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Health Effects and Toxicity of Phosgene : Scientific Review

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ABSTRACT

The chemistry and toxicology of phosgene are reviewed at length. Manufacture, physical and chemical properties and industrial application of this important chemical intermediate are presented. Both acute and chronic exposure studies on animals and some human exposure data are also discussed. Pathology of phosgene poisoning and reliable therapeutic measures are critically examined.

1. INTRODUCTION

Phosgene, an extremely toxic chemical, also known as carbonyl chloride, has always been treated with great respect by its producers. Their concern over dangers associated with handling this versatile product, used as the first poisonous gas in World War I (later replaced by mustard gas), led to the formation in 1972 of the Chemical Manufacturers Association's first Chemical Safety Panel.[1]

Phosgene is under intense scrutiny, worldwide, in part because it is the key reactant, together with methylamine, for producing toxic methylisocyanate (MIC). The detrimental effects of MIC came to light in Bhopal, India.[1,2] Since that accident, many phosgene manufacturers and their customers have been reassessing their procedures for handling and using this important but hazardous chemical. Phosgene also can be produced from the burning of some PVC–type plastics along with other chemicals. Attempts are being made to eliminate those plastics from use as building materials.[2]

2. PHYSICAL AND CHEMICAL PROPERTIES

Phosgene is a colourless, low–boiling liquid with an odour at 0.5 ppm in air resembling that of new–mown hay. Phosgene is soluble in aromatic and aliphatic

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hydrocarbons as well as organic acids and esters. It is slowly hydrolyzed by pure water. Table 1 lists some of its other physical properties.

Table 1. Some physical properties of phosgene[3].

Property	Value
Molecular Weight	98.92
Melting Point, °C	127.84
Boiling Point, °C	7.48
Specific gravity at 4°C	1.39
Vapour Pressure at 20°C, psi	
Vapour Desnity (air=1.0)	3.40
Structure *Cl-C-Cl*	

3. MANUFACTURE

Phosgene is manufactured from highly refined carbon monoxide which is produced from synthetic gas, coke or charcoal, or natural gas. High purity carbon monoxide is reacted with chlorine gas in the presence of activated charcoal. The reaction with chlorine is rapid and exothermic. After condensation of phosgene, the remaining product gases are scrubbed with sodium hydroxide solution to destroy any uncondensed phosgene. Product specifications and standards are as follows[3-5]. phosgene (min.), 99%; chlorine (free), max., 0.1 per cent; *HCl*, max., 0.2 per cent.

The output of phosgene is high and has been estimated to be 2.122 billion pounds in 1986 alone.[1] With few exceptions U.S. phosgene producers use virtually all of their output captively as an intermediate to synthesize toluene diisocyanate (a polyurethane building block), polycarbonates, drugs and pesticides. Phosgene is classified as a Class A poison and shipping it by truck or rail requires special containers. The procedure is both hazardous and costly.[1] As another alternate to the shipment of phosgene, modules are available that permit even small chemical manufacturers to install a phosgene generator on site.

In addition to reducing the chance of a release of phosgene, many producers are reducing inventory by as much as 50 per cent and are interested in developing less toxic alternatives to phosgene. For Example, diphenylcarbonate is not as toxic, requires no waste treatment, and makes a readily transportable product. However, diphenylcarbonate costs more than three times as much as phosgene. Carbonyl

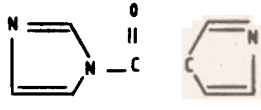


Figure 1.

diimidazole (Fig. 1) is another subsitute for phosgene, but it is unstable and expensive. It does not appear probable that there will be any large-scale replacement for phosgene.

4. COMMERCIAL USES OF PHOSGENE

Most of the phosgene produced in industry (approximately 85 per cent) is used to synthesize organic isocyanates by reaction with amines. Polycarbonate formation via reaction with Bisphenol A is responsible for approximately 6 percent of the annual total, with the remainder of the phosgene being used to synthesize other chemical intermediates, drugs, and pesticides.[6] Some typical reactions of phosgene are shown in Table 2.

Table 2.Typical reactions of phosgene

Reactant	Product
Cadmium Sulfide	Carbonyl Sulfide
Calcium Oxide	Calcium Chloride
Titanium Oxide	Titanium Chloride
Ferric Phosphate	Phosphorous Oxychloride
Aluminum Chloride	Complex
Ammonia	Urea, Cyanuric Acid, Cyanelide
Primary Amines	Isocyanates
Secondary Amines	Carbamoyl Chlorides
Amino Acids	Chloroformate Derivatives
Polyols	Polycarbonates
Carboxylic Acids	Acid Chlorides
Water	Hydrochloric Acid

(i) Organic Isocyanates

The prominent polyfunctional isocyanates manufactured by reaction with the appropriate amine are : Toluene diisocyanate (TDI) (Fig. 2) and Methylene bis–phenylisocyanate (Fig. 3).

