

**AMMA JOURNAL VOL 13 ISSUE 2**  
**OCTOBER 2004**  
**CHEMICAL AGENTS**  
**Phosgene – A Research Review<sup>1</sup>**

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**ABSTRACT**

Phosgene is a toxic substance which causes fatal permeability-type (non-cardiogenic) pulmonary oedema on inhalation. Phosgene is a simple low-molecular-weight synthetic chemical which was used as a chemical warfare agent in World War I. Phosgene attacks the epithelial lining of the respiratory tract. This paper summarises the current state of knowledge about the actions of phosgene and the treatment of its effects, as found in a recent review and recent research papers.

**INTRODUCTION**

Phosgene (COCl<sub>2</sub>; MW = 98.9) is a highly reactive gas that was used extensively as a chemical warfare agent in World War I. It is still considered to be a threat agent, although the probability of its use is low<sup>1</sup>. It has a boiling point of 8°C and a high density as a liquid and gas, which makes it useful as a chemical warfare agent, as it will remain at ground level for prolonged periods. Phosgene is a hazard industrially: not only is it an important intermediate in the manufacture of agricultural and pharmaceutical products, but it is formed on combustion of foamed plastics, e.g., polyvinyl chloride (PVC)<sup>1</sup>.

Mathur and Krishna<sup>1</sup> have published a comprehensive but concise review of phosgene covering its history, physical and chemical characteristics, metabolic formation, effect of phosgene exposure, course after poisoning, mechanisms of lung damage and therapy of phosgene poisoning. A brief summary of the important points follows; the review should be consulted for further details.

Phosgene causes non-cardiogenic pulmonary oedema in humans and increases lipid peroxidation and vascular permeability. Inhalation of phosgene produces initial symptoms of irritation of eyes and upper respiratory passages, and these are followed by a symptom-free clinical latent period. As pulmonary oedema develops, the symptoms return with coughing, shortness of breath, tightness of chest and other symptoms, and death occurs within 48 hours in fatal cases, although patients may die later of infections consequent upon phosgene exposure. The pulmonary oedema regresses in survivors within a few days, but complete recovery may take up to several years. The lavage fluid from the lungs has a high protein content and increased total cell count, and other biochemical changes are in serum lactic acid dehydrogenase, lung glucose-phosphate dehydrogenase and nonprotein sulphhydryl content (all increased). ATP and Na-K ATPase (both decreased), and acyl (palmitoyl) transferase, which increases after an initial decrease. This last-mentioned enzyme is involved in the synthesis of surfactant; an intact surfactant system is essential for the maintenance of the integrity of the alveolar membrane and prevention of the development of pulmonary oedema. Na-K-ATPase is a membrane-bound enzyme that has a key role in the active transport processes that regulate homeostasis and fluid balance.

The toxic effects of phosgene are not due to its hydrolysis and conversion to HCl in the aqueous medium of the exposed mucous membranes of the respiratory tract. Lipooxygenase intermediates, derived from arachidonic acid, may be involved in phosgene induced lung damage, presumably by increasing systemic vascular permeability. Accordingly, specific leukotriene-receptor blockers or inhibitors of leukotriene synthesis have been found to counter the development of oedema. The lung damage can also be blocked by various agents which increase cellular cyclic adenosine monophosphate. Other means of countering phosgene toxicity include glucocorticoids, positive pressure oxygen ventilation, sodium bicarbonate to correct metabolic acidosis, diuretics, antibiotics to counter subsequent infection, and physical rest. However, despite all these measures, Mathur and Krishna<sup>1</sup> claim

that no antidote for phosgene is known, although hexamethylenetetramine is an effective prophylactic agent in rabbits.

Additional information on phosgene from other sources is discussed below.

### TOXICITY

Table 1 lists the LCt50 of phosgene by inhalation in various species. The LCt50 is the dose of the toxicant that is lethal to 50 percent of the exposed population. Concentrations below 5 ppm did not cause alveolar oedema in rats, regardless of the length of exposure. However, there was no threshold concentration of phosgene (down to 0.1 ppm) for an increase in pulmonary lavage protein content or widening of pulmonary interstices. At low concentrations (0.1-2.5 ppm) pulmonary damage in the rat was primarily located at the transition for terminal bronchioles to the alveolar ducts, whereas at higher concentration (5 ppm) damage to the alveolar pneumocytes (Type 1) was more conspicuous<sup>2</sup>. These results are consistent with the review by Cucinell<sup>3</sup> which reported that prolonged exposure of animals to 0.2-1 ppm phosgene caused lung lesions. Phosgene is excreted via the lungs and kidneys.

