PHOSGENE

Information on Options for First Aid and Medical Treatment

Last Revised January 2020
Check http://www.americanchemistry.com/phosgenepanel for Potential Updates

Contents

1.0 INTRODUCTION AND LEGAL DISCLAIMER

This document is presented by the American Chemistry Council's Phosgene Panel to assist persons already sophisticated and experienced in first aid and medical treatment of phosgene exposure. In January 2013, the International Isocyanate Institute (III) issued an updated document on phosgene exposure evaluation and treatment, "Phosgene: information on options for first aid and medical treatment." ACC has been given permission by III to use their document as the basis for the information presented in this ACC document. This document was updated January 2020 and replaces the last version dated January 2019.

The document is intended to assist such readers in their understanding of various options related to first aid and treatment. It is intended that the document will facilitate in-depth dialog and analysis concerning the issues presented. Readers are encouraged to consider information presented in the document as they evaluate and develop their own programs and procedures. The development of protocols to address phosgene exposure can assist companies and health care providers in their provision of timely and helpful first aid and medical treatments. Although this document may be used to facilitate the development of such protocols, the material herein is very clearly not proposed, and is not to be interpreted, as a specific standard or protocol. This document is not intended to be a substitute for in-depth training or specific requirements, nor is it intended to define or create legal rights or other obligations. The document is not intended as a "how-to" manual, nor is it a prescriptive guide. Because this document is necessarily general in nature, each reader has an independent obligation to evaluate whether information and options contained in it are appropriate based on the particular factual circumstances of the individual.

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2.0 QUICK REFERENCE GUIDE AND DECISION TREE

The following guide is included to expedite preparations necessary to efficiently evaluate and treat individuals exposed to phosgene, according to initial presentation and suspected severity of exposure. Additional detail is provided in subsequent sections of this document.

Emergency Response	
Decontamination	For patients whose clothing or skin is contaminated with liquid phosgene or solvent solutions containing phosgene: Exposed skin and hair should be washed copiously with plain – preferably lukewarm - water for at least 15 minutes, unless the patient is showing signs or symptoms of respiratory distress. Clothing suspected to be contaminated should be completely removed as soon as possible and double-bag the clothing for proper disposal. Patients transiently exposed only to phosgene gas should not pose a significant risk of secondary contamination and thus generally do not need decontamination. However, it is still advised to substantiate that a person does not need decontamination before transport.
Rest	Physical rest is regarded as an important measure to reduce the risk of development of pulmonary edema from phosgene inhalation of 150 ppm-min or greater.
Oxygen	Oxygen should not be routinely given after a phosgene inhalation even if irritant effects are present unless there are signs of hypoxemia or respiratory distress.

Medical Evaluation & Monitoring

All patients with the following should be evaluated by a physician & monitored for at least 8 hours:

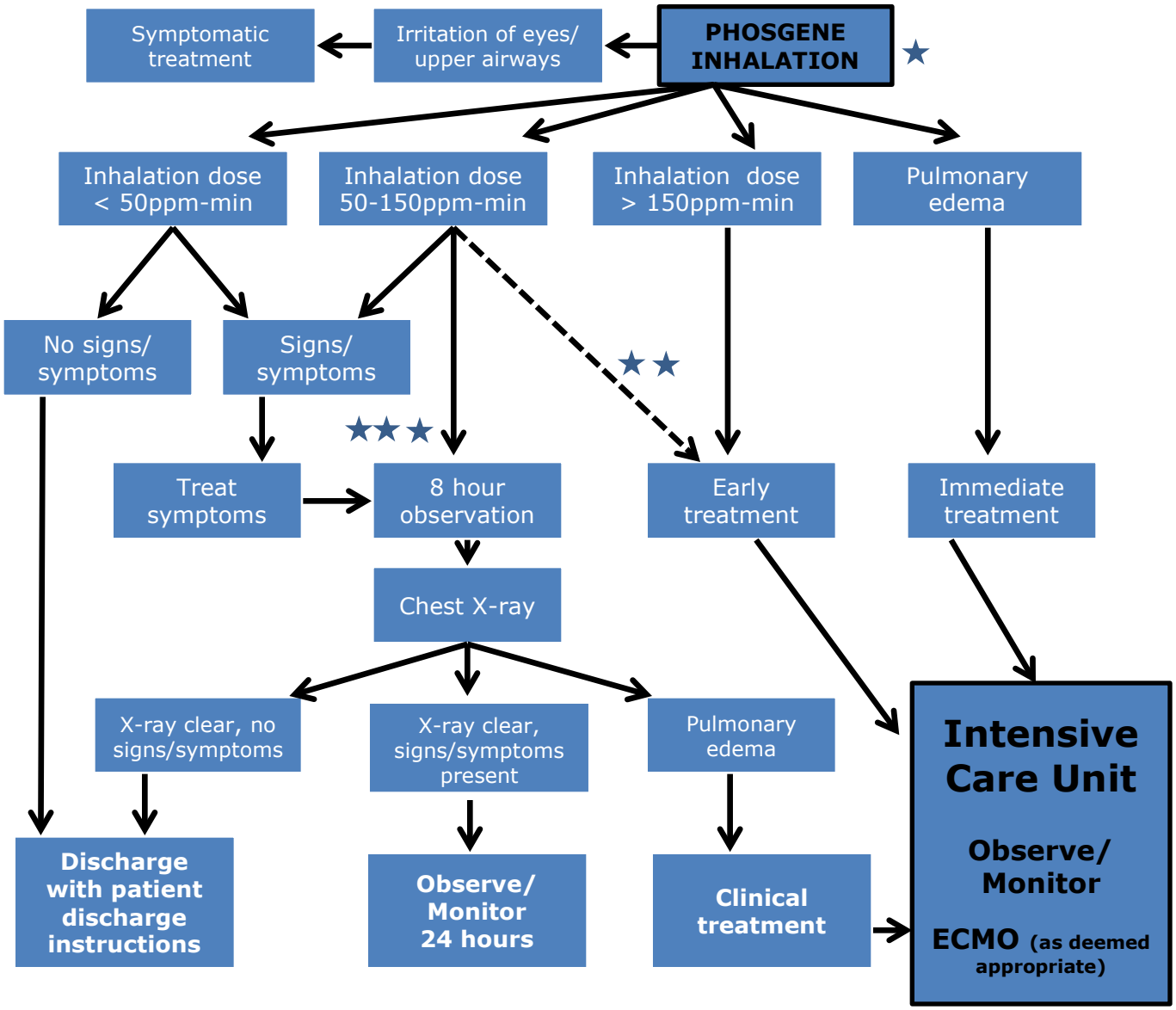
- Exposures of 50 ppm-min or above.
- Unknown exposures.
- Exposures consisting of liquid phosgene, or phosgene in solvent, to the facial area.
- Significant, especially respiratory, symptoms.