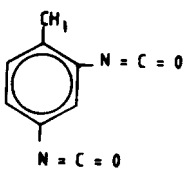


Figure 2.

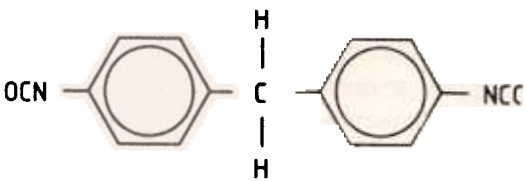


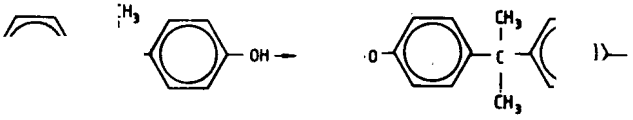
Figure 3.

These and other polyfunctional isocyanates are reacted with glycols to form polyurethanes, useful in forming elastic fibers, tough coatings, and synthetic leathers.

Methylisocyanate (MIC), CH_3–N=C=O, the chemical released in Bhopal, is an intermediate in the production of pharmaceuticals and such large scale pesticides as the nematocide carbofuran.

(ii) Polycarbonates

Phosgene is reacted with a polyol, usually Bisphenol A, to form the polycarbonates, which have widespread use in food contact, automotive, medical, and construction markets.



The polymers are used in numerous molded and extruded products such as street light covers, safety helmets, and break–resistant windows.

(iii) Others

The chloroformates are versatile chemical intermediates. The carbonic esters have significant uses in pharmaceuticals. Cyclic ethylene carbonate is often used in preparing solutions of polymers.

5. WORKPLACE EXPOSURE

Large-scale production of phosgene began only in the 1950s with the advent of the polyurethanes and the polycarbonates. National Institute of Occupational Safety and Health (NIOSH) estimated that 10,000 U.S. workers are potentially exposed to phosgene, especially during its production and subsequently during the synthesis of toluene diisocyanate.[7] Phosgene levels in the air in workplaces where synthetic processes involving phosgene take place are reported to be as high as 0.4 ppm. The Occupational Safety and Health Administration has not issued a workplace exposure standard for phosgene, but the Agency has put into effect a special emphasis program that includes phosgene facilities.[7]

Because of its irritating effects on the respiratory tract at levels slightly above 0.1 ppm, a time-weighted average Threshold Limit Value (TLV) of 0.1 ppm is recommended by American Conference of Governmental, Industrial Hygienists (ACGIH). These levels have been shown to include tolerance.[8] Personnel in industry are trained to recognize the odour of phosgene (odour detection limit is considered to be 0.5 ppm) and to report any such odour immediately. The U.S. National Academy of Sciences lists a 90-day atmospheric limit for use in Submarines of 0.05 ppm and a

Douglas Aircraft continuous atmospheric limit of 0.04 ppm.[9] Most other countries, including the USSR and the Council for Europe, have adopted 0.1 ppm or its mg/m^3 equivalent Belgium, Holland, Romania, Sweden, and Switzerland have opted to adhere to a 0.05 ppm limit.[9]

Exposure to phosgene may result not only from its use in the chemical industry, but also as a result of the decomposition in air of chlorinated organics. Hydrogen chloride is usually the principal decomposition product from such compounds, although a static system of PVC heated to high temperatures produced 0.2 to 1.6 milligrams of phosgene per gram of PVC.[6] Phosgene may be the chief product of photodecomposition. Vapours of degreasing chlorocarbons in air near heliarc welding of aluminum may be largely converted to phosgene (1 to 3 ppm levels have been detected). While the rate of formation of phosgene often is not known, mathematical modeling has suggested that, for example, in PVC combustion, phosgene formation in considerable amounts but at slow rates can occur at temperatures of about 600°C. However, if the gases came in contact with metallic chlorides which are formed from copper, iron and elemental carbon in the form of soot or carbonized materials, the rates of formation of phosgene would be greatly enhanced via a catalytic action. Similarly, under conditions of combustion, dangerous levels of phosgene can be reached within a fraction of a minute.[10]