At very high doses (200 ppm), phosgene passes through the blood-air barrier, reaches the lung capillaries and react with blood constituents. Haemolysis in the pulmonary capillaries occurs with haematin formation, congestion by erythrocyte fragments, and stoppage of capillary circulation. Death follows within a few minutes from “acute cor pulmonale” (acute overdistension of the right heart), often before pulmonary oedema can develop.

Guinea pigs and cats can develop tolerance to phosgene after exposure to low doses over 7-40 days. In particular, tolerant cats were able to survive a low-dose/long-exposure Ct that was 4.5 times the high-dose/short exposure LCt50. On the other hand, rats exposed to 1 ppm phosgene for only 6 hours did not developed increased resistance to phosgene, although they were capable of surviving normally lethal does of ozone and nitrogen dioxide”.

SPECIES	LCt.0	REFERENCE
Mouse	3400 mg.min.m	Cucinell, 1974 <sup>3</sup>
Rat	1500-2400 ppm.min	Clayton, 1977 <sup>5</sup>
	1400-6500 m_&min. n-1	Cucinell, 1974 <sup>3</sup>
Guinea Pig	2200-2800 mg.min. n-1	Cucinell, 1974 <sup>3</sup>
Dog	4200-8400 mg.min. n-1	Cucinell, 1974 <sup>1</sup>
Sheep	13300 mg.min. <sup>3</sup>	Keeler <i>et al.</i> , 1989 <sup>6</sup>
Monkey	1000 mg.min. n-1	Cucinell, 1974 <sup>1</sup>
Human	500-1600 EE_m.min	Mathur and Krishna, 1992
	3200 mg.min. n-1	Cucinell, 1974 <sup>3</sup>

Table 1. LCt50 of phosgene to inhalation for various species.

### CLINICAL MANIFESTATION

The clinical manifestations of phosgene exposure in humans are summarized in Table 2<sup>1</sup>.

EXPOSURE	OBSERVATIONS
>0.4 ppm	Perception of odour
>1.5 ppm	Recognition of odour
>3ppm	Irritation in eyes, nose, throat and bronchi
>3ppm.min	Beginning of lung damage
>150ppm	Clinical pulmonary oedema
-300 ppm.min	LCt,
-500 ppm.min	LCt50
-1300ppm.min	LCt100

Table 2: Clinical manifestation of phosgene exposure in humans

LCt, LCt50, and LCt100 are the concentrations required to kill one percent, 50 percent and 100 percent of the population respectively.

### MECHANISM OF ACTION

The involvement of enzymes and mediators in the action of phosgene has been investigated in several studies. Hurt et al<sup>7</sup> produced results consistent with toxic oxygen species being a partial or major source of lung injury, while not discounting other mechanisms or excluding other effects with drugs having more than one mode of action. Frosolono and Pawlowski<sup>8</sup> fractionated lungs into nuclear debris, mitochondrial lysosomal, microsomal and soluble (cytoplasmic) fractions 0, 30 and 40 min after exposure of rats to phosgene concentrations within the LCt50 range. They found that activities of the enzymes p-nitrophenylphosphatase, cytochrome C oxidase and ATPase decreased, with serum lactate dehydrogenase increased in response to phosgene. Madren-Whalley and Werrlein<sup>9</sup> studied the effect of phosgene directly on contiguous sheets of sheep pulmonary artery endothelial cells in vitro that mimicked in vivo organisation of endothelial tissues. They concluded that phosgene increased permeability in a dose-dependent fashion, with an immediate onset inconsistent with the clinical latent phase of phosgene poisoning. Results of other experiments with this preparation suggested that specific cell responses to phosgene may be linked by F-actin lesions to altered expression of antigenic markers, immunosuppression and response to drug therapy.

