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CHEMICAL AGENTS
Phosgene – Chemical Weapon and Industrial Chemical[1]

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PHOSGENE IS USED IN industry widely and has potential use as a chemical weapon. In this paper, its chemistry, uses and effects will be reviewed.

CHEMISTRY

Phosgene ($COCl_2$) was first synthesised by Davy in 1812 from carbon monoxide, chlorine and activated charcoal in the presence of sunlight. At room temperature and normal atmospheric pressure, phosgene is a colourless, non-flammable, highly toxic gas with an odour like musty hay in low concentrations[1]. In high concentrations, it is pungent and irritating. As a gas it is heavier than air and only slightly soluble in water. Phosgene is readily liquefied to a light-yellow liquid and may be shipped in steel cylinders[2].

Phosgene's recommended Threshold Limit Value (TLV) is 0.1 ppm (0.4 $mg.m^3$).
Diller[3] notes the following concentration-effect relationships in reference to 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 of lung damage > 30ppm clinical pulmonary oedema > 150 ppm Phosgene's molecular pathology was initially thought to exclusively be the result of the action of HCI, produced by the aqueous hydrolysis of the inhaled gas.

COCL2 + H20 C02 + 2HCI
Diller[3] notes, however, that this theory has been abandoned for a number of reasons:

a. Phosgene is about 800 times more toxic than equivalent amounts of HCI. The small amounts of HCI produced are easily buffered by the lung tissue.
b. Phosgene inhibits Co-enzyme 1 while an equivalent amount of HCI does not.
c. Hexamethylenetetramine, free a mines and thromboplastin protect against phosgene, but not against HCI poisoning.
d. Ketene, which resembles phosgene in toxicity and chemical constitution, contains no chlorine atoms and thus cannot release HCI.

It is likely that some of the effects are due to the acylation reactions of phosgene with -NH2, -OH and -SH groups.

INDUSTRIAL USES

Phosgene was initially used by the Germans as a chemical warfare agent in 1915. Phosgene is used today in the manufacture of dyestuffs based on triphenylmethane, coal tar and urea; in the organic synthesis of isocyanates, carbonic add esters and acid chlorides; and in metallurgy and in the manufacture of some pesticides and pharmaceuticals[5]. Phosgene may also be liberated when halogenated hydrocarbons are heated. An example of this process is welding in an area where

degreasing agents like trichloroethylene or carbon tetrachloride are being used[6]. It may also be seen in firefighting where portable fire extinguishers containing carbon tetrachloride are used on hot surfaces, producing phosgene gas.

RESPIRATORY EFFECTS

Pathophysiology

Phosgene poisoning can be divided into several distinct phases[3]

Initial Reflex Syndrome. Phosgene inhaled in concentrations greater than 3 ppm often triggers a bioprotective vagal reflex by interaction with sensory receptors in the bronchial tree. This leads to frequent shallow respirations, decreased respiratory volume, decreased vital capacity and a drop in arterial oxygen partial pressure. Arterial carbon dioxide partial pressure may rise with a drop in pH. Also, a bradycardia and a fall in systemic blood pressure may occur.

The intensity of these reflexes varies greatly between individuals, and Coman et al[3] notes that the response is not strictly in proportion to the inhaled dose of phosgene.

Phosgene inhaled in concentrations greater than 3 ppm seems to undergo partial hydrolysis within the aqueous film covering the mucus membranes of eyes, nose, throat and bronchi. The small amounts of HCl produced interact with the sensory receptors, precipitating signs and symptoms of eye and upper airways irritation. There may be an overlap with the vagal reflex[3].

Phosgene concentrations greater than 200 ppm produce apnoea of short duration, bronchoconstriction[4], bronchial epithelial desquamation and inflammatory bronchiolar changes[3].

Clinical latent Phase. The inhaled phosgene reacts with extracellular substances and all constituents within the respiratory tract. Presently there is no consensus as to the exact localisation of the action of phosgene. Gross et al, Coma n et al and Pawlowski and Frosolono[3] reported that histological changes first occurred in the respiratory bronchioles while Diller *et al*, Short, and Cameron and Courtice[3] noted that the first histological changes were more distal at the blood-air barrier, where swelling of alveolar cells and later rupture of endothelial cells were seen. Gross et al[3] suggests that the apparent disparity derives from different phosgene dose - small doses producing changes in the respiratory bronchioles while larger doses produced changes in the alveolar region.