Since extensive precautions are taken by those who use phosgene, most incidences of high exposure occur as a result of leaks and spills. One large plant manufacturing MIC reported a total of 107 in-plant losses of phosgene during a recent five-year period.[11]

6. TOXICOLOGY

The toxicity of phosgene in animals and dose response relationships have been reviewed in detail elsewhere. Observations clearly indicate that the sensitivity to phosgene toxicity varies with the species and increases where comparisons have made in the following order: < goat, < rat, < mouse, < man, < cat, < monkey.[12]

(i) Animal Exposures

Most studies on phosgene toxicity have been carried out on rats.[12,13]

(a) Acute Exposures

Alveolar pulmonary edema was observed[13] in rats 48 hours after exposure to 5 ppm for 10 minutes. The lowest dose rate to produce a widening of pulmonary interstices was 25 ppm per minute.

Concentrations as low as 0.5 ppm for 2 hours caused definite pathological changes in the lungs of rats sacrificed 96 hours after exposure. Some abnormalities were still present 3 months after a 2 ppm esposure for 80 minutes [12]

From a wide variety of studies[12] it became clear that differences in airway structures have to be taken into account when extrapolating from animals to man. For example, absorption occurs mainly in the nasal passages of rabbits and

comparatively little reaches the lung as a result of the complicated structure of the rabbit's nasal airway. In man where the nasal structure is less complex phosgene can reach and damage the deeper regions of the lung.[14]

Several studies have demonstrated[13] that phosgene inhaled at low concentrations by test animals results in a decreased susceptibility to subsequent and otherwise acute, edema-producing doses. Phosgene at 1 ppm for 6 hours not only induced tolerance against the acute effects of a subsequent exposure, but also protected the host against other edema-producing agents such as ozone.[15] This development of tolerance, however, is thought to be the triggering mechanism of irreversible lung changes when there is daily exposure to low levels that produce no obvious acute response.

(b) Chronic Exposures

Phosgene has not been adequately studied with respect to chronic toxicity, including carcinogenicity and mutagenicity. Probably this lack of satisfactory data reflects the difficulties attendant to conducting valid tests with a highly reactive, acutely toxic compound which produces corrosive *HCl* on contact with water. Phosgene may not be systemically absorbed, but rather is thought to react with tissues at the site of contact. Prolonged exposures in the workplace to phosgene will probably not occur above levels of 3 to 4 ppm since immediate eye and respiratory irritation can result at this level.

Cameron and associates[16] reported that exposure at 0.2 ppm, for 5 hours/day, for 5 consecutive days caused pulmonary edema and histopathological abnormalities in 41 per cent of the exposed animals (goats, cats, rabbits, guineapigs, rats, mice). ACGIH cited these data as a major consideration in recommending a TLV of 0.1 ppm. Repeated exposures of cats to 5 to 6 ppm for 10 minutes every day caused no greater lung damage after 40 days than after 2 days.[1]

(ii) Human Exposures

The poisonous effects of phosgene in man were first seen during World War I when thousands of soldiers were exposed to the gas.[17] Follow-up examinations of these soldiers were not informative since it was impossible to identify unequivocally the noxious gas to which the individual was exposed; in many cases gas mixtures such as chlorine plus phosgene and subsequently nitrogen mustards were involved.

At present, toxic phosgene exposure involves isolated accidents where workers in the process of manufacturing and use of phosgene are exposed to the gas. Occupational or bystander exposure to phosgene occurs primarily via inhalation.

It is generally accepted that phosgene may cause chronic lung disease in man though no quantitative data are available on the dosage which may produce permanent pulmonary damage.[18]

6.1 Vagal Reflexes

In most cases phosgene poisoning may involve the inhalation of doses below 3 ppm.[19] Mild symptoms of irritation occur such as tickle in the throat, irritant cough

and retrosternal pressure pain; patients also complain of weakness at the knees and watering eyes. These symptoms abate rapidly, however, within 24 hours and the patient is then relatively free from symptoms throughout the clinical latent phase.[19]

Phosgene inhaled in concentrations of 3 ppm can trigger a vagal reflex within the bronchial tree.[20,21] Respiration becomes frequent and shallow; arterial oxygen is decreased. The partial pressure of arterial carbon dioxide ($PaCO_2$) shows a tendency to increase and blood pH decreases. Bradycardia and occasionally sinus arrhythmia occur and the systemic blood pressure tends to drop.[22-24]