Treatment

Irritant Effects	• Eye exposure to liquids containing phosgene requires thorough rinsing (decontamination). Check for corneal abrasion/burn if irritation continues. Refer to ophthalmologist if ocular signs and symptoms continue. Persistent irritation of the eyes due to gaseous phosgene exposure may benefit from lubricant eye drops. • Cough may require throat lozenges or a non-narcotic anti-tussive. • Wheezing/bronchospasm will require aerosolized bronchodilator therapy as per standard treatment for asthma. • Oxygen (humidified if possible) should be added to inspired air (by mask or nasal catheter) for dyspnea, wheezing, or pulse oximetry indicates SpO_2 <92%. Pure (100%) oxygen should be avoided.
Subjective Effects	• Anxiety can be a normal reaction to the often dramatic circumstances of a phosgene accident. A calming, informative talk with medical personnel may help. In patients who manifest moderate to severe anxiety a light sedative may be considered.
Early "prophylactic" treatment of pulmonary effects	Phosgene exposures estimated as 150ppm-min and above, unknown exposure, or liquids with phosgene to the facial area; and if any signs of respiratory distress or pulse oximetry less than 92%: **Use of positive pressure ventilation (such as Continuous Positive Airway Pressure (CPAP) within the first hour post exposure**

	Steroids: Intravenous: 1000 mg methylprednisolone; or/and Aerosolized: Maximal dosage according to the specific corticosteroid used and if available; Note: If intravenous and/or aerosolized corticosteroids are not available, oral or intramuscular application may be considered Note: Above may be considered for exposures <150 ppm-min based on the discretion of the treating physician and the circumstances of the exposure.
Pulmonary Edema	Treat per recommendations of specialist in the area of ARDS treatment (such as intensivist, pulmonologists, etc.) Intensive Care Unit (ICU) care Adult Extracorporeal Membrane Oxygenation (ECMO), early in cases of significant exposure with resulting pulmonary edema, especially if such person is not responding to conventional treatment. Note: The decision of whether or not, and when to use ECMO in cases of phosgene induced pulmonary edema should be made by experts with ECMO experience, such as a pulmonologist or intensivist.

Decision Tree
Summary of Recommended Approaches Based on Estimated Phosgene Dose



★ If information (such as a badge) to estimate the actual exposure is not available or not clear, or if there is liquid phosgene or phosgene in solvent exposure to the facial area, then it would be prudent to assume that an exposure of 150 ppm-min or greater occurred.

★★ The dotted line indicated that treatment at levels as low as 50ppm-min may be considered.
Note: the exposure level at which treatment is warranted is undetermined.

★★★ For inhalation doses <50 ppm-min only significant, especially respiratory symptoms, need to be observed for 8 hours, and not minor irritant or subjective symptoms.

3.0 SUBSTANCE INFORMATION

Phosgene ($COCl_2$), CAS 75-44-5
Synonyms: carbonic acid dichloride, carbonic dichloride, carbon oxychloride, carbonyl chloride, chloroformyl chloride

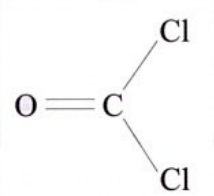


Figure 1. Chemical Structure of Phosgene

Phosgene has a boiling point of 7.56°C (45.6°F) and at room temperature and pressure is a colourless, non-flammable gas. Below its boiling point phosgene is a colourless liquid (ACC, 2006). Phosgene gas is heavier than air and may travel along the ground (CDC, 2005). Phosgene reacts slowly with water (including humidity in air and on mucous membranes) to form hydrochloric acid and carbon dioxide (IPCS, 2002).

Phosgene is used as an intermediate in the manufacture of many chemicals including isocyanates, polycarbonates, dyes, crop protection products and pharmaceuticals. It is often used as a solution in organic solvents. At low concentrations, its odor is similar to that of green corn or newly mown hay; at high concentrations, its odor can be sharp and suffocating. There may be perceived odors at the lower threshold value but recognition of the odor as phosgene is usually at a higher value. (See Table 1)

4.0 MECHANISM OF PHOSGENE INJURY

After human inhalation exposure to phosgene, several different reactions have been postulated. The two most often noted include:

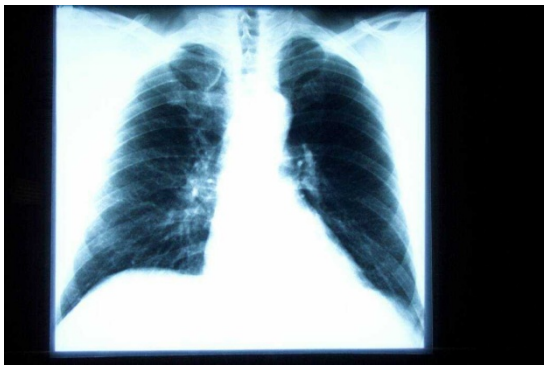
a) Slow and limited hydrolysis with the formation of HCl. This may, in cases of higher concentration exposures, cause irritation of the eyes, nose and throat, with burning sensation, cough and chest oppression. Signs and symptoms will appear soon after the inhalation will vary according to the inhaled phosgene concentration and will usually dissipate within a few hours. This mechanism is less likely to play a causal role in development of pulmonary edema (Borak and Diller, 2001; Pauluhn et al., 2007).

   Direct acylating reactions of phosgene with nucleophilic structures of cells and their products which will deplete nucleophiles such as glutathione, increase lipid peroxidation and cause metabolic disruption. These reactions may result in damage of the terminal bronchioli and alveoli, impairment of the surfactant film, increase in the production of arachidonic acid and leukotrienes and depletion of cyclic adenosine monophosphate (cAMP). The above mechanisms activate an inflammatory cascade resulting in the formation of reactive oxygen species adversely impacting alveolar and capillary integrity resulting in a compromised blood air-barrier. Fluid will be extravasated into the interstitial space between capillary and alveoli. This increases the distance to be crossed by oxygen to reach the blood, and thus results in hypoxemia. In the further course of the edema formation, flooding of the alveoli will occur (non-cardiogenic "pulmonary edema").

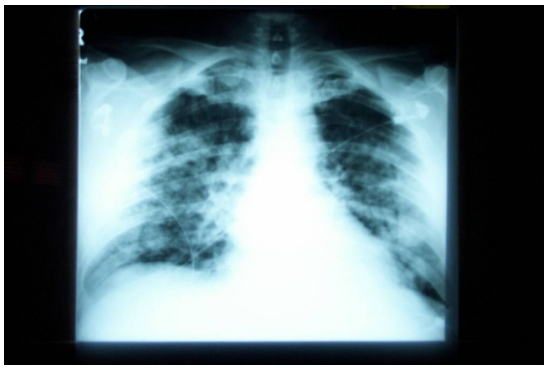
   Although the process described above starts immediately with exposure, the actual onset of the pulmonary edema, if it occurs, is delayed – "clinical latency period". The length of this "clinical latency period" is inversely related to the inhaled phosgene dose: the higher the inhaled dose, the shorter the latency period.

Picture 1: Sequential radiographs demonstrating development and resolution of pulmonary edema after a severe phosgene exposure (Steffens, 1991).

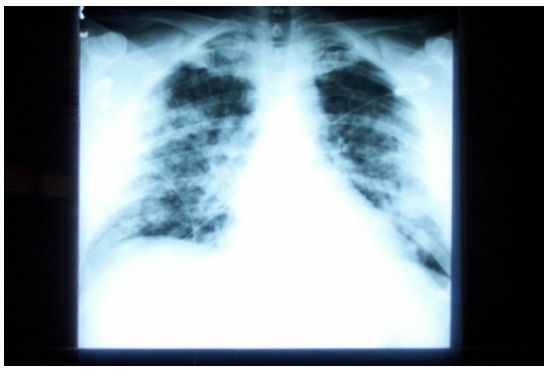
The case involved an unknown exposure dose. Initial treatment included early administration of high dose aerosolized corticosteroids, high dose intravenous corticosteroid and hospital admission after 4 hours. Hospital treatment was continued with high dose aerosolized and intravenous corticosteroids, but no mechanical ventilation.



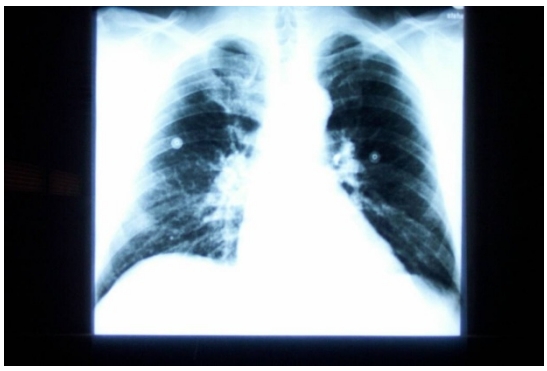
4 hours



24 hours



40 hours



108 hours

4 hours:	Slightly blurred hili, clinically some wheezing.
24 hours:	Full blown pulmonary edema with opacities all over the lungs.
40 hours:	Further deterioration of pulmonary edema.
108 hours:	Pulmonary edema resolved, patient survived.

5.0 ROUTES OF EXPOSURE

There are three possible routes of exposure to phosgene:

Inhalation
Inhalation is the most common route of phosgene exposure. Inhalation exposures may result in irritant and pulmonary effects (Section 6.0).

Contamination with phosgene in solvent solution may lead to significant off-gassing and continuous (inhalation) exposure of the victim or secondary exposure of others.

Phosgene is heavier than air and may cause asphyxiation in poorly ventilated, low-lying or enclosed spaces.

Skin/Eye Contact
When phosgene gas contacts moist or wet skin or eyes, it may cause irritation and reddening. Liquid phosgene may cause severe burns.

Contamination (for example of clothing) with phosgene in solvent solution may lead to significant off-gassing and continuous (inhalation) exposure of the victim or secondary exposure of others.

Ingestion
Ingestion of phosgene is unlikely because it is a gas at room temperature. No information is available about the sequelae of swallowing phosgene-containing solvents.

6.0 EXPOSURE-EFFECT RELATIONSHIPS

As a consequence of the different underlying mechanisms of phosgene injury caused by inhalation exposure, the health effects depend both on the phosgene concentration and the inhaled dose. Other factors including the susceptibility of the exposed person may also affect the response. Additionally, it should be noted that since it is very difficult to accurately estimate the actual inhalation exposure dose (see section 7.0) there cannot be absolute certainty in predicting exposure-effects in humans. The summary of exposure-effects in Table 1 is based on experience and is for guidance purposes - the attending physician should assess each case individually.

The unit for phosgene concentration in air is "part per million", abbreviated "ppm". The inhalation exposure dose is the product of exposure concentration (in ppm) and exposure time (in minutes), thus the unit of ppm-min.

Table 1: Summary of exposure-effects for phosgene

Phosgene Concentration	**Effect**
> 0.125 ppm	Odor perception
> 1.5 ppm	Recognition of odor
> 3.0 ppm	Irritation of eyes, nose, throat, bronchi
Inhalation Exposure dose of Phosgene*	**Pulmonary Effect**
< 50 ppm-min	No clinical pulmonary effect
50 – 150 ppm-min	Subclinical pulmonary reactions. Edema unlikely
150 ppm-min or above	Pulmonary edema probable
300 ppm-min or above	Life-threatening pulmonary edema expected
Note: for unknown exposures: assume exposure of 150 ppm-min or greater *Represents dose effect relationships based on average responses and accurate assessment of dose, not badge readings only.	

The clinical presentation from a phosgene exposure may vary significantly, dependent on many factors including the phosgene concentration, duration of exposure and underlying medical condition of the person exposed. Presentations can be generalized into three categories: subjective, irritant and pulmonary effects.

Subjective effects: May include such symptoms as headache, nausea and anxiety. These symptoms are believed to be due to the person experiencing the event and not a direct effect of the chemical.

Irritant effects: May include such symptoms as irritation of the mucous membranes (eyes, nose, mouth & throat), tearing of eyes, coughing and even shortness of breath and wheezing (especially in an individual with previous respiratory issues). These effects are generally present immediately after the exposure and are related to the concentration of the gas, and can resolve relatively quickly and not be life-threatening.

- Pulmonary effects: May include symptoms consistent with pulmonary edema. These symptoms are latent (delayed), starting hours after the exposure and are related primarily to the exposure dose. The length of the "latency period" (delayed response) can provide some insight as a prognostic indicator, because typically the shorter the latency period, the worse the prognosis is likely to be.

There is no specific diagnostic test to predict the development of pulmonary edema, which is a continuous process initiated by the actual inhalation.

The following theoretical scenarios are presented to illustrate possible clinical variations based on concentration and exposure:

- after the inhalation of 2 ppm (odor recognition) for 1 minute - a dose of 2 ppm-min: no signs or symptoms.
- after an inhalation of 5 ppm (odor recognition and irritation effects) for 3 minutes - a dose of 15 ppm-min: odor recognition and early eye and upper airways irritation.
- after an inhalation of 2 ppm (odor recognition) for 80 min - a dose of 160 ppm-min: odor recognition, no upper airways irritation, but delayed pulmonary edema.
- after an inhalation of 5 ppm (odor recognition and irritations effects) for 50 min - a dose of 250 ppm-min: odor recognition, significant upper airway irritation and pulmonary edema.
- after an inhalation of 1 ppm (odor perception) for 600 min - a dose of 600 ppm-min: no odor recognition, no upper airways irritation, but pulmonary edema and death.
- after an inhalation of 20 ppm (odor recognition and irritation effects) for 40 min - a dose of 800 ppm-min: odor recognition, severe upper airways irritation; pulmonary edema and death.

Possible scenario	Exposure ppm-min	Odor perception	Odor recognition	Irritant effects	Pulmonary edema	Death
2 ppm for 1 minute	2	X	X			
5ppm for 3 minutes	15	X	X	X		
2ppm for 80 minutes	160	X	X		X	
5ppm for 50 minutes	250	X	X	X	X	
1 ppm for 600 minutes	600	X			X	X
20 ppm for 40 minutes	800	X	X	X	X	X

X = EXPECTED

The above scenarios are consistent with the following:

- Odor recognition is an unreliable warning mechanism.
- Odor recognition, upper airways irritation, pulmonary edema and death may be independent from each other.
- Upper airways irritation does not necessarily precede pulmonary edema or death.
- Observed signs and symptoms of pulmonary edema will usually be delayed by at least several hours.
- Symptoms such as headache, nausea and anxiety can occur after any perceived exposure but may not be directly related to phosgene (either concentration or exposure dose).

A published article *"Results from the US Industry-Wide Phosgene Surveillance: The Diller Registry" (Collins et al., 2011)* found no relationship between phosgene exposure and the presence of symptoms 30 days after exposure, thus lending credence to the theory that prolonged respiratory effects do not occur after phosgene exposures less than 150 ppm-mins. Reports of long term effects from phosgene exposure generally are based on mixed chemical exposures.

7.0 ESTIMATION OF INHALED DOSE

Phosgene concentration (expressed either in parts per billion – ppb, or in parts per million - ppm) in the atmosphere can be detected by sensitive phosgene gas monitors. Phosgene badges can detect a possible exposure dose (ppm-min). The phosgene badge turns color depending on dose and is read by using a color comparator. It is recommended that the badge be worn near the breathing zone to best approximate to the actual exposure. The color of the badges, in many cases, may likely be the only information on which to estimate actual exposure. Badge dose readings are commonly used to estimate the exposure dose but may not necessarily be reflective of the actual inhalation exposure. Factors affecting the estimated exposure include use of personal protective equipment (PPE), breath holding and the relationship of badge to mouth/nose and the exposure source. Further, badge readings may vary depending on the manufacturer, the comparator used, the person's ability to read the badge, certain environmental conditions such as humidity, as well as the presence of other gases, e.g. hydrogen chloride or chloroformates (cross-sensitivities). Thus it should be noted, in recognition of the influences discussed above, an exposure estimate based on a badge reading should be balanced with additional information especially as it relates to treatment considerations.

While estimating an exact exposure dose using a phosgene detection badge can be imprecise, it does provide extremely useful information not otherwise available. Additionally, since exposure - effects are known (section 7) and medical evaluation and treatment is based on exposure dose estimations (section 2), the use of phosgene detection badges when working in situations where a phosgene exposure is possible is highly recommended by medical professionals with experience in caring for patients exposed to phosgene.

If information (such as a badge) to estimate the actual exposure is not available or not clear, or if there is liquid phosgene or phosgene in solvent exposure to the facial area, then it would be prudent to assume that an exposure of 150 ppm-min or greater occurred.

8.0 EMERGENCY RESPONSE

Patients, whose clothing or skin is contaminated with liquid phosgene, or solvent containing phosgene, can continue inhaling and/or secondarily contaminate other people by direct contact or through off-gassing phosgene. Thus, such patients need decontamination to stop further exposure to themselves or exposure to others. Patients transiently exposed only to phosgene gas should not pose a significant risk of secondary contamination and thus generally do not need decontamination. However, if there is suspicion that gaseous phosgene may have saturated the clothing, then decontamination as above should be done. To reduce the risk of secondary contamination, the absence of off-gassing can be verified prior to transport using a fresh phosgene badge or detector tape. For patients with an estimated exposure of 150 ppm-min or greater it is important to minimize physical stress.

8.1 Decontamination

Clothing suspected to be contaminated with liquid or gaseous phosgene, or solvents containing phosgene should be completely removed as soon as possible and double-bagged for proper disposal.

For patients whose skin is contaminated with liquid or gaseous phosgene or solvents containing phosgene, exposed skin and hair should be washed copiously with plain – preferably lukewarm - water for at least 15 minutes, unless the patient is showing signs or symptoms of respiratory distress. The eyes should be protected during flushing of skin and hair.

Eye exposure to liquids containing phosgene requires decontamination by irrigating with plain water or saline for at least 15 minutes unless the patient is showing signs or symptoms of respiratory distress. Contact lenses should be removed if this can be done easily without additional trauma to the eye.

For patients with an estimated exposure of 150 ppm-min or greater it is important to minimize physical stress (see 8.2) during decontamination. In addition, in cases with presence of significant symptoms or suspicion of imminent or manifest pulmonary edema, the decontamination period can be shortened to allow for prompt initiation of medical treatment and transport to a facility capable of a higher level of care, as long as this shortened decontamination does not compromise efforts to avoid secondary phosgene exposure.

8.2 Rest

Physical rest and avoidance of overexertion are regarded as important considerations in the management of cases of phosgene inhalation of 150 ppm-min or greater, as discussed below.

As controlled studies remain absent, the role of stress and rest in development and severity of phosgene toxicity are based on clinical experience and judgment. However, the importance of physical and psychological rest as a method of reducing the risk of developing pulmonary edema from phosgene exposure has been described since World War 1 (Flury and Zernik, 1931). Published articles from that era through to the present day have hypothesized that an increase in oxygen consumption may be an important factor in development of pulmonary edema. Physical activity was regarded as detrimental after phosgene inhalation (Cook, 1999), with further support provided by animal experiments on chemically induced pulmonary edema and potentiation of its occurrence and severity by exertion (Moore and Wall, 1991; Lehnert et al., 1995; Cheng 2004). A review of recent literature indicates physical rest is regarded as very important or mandatory for phosgene exposure victims (Urbanetti, 1997; IPCS, 1998; Wang and Li, 1998; Pallapies and Diller, 1999; Borak and Diller, 2001; Cheng, 2004; Wang and Cheng, 2004; Grainge and Rice, 2010). However, there are no studies comparing outcomes between victims prescribed rest versus activity. Although there is a lack of evidence, there is strong professional opinion that victims of phosgene exposure of 150 ppm-min or greater should avoid strenuous activities.

8.3 Oxygen

Oxygen should not be routinely given after a phosgene inhalation even if irritant effects are present unless there are signs of hypoxemia or respiratory distress

Oxygen has been advocated as early supportive treatment following phosgene related lung injury since World War I (Diller, 1985; Grainge, 2004; Russel et al., 2006), but it is also known that excessive oxygenation can generate harmful reactive species (Manning, 2002). After an extensive review (Grainge & Rice, 2010), they found that *there is a threshold concentration of oxygen required to improve survival that will reduce the severity of the underlying lung injury and suggest that the administration of oxygen can be safely delayed until the delayed signs and symptoms of phosgene inhalation become apparent thus avoiding risks of immediate oxygen induced toxicity.* Their research also indicates that delayed therapy is not demonstrably inferior to immediate therapy. They recommended "*if the SaO_2 falls below 94%, patients should receive the lowest concentration of supplemental oxygen to maintain their SaO_2 in the normal range".* Other sources (ACC, 2006) have recommended treating with oxygen if the pulse oximetry falls below 92%. Since pulse oximetry values consistent with survival range from 88-94%, an exact number within this range may be somewhat arbitrary and practitioners may treat based on their own clinical experience. However, if SaO_2 is 94% or above, then no oxygen should be given unless signs of respiratory distress exist.

9.0 MEDICAL ASSESMENT

Utilizing badge readings and other sources of information e.g. on PPE used, to estimate the exposure dose is an important component in the medical assessment (Section 7.0). The gradation of exposures against clinical outcome in this document is offered to aid decision making, but at all times clinical judgment should be paramount. As discussed in Section 6.0, when symptoms occur from exposures below 50ppm-min they are limited to subjective and irritant effects and do not progress to pulmonary edema. If a patient shows symptoms like wheezing, signs of dyspnea, etc, a physical exam and vital signs should be obtained. If these are normal, and subjective and irritant effects are addressed, then the patient may be discharged (Section 11.0). Due to imprecise methods of exposure estimation (Section 7.0), it must be left to the discretion of the treating physician as how best to evaluate patients with lower exposure doses.

As a general guideline, all patients with any of the following should be evaluated by a physician:

- Exposures of 50 ppm-min or above. Note: since inhalation exposure dose estimation is imprecise (Section 7) many practitioners recommend having patients evaluated by a physician at lower exposures.
- Unknown exposures.
- Exposures consisting of liquid phosgene or phosgene in solvent to the facial area.
- Significant, especially respiratory, symptoms.

For patients meeting any of the four criteria above, medical monitoring (listed below) and ongoing evaluation is recommended. Some authorities indicate that patients with an exposure dose of 50 ppm-min or more, or with unknown inhalation exposure, who have a normal examination and no signs or symptoms of toxicity after observation for 8 hours post exposure and have no signs of acute pathologic findings (specifically any signs of pulmonary edema) on chest X-rays at least 8 hours after exposure may be discharged with appropriate discharge instructions. If any one of these criteria is not met, medical monitoring for a longer period, (such as 24 hours) should be considered before discharge. This monitoring may be done initially on site if there are appropriate medical facilities, or in a hospital Emergency Department, intensive care unit (ICU), or medical unit where close monitoring can be done.

9.1 Medical Monitoring

Medical monitoring may include the following:

- Standard intake history.
- Exposure history with consideration of reading of badge and other appropriate exposure related information.
- Periodic vital signs, such as every 30 minutes.
- Physical examination (with specific emphasis on the respiratory system - auscultation).
- Pulse oximetry monitoring.
- Chest X-ray (posterior-anterior and lateral), as indicated by a physician.
- Baseline blood work for complete blood count, electrolytes, liver and kidney function (in hospital).

If pulmonary edema is anticipated (after an inhalation dose of 150 ppm-min or higher, or a strong suspicion thereof, unknown exposure or liquids with phosgene exposure to facial area), intensified medical monitoring is important. Such monitoring is best done in a hospital setting with intensive care capabilities.

- Baseline arterial blood gases.
- Continuous pulse oximetry.
- Frequent vital signs, such as every 15 minutes.
- Frequent chest auscultation by a nurse or physician.
- Serial Chest X-rays, initially and eight hours post-exposure.

10.0 TREATMENT OPTIONS

Treatment for cases of phosgene exposure generally can be placed into the following categories:

1. Treatment of subjective and irritant symptoms.
2. Early, "prophylactic" treatment intended to minimize the pulmonary effects by affecting the inflammatory cascade caused by higher levels of phosgene exposure.
3. Treatments addressing the pulmonary effects – pulmonary edema and acute respiratory distress syndrome.

10.1 Treatment of Irritant & Subjective Effects

Immediate symptoms are mainly due to irritation and are concentration-dependent (Section 6). Such symptoms generally include eye and throat irritation cough and chest tightness. Additionally, subjective symptoms, such as anxiety, nausea and headaches that are generally due more to the event around the exposure rather than the direct effects of phosgene, may also occur and need to be addressed.

10.1.1 Treatment of Irritant Effects

Irritant effects from phosgene exposure are generally transient and generally do not require specific medical treatment

- Eye exposure to liquids containing phosgene requires thorough rinsing (decontamination). Check for corneal abrasion/burn if irritation continues. Refer to ophthalmologist if ocular signs and symptoms continue.
- Cough may require throat lozenges or a non-narcotic anti-tussive.

- Wheezing/bronchospasm generally will require aerosolized bronchodilator therapy as per standard treatment for asthma. These symptoms, when immediate, are generally due to the irritant effects of the phosgene or the HCl from hydrolization in air, to someone with a past history of asthma/asthma-like medical issues.
- Oxygen (humidified if possible) should be added to inspired air (by mask or nasal catheter) for dyspnea, wheezing, or pulse oximetry indicates SpO_2 <92%. 100% oxygen should be avoided (Section 8.3).

Patients should be kept under medical supervision until significant signs and symptoms abate (see medical monitoring and patient discharge information). Mild irritant symptoms such as sore throat and a dry periodic cough may persist for several days.

Persistent or increasing signs and symptoms of respiratory impairment, including the appearance on auscultation of wheezing without a previous history of wheezing or asthma, may signal the onset of pulmonary edema.

10.1.2 Treatment of Subjective Effects

- Anxiety can be a normal reaction to the often dramatic circumstances of a phosgene accident. A calming, informative talk with medical personnel may help. In patients who manifest moderate to severe anxiety a light sedative may be considered.
- Other – Symptoms such as headache and nausea usually dissipate, but symptomatic care for those symptoms persisting may be appropriate.

10.2 Early "prophylactic" Treatment of Pulmonary Effects

With respect to pulmonary effects and depending on the inhaled dose, there may be a symptom free period of up to 24 hours. During this latency period biochemical changes may occur which will result in inflammation and changes in lung permeability. The process leading to overt pulmonary edema starts with the inhalation, but becomes clinically visible only at a later stage. There is no specific antidote to be administered to counteract the effects of phosgene. Treatment consists of supportive measures based on symptoms, but consideration may also be given to early post exposure "secondary prophylaxis" based on estimation of inhaled dose (Section 7.0). Treatment options are primarily based on animal studies and anecdotal experiences. Therefore, the health care professional should consider specific treatment on a case by case assessment based on their own

professional judgment, local medical practice, available information from the literature and availability of medical technologies. Symptoms, estimated inhaled dose, pre-existing medical conditions and clinical findings from medical monitoring are key components in this decision making process.

Note: Treatment options are provided in this document that are based on the opinions of physicians with experience in treating phosgene patients and lung specialists. Because this document is necessarily general in nature, each reader has an independent obligation to evaluate whether information and options contained in it are appropriate based on the particular factual circumstances of the individual.

Although there is no specific antidote against phosgene-induced lung injury, clinical experience seems to indicate that during the latency period, efforts to block the inflammatory cascade resulting from significant phosgene exposure may be more effective than the treatment of clinically overt pulmonary edema later on. Additionally, there exists information that using ambient air continuous positive pressure (CPAP) support before overt signs of exposure become manifest would reduce or ameliorate lung injury following exposure to phosgene (Graham et al., 2017). Thus, a stepwise type of early therapy, depending on the suspected phosgene inhalation dose is suggested. After an inhalation exposure of 150 ppm-min or above, or liquid phosgene to the facial area, early "prophylactic" treatment may be considered along with the medical monitoring detailed in Section 9.0. Some practitioners suggest that such an approach is warranted for lower inhalation exposures due to the imprecise methods to estimate inhalation exposure.

The exposure level at which treatment is warranted is undetermined. However, after the inhalation of a phosgene exposure dose of 150 ppm-min or greater, or the suspicion thereof (e.g. facial contamination with phosgene in solution, severe or therapy-resistant irritation of upper airways, sustained drop of oxygen saturation below 92%), it can be critical that all possibilities to combat impending pulmonary edema are used immediately. According to anecdotal clinical observations and/or information from animal experiments, the following therapeutic measures may be beneficial and merit consideration. These options are experience-based and not evidence-based and most of the information has been derived from case reports, case series, or animal studies. Therefore, the decisions for post-exposure early treatment should be left to the attending physician.

10.2.1 Positive airway pressure ventilation and Continuous Positive Airway Pressure

For cases where pulmonary edema is expected to develop, the early use of positive airway pressure when signs of respiratory distress or pulse oximetry of <92% exists is recommended.

Some authorities have previously recommended early (prophylactic) use of positive pressure ventilation (CPAP / EPAP / BiPAP) during the latency period as a means to prevent or minimize phosgene induced pulmonary edema (Schölmerich et al., 1980; Diller, 1985). Historically, this approach was not always consistent with current practices of many pulmonologists/intensivists who do not start positive pressure treatment during the latency period, but rather wait until pulmonary edema begins to develop (Section 10.3). With the availability of noninvasive methods to provide positive airway pressure, as well as further discussions on the topic, practitioners with experience in treating significant phosgene exposures are recommending earlier use of positive pressure ventilation, i.e. as soon as any deterioration of respiratory status occurs, specifically for exposures which pulmonary edema is expected. Graham et al. in an article in Toxicology Letters 2017,11.001., demonstrated in a large animal study that CPAP (commercially off the shelf therapy) using ambient air initiated before overt signs of exposure become manifest, significantly improved survival as well as improving some clinically relevant physiologic measures of phosgene induced lung injury over 24 hours. Thus, instituting such treatment within the first hour post exposure for significant phosgene exposures (cases of phosgene exposure for which pulmonary edema should be expected), even if symptom free, is being added to the Treatment Chart under Early Prophylaxis. While the use of positive airway pressure ventilation before signs of pulmonary edema develops is recommended by practitioners with experience in treating significant phosgene exposures, its use is left to the discretion of the attending physician.

Since the care for patients exposed to phosgene, especially those with significant exposures, crosses various levels of care, it is strongly recommended that discussions occur in advance with plant sites, EMS services, hospitals and specialists experienced in the treatment of ARDS. Included in such discussions are the concept of early use of positive airway pressure ventilation into phosgene evaluation and treatment guidelines.

10.2.2 Sedation

Sedation, e.g. by diazepam, may be considered after significant exposures, such as exposures of 150 ppm-min or greater, or liquid exposures to the facial area, especially if the exposed individual is exhibiting extreme anxiety.

As discussed in Section 8.2, it is important, that physical stress or exercise be avoided after significant phosgene exposure. Morphine has been critically discussed for sedation in humans after phosgene inhalation due to its respiratory depressive effect. However, no such respiratory depressive effect of morphine was noted, but rather an increase in survival (about 13%) in animal experiments was evident from an evaluation of the studies. For human cases, the benefit, if any, of morphine was regarded as equivocal. A dose of morphine as small as possible to achieve a reduction of the struggle for air was advocated. Freeman S, Grodins FS, Kosman AJ (1945a): Sedation in the treatment of phosgene casualties. National Research Council, Committee on Treatment of Gas Casualties (Ed.): Fasciculus on Chemical Warfare Medicine vol.2, 1945, 510-520

In contrast, initial investigation of anesthetic doses of barbiturates were found not to be beneficial, but seemed to increase mortality (Freeman et al., 1945), while later papers showed positive effects (Bean and Zee, 1966; Maly, 1970).

The application of sedatives, at least during transport of the patient, was suggested in the 1970s and 1980s. In China, where physicians encountered a significant number of phosgene poisoning cases (in the hundreds), sedation of patients, usually with intramuscular diazepam, is a standard part of treatment regimens (Zhu, 1985; Wang and Li, 1998; Cheng, 2004; Wang and Cheng, 2004; Chen et al., 2006).

10.2.3 Steroids

While many practitioners with experience in treating significant phosgene exposures suggest strong consideration for the use of steroids for phosgene exposures of 150 ppm-min or greater, the decision is left to the discretion of the attending physician. There is no evidence-based requirement to use corticosteroids in phosgene poisoning.

While for many experts corticosteroids still are considered beneficial in the early treatment of significant phosgene exposures and are applied regularly in phosgene inhalation cases worldwide (Zhu, 1985; Albrecht, 1997; Steffens et al., 2003; Chen et al, 2006; Shi, 2006; Wang and Li, 2006), other experts regard them as being equivocally substantiated (Diller, 1985), or as being without definite proof of efficacy in humans and in animals without benefit or even potentially detrimental (Sangster and Meulenbelt, 1988; Meulenbelt and Sangster, 1990; Meulenbelt and Sangster, 1994; de Lange and Meulenbelt, 2011; Luo et al., 2014; Liu et al., 2014). Thus, there use is still regarded as opinion-based (Diller, 1999).

Phosgene-related data:
After phosgene inhalation in animals, edema reduction results from inhaled **corticosteroid application** were equivocal, reduction of mortality was not significant and high doses were even deleterious (propellant gas and hypoxia effects were assumed). Reduced mortality and prolonged survival were described in an overview (Diller and Zante, 1985), while recent experiments in pigs showed neither an improved outcome nor detrimental effects. A recent review article recommended that intravenous bolus high dose steroids may be considered if presentation is less than 6h after exposure. (Grainge and Rice, 2010). For human cases of phosgene inhalation there are only case reports for corticosteroid inhalation. Negative effects have not been described.

Parenteral application of corticosteroids in animals after phosgene inhalation also gave equivocal results regarding survival time and edema formation. A study in pigs found neither positive nor detrimental effects. Earlier application may be required. (Smith et al., 2009; Grainge and Rice, 2010).

In humans there are recommendations in favor of parenteral corticosteroid application from all over the world, but only case reports are available.

Other lower airway irritants
As the data for phosgene itself are scarce, consideration of other lower airway irritants is useful (e.g. ozone, nitrous oxides, chlorine, zinc oxide fume)

For corticosteroid inhalation in animals, older studies found beneficial effects in such scenarios, though observation time was often short. Case reports and case series relate positive effects in humans. In particular, there are several case series papers describing lung edema formation only in patients not receiving corticosteroid aerosol. For parenteral application small and inconsistent, and in part contradictory, effects were reported in animal studies. Some even report deleterious effects (de Lange and Meulenbelt, 2011). In humans, there are few reported cases with contradictory outcomes.

Acute lung injury (ALI) and Acute airway dysfunction syndrome (ARDS) of non-phosgene origin

As phosgene poisoning is a subtype of ARDS and ALI, the issue of corticosteroid use in these syndromes is briefly reviewed here, but with respect to early use only.

Inhalation:

Inhaled corticosteroids have not been clinically used in ALI/ARDS. There is some animal experimental evidence from chlorine inhalation of certain benefits including attenuation of lung edema formation and improvement of clinical indices of lung injury. Based on this, a Phase II study has been suggested. (Reade and Milbrandt, 2007).

Parenteral application:

Several meta-analyses on corticosteroids in ALI and/or ARDS are available. Results both in animal experiments and clinical trials have been found to be equivocal or contradictory, with newer studies indicating no efficacy or beneficial effect (Metz and Sibbald, 1991) high dose steroids not showing differences in mortality (Adhikari et al, 2004), and not recommending steroids for prevention of ARDS in at-risk patients, and warning against high doses. One study seemed to indicate a benefit of early phase low dose infusion (Annane, 2007).

Other studies overviews showed a benefit or positive trends of corticoid therapy in ARDS for early application (Meduri et al., 2008; Tang et al., 2009; Peter et al., 2008), though not for prevention (Peter et al., 2008).

Conclusion:
The data for corticosteroid use in phosgene inhalation, be it as aerosol or as i.v. injection, is contradictory. Yet there seems to be limited evidence for at least some positive effects, especially for significant phosgene inhalation exposures. Detrimental effects have rarely been described in animals and never in humans – rather corticosteroids might be without effect. Positive effects have been seen in some studies with other lower airway irritants, and in ARDS/ALI. More recently a few studies have also hinted at the possibility of positive effects. What is clear from literature is if corticosteroids are to be used, it should be as early as possible and before the onset of pulmonary edema.

10.2.4 N-Acetyl Cysteine

N-acetyl cysteine is generally not recommended as a prophylactic treatment for phosgene inhalation.

N-acetylcysteine (NAC) has been suggested as a therapeutic intervention for phosgene inhalation and for ALI from other toxicants, though mostly for pre-exposure use only. Few publications address post-exposure effectiveness of NAC given after phosgene inhalation or after other inducers of toxic lung edema. Lung weight gain, leucotriene concentration, protein flux and protein ratio were reduced and glutathione concentration in lung tissue was preserved (Schroeder and Gurtner, 1992; Sciuto et al., 1995; Ji et al., 2010). NAC thus seems to increase membrane stability and at least inhibits fluid transudation into the alveoles (Sciuto and Hurt, 2004). Yet there are also publications showing NAC i.v. or L-cysteine aerosol to be ineffective (Sciuto and Gurtner, 1989; Pauluhn and Hai, 2011).

In animal experiments using other substances inducing lung edema and ALI, positive effects were seen (Davreux et al., 1997; van Helden et al., 2004). Early application is advocated (McClintock et al., 2002; McClintock et al., 2006).

The positive effects in test animals could in part be confirmed in humans with ARDS from septic shock (Bernard, 1991), while other randomized studies in ALI/ARDS did not always confirm positive effects (Jepsen et al., 1992; Domenighetti et al., 1997). In reviews

and meta-analyses of some of these studies, NAC is usually not to be considered a viable treatment for ARDS (Adhikari et al., 2004; Bream-Rouwenhorst et al., 2008), though some reviewers recommend it (Gilissen and Nowak, 1998).

There is one unpublished report on a phosgene poisoning with toxic lung edema that was treated with NAC intravenously as suggested for acetaminophen poisoning. The patient recovered from therapy refractory lung edema after application (Suputtitada, 2005).

Recent papers on treatment of phosgene poisoning recommend consideration of application of 0.5 -1-2 g nebulized NAC (Borak and Diller, 2001; Grainge and Rice, 2010), while for ARDS the situation is not yet clear (Kopp et al., 2003).

10.2.5 ß2-Adrenergic Agonists

Beta-agonists, such as salbutamol 5 mg by nebulizer every 4 hours, should be used for bronchospasm. However, in the absence of bronchospasm its general use for prophylactic treatment of phosgene inhalation use is not recommended.

Phosgene Related Data:
After direct phosgene exposure in animal studies, isoprenaline (isoprotenerol) was reported to suppress the synthesis of lipoxygenase mediators, known inflammatory mediators triggered by phosgene exposure and upregulate intercellular cyclic AMP (Sciuto et al., 1998). Terbutaline and isoprenaline were also studied in a rabbit isolated lung model and were found to reduce lung weight (Kennedy et al., 1989). This was not duplicated in a pig model in which nebulized salbutamol was administered equivalent to 4 mg human dose in repeated doses following lung injury from phosgene exposure. This treatment did not improve survival, and worsened physiological parameters such as heart rate and arterial oxygenation. Although it reduced neutrophil influx into the lung, its sole use following phosgene exposure was not recommended (Grainge et al., 2009).

The conflicting data in animals demonstrate that it is difficult to extrapolate from animals to human and the clinician must decide whether the proven anti-inflammatory effect in animals as well as the

known properties of beta-agonists to reduce airway resistance and improve the inotropic support in the circulation warrant treatment with beta-adrenergic agents while keeping in mind side effects such as arrhythmia. Once oxygen is required, a dose of nebulized salbutamol of 5 mg every 4 hours, preferably starting one hour post-exposure, has been recommended to reduce inflammation (Grainge and Rice, 2010).

Post treatment of rabbits exposed to lethal doses of phosgene with IV and intra-tracheal isoprenaline attenuated in-situ markers of pulmonary edema attributable to reduced vascular pressure and capillary permeability (Sciuto et al., 1998).

There are no human trials on post-exposure prophylaxis with ß2-adrenergic agonists following exposure to phosgene. Many authors agree on the use of bronchodilators for the treatment of wheezing due to early irritation. In a review of 75 confirmed cases of phosgene inhalation, isoproterenol and epinephrine was utilized among other modalities for two of the more serious cases with clinical pulmonary edema, and both cases improved (Regan, 1985).

Acute lung injury (ALI) and acute airway dysfunction syndrome (ARDS) of non-phosgene origin

Beta-2 agonists have been studied in animal models as well as in clinical trial for prevention of human lung injury. An extensive review of animal studies considered the effects of beta agonists on three mechanisms of improvement in ALI and ARDS: edema clearance, anti-inflammatory effects and bronchodilation. The authors concluded that they were beneficial on all three and recommended randomized human trials to study the effects of β2 agonists in humans (Groshaus et al., 2004). Results of clinical trials of β-agonist therapy for ALI/acute respiratory distress syndrome (ARDS) have been inconsistent. Sustained infusion of i.v. salbutamol (albuterol) was found to reduce extravascular lung water in double blind randomized controlled trial of patients with ALI and ARDS (Perkins et al., 2006). However another randomized, placebo-controlled trial for the treatment of ALI did not find improved clinical outcomes after treatment with the aerosolized β2-adrenergic agonist, albuterol

(Matthay et al., 2011). Strikingly, in the Beta-Agonist Lung Injury Trial investigators stopped intravenous salbutamol early because of safety concerns (Gao Smith, 2012). The salbutamol group had increased mortality and the authors concluded that intravenous use of β2-agonists early in the course of ARDS cannot be recommended, although they acknowledged study limitations.

10.2.6 Ibuprofen

Whereas some have previously proposed ibuprofen administration as prophylaxis (Borak and Diller, 2001) based on various animal studies reported in the 1990s, this approach is generally not recommended. There does not appear to be any reported clinical studies with the administration of ibuprofen in humans. To provide a dose comparable to that shown to be effective in animals it would be necessary to administer at least 25-50 mg/kg by mouth (Borak and Diller, 2001), which is above recommended doses for humans.

10.3 Treatment of Clinical Pulmonary Edema

It is recommended that phosgene induced pulmonary edema be treated by specialist in ARDS such as intensivist and pulmonologist. (Grainge and Rice, 2010).

It is recommended that phosgene induced pulmonary edema be treated by experts in this area, such as pulmonologist or intensivist, especially since said treatment, including the use of positive pressure ventilation, would be similar to that utilized for pulmonary edema from ARDS. The specifics of such treatment should be left to the physician with expertise in caring for ARDS.

10.3.1 ECMO (Adult Extracorporeal Membrane Oxygenation):

There are recent reports of ECMO improving the prognosis of patients with life threatening pulmonary edema from phosgene exposures as well as significant literature support for the use of ECMO in ARDS. (Zhonghua Wei Zhong Bing Ji Jiu Yi Xue, 2019) ECMO is now included in treatment considerations for significant phosgene exposures, early in the course of pulmonary edema, especially if such person is not responding to conventional treatment. The decision of whether or not, and when to use ECMO in cases of phosgene induced pulmonary edema should be made by experts with ECMO experience, such as a pulmonologist or intensivist.

ECMO, which is generally available only in select tertiary care centers, provides for external blood oxygenation and reintroduction of oxygenated blood via a veno-venous or veno-arterial circuit, the former being the option recommended for ARDS type conditions. ECMO in itself is not so much a treatment as a support to significantly injured deep lung tissue to allow for lung recovery or for other treatment approaches to work. ECMO has been used successfully in the care of other life threatening ARDS type situations (Combes 2018). In the 2017 version of these Guidelines, it has been postulated that ECMO may be beneficial in the treatment of pulmonary edema from phosgene exposures, and many practitioners with experience in treating significant phosgene exposures suggested consideration for having the option for ECMO available for cases of life threatening phosgene exposures, especially for pulmonary edema not responding to conventional treatment.

In February 2019, a paper (Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019) was published in Chinese on the successful use of ECMO in 4 cases of ARDS from phosgene exposure, not responding to conventional treatment. Its conclusion was that "*early ECMO treatment can significantly improve the oxygenation of patients with severe ARDS caused by acute phosgene poisoning, remove excessive CO2 in the body, and reduce ventilator-associated lung injury, thus improving the prognosis."* Based on these reports and prior treatment considerations, ECMO is included in the treatment considerations for significant phosgene exposures, early in the course of pulmonary edema, especially if such person is not responding to conventional treatment. The decision of whether or not, and when to use ECMO in any specific case of phosgene induced pulmonary edema should be made by experts with ECMO experience, such as a pulmonologist or intensivist.

Information and location of ECMO capable facilities can be found at the Extracorporeal Life Support Organization (ELSO) at the following website: http://elso.org.

It is recommended that discussion with the ECMO center occur in advance of any emergency situation, so as to more effectively integrate this option into local protocols. Included in such protocols would be referral criteria for severely phosgene exposed individuals and the logistics of transferring the patient. Potential referral criteria during the latency period used by some authorities include: suspected exposure of the respiratory tract to 150 ppm-min or greater of phosgene; spray to the face and/or anterior chest without respiratory protection to high concentrations of phosgene (such as liquid and/or in a solvent); or suspected significant exposure to the respiratory tract when there is no badge or other means of determining exposure. Other referral criteria may be appropriate depending on the situation. Although if a severely phosgene exposed patient is to be transferred, doing so during the latent period is desirable, transferring severely phosgene exposed individuals in early pulmonary edema to an ECMO center may also provide benefit. It is recommended that appropriate logistics of transferring be addressed in advance. Depending on the location and geography, various options may also exist, such as going directly to the ECMO center versus a local facility first; ground versus air transport; and having the ECMO team coming to the patient before transport.

11.0 CONSIDERATIONS REGARDING DISCHARGE

In the opinion of some medical authorities in the area of phosgene exposures, patients with an estimated dose lower than 50 ppm-min can be discharged if they have a normal examination ***and*** no significant signs or symptoms of toxicity after observation.

Additionally, some authorities indicate that patients with an exposure dose of 50 ppm-min or more or with unknown inhalation who have a normal examination and no signs or symptoms of toxicity after observation for 8 hours and have no signs of acute pathologic findings (specifically any signs of pulmonary edema) on chest X-rays 8 hours after exposure may be discharged with appropriate discharge instructions. If any one of these criteria is not met, medical monitoring for a longer period, such as 24, hours should be considered.

Patient Discharge:
Upon discharging a patient after initial evaluation or from a hospital ER, it is suggested that written discharge instructions be given which may include:

- Information on signs/symptoms of concern.
- Whom to contact in case of concerns.
- Follow-up instructions.
- Recommendations to avoid heavy physical exertion for 24 hours.
- Recommendations to avoid exposure to cigarette smoke for 72 hours.

12.0 POSTSCRIPT- DIFFERENCES WITH OTHER REFERENCE SOURCES

A number of resources are available related to phosgene medical evaluation and treatment, some of which are located in the Reference section. There may be differences between what is presented in this document versus what is presented elsewhere, and these apparent differences can be confusing. Therefore, it is important to understand that each medical professional must make their own decisions and not use this document as a "how to guide." The reasons for the apparent differences are that various resources may come from different perspectives, thus explaining some of the differences. One significant reason may be that many of the literature articles, and the reference materials using these articles, are related to case reports. In these case reports the concept of level of exposure may be absent because in many countries badges or other means of estimating exposures may not be used. Thus, the exposure is not differentiated by exposure levels. When an exposure which cannot be differentiated by an exposure level occurs, all findings are generally related to an exposure occurring. Additionally, some sources use references for exposures which occurred during military actions when exposures were not differentiated by level of exposure, but also, and especially those from WWI, actually were from mixed chemical (including chlorine) exposures. If one does not know the level of exposure, then such decisions as: How long before a patient can be discharged, How best to evaluate and treat and long term effects from acute exposure become more difficult to differentiate. This document attempts to provide some additional clarity based on specific exposure levels when known.

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