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Phosgene: information on options for first aid and medical treatment

III Phosgene Medical Group

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1. QUICK REFERENCE GUIDE AND DECISION TREE

Quick Reference Guide

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

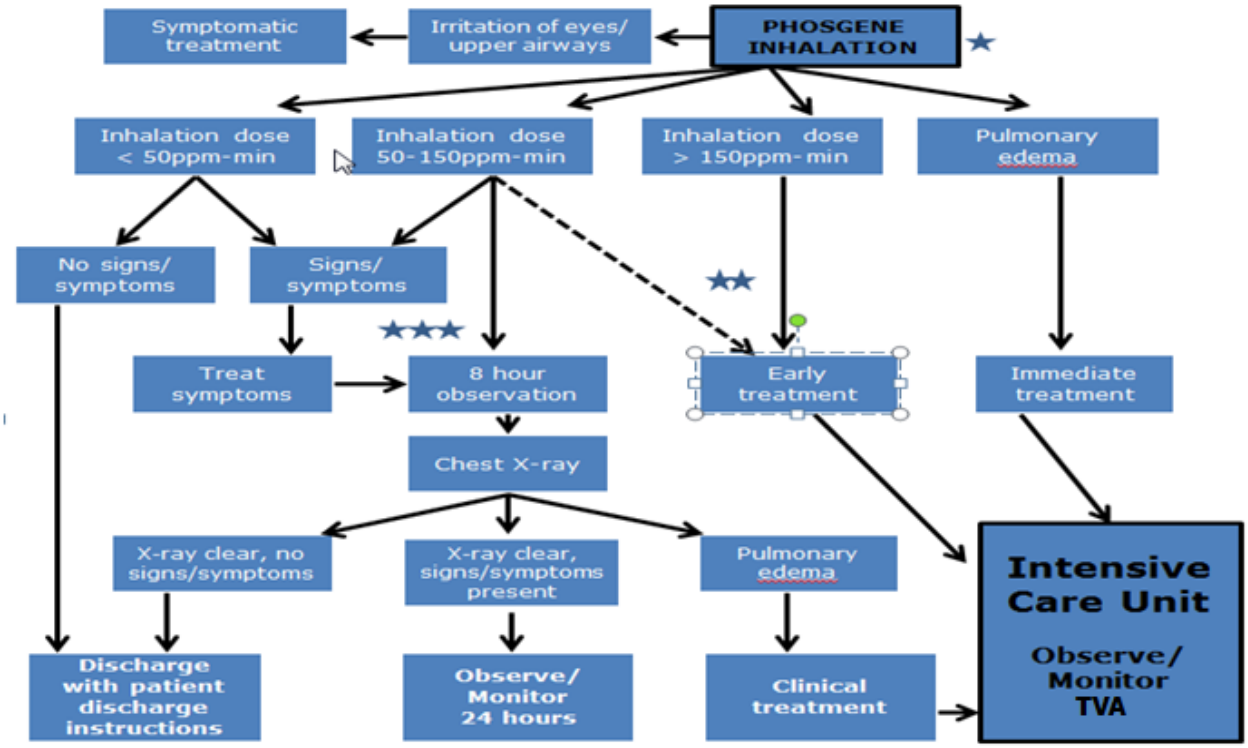
Treatment

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 "prophylatic" treatment of pulmonary effects	Phosgene exposures estimated as 150ppm-min and above, unknown exposure, or liquids with phosgene to the facial area: Steroids: Aerosolized: Maximal dosage according to the specific corticosteroid used and if available; and/or Intravenous: 1000 mg methylprednisolone Note: If intravenous and/or aerosolized corticosteroids are not available, oral or intramuscular application may be considered If symptomatic, consider Tiered Ventilation Approach, starting with use of positive pressure ventilation (such as CPAP) if any signs of respiratory distress or pulse oximetry less than 92%.

	Note: Above may be considered for exposures <150ppm-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) may merit consideration, but left to the discretion of the attending specialist. For severe cases the suggested Tiered Ventilation Approach (TVA, see section 11.) has been developed.

Decision Tree

Summary of recommended approaches based on estimated phosgene dose



Note: the exposure level at which treatment is warranted is undetermined. The inhalation dose gradations indicated in this scheme are for guidance only. Clinical judgement must be used in all cases.

★ 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 indicates that treatment at levels as low as 50ppm-min may be considered.

★★★ 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.

2. INTRODUCTION

The Phosgene Medical Group (PMG) of the International Isocyanate Institute (III) comprises physicians from various countries with knowledge and actual experience of phosgene inhalation cases. The PMG developed this document as a global consensus on phosgene exposure evaluation and treatment. It is desirable that companies and health care providers will develop their own protocols for dealing with phosgene exposure. Although this document may be used to facilitate the development of such protocols it is very clearly not proposed as a specific standard or protocol. Because this document is necessarily general in nature, readers have an independent obligation to evaluate whether information and options described herein are appropriate for the given situation based on their own particular situation and circumstances.

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 need for a reference resource to provide clinicians with information on the evaluation and treatment of individuals with phosgene exposure has long been recognized. In 1982 the *International Symposium on Phosgene Induced Edema: Diagnosis and Countermeasures* was held with the papers from this symposium later published. In 1994 the physicians of the Phosgene Panel of the Chemical Manufacturers Association (CMA) now called the American Chemical Council (ACC) compiled a booklet, *Phosgene Pulmonary Exposure Information*, in order to assist other physicians who may be called upon to evaluate and treat patients after phosgene exposure. The information was compiled from relevant medical literature review and from consultations with occupational physicians experienced in the evaluation and treatment of phosgene-exposed patients. This information was updated with the latest version *Phosgene: Information for Emergency Responders and Health Care Providers*, released in 2002. The III released two documents in 1999 - *Critical Review of the Medical Management of Acute Phosgene Poisoning* by WF Diller and *Options for the Medical Management of Phosgene Poisoning* by D Pallapies and WF Diller. In 2004, the PMG developed a consensus document, *Phosgene - Information on Treatment Options for Emergency Responders and Health Care Providers* which is the basis for the current update. Review articles on this topic have been published periodically including the 2001 paper *Phosgene Exposure: Mechanisms of Injury and Treatment Strategies* in the *Journal of Occupational and Environmental Medicine* and the 2010 paper *Management of phosgene-induced acute lung injury* in *Clinical Toxicology.* Additionally, a paper on the results of a US phosgene registry was published in 2011 in the *Journal of Occupational and Environmental Medicine - Results from the US Industry-Wide Phosgene Surveillance: The Diller Registry (Collins et al, 2011)*. Information from discussions with clinicians and researchers has been added in 2017.