The use of glucocorticoids (corticosteroids) in an attempt to counteract phosgene toxicity was mentioned above, in the context of the review by Mathur and Krishna. Such steroids have been investigated in a variety of models of pulmonary oedema, and in the treatment of human acute lung injury of widely different aetiologies, partly because of the ability of the corticosteroids to block increases in microvascular permeability<sup>12</sup>. The effects of steroids have been reported to be beneficial, without effect, and even harmful. These conflicting results may be when given after lung injury, including, in humans, increased susceptibility to infection and, in animals, increased due to the corticosteroids preparation, the dose, time and duration of its administration, the agent producing the lung injury, the extent of lung injury, the animal species under study, the parameter under investigation (a biochemical or physiological change, or survival) and the design of the experiments. The most important of these factors is possibly the timing of steroid administration. Several studies<sup>10, 11</sup> have demonstrated that corticosteroids have most benefit when given early, i.e., before the oedema-causing mechanisms have progressed beyond a certain, though ill-defined, point. There are no data suggesting that corticosteroids can reverse pre-existing lung damage, although they may prevent additional injury. Moreover, corticosteroids may have adverse effects mortality and lung injury with prolonged administration.<sup>12, 13</sup>

### THERAPY

Little can be added to the current state of knowledge of therapy of phosgene poisoning as outlined by Mathur and Krishna! Esters of cysteine have been found to selectively elevate pulmonary cysteine levels and provide prophylactic protection against perfluoroisobutylene, presumably by direct chemical reaction with it<sup>16</sup>, However they are less effective against phosgene<sup>17</sup>. Anderson et al,<sup>18</sup> suggested that N-acetyl cysteine and phosgene exposure. This suggestion was based on the ability of these compounds to inhibit the effect of phosgene on the human monocyte/ macrophage U937 cell line in vitro.

### REFERENCES

1. Mathur BB, Krishna G. Toxicodynamics of phosgene. In: SM Somani (cd.) Chemical Warfare Agents. San Diego and London: Academic Press; 1992: 237-254.
2. Diller WF, Bruch j, Dehnen W Pulmonary changes in the rat following low phosgene exposure. Arch Toxicology 1985; 57:1984-1990.
3. Cucinell A. Review of the toxicity of long-term phosgene exposure. Arch Environ Health 1974; 28:272-275.
4. Diller WF Pathogenesis of phosgene poisoning. Tox Ind Health 1985; 1:7-15. 1977; 21:255-267.

5. Keeler JR, Hurt HH, Nold JB, Lennox Wj. Estimation of the LC<sub>50</sub> of phosgene in sheep. USA MR! CD-TR-89-07. Maryland, USA: US Army Medical Research Institute of Chemical Defence; 1989.
6. Hurt HH, Hernandez SA, Baze WB, Tezak-Reid TM, Keeler JR. Pathophysiological mechanisms of three pulmonary chemogenic compounds: the role of toxic oxygen species. USA MR! CD-TR-92-02. Maryland, USA: US Army Medical Research Institute of Chemical Defence; 1992.
7. Frosolono MF, Pawlowski R. Effect of phosgene on rat lungs after single high-level exposure. *Arch Exp Health* 1977; 32:271-277.
8. Madren-Whalley JS, Werrlein Rj. Ultrastructural studies and transendothelial resistance of phosgene-exposed endothelial cells. 1993 Medical Defense Bioscience Review, May 10-13. US Army Medical Research and Development Command; 1993: 1215-1221.
9. Werrlein RJ, Madren-Whalley, Kirby SD. Phosgene-induced expression of dendrite cells from rat tracheal explants. 1993 Medical Defense Bioscience Review, May 10-13. US Army Medical Research and Development Command; 1993: 1197-1204.
10. Werrlein R, Madren-Whalley, Kirby SO. Phosgene effects on F-actin in cells grown from pulmonary tissues. 1993 Medical Defense Bioscience Review, May 10-13. US Army Medical Research and Development Command; 1993: 1205-1213.
11. Robertson C. A review of the use of corticosteroids in the management of pulmonary injuries and insults. *Arch Emerg Med* 1985; 2:59-65.
12. Smith LJ. The effect of methylprednisolone on lung injury in mice. *J Lab Clin Med* 1983; 101:629-640.
13. Bihari OJ, Tinker J. Steroids in intensive care. *Brit Med J* 1982; 28:323-330.
14. Brigham KL, Bowers RE, McKeen CR. Methylprednisolone prevention of increased lung vascular permeability following endotoxemia in sheep. *Clin Invest* 1981; 67:1103-1110.
15. Lailey AF, Hill L, Lawton IW, Stanton D, Upshall DG. Protection by cysteine esters against chemically induced pulmonary oedema. *Biochem Pharm* 1991; 42: S47-S54.
16. Upshall DG. Personal communication.
17. Anderson OJ, Davidson C, Gurtner G H. In-vitro phosgene exposure inhibits superoxide production by a human macrophage cell line: Protective effects of methylprednisolone or N-acetyl cysteine. 1993 Medical Defense Bioscience Review, May 10-13. US Army Medical Research and Development Command; 1993: 1241-1251.