Phosgene Handling

General Safety Guideline,

Best Industrial Practices and

Medical Approach

Compiled by

Indian Phosgene Council

Disclaimer:

The Sole purpose of this document is to share general knowledge about Phosgene.
All the information of this report is meant for general guidelines only and should not be treated as conclusive in any of its mean.
It is likely that steps, procedures and other guidelines described here may differ depending upon local and other legislative criteria enforced by regulating authorities. In such cases local and other legal guidelines are to be followed.

Table of contents:

Introduction:

Phosgene is also known as carbonyl chloride having C.A.S. # 75-44-5, U.N. # 1076. It is categorized as toxic chemical having typical pungent smell; however it must be noted that its odour threshold concentration is above its threshold limit value. it is colorless and non-flammable. It decomposes in bio-degradable compounds.

Besides of gaseous form, Phosgene also may be used or handled either in dissolved or in condensed form.

Gaseous Phosgene is produced by chemical reaction in between Carbon Monoxide (g) & Chlorine (g). Di-phosgene and tri-phosgene are other sources of Phosgene in industrial processes. During most of the industrial uses of Phosgene, it is immediately consumed in 'Phosgenation' section and never stored. The overall plant hold-up of Phosgene should be kept at minimum. If for what so ever reason Phosgenation section is not being operated then production of Phosgene should also be stopped.

Phosgene is mainly used as intermediate for production of aromatic diisocyanates such as MDI & TDI, aliphatic diisocyanates such as HDI and Polycarbonates. It is also used as an active ingredient in the pharmaceutical, agricultural industries.

As mentioned earlier Phosgene is highly toxic gas and its exposure may lead to death.

1. Safety Management System:

A detailed and stringent Safety Management System (SMS) is needed for Phosgene producing facilities. Followings are some but not all, of the basic elements that constitutes good safe working environment when dealing with Phosgene.

The roles, responsibilities, accountability, authority and interrelation of all personnel who manage, perform or verify work affecting phosgene safety should be defined. Senior management should commit to achieving the high standards of hazard control (see Chapter 1.3.1 & 1.3.2).

Employees and others present at the establishment, for example contractors, should be involved in the arrangements for managing major hazards and their implementation. Particular attention should be paid to contractors to ensure they receive the necessary information and training.

The Plant Operating Company should develop and implement procedures to systematically identify and evaluate hazards arising from their activities (in both normal and abnormal conditions), and from the substances and materials handled or produced in them. The procedures should be described in the SMS. There should also be systematic procedures for defining measures both for the prevention of accidents and for the mitigation of their consequences.

The Plant Operating Company should prepare, keep up to date and have readily available the information on process hazards, design limits, operational limits and controls coming from the hazard identification and risk evaluation procedures. The SMS should describe documented procedures to ensure safe design and operation of plant, processes, equipment and storage facilities. Safe working practices should be defined for all activities relevant to operational safety.

Procedures, instructions and methods of work should be developed in cooperation with the people who are required to follow them, and should be expressed in a form they can understand. The operator should ensure these procedures are implemented and provide the training necessary.

The Plant Operating Company should adopt, and implement, management procedures for planning and controlling all changes in people, plant, processes and process variables, materials equipment, procedures, software, design or external circumstances which are capable of affecting the control of major accident hazards. This approach should cover permanent, temporary and urgent operational changes as well as changes to the management arrangements themselves.

The SMS should include the procedures necessary to ensure that an adequate emergency plan is developed, adopted and implemented. Scenarios for hypothetical accidents shall be developed, here the release of the largest connected mass should be considered together with effective mitigation measures.

The SMS should describe how the plant operator maintains procedures to ensure that safety performance can be monitored and compared with the safety objectives defined.

In addition to the routine monitoring of performance, the plant operator should carry out periodic audits of the SMS as a normal part of its business activities.

1.1 **Rules & regulations**: phosgene producing facility must comply with all the local and national rules & regulations. In addition to that other international norms also may be adopted to support best working environment. Prior to the start of construction (or operation), a notification must be sent to the authority containing details on registered place for plant operation, information about all the chemicals being handled in plant premises along with its quantity being handled, information about storage facilities of various raw material etc.

1.2 **Phosgene work area definition**:

Phosgene areas are typically those sections of a unit containing phosgene and mixtures in liquid or gaseous form, Other toxic gases such as carbon monoxide and chlorine could also be used in the phosgene work area.

1.3 **Safety management**:

1.3.1 Plant and Process hazard analysis:

Central to phosgene safety is a comprehensive, well-defined, communicated and enforced management system. All properties of the management system must comply with national and local requirements. Safe operation must be ensured by adherence to procedures and rules. These must be reviewed and updated on a regular basis

The detailed safety review should be performed as a plant and process hazard analysis. Several methods for detailed safety reviews have been developed:

- Failure Mode and Effect Analysis (FMEA, mostly used in the automotive industry)
- Fault Tree Analysis
- Inherent Safety Review
- Layer of Protection Analysis (LOPA) / Lines of Defense

- Quantitative Risk Assessment (QRA)
- Hazard Identification and Risk Assessment (HIRA)
- Hazard and Operability Study (HAZOP)

All methods follow the same main principle:

- Systematic identification of hazards
- Assessment of the risks involved
- Definition of adequate safety measures

The formation of an investigation team with very experienced participants from the necessary functions (unit manager, plant and E&I engineers, production experts, unit operators, HSE expert, fire brigade and a plant and process safety specialist as moderator) is essential to make the right evaluation and assessment of the identified risks, followed by definition of appropriate and efficient safety measures.

1.3.2 Safety reviews:

Plant and process safety reviews should be developed in different levels of detail during process development and plant life cycles. Design, engineering and modification phases of phosgene plants or their operation must be accompanied by safety reviews to identify significant risks for people and environment and to eliminate or minimize potential

Safety reviews should be established during different stages of process development, detailed engineering, and unit construction and operation. Every safety review must be finished with an appropriate documentation/certificate:

- Preliminary safety reviews

Preliminary safety reviews should be performed during process development or concept stages to determine safety data for the involved substances, mixtures and reactions and to compile process parameters and boundary conditions like waste treatment.

- Safety design reviews

At the unit design stage, a systematic safety design review should be performed to address all main process and unit safety issues. At the end of this step, all safety-relevant information that is necessary for the beginning of the detailed design phase have to be compiled and a basic safety concept must be developed.

- Detailed safety reviews / HAZOP (Hazard and Operability Study)

Detailed safety reviews should be performed before the plant construction phase in the form of a process hazard analysis (see also Chapter 4.2.2). This analysis must be moderated by an experienced process safety specialist based on detailed process descriptions, technical drawings (PI diagrams, PCT information, piping and equipment specifications, plant layout plans, etc.) and process safety data.

- Prestart-up reviews

During this safety review, the realization of the overall safety concept must be checked and certified before the initial start-up of a phosgene unit. This must be done through unit inspections and functional equipment testing. Unresolved items that require action must be documented. It must be clearly defined which action items need to be solved prior to start-up.

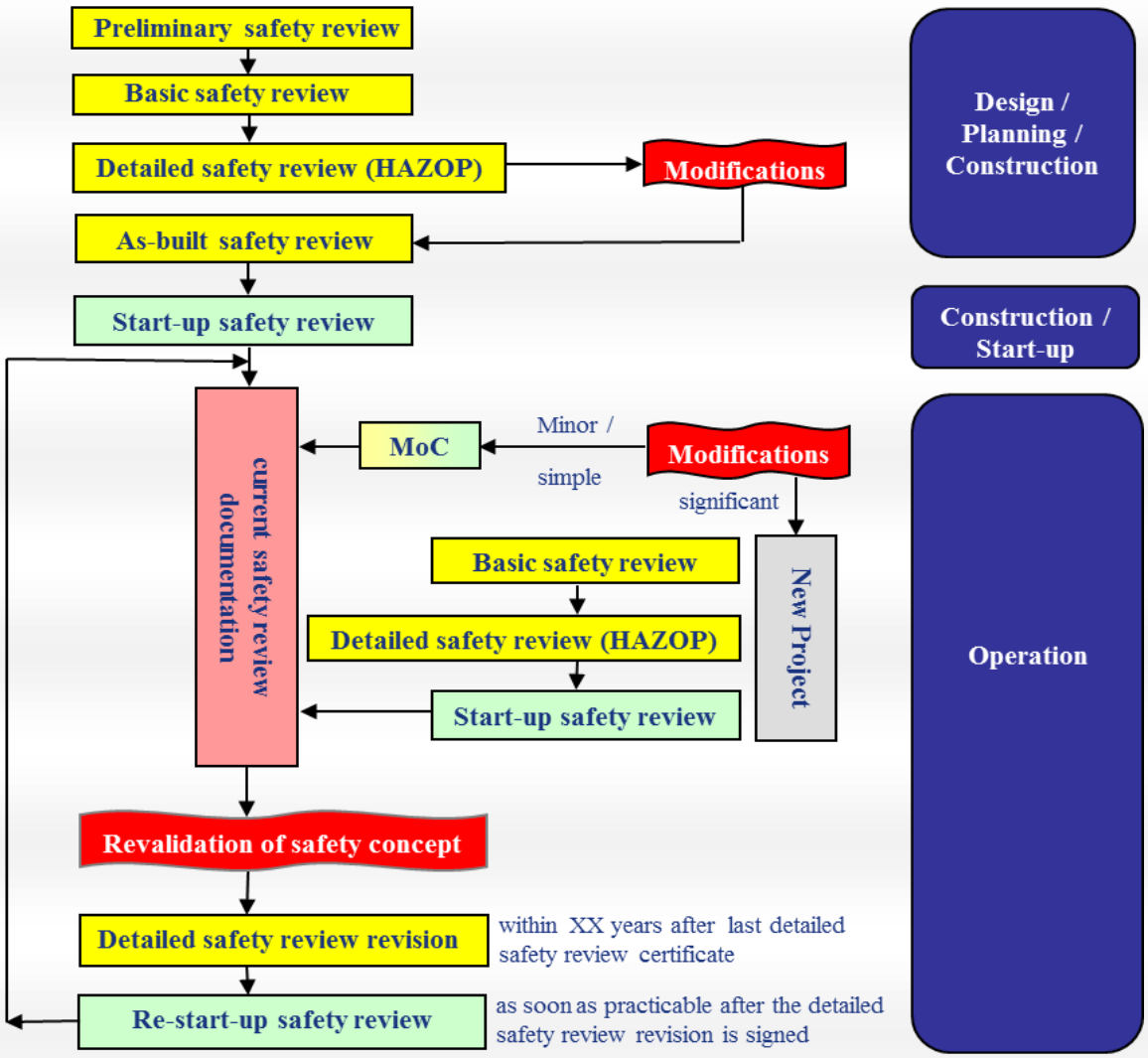
- Safety reviews for process and unit modifications

Prior to any modifications of a process, substance or equipment at an existing unit, it must be evaluated if this change may have an impact on the existing safety concept. If so, a detailed safety review must be executed for the operation concerned. Smaller modifications may be documented via a management of change (MOC) procedure. Important and complex changes should be handled as a project for a new process or unit and **need a** new comprehensive process hazard analysis.

- Periodic safety reviews

Periodic revalidation of the detailed safety review (process hazard analysis) for existing phosgene units is strongly recommended. A five-year period for revalidation of the process hazard analysis is good practice in the chemical industry.

Safety Review Flow Chart:



2. Basic engineering concepts:

Basic engineering concepts should be followed for safe installation of phosgene producing facilities. Some of the important basic concepts are recommended as under.

2.1 **Plant lay out**: Phosgene producing facilities should be installed as far as possible from local populations. During construction of various plant sections local wind direction and other meteorological data should be considered. It is advisable to construct phosgene carrying sections as near as possible to each other so as to reduce phosgene hold up of carrying lines, equipments etc. Wind indicators, phosgene sniffers, Manual Call Point (MCP) etc. should be installed at all the strategic locations of plant.

2.2 **Design concepts**: Plants should be designed on the basis of failsafe design or should be protected by proven technical safety measures. Design concepts should take care of all the hazardous conditions that may arise during operation of plant at well in advance during designing stage of the plant. Phosgene generation and processing units are recommended to designed and operated according to a dual safety measure concept:

Layer of Safety Protection: there are two layers of safety are defined as per following

1. Primary Safety Measures (PSM) are of preventing nature i.e. primary safety measures mainly focus on prevention methodology.

2. Secondary Safety Measures are of mitigating nature i.e. secondary safety measures mainly focus on mitigation methodology unlike of PSM.

2.2.1 **Primary Safety Measures**: Piping, equipment, pumps, PCT equipment and process controls must be designed in accordance with the requirements described in this manual. In addition, the following items must be in place to complete the first measure:

- A system for the safe control of deviations in the process
- Decomposition systems for all phosgene containing waste gas streams *
- Safety procedures must be in place (e.g. training, MOC, SOP, work permit, ERP, etc.)
- A compact layout design for phosgene service equipment
- Process design that minimizes phosgene holdup

*** For details refer Chapter 2.8.1**

Secondary safety measures

The second measure must be one of the following solutions:

- To contain release of phosgene all the phosgene carrying equipments, pipelines etc. should be under completely contained chamber equipped with phosgene sensors and connected with phosgene scrubbing system.
- Phosgene carrying equipment, pipelines etc. are surrounded with steam-ammonia curtain system to decompose the phosgene whenever it comes in contact with the steam-ammonia gas mixture during release **(Not recommended now a days)**.
- Fully jacketed equipment and piping systems should be used preferably with nitrogen as jacketing media.
- **OR** combination of the solutions above or others which have to be explicitly defined.

*** For details refer Chapter 2.8.2**

The selection of the secondary measure is based on the type of process, the size of the phosgene-containing unit area, the size and complexity of the equipment and piping. All the solutions are of equal value.

Followings are some of the point related with primary containment. Probable excursions (upsets) from normal operating conditions must be taken into account when designing systems containing phosgene.

- Metallic piping and equipment must be designed for full vacuum conditions
- Temperature and pressure ratings of lines, equipment etc. should be considered during detailed engineering phase, so that even under upset conditions their mechanical integrity is maintained.
- Construction materials, wall thickness, fluid velocity and pipe routing must be selected to prevent or minimize corrosion and/or erosion caused by the raw materials, product, intermediates and/or potential impurities.
- No brittle material should be allowed in phosgene service
- Threaded connections should not be used for process connection to minimize risk of phosgene leakage. Instead, flange connections should be used.

- Despite of its flexibility hose whether braided or not should not be used for phosgene carrying services.
- In order to minimize possible emissions to the environment, all phosgene-containing services must be conveyed within the system by either gravity flow, inert gas pressure or shaft seal-less pumps (i.e. canned motor pumps or magnetically coupled pumps)..
- Plant should be designed in such a way that use of flanges, sight glass, expansion joints etc. are at its minimum as these elements are more prone to fail and leading to phosgene release.
- All the valves used in phosgene carrying system should be of bellow seal type.
- All the weld joints of phosgene carrying equipment should undergo NDT at regular interval of time.
- All process vents and pressure relieving devices should be routed to phosgene scrubbing system and all the rotary equipments of this scrubbing system should have back up of emergency power supply.

2.2.2 **Process conditions**: necessary standard engineering practices is to be followed to cater with high temperature and pressure conditions.

Phosgene holds up or inventory should be at its minimum at any given condition of plant. . Pure Phosgene should not be condensed and stored at any stage of plant operation. Condensation of phosgene into a solvent to prepare a defined phosgene solution for the phosgene reaction is preferred.

To avoid chances of water / steam ingress to process side other process – inert fluid should be used as heating or cooling media instead of conventional water / steam. If heat exchangers with double tube sheets are used, steam heating may be accepted. The steam condensate must be continuously monitored for possible leakages (e. g. conductivity analyzer)

2.2.3 **Equipments:** Followings are some of the considerations that should be accounted during fabrication of equipments.

2.2.3.1 **Pressure vessel Considerations** – Factory Act 1948 defines a pressure vessel as 'a vessel that may be used for containing, storing, distributing, transferring, distilling, processing or otherwise handling any gas, vapor or liquid under pressure greater than the atmospheric pressure and includes any pipeline fitting or other equipment attached'.

Fabrication of such vessel should be done only by approved vendors.

It is advisable to design pressure vessels with a minimum number of connections to decrease the number of potential sources of leaks

All vessels have to be designed for full vacuum

It is recommended to design pressure vessel according to temperature and pressure conditions of operating plant. Corrosion allowance is to be added during calculation of wall thickness of vessels and connected nozzles.

To protect vessel against high built up pressure, rupture disk and/or pressure relief valve should be attached with vessel having its outlet connected to phosgene scrubbing system or other suitable process equipment (e. g. surge vessel which can contain the pressure relief).

Connecting flanges of vessel should be of type tongue & groove, raised face, flat face or any special design suitable for service of phosgene.

All welds using at least 2 passes and butt welds that are full penetration welds welded with a cap weld pass if possible are optimal. Weld joints should be accessible for testing by NDT techniques easily. Hidden weld joints should be avoided.

Equipment that are designed for non-phosgene services should be avoided for phosgene service unless they are carefully inspected, tested and declared fit for use.

MOC for vessel, pipelines and other attachments should be compatible with phosgene service at its operating conditions. Material with good ductility may be used.

Phosgene service vessel should be tested internally / externally as per local and other governing laws and regulation. All the butt welds should be 100% radio graphed. Beside of that regular inspection schedule should be prepared and followed at company level.

Good safety considerations require that pressure vessels be protected by adequate E&I instrumentation and/or with a pressure relief device that discharges to a phosgene destruction system in case the design pressure is exceeded.

2.2.3.2 **Heat Exchangers considerations** – heat exchangers should follow the same considerations that of pressure vessels as mentioned earlier.

Besides of that, seamless tubes are recommended for fabrication of exchangers. Welded tubes should be radio graphed. To improve mechanical stability of tubes it should be roller expanded.

Double tube sheet heat exchangers are recommended for phosgene services.

To avoid corrosion due to water being other media, water analysis and/or monitoring should be carrying out. Addition of corrosion inhibitors to cooling water is a good practice to follow. An online pH monitoring system or conductivity monitoring system (preferred) should be installed for monitoring cooling water quality where process side pressure is more than cooling water.

Air cooled heat exchangers should be avoided for phosgene services.

2.2.3.3 **Rotating equipment considerations** – pumps, compressors, agitator and vacuum pumps fall under category of rotating equipments. It is preferable to use seal less rotary equipments to avoid phosgene leakage.

Casting area of equipment viz. has highest stress during operation, area which may have porosity or inclusion, have curvature, nearby area of flange should be radio graphed.

Dye penetration, helium leak test is recommended for inspection of internal and external surfaces.

Seal less pump or MAG drive pump are best suited equipment for phosgene services. While seal pump or double seal pumps should be avoid.

Equipment should be of compatible material of construction with process fluids. As far as possible dead zones should be avoided inside the equipment as these areas are difficult to drain, purge or to be open for cleaning.

2.2.3.3.1 **Centrifugal Pumps:** as mentioned earlier seal less MAG drive or canned pump should be used for phosgene service with instrumentation to monitor dry running of pump, dead heading, bearing flush backflow, motor winding temperature etc.

If seal less pumps are not being used then double mechanical seal pumps might be an option, with seal buffer fluid circulated between the seal, which is compatible with the process and at a higher pressure than the process pressure, will ensure that any inner mechanical seal leaks will go into the process and not to the environment. The seal liquid level must be monitored and equipped with a low level switch.

If a buffer fluid pot is used, monitoring of the level and pressure of the buffer fluid will indicate a seal leak. Dependent on the seal plan selection, it could do the same with a flow measurement.

2.2.3.3.2 *Compressors:* it is good to avoid use of compressors for phosgene services but if required then special design considerations are required.

2.2.3.3.3 *Vacuum pumps:* liquid ring pumps operated with solvent as a seal fluid is recommended for phosgene services. Used solvent fluid should be compatible with process conditions.

2.2.3.3.4 Agitators: It is important that the mounting flange, considered as part of the tank wall, be made of same construction materials as the tank. Other requirements are defined in the pump section

2.2.3.4 **Nonmetallic equipments**: generally being used in small scale units. This type of equipments is suitable to handle aqueous liquids with organic components and other services that are corrosive in nature.

These equipments should be tested for healthiness of inner linings with well established methods. Weld joints and its nearby area should be tested with spark testing method.

The temperature rating of the lining material is critical.

2.2.3.4.1 **Glass vessels**: The use of equipment made of glass in phosgene service is not allowed except in laboratory applications due to the possibility of catastrophic failure.

2.2.3.4.2 **Glass lined steel vessel:** this type of vessels are typically used in fine chemicals and can be suitable for phosgene services also.

2.2.3.5 **Composite material / plastic lined steel vessel**: Steel equipment lined with ECTFE (Ethylene Chloro-TriFluoro-Ethylene) is most suitable for phosgene service that may be operated up to 100 °C. Above 100°C this material may deteriorate.

PVDF (PolyVinylidene Fluoride) is considerably less suitable as a lining material for steel because of its poorer ability to process (higher stiffness), its high water vapor permeability and its high thermal expansion coefficient.

2.2.3.6 ***Graphite heat exchangers***: heat exchanger made of graphite has been used for decades. If properly installed and operated then there are fewer chances of these exchangers to become defective.

Impregnated graphite is good choice for the material of construction for heat exchangers due to its high chemical resistance, good thermal conductivity and mechanical processing. Due to its passive surface, it is also less susceptible to contamination than metal.

Testing: it is a good practice to carry out pressure test of vessel after on floor installation to ensure that no part is damaged either during transportation or installation.

To start with pressure test, all the components of vessel should be tightened properly as per manufacturer's torque guidelines. After that pressure is to be increased slowly and gradually and reaching up to final test pressure. To have final test pressure again manufacturer's manual is to be referred.

The graphite material normally does not undergo any changes. Periodic pressure tests are recommended

Special installation Requirement: graphite is brittle and quite sensitive to pressure surges. Due to this care should be taken during normal operation even at lower pressure.

To avoid pressure surges valves to be used that having slow opening and closing characteristic. Avoid trapping the media in heat exchangers as it may lead to high pressure inside exchanger due to thermal expansions.

Flow should be controlled at upstream of heat exchangers and if possible then valves should be avoided at outlet. As if flow is established against close isolation valve at outlet then it may damage heat exchanger.

2.2.4 **Piping System**: a piping system is defined as pipe, piping components including miscellaneous items contained within the system.

2.2.4.1 **Piping Design**: piping design should be as per national and other local regulations. Standard engineering practices should be followed. Followings are some of the criteria for optimal piping design.

Metallic piping should be of specific schedule number. Seamless piping and its fittings are recommended for phosgene services.

Piping having MOC of CS is accepted but higher alloy are also recommended considering specific operational conditions.

As far as possible threaded connections are to be avoided as they are more likely to leak. Phosgene carrying piping should be minimum of 1" NPS diameter is recommended. 1" NPS diameter is also recommended for instrument and sample connection flanges.

As per safety point of view all the butt welds should be of two passes and 100% radio graphed. Use of expansion joints and flexible hoses are to be avoided.

To reduce leakage possibility number of flanges, isolation valves, remotely operated valves etc. should be kept at minimum as far as practical.

To avoid chances of corrosion of piping heating or cooling with water media is not advisable. Instead of that other process inert media should be used.

Consider using either stainless steel or carbