which are distributed and eliminated according to normal physiological processes [1]. The generation of hydrochloric acid does not play a key role in the toxicity of phosgene [2].

Sources and route of exposure

There are four potential sources of phosgene in the environment: combustion of chlorinated hydrocarbons, photo-degradation of organochlorine compounds, fugitive release and deliberate release. Combustion of chlorinated hydrocarbons such as methylene chloride (paint stripper), trichloroethylene and tetrachloroethane may liberate smoke and fumes containing phosgene. Contact of chlorinated solvents with hot metal surfaces may also liberate significant quantities of phosgene, for example, during the welding of metal that has been prepared by cleaning with chlorinated solvents [3]. Organochlorine pollutants such as chloroform and tetrachloroethylene and polymers such as polyvinyl chloride (PVC) may decompose in the atmosphere (on exposure to solar radiation) to form significant quantities (several hundred thousand tonnes) of phosgene each year [1].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

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]. The threshold toxicity levels for phosgene are summarised in Table 1.

Table 1: Estimated threshold toxicity values for human (inhalation) exposure to phosgene. LCt values refer to the dose that would result in 1, 50 or 100% fatalities in an exposed population. Dose expressed as Ct; the product of concentration and time of exposure. Data from EHC 193 [1].

Concentration		Effect(s)
ppm	mg m ⁻³	
0.4	1.6	Perception of odour
1.5	6	Recognition of odour
3	12	Irritation of eyes, nose and throat
Dose		
ppm min	mg min m ⁻³	
>30	>120	Onset of lung damage
>150	>600	Pulmonary oedema
~300	~1200	LCt ₁
~500	~2000	LCt ₅₀
~1300	~5200	LCt ₁₀₀

Phosgene generally conforms to Haber's rule in that certain physiological effects of exposure (e.g. lung damage or death) are proportional to the product of concentration and duration of exposure (Ct), although deviation from Haber's rule occurs following chronic exposures [2]; (see animal section on chronic health effects, below).

Inhalation

There are three, distinct phases associated with the inhalation of phosgene at levels ranging from 30 – 300 ppm min (120 – 1200 mg min m⁻³), viz., an initial reflex syndrome, clinical latent period and clinical oedema phase [1]. During the initial phase, an individual may experience eye, nose and throat irritation and pain, dyspnoea and coughing. The duration of the latent phase is generally proportional to the level of exposure, generally lasting from 30 minutes to 24 hours [4]. However, 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.

Ingestion

Not relevant.

Dermal / ocular exposure

At concentrations above 3 ppm, exposure of (moist) skin to phosgene may cause skin irritation and erythema. Ocular effects may also occur, such as lacrimation and inflammation (conjunctival hyperaemia). Splashes of liquefied phosgene may cause frost-bite and complete corneal opacification [1].

Delayed effects following an acute exposure

A single, acute exposure to phosgene is not generally associated with long-term sequelae. However, sensitive individuals (particularly smokers and those with a pre-existing pulmonary dysfunction such as emphysema) and those exposed to high concentrations may exhibit persistent, chronic signs such as shortness of breath and reduced physical capacity (exertional dyspnoea). 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 lower-leg paralysis) [1].

Animal Data

The acute effects of phosgene observed in animal models are consistent with those described for human. 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 laboratory species, the lethal dose (LC₅₀) phosgene is 1000 – 2000 mg min m⁻³ [1].

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) [5, 6].

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 long-term illness or deaths were attributable to phosgene exposure [7]. The average concentration of phosgene measured in the factory was 0.01 mg m^{-3} , equating to a Ct of $4.8 \text{ mg min m}^{-3}$ [1.2 ppm min] for an 8 hour working day.

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 [8, 9].

Genotoxicity, carcinogenicity, reproductive and developmental toxicity

There is no evidence to suggest that phosgene is carcinogenic or mutagenic. It is unlikely that biologically relevant quantities of phosgene will be systemically absorbed following inhalation exposure due to the very rapid hydrolysis of phosgene to hydrochloric acid and carbon dioxide [1]. Similarly, there have been no reports associating phosgene exposure with adverse reproductive or developmental effects [1].

Animal and In-Vitro Data

Inhalation

There are no reports on the long-term exposure of animals to phosgene, although the effects of repeated exposure have been subject to limited investigations. In one study, dogs were exposed 1 – 3 times per week to $96 - 160 \text{ mg min}^{-3}$ for up to 12 weeks. The main effects were chronic bronchiolitis and emphysema [1]. In a more recent study, “adaptation” to chronic phosgene exposure (up to 1 ppm, 6 hours per day, up to 5 days per week) was observed if the dose was not overwhelming and repeated daily [10]. Thus, whilst phosgene obeys Haber’s rule for short to medium term exposures, this is not the case for chronic exposures [2].

Immunotoxicity

Given that the pulmonary system is the target organ for phosgene, studies have investigated the effect of exposure on susceptibility to respired pathogens. Overall, there was a decrease in host resistance in response to various pathogens (Table 3).

Table 3: Effect of phosgene exposure on pulmonary immuno-competence in animals. N.s. = not specified. Data from [1].

Species	Dose		Effect
	C (mg m ⁻³)	T (hours)	
Rat	0.4 – 4	4	Decrease in pulmonary natural killer cells (≥ 2 mg m ⁻³).
Rat	4	4	Blood titre of rat-adapted influenza virus significantly higher than control up to 4 days post infection.
Rat	0.4 – 0.8	6	Significant decrease in pulmonary clearance of bacteria (<i>Streptococcus zooepidemicus</i>).
Mice	0.04 – 0.4	4	Significant elevation in mortality following infection with a <i>S. zooepidemicus</i> and melanoma tumour cell mixture (≥ 0.1 mg m ⁻³).
Rat	0.2 - 4	n.s.	Decrease in concentrations of prostaglandin E2 and leukotrienes (≥ 0.4 mg m ⁻³).
Rat	0.4 – 0.8	6h/day, 5days/week, 4 or 12 week duration	Decreased clearance of bacteria. Resolved 4 weeks after cessation of exposure.

It is not possible to interpret these animal studies in terms of potential health effects in humans due to the lack of adequate human data. However, it would seem prudent to assume that exposure to phosgene may affect susceptibility to respiratory infections in humans.

Genotoxicity

No available data.

Carcinogenicity

One study reported no increase in neoplasms in guinea pigs (n=20) and rats (n=20) following exposure to phosgene over 18 and 24 months, respectively. However, this study is inadequate to draw any conclusions regarding the carcinogenicity of phosgene [1]. There are no other studies reported.

Reproductive and developmental toxicity

There are no reports available on the reproductive effects of phosgene in any animal model.

References

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.