The alveoli and interstices slowly fill with blood plasma. Depending on the dose, the alveolar oedema may occur within a few minutes, commencing in the region of the large bronchi. There is a substantial increase in lymph drainage from the lungs. Haematocrit initially falls and then later rises. The arterial oxygen pressure tends to remain normal until the end of this phase and any ventilation-perfusion mismatch is well compensated for until a protracted right-left shunt occurs at the end of this phase.

Many enzyme systems are inhibited by phosgene, although glycolysis in the lung appears only to be slightly disturbed. Histamine is liberated but with little symptomatic effect.

Also, some enzymes are released by anoxaemia and cellular decay, e.g. LDH. The lining of the lungs becomes stiffer, and compliance decreases[3].

Clinical Oedema Phase. The oedema fluid gradually rises from the alveoli into the proximal regions of the respiratory tract, and gas exchange becomes insufficient[3]. The protein content in the fluid rises due to increasing defects in the blood-air barrier, and the increased respiratory movements agitate this fluid into a froth. The mucus membranes of the bronchi become necrotic and are shed, leading to further restriction of respiration. Boyd and Perry[3] note that the pulmonary artery pressure remains normal up to the terminal phase. At this point the heart rate is increasing, peripheral arterial pressure falling and venous pressure increasing. Cause of death is usually paralysis of the respiratory centre due to anoxaemia, cessation of a cardiac function being a secondary role. Patt et al[3] note, however, that, if anoxaemia is treated effectively, circulatory shock may become an important factor.

Hyperacute Poisoning. At very high doses (greater than 200 ppm) phosgene pass directly with the blood constituents. The resultant haemolysis produces haematin formation, congestion by erythrocyte fragments and cessation of capillary circulation. Death occurs within a few minutes from acute corpulmonale often before pulmonary oedema can result'.

Sims and Symptoms

Clinical symptoms depend on the dose inhaled and to some extent on the phosgene concentration in the atmosphere. The rare extremely high doses of inhaled are usually followed rapidly by death from acute corpulmonale. Most frequently small to medium doses are inhaled and at> 3 ppm, the HCI in solution produces mild symptoms of irritation[3].

The symptoms include catching of the breath, choking, tightness of the chest, lacrimation, difficulty and pain in breathing and subjective weakness of the legs[3]. These complaints usually disappear rapidly, and the symptoms produced by even a fatal dose may be relatively mild. There is a following latent phase, the duration of which is inversely proportional to the dose inhaled. After relatively large doses it maybe 1 to 4 hours and after small doses, 8 to 24 hours[3].

Bruner and Coma[3] note that a gradual collection of oedema fluid may be seen on chest x-ray even during the latent phase. The clinical oedema phase is marked by crepitations across the lower lobes and lengthening of respiration. The symptoms are dizziness, chills, discomfort, thirst, increasingly tormenting cough and viscous sputum. Sputum may then become thin and foamy, dyspnoea, a feeling of suffocation, tracheal rhonchi and grey-blue cyanosis may follow[5]. Blood pressure falls, heart rate increases and the terminal phase is one of extreme distress where the intolerable dyspnoea finally passes into a respiratory standstill[3].

Late Sequelae

If the patient survives the poisoning, clinical and radiographic oedema usually regresses within a few days, and blood gases and CO diffusion capacity return to normal within a week[3]. In the absence of adequate antibiotic prophylaxis, secondary pneumonia may develop. Exertional dyspnoea and increased bronchial resistance may persist for several months[7]. After an acute episode, Diller notes that complete recovery may require up to several years in healthy patients while those with pre-damaged lungs (e.g. cigarette smokers) may experience continued deterioration or their lung functions with increased emphysema and chronic bronchitis. Waldron[7] notes that repeated acute episodes can lead to chronic lung disease.

With regard to chronic exposure, Diller[8] notes some of the Russian literature that reports that chronic exposure to phosgene at 0.1 ppm (and occasionally over this) does not produce detrimental health effects in humans. However, Sittig' suggests that chronic exposure to phosgene, although

providing some tolerance to acute doses, may cause irreversible pulmonary changes of emphysema and fibrosis. Sittig did not specify at what level this chronic exposure might be.

CONCLUSION

Phosgene, which can be a workplace contaminant in a number of industries, poses a major respiratory hazard because of its highly irritating, oedemogenic and potentially lethal effects. As there is a suggestion that even at low levels it may have some chronic effects on the lung, a concerted effort should be taken to maintain concentrations below the TLV of 0.1 ppm.

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