3. SUBSTANCE INFORMATION

Phosgene ($COCl_2$), CAS 75-44-5

Synonyms: carbonic acid dichloride, carbonic dichloride, carbon oxychloride, carbonyl chloride, chloroformyl chloride

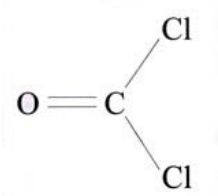


Figure 1. Chemical Structure of Phosgene

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 Phosgene Panel, 2006). Phosgene gas is heavier than air and may travel along the ground (CDC 2012). Phosgene reacts slowly with water (including humidity in air and on mucous membranes) to form hydrochloric acid and carbon dioxide (ICSC 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. Values quoted for the odor threshold of phosgene range between 0.125ppm and 1ppm (US DHHS 1978).

4. MECHANISM OF PHOSGENE INJURY

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

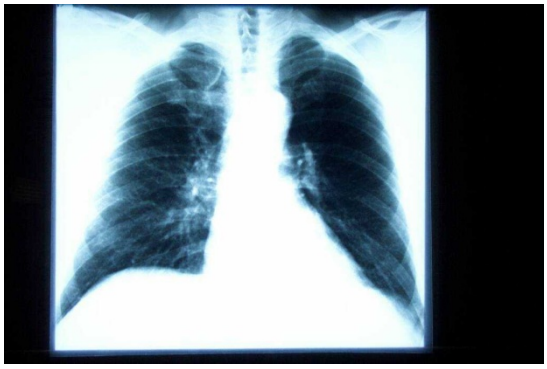
a) Slow and limited hydrolysis with the formation of HCl. This may, in cases of higher concentration exposures, cause irritation of the eyes, nose and throat, with burning sensation, cough and chest oppression. Signs and symptoms will appear soon after the inhalation will vary according to the inhaled 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).
b) 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 adenoside 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”).

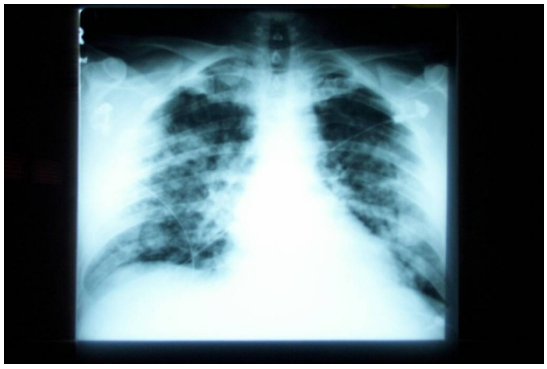
Although the process described above starts immediately with exposure, the actual onset of the pulmonary edema, if it occurs, is delayed – “clinical latency period”. The length of this “clinical latency period” is inversely related to the inhaled phosgene dose: the higher the inhaled dose, the shorter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

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

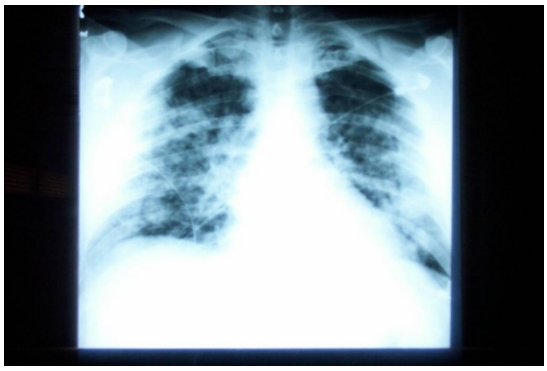
The case involved an unknown exposure dose. Initial treatment included early administration of high dose aerosolized corticosteroids, high dose intravenous corticosteroid and hospital admission after 4 hours. Hospital treatment was continued with high dose aerosolized and intravenous corticosteroids,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



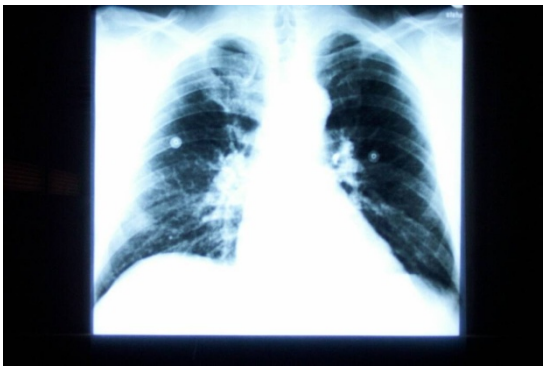
4 hours



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. 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).

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. 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) there cannot be absolute certainty in predicting exposure-effects in humans. The summary of anticipated 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 anticipated exposure-effects for phosgene

Phosgene Concentration	**Anticipated 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*	**Anticipated 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. These effects will resolve relatively quickly and are not 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 recently 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 would not be expected to 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. 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, a 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 related 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. EMERGENCY RESPONSE

Patients whose clothing or skin is contaminated with liquid phosgene, or solvents 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 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 judgement. 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 hypothesised 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. For a detailed text and literature list on this topic, see Appendix 1.

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 1 (Diller 85, Grainge 2004, Russel Blain Rice 06), but it is also known that excessive oxygenation can generate harmful reactive species (Manning 2002). After an extensive review Grainge & Rice (2010) the authors 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, no oxygen should be given.

9. MEDICAL ASSESSMENT

Utilising badge readings 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). 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, when symptoms occur from exposures below 50ppm-min they are limited to subjective and irritant effects and are not expected to 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 can be discharged (Section 11). Due to imprecise methods of exposure estimation (Section 7), it must be left to the discretion of the treating physician to evaluate patients with lower exposures.