6.2 Pathology of Phosgene Poisoning

Toxic injury to the lung from phosgene poisoning results in increased water permeability of the lung capillaries to the endothelium and edema.[19,25] Initial increase in water efflux capillary to interstitium are mostly compensated by increased lymphatic clearance. When the lung's ability to clear excess fluid is exceeded, fluid volume in the lung interstitium rises and water leaks through the alveolar epithelium into the alveolar spaces.[18] When a sufficiently large amount of fluid has collected in the lung, edema becomes apparent both directly and indirectly. Gas exchange becomes insufficient, and the fluid gradually rises from the alveoli into the proximal segments of the respiratory tract. Due to increasing defects within the blood-air barrier, the edema fluid becomes richer in protein content. The mucous membrane of the bronchi becomes necrotic and is shed, further impeding respiration. Leucocytes migrate into the bronchiole walls and into the alveolar interstices.[18]

The pulmonary toxic effects begin immediately upon inhalation of phosgene.[18,19,26,27] A report on cardiopulmonary pathophysiology[20] suggests that the terminal airways, alveolar lining layer and alveolar epithelial layer are affected first. Initial damage at these anatomical sites is supported by the findings of histopathological abnormalities at the air-blood barrier[20,28] and in the terminal airways.[29] Pulmonary edema is considered a late pathologic effect of phosgene exposure except at very high and low doses. High exposure levels can result in death before pulmonary edema develops[20] and low exposure produces localized acute inflammation of the lung.[15]

A very high doses (200 ppm) in acute poisoning phosgene passes through the blood-air barrier, reaches the lung capillaries and reacts with blood constituents. Hemolysis in the pulmonary capillaries occurs with hematin formation. Congestion by erythrocyte fragments, and stoppage of capillary circulation is observed. Death occurs within a few minutes from acute overdistension of the right heart, often before pulmonary edema can develop.[30] A summary of the symptoms observed at various dose levels of phosgene poisoning is shown in Table 3.

7. THERAPEUTIC APPROACHES IN PHOSGENE POISONING

Each instance of phosgene poisoning must be considered as a highly individualized situation. The therapy must be adjusted to the particular clinical situation.

Table 3. Effects of inhaled phosgene

Effect	Concentration of Phosgene	
Perception of odour	0.4	ppm
Recognition of odour	1.5	ppm
Signs of irritation in eyes, nose, throat and bronchi	3	ppm
Beginning lung damage	30	ppm-min
Clinical pulmonary edema	150	ppm-min
LCT_{50}	500	ppm-min
LCT_{10}	1300	ppm-min

7.1 Positive Ventilation With Oxygen

There are clinical reports which show the beneficial effects of positive pressure ventilation with oxygen during phosgene exposure.[30-32] The action is assumed to be due to the elevated alveolar pressure whivh counteracts the filtration pressure of the lung capillaries, reopens collapsed alveoli, reduces shunt volume, enlarges functional residual capacity and improves oxygenation of the blood. The disadvantages of positive pressure ventilation with oxygen are a reduction of cardiac output, an increase in lung water due to impeded drainage, an overdistension of normal alveoli and a potential of damaged alveolar walls which can result in pneumothorax.[33]

7.2 Glucocorticoids

Clinical reports on the effect on glucocorticoids are promising[34,35] though controlled (blind) studies are lacking. While a few clinicians suggest the inhalation of glucocorticoid-aerosol, the majority favors combined inhalation and systemic administration, due to the uncreatainty weather the inhaled glucocorticoids reach the affected alveoli in adequate amounts. The general recommendation is to administer glucocorticoids as early as possible after the phosgene inhalation

The beneficial effects of glucocorticoids in phosgene induced edema may be due to the increase of macrocortin synthesis (leading to inhibition of phospholipase A_2 activity and to inhibition of prostaglandin E_2 release); stabilization of lysosomes; inhibition of plasminogen-activation; inhibition of tissue-macrophages; enhancement of prostaglandin E_1 activity; and positive inotropic effect of myocardium.[34,35]

7.3 Sedatives and Analgesics

These agents have been recommended for all forms of pulmonary edema. They lower basal metabolism and thereby oxygen demand; on the other hand some like morphine depress the respiratory center.[36,37]

7.4 X–ray

Chest X-ray radiograms facilitate the early diagnosis of beginning pulmonary edema.[38]Since the speed of development of toxic pulmonary edema is inversely proportional to the inhaled phosgene dose, such X-ray photographs must be taken about 2 hours after the inhalation of very high doses of phosgene. A radiogram taken 8 hours later will suffice if exposure to low concentrations has occured. Strategy of therapy is related to dose. Exposure doses below 25 ppm/mın can be regarded as harmless.[30]

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