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, and later in the intensive care unit (ICU) or medical unit where close monitoring can be done.

Medical Monitoring

Medical monitoring may include the following:-

- Standard intake history.
- Exposure history with consideration of ~~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 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. 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 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 dyspnoea, wheezing, or pulse oximetry indicates SpO_2 <92%. Pure (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). 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 judgement, 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: Suggestions provided in this document 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. 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 should be considered along with the medical monitoring detailed in Section 9. 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 Sedation

Sedation, e.g. by diazepam, may be seriously considered after significant exposures, such as exposures of 150 ppm-min or greater, or liquid exposures to the facial area.

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 et al. 1945a). In contrast, initial investigation of anaesthetic doses of barbiturates were found not to be beneficial, but seemed to increase mortality (Freeman et al. 1945a), 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 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).

10.2.2 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 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, in animals without benefitor 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). So their use still must be 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 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 treands 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.

For a more detailed review and literature list see Appendix 2

10.2.3 N-Acetyl Cysteine

Treatment with nebulized NAC, still part of several treatment recommendations, is no longer recommended according to pulmonology experts.

N-acetylcysteine (NAC) had been suggested as a therapeutic intervention for phosgene inhalation and for ALI from other toxicants, though mostly for pre-exposure use only. Few publications addressed 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 1998, Sciuto et al. 1995, Ji et al. 20109). NAC thus seems to increase membrane stability and at least inhibits fluid transudation into the alveoles (Sciuto 2004). Yet there are also publications showing NAC i.v. or L-cysteine aerosol not to be effective (Sciuto and Gurtner 1989, Pauluhn and Hai 2011).

In animal experiments using other substances inducing of 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 N 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 as suggested for acetaminophen poisoning. The patient recovered from therapy refractory lung edema after application (personal communication Dr. Suputtitada, Rayong Hospital).

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).

For a more detailed review and literature list see Appendix 3.

As NAC use may prompt allergic reactions, and the benefit is not clear, its use is no longer recommended.

10.2.4 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. Intravenous administration is not recommended

Phosgene Related Data:

In direct phosgene exposure in animal studies, terbutaline and isoprenaline (isoprotenerol) have been reported to suppress the synthesis of lipoxygenase mediators, known inflammatory mediators triggered by phosgene exposure and upregulate intercellular cyclic AMP (Sciuto et al,1996). They 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 isuprenalin attenuated in-situ markers of pulmonary edema (Sciuto et al 1998) attributable to reduced vascular pressure and capillary permeability.

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 u~~n~~tilized 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 2011). Strikingly, in the Beta-Agonist Lung Injury Trial investigators stopped intravenous salbutamol early because of safety concerns (Fang 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.

10.2.5 Positive airway pressure ventilation

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

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 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. Thus for cases of phosgene exposure which pulmonary edema should be expected, the use of positive pressure ventilation before pulmonary edema develops merits consideration, but its use is left to the discretion of the attending physician.

Since the care for exposed patients with 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 specialist experienced in the treatment of ARDS. Included in such discussions is the concept of early use of positive pressure ventilation into phosgene evaluation and treatment guidelines. In the appendix, there is an example of a tiered ventilation approach, which may be helpful in your consideration but should not be seen as per se instructions (see 11).

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 specialists in ARDS such as intensivists and pulmonologists. (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.

10.3.1 ECMO (Adult Extracorporeal Membrane Oxygenation): There are no sufficiently reported cases of ECMO being used to treat in the care of life threatening pulmonary edema, thus such care should still be regarded as unproven for cases of phosgene exposure. The decision of whether or not to use ECMO in cases of phosgene induced pulmonary edema should be made by experts in this area, such as pulmonologist or intensivist. However, many practitioners with experience in treating significant phosgene exposures suggest consideration for having the option for ECMO available for cases of life threatening phosgene exposures.

ECMO, which is available only in select tertiary care centers, provides for external blood oxygenation and reintroduction of oxygenated blood via a veno-venous or arterio-venous 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. Although there are no sufficiently reported cases of ECMO being used in the care of life threatening pulmonary edema from a phosgene exposure, such support has been used successfully in the care of other life threatening ARDS type situations, also from life-threatening exposures with e.g. aluminum phosphide/phosphine.

Information and location of ECMO capable facilities can be found at the Extracorporeal Life Support Organization (ELSO) at the following website: http://www.elso.med.umich.edu/. Further information is given in Appendix 4.

If transfer to an ECMO center is considered to be a possibility, it is recommended that discussion with the ECMO center occur in advance, so as to more effectively integrate this option in 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 merit consideration. It is recommended that appropriate logistics of transferring be addressed in advance. Depending on the location and geography, various options may 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. Tiered Ventilation Approach – TVA

In discussions with pulmonologists in several countries an example of a suggested tiered ventilation approach has been developed – largely based on ARDS net recommendations, which may serve as a possible suggestion, if needed, while the decisions should be:

Inhalation dose of 150 ppm*min or more and symptoms and all cases with an inhalation dose of 300 ppm*min or more:

- In order not to lose time, in case the patient status should develop into a critical phase, early transfer to a specialized hospital with an experienced pulmonology, anesthesiology, or at least cardiac surgery department, in any case with equipment for and experience in long-term venous-venous ECMO in adults is advisable. Stable, asymptomatic patients with 150 ppm*min or more plus symptoms, and all cases with 300 ppm*min and above, should be transferred as soon as possible. Sites, site medical departments, and primary hospitals close to the site should seek an agreement with a specialized hospital as described above and clarify communication and transport procedures in advance. Such specialized hospitals should be identified for all sites handling phosgene. The respective department heads should be visited, the approach should be discussed and agreed upon, if possible, and communication and transport procedures should be clarified. In the specialized hospital close monitoring is required. If the patient is unstable, e.g. shows decreased oxygen saturation or develops clinical symptoms,

- non-invasive ventilation (preferably BiPAP, if not available CPAP or EPAP) should be started. The PEEP should be adjusted according to usual practice. Cautious sedation with morphine, which in addition would decrease the cardiac afterload, can be considered, if the patient is agitated (see above).
  If this does not stabilize the clinical situation and/or the oxygen saturation (pulse oximetry) within 30 minutes, or if more than 70%

oxygen are required in the ventilation gas to keep the patient stable, or if the P/F ratio is below 200,

⇓

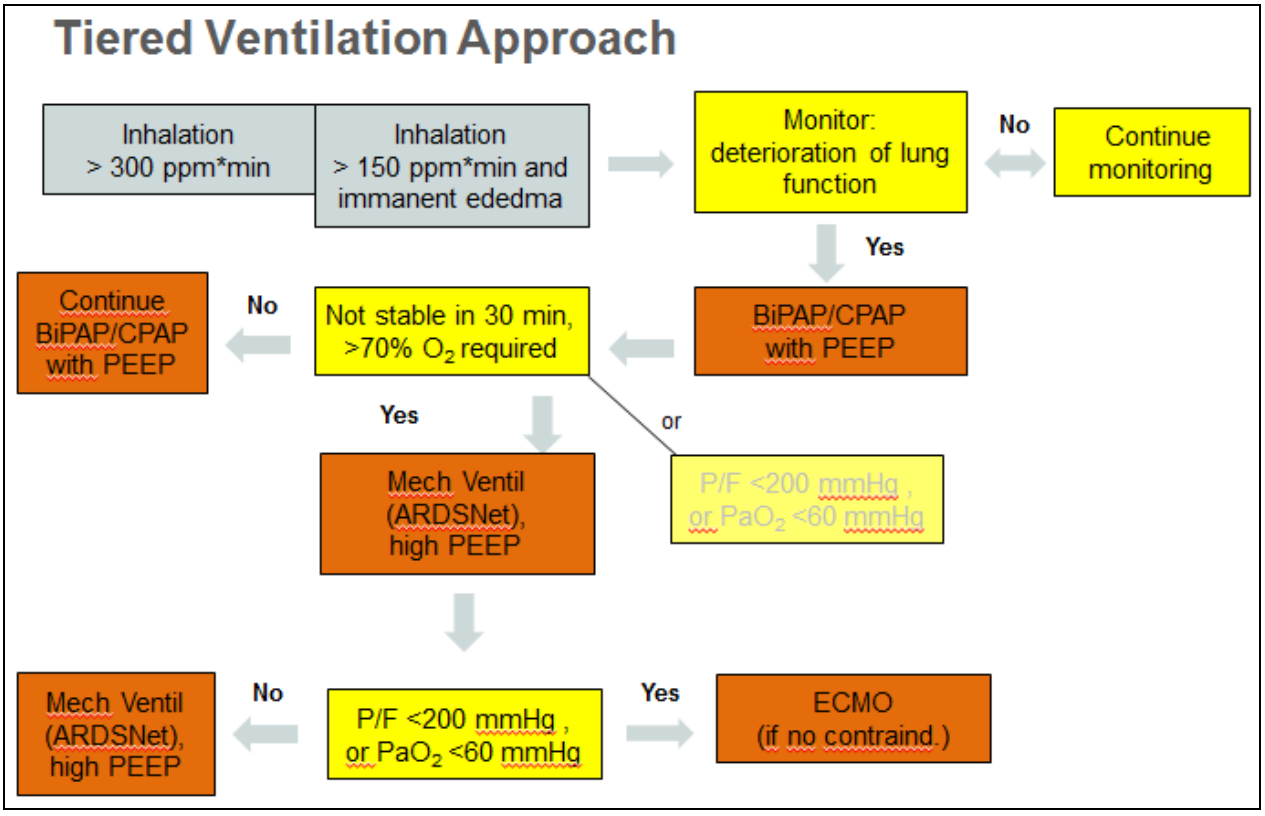
- Mechanical ventilation according to the current ARDSNet protocols, e.g. low tidal volume, supine position, etc., should be installed. PEEP should be used correlated to the oxygen concentration in blood. Even high PEEP might be considered by the attending physician in case of manifest severe lung edema.
  If the P/F-ratio is below 200 at a FiO_2 of 100% O_2 , or if the PaO_2 is below 60 mm Hg, either of which for more than 1 hour, and if there are no contraindications

⇓

- ECMO can be considered.

Note: the decisions as above can only be taken by an experienced pulmonologist, anesthesiologist or cardiac surgeon, not by occupational physicians.

To clarify this approach, a flow chart is provided:



12. 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.

If a patient who develops pulmonary edema survives the initial 48 hours after exposure, recovery is likely.

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14. APPENDICES

APPENDIX 1

Rest and sedation after phosgene exposure – detailed review

All authors during and after World War 1 (WW 1) stressed that in order to reduce oxygen consumption, and because stress and strain enforce development of lung edema, absolute physical rest was mandatory. A caveat might be, that in WW 1 little phosgene was used on its own, as it was usually combined with chlorine. However, pulmonary edema as consequence of both pure phosgene and the mixture exposures has been vividly described. No physician ever had to gain as much experience on toxic lung edema as the physicians on both sides of WW 1 did.

Canadian sources clearly relate that the more activity a soldier carried out, the quicker his lungs filled up with fluid and he collapsed and died [Cook 1999]. This has been supported by animal experiments on chemically induced pulmonary edema and exertion potentiation of its occurrence and severity [Moore and Wall 1991, Lehnert et al. 1995, Cheng 2004].

The very few recent phosgene cases also seem to indicate that physical "exertion" (i.e. continuation of normal activities) or rather the lack of rest, may have contributed to edema severity and possibly even fatal outcomes. Unfortunately these cases have not been published in scientific literature [Bagur, Argentina 2007, Wang, China 2008, Zilker, Germany 2010, Calhoun, USA 2011].

During and after WW 1 physical rest was consistently stressed as a key measure. It was said that the victim had to be carried from the site of inhalation, that walking on his own was strictly prohibited, that full immobilization was indispensable [Army War College 1918, Medical Research Committee 1917, Flury and Zangger 1928, War Office 1930, Blum 1934, Gillert 1934, War Office 1940, Richter 1941, Cook 1999]. There were even warnings against any active movement [Fitch 1942], sitting upright [Herringham 1920], chewing of bread, undressing oneself [Leschke 1933], longer transport [Flury and Zernik 1931], or transport on uneven roads [Gillert 1934]. Some patients were even strapped to their beds [Cook 1999]. The importance of additional psychological rest was also stressed [Flury and Zernik 1931].

However, in an overview several animal studies in mice, rats and dogs were reviewed, which showed no deleterious effect of moderate exercise after phosgene and diphosgene inhalation in a range of the LC50. Still from a clinical point of view the authors recommend maximum rest based on WW 1 reports [Freeman et al. 1945b].

Around 1960 full rest, even avoidance of unnecessary questioning, was advised from industry [Andrieu et al. 1959, Ehrlicher 1961]. Later physical rest was still very clearly advised for severe inhalations [Faure et al. 1970, Diller 1974, Klimmek et al. 1983, Diller 1985, Diller and Zante 1985, Zhu 1985].

Physical rest has been stressed as important or mandatory in all recent publications, too [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]. There is no doubt that it still is one of the basic measures to be taken.

Sedation

From British chemical industry the advice of absolute rest for 24 to 48 hours after all inhalation cases with phosgene (and other irritant gases) was given. Morphine should be avoided due to its suppressive effect on respiratory function [Jones 1940]. In contrast, initial US recommendations included the use of “morphia” to calm down restless gassed soldiers [Army War College 1917]. Later advice was given against its use except for very severe cases [US Army 1918].

However, no such respiratory depressive effect of morphine, but an increase in survival (about 13%) in animal experiments was derived from an overview and evaluation of the studies [Freeman et al, 1945a]. For human cases, however, the benefit, if any, of morphine was regarded as dubious. A dose of morphine as small as possible to achieve a reduction of the struggle for air was advocated.

In contrast, anesthetic doses of barbiturates were not found to be beneficial, but increased mortality. For sedative barbiturate doses there was insufficient evidence, as was for other forms of sedation. In consequence, advice was given against the use of barbiturates [Freeman et al. 1945a]. In contrast later animal experiments in rats showed an inhibitory effect of urethane-, pentobarbital-, propylene glycol- or chloralose-narcosis on edema formation or lung weight to body weight ratio, which confirmed earlier results [Bean and Zee 1966, Maly 1970].

In an overview paper the application of narcotics even morphine and sedatives were recommended based on the theory that the genesis of the pulmonary edema may be “neurogenic”, assuming there is a reflex arc from hypertension caused by adrenaline to a sudden increase in permeability of the pulmonary vessels [Belknap 1951]. However, this has largely remained a theory. In a similar framework atropine was regarded as contraindicated, as by depressing the vagus and thus pulmonary reflexes it was assumed to cause relatively sudden pulmonary edema [Jones 1940].
The application of sedatives at least during transport was suggested in 1983 [Klimmek et al. 1983]. A US publication in 1985 reported the use of valium sedation in 2 severe cases [Regan 1985]. Also for toxic lung edema from nitrous oxides sedation has been used successfully [Queck et.al 1975]. In

China, where physicians overlook 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].

In experimental lung edema in rabbits, induced by adrenaline, sedatives/narcotics prevented fatalities – in particular chloral hydrate and papaverine, but also morphium and barbiturate [Luisada 1928]

Conclusion – rest and sedation

From the historic and recent evidence phosgene exposed patients should be kept at rest as far as possible. This would include, if at all possible, to rescue them from exposure (under breathing protection), and at least to help them with decontamination or even apply passive decontamination like showering on a stretcher.

Sedation, e.g. by diazepam, should at least be seriously considered. In the light of animal experiments it seems to be favorable.

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APPENDIX 2

Use of steroids after phosgene exposure – detailed review

For many experts corticosteroids still are indispensable in the treatment of phosgene poisoning [Klimmek et al. 1983, ACC 2006, Muskat 2008, Solinska-Lewna and Hermelin 2010, BASF 2010a and b], and are applied regularly in phosgene inhalation cases worldwide [Zhu 1985, Albrecht 1997, Steffens and Hoffarth 2003, Chen et al. 2006, Shi 2006, Wang and Li 1998].

The rationale for cortisone treatment of phosgene inhalation is given in a dissertation cited by [Diller 1985], that reported equivocal animal experiments with positive effect on lung edema formation, but no effect on mortality. The best mode of application remained unclear, with some clinicians favoring aerosol inhalation alone, others rejecting it, and many preferring aerosol plus systemic administration.

In total, the use of steroids for phosgene and other irritant gases inhalation poisoning treatment is regarded by a group of authors as being without definite proof of efficacy in humans, in animals even potentially detrimental [Sangster and Meulenbelt 1988, Meulenbelt and Sangster 1990, Meulenbelt and Sangster 1994, de Lange and Meulenbelt 2011]. So still it must be regarded as opinion-based [Diller 1999].

In a general overview unrelated to toxic pulmonary edema immediate effects achievable with rapid IV injection of corticosteroids at high doses (1 g/day prednisolone or equivalent) have been described. These effects were due to direct physico-chemical effects on cellular membranes, possibly transmitted by receptors on the membranes. Also high dose corticosteroids are supposed to inhibit the liberation of oxygen radicals, thus stabilizing endothelial integrity [Buttgereit et al. 1996].

A2.1 Corticosteroid administration by inhalation:

Animal experiments:

Animal testing of dexamethasone-isonicotinate aerosols sprays showed reduced edema formation, if given immediately after phosgene inhalation. Efficacy decreased with increasing delay of application. Longer or repeated therapy increased the edema. Reduction of mortality and increase in survival time were seen, but were not significant [Brand 1971]. However, further experiments by the same group showed but little edema reduction [Wimmer 1972].

After inhalation of phosgene gas at near lethal doses dexamethasone-isonicotinate aerosol spray in rats every 30 seconds was fatal, while application every 90 seconds was tolerated. This was supposed to be due to a combination of high doses of carrier gas from the spray and hypoxia. No positive effects were seen [de Rooij et al. 1981].

An overview indicated both reduction and increase of pulmonary edema, but also reduced mortality and prolonged survival after dexamethasone inhalation. Phosgene doses were between 210 and 900 ppm-min [Diller and Zante 1985].

In pigs the effect of budesonide (2ml of a 0.5 mg/ml solution) given 1, 6, 12 and 18 hours after an inhalation dose 488 ppm-min phosgene over 24 hours was assessed. No differences to the control group (glucose saline inhalation) were found for mortality, lung edema, shunt fraction, BAL parameters, mediators of inflammation, or cardiovascular parameters. Budenoside did not improve the outcome, but was not detrimental either [Smith et al 2009]. Application of higher aerosol doses earlier than 1 hour after phosgene inhalation may be required to be effective [Grainge and Rice 2010].

Experiences in humans:
The use of corticosteroid aerosols in chlorine and phosgene inhalation was recommended based on experiences with 99 cases [Faure et al. 1970].

A non-peer reviewed German paper addressed the use of dexamethasone-21-isonicotinate as antidote against lung irritant poisonings, of which only 3/4099 were phosgene cases [Daunderer 1986]. In total the paper gives no scientific rationale for the use of corticosteroid aerosol for prevention or treatment of phosgene poisoning.

Further casuistics reported efficacy of a regimen including aerosols [Fabre et al 1983].

In a congress poster the use of beclametasone spray was described in 40 patients after potential phosgene inhalation. However, as their symptoms were of irritation only, it is not clear whether there was actual phosgene inhalation [Zilker et al. 2010].

A2.2 Corticosteroid administration orally:
Animal experiments:
After 1880 ppm-min phosgene dogs were given 40 mg/kg cortisone orally, 3mEq/kg sodium bicarbonate orally, and 100% oxygen over 30 minutes and were observed for 2 hours. Oxygen increased PaO_2, while cortisone and bicarbonate had so such effect. However, observation time was considered to be too short to see a cortisone effect [Mautone et al. 1985].

Experience in humans:
Application of cortisone allegedly contributed to survival of a patient with lung edema from phosgene inhalation [Gerritsen and Buschmann 1960]. Application of 100 mg hydrocortisone daily supported recovery in a probable phosgene poisoning from heated paint stripper. It is not clear, whether the application was orally or IV [English 1964].

A2.3 Corticosteroid administration parenterally:
Animal experiments:

In mice intraperitoneal injection of 1.5 to 10 mg/kg methylprednisolone after phosgene inhalation showed positive effects (mortality and survival time) only for the 1.5 mg/kg dose and for application 2 and 4 hours after exposure. Other doses and time had no or even a negative effect on mortality, though they all reduced edema formation [Gruner 1972].

No increase in survival time was seen after intraperitoneal injection to mice of 10 or 20 mg/kg methylprednisolone or the equivalent dose of dexamethasone after a phosgene dose of about 118 ppm-min (470 mg/m^3-min, about at the LD_{50}) [de Rooij et al.1981].

Hydrocortisone at a dose of 40 mg/kg increased survival time, but did not reduce lung edema in rabbits [Frosolono et al.1978].

In an overview equivocal results for mortality have been reported for intraperitoneal application of 6-methylprednisolone at doses between 1.5 and 20 mg/kg b.w. after phosgene doses between 340 and 1,200 ppm-min. Pulmonary edema was addressed in only one publication assessed, which found a decrease. No dose-effect correlation of corticosteroids can be derived from the tables [Diller and Zante 1985].

6 hours after exposure to ca 488 ppm-min (2,000 mg/m^3-min) phosgene methylprednisolone (12.5 mg/kg) was given to anesthetized pigs and biochemical and physiological parameters were monitored to 24h. No differences to the control group were seen for mortality, lung edema, shunt fraction, BAL parameters, inflammatory mediators or cardiovascular parameters. Methylprednisolone did not improve the outcome, but was not detrimental either [Smith et al 2009]. Earlier application may be required to be effective [Grainge and Rice 2010].

Experience in humans:
German papers assessed corticosteroids as being effective based on casuistics [Fruhmann 1974, Fruhmann and Jahn 1974]. Older textbooks on Occupational Medicine recommend the use of corticosteroids IV [Ehrlicher 1961]. Similarly, reports from France reported efficacy of a regimen including corticosteroids by injection [Fabre et al 1983], or as aerosol and IV injection combined [Faure et al. 1970]. Corticosteroids were given in successful regimens in the USA [Everett and Overholt 1968, Regan1985]. Lim et al (1996) reported from Korea that two patients treated with methylprednisolone survived while death resulted in one patient without such therapy, albeit with more severe symptoms, were reported.
In China 156 patients with phosgene inhalation poisoning, of which 35 were with pulmonary edema, were successfully treated with a regimen including corticosteroids, but no mechanical ventilation. However, application route, dose and timing were not described [Zhu 1985]. Also, in other Chinese papers with smaller numbers of patients use of corticosteroids like dexamethasone (140 mg) is described and regarded as effective in successfully treated severe cases [Chen et al. 2006, Shi 2006].

In a further case from Germany initially corticosteroid aerosol was given as prophylaxis. The patient still developed pulmonary edema, but fully recovered with 1000 mg prednisolone IV twice daily without mechanical or positive pressure ventilation [Steffens and Hoffarth 2003].

Two more cases of toxic lung edema from phosgene were successfully treated with repeated doses of 1 g methylprednisolone without mechanical ventilation. Treatment was started only, when there was full-blown lung edema [Zilker 2010, Zilker et al. 2010].

A2.4 Experience with other lower airway irritants

As the data for phosgene itself are scarce, consideration of other lower airway irritants is useful.

Corticosteroid inhalation:

Animal experiments:

A reduction of lung edema in rats by prednisolone intraperitonally after inhalation of ozone or nitrous gases reduced lung edema formation in rats by 50% [Henschler and Jacob 1958].

After nitrous gas inhalation increased survival time and decreased lung edema formation were seen in rats from inhalation of dexamethason-isonicotinate. [Wimmer 1972].

After chlorine exposures (140 ppm over 10 minutes) in pigs 10 µg/kg nebulized beclomethasone-dipropionate given immediately and after 30 minutes improved lung parameters and cardiovascular function and reduced lung edema,. Application 60 minutes after chlorine was less effective [Gunnarsson et al 2000, Wang et al. 2002]. The positive effects could be increased by combination of budesonide (0.1 mg/kg) and terbutaline (0.1 mg/kg) [Wang et al. 2004]. In all these studies observation time was only 5-6 hours. However, also with an observation time of 23 hours similar positive effects were seen both for beclomethasone and for betamethasone IV (2.5.mg/kg) [Wang et al. 2005].

Experience in humans:

In cases of both severe chlorine and nitrous oxides inhalations good results have been reported [Tilling and Knick 1960]. In a mass poisoning with a combination of nitrous oxides, nitrosyl chloride and hydrogen chloride (n=146) treatment on location was done with high dose dexamethanson-21-isonicotinate aerosol application (150 puffs/2-3 hours). Lung edema was only seen in one person, who left the site without treatment [von Clarmann 1975]. No positive effect of inhaled corticosteroids was seen in a very case of severe lung edema from nitrous gases [Bur et al. 1997].

The German Army has reported experiences with the use of inhalable dexamethson-21-isonicotinate (aerosol) and of very high doses of parenteral methylprednisolone after zinc oxide smoke inhalation Earliest possible application is key, as is the correct dosage of the aerosol (doses too high increase edema formation). In 25 cases lung edema was only seen if there was no or delayed aerosol application. The recommendation clearly is to give

corticosteroids by inhalation and iv injection regimen also for other lower airway irritants [Helm 1969, Helm et al. 1971, Schmahl 1974, Helm 1980].

Parenteral application:

Animal experiments:

8 mg/kg methylprednisolone intraperitoneally in mice shortly after inhalation of sublethal doses of nitrous gases and before onset of lung edema symptoms reduced lung edema [Henschler and Ross 1961]. This had been shown for chloropicrin and thiourea before, too [Henschler and Reich 1959]. The same methylprednisolone dose slightly reduced mortality with unchanged survival time and lung edema formation after nitrous gases or ozone [Vitting 1963].

In contrast, a trend to increased lung edema and mortality was seen from corticosteroids directly after nitrous gas exposure in guinea pigs [Vassilyadi and Michel 1989]. No effect on lung injury from nitrous gases was seen from intramuscular application of dexamethasone in rats and rabbits [Meulenbelt 1994].

Dexamethasone (20 mg/kg intraperitoneally) significantly reduced lung edema formation in guinea pigs exposed to ozone [Toward and Broadley 2002].

A Dutch group from a literature review pointed repeatedly at an increased collagen synthesis once high-dose corticosteroid treatment is stopped in rats after butylated hydroxytoluene inhalation. Alveolar cell type II proliferation was inhibited by short application (2 days), while the proliferation as well as lung damage and mortality were increased by longer (5 days) application [Sangster and Meulenbelt 1988, Meulenbelt and Sangster 1990, Meulenbelt and Sangster 1994, de Lange and Meulenbelt 2011].

Experience in humans:

Steroid therapy (unspecified) was said to have had an early and good effect on 6 patients presenting with toxic lung edema [Becklake et al. 1957]. Other casuistics report a beneficial effect of prednisolone on the lung edema caused by nitrous gases [Lachnit 1958], or for the prevention of lung edema after inhalation nitrous gases, if given quickly [Queck et al. 1975]. No improvement of a very severe lung edema after inhalation of “nitric acid” (*viz* nitrous gases) was seen from 4 x 250mg methylprednisolone IV per day [Bur et al. 1997].

A2.5 ALI and ARDS of different origin

Phosgene poisoning is a subtype of ARDS or ALI. Therefore the issue of corticosteroid use in these syndromes is shortly addressed, but only for early use.

Inhalation:

Inhaled corticosteroid have not been clinically use in ALI/ARDS. There is evidence, however, from experiments of certain benefits, including attenuation of lung edema formation, and improvement of clinical indices of

lung injury in chlorine inhalation. 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]. A Cochrane review considered only 2 studies with high dose steroids, and found no difference in mortality. Other parameters like duration of mechanical ventilation could not be assessed [Adhikari et al. 2004].

A further meta-analysis came to the conclusion that for prevention of ARDS in risk patients the use of steroids is not recommended, and high doses are harmful. One study seemed to indicate a benefit of early phase low dose infusion [Deal et al 2008]. Also low-dose treatment (1mg/kg/day of methylprednisolone) starting latest 72 hours after onset of ARDS with tapering showed positive results [Meduri et al. 2007]. Such corticosteroids us was advocated, but a recommendation was given against high initial doses [Annane 2007].

In a review of 5 studies a clear benefit of corticosteroid therapy in ARDS was found, both for early and for prolonged application [Meduri et al. 2008]. This was confirmed in 9 more studies, where a clear benefit of low-dose (40-250 mg/d) methylprednisolone or equivalent was stated, including two of these studies in which steroids were given at onset of ARDS. No increase in adverse events was seen [Tang et al. 2009]. In another meta-analysis a non-significant negative effect trend was seen for preventive steroids. There were more frequent development of ARDS and fatalities. Once there was ARDS present, a positive trend was seen [Peter et al. 2008].

Other authors regard the use of corticosteroids as of no long-term beneficial outcome and thus not indicated [Calfee and Matthay 2007]. A clinical trial of inhaled corticosteroids in ARDS is advocated [Reade and Milbrandt 2007].

A2.6 Conclusion:

The data situation for corticosteroid use, be it as aerosol or as IV injection, is contradictory. Yet there seems to be evidence for at least some positive effects. Detrimental effects have rarely been described – rather there are indications that corticosteroid might be void of an effect. What is clear from literature is the need to apply corticosteroids as early aspossible – before onset of pulmonary edema. So the use is recommended, but left to the discretion of the attending physician(s). There is no evidence-based requirement to use corticosteroids in phosgene poisoning.

References: Appendix 2

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APPENDIX 3

Use of *N*-acetylcysteine after phosgene exposure – detailed review

N-acetylcysteine (NAC) has been suggested as a therapeutic intervention for phosgene inhalation.

However, most publications finding it to be effective against toxic lung edema and underlying mechanisms have used it for pretreatment, this is before phosgene exposure. The transferability of these results to real-life situations with application after phosgene exposure is questionable [Bernard 1991, Lailey at al. 1991, Särnstrand et al. 1995, Jansson et al. 2005, Chuang et al. 2007, Mitsopoulos et al. 2008]. The same is true for studies in acute lung injury (ALI) from other compounds [Rhoden et al. 2004, Kao et al. 2006].

Few publications address post-treatment effectiveness of NAC given after phosgene inhalation or after other inducers of toxic lung edema.

From 45 to 60 minutes after 1500 ppm-min phosgene the intratracheal application of 40 mg/kg NAC to isolated perfused rabbit lungs the lung weight gain was reduced compared to phosgene alone, as were leukotrienes in perfusate. The pulmonary artery pressure was decreased, tracheal pressure was reduced, glutathione concentration in lung tissue was preserved [Sciuto et al. 1995]. NAC thus seems to increase membrane stability and at least inhibits fluid transudation into the alveoles [Sciuto and Hurt 2004].

NAC given i.p. after 500 ppm-min phosgene inhalation at 50, 100 and 200 mg/kg b.w. decreased lung wet/dry ratio, thus edema formation, in a dose-dependent manner. Markers of oxidative stress were also decreased [Ji et al. 2010].

An examination of the effectiveness of aerosolized L-cysteine (not NAC) given immediately after phosgene exposure (225 ppm-min) for 5 and for 15 minutes at the maximum technically attainable concentration, mostly as a dry aerosol was reported [Pauluhn and Hai 2011]. Lung weight and BALF-protein 1 day after exposure and treatment were analyzed and did not show a positive effect of L-cysteine application.

The LPS (lipopolysaccharide, endotoxin) effect on rat lungs was assessed by albumin leakage, myeloperoxidase content and BALF (bronchoalveolar lavage fluid) cell counts, lipid peroxigenation and histology of the lung. NAC by i.p. injection attenuated the increase in lung permeability and reduced the increase in lipid peroxidation, even if given 2 hours after exposure. Suggested mechanisms are free radical scavenging and inhibition of the neutrophile oxidative burst [Davreux et al. 1997]. At 4 and 8 hours after inhalation of perfluoroisobutene by rats NAP (1000mmol/kg i.p.) increased

the survival rate, reduced the inflammatory processand the BALF protein, but not lung wet weight [van Helden et al. 2004].

In humans the application of NAC to patients with septic shock and ARDS increased glutathione and improved cardiovascular function including X-ray lung edema scores [Bernard 1991]. Randomized studies with NAC in ALI/ARDS patients gave contradictory results – positive like shortening of ARDS without reducing lethality [Bernard et al. 1997], improved oxygenation and reduced need for ventilatory support [Suter et al. 1994], protective effects on lipid peroxidation in ARDS [Ortolani et al. 2000], significantly improved oxygenation and decreased mortality [Moradi et al. 2009], or no significant positive effect [Jepsen et al. 1992, Domenighetti et al. 1997]. In reviews and meta-analyses of some of these studies NAC is not considered as a viable treatment for ARDS [Adhikari et al. 2004, Bream-Rouwenhorst et al. 2008].

- There is only one unpublished report on a phosgene poisoning with toxic lung edema from Thailand that was treated with NAC as suggested for acetaminophen poisoning [personal communication Dr.Suputtitada, Rayong Hospital, 2005]. Details are:
- phosgene leakage, concentration up to 1000 ppm, spread over a 3 km radius
- 43y male affected with cough, dyspnea, nausea, vomiting after smelling musty hay for 5 minutes (d0)
- d1 – lung edema, ARDS. Moved to Intensive Care Unit, mechanical ventilation (100% O_2, PEEP 5 cm H_2O), hydrocortisone, aminophylline
- d2 – increasing edema, clinical deterioration
  - upon recommendation of Bangkok Poison Control Centre, NAC 7500 mg as IV drip over 4 hours
  - improvement after 4 hours
  - NAC 2400 mg as IV drip over 8 hours
- d 3 – edema resolved
- d 7 – moved to normal ward
- d 10 – discharge

Some papers on treatment of phosgene poisoning recommend consideration of application of 1-2 g nebulized NAC [Grainge and Rice 2010], while for ARDS the situation is not yet clear [Kopp et al. 2003].

Taken together literature on nebulized/inhaled NAC for phosgene inhalation is scarce and based on one animal study with intratracheal application. For ALI/ARDS there are no studies on nebulized NAC. A second study used largely a dry aerosol of L-cysteine and found it not to be effective.
As NAC inhalation may cause bronchoconstriction, pulmonologists rather advise against its use.

For parenteral application the data situation for toxic lung edema, not for phosgene, from animal experiments is hardly better – yet there seems to be an effect. For humans there is only one casuistic with phosgene and toxic lung edema. As mentioned above, the risk of potential allergic reactions and

the doubtfulness of effect prompted lung specialists to advise against the use of NAC.

For ALI/ARDS there is no clear benefit according to meta-analyses and reviews. However, several papers show a tendency or even significance for improvement of different parameters of lung injury.
In regard of potential sude effects, injection or even infusion of NAC is no longer recommended by pulmonologists.

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APPENDIX 4

Suggested Minimal Medical Program Requirements for a Phosgene Using or Producing Site:

i. The site/plant should have its own site-specific emergency medical response plan. The plan may reference this document, but should not rely on it as it own plan.

ii. The site/plant should have emergency responders on site whose members are trained and drilled on the effects of phosgene and the site/plant's specific emergency medical response plan.

iii. The support of a physician familiar with the site's emergency medical response plan and the toxic effects of phosgene should be available to the responders covered by the site/plant's emergency medical response plan within less than 30 minutes. Access by telephone suffices.

iv. Time from call to arrival on-site of an ambulance should be less than 20 minutes.

v. Travel time from the site to a Medical Facility with an emergency department with 365 days/year physician staffing should be 30 minutes or less.

Should the site/plant be located where (iv) and (v) criteria are not met by external resources, internal resources will need to be augmented, i.e. an on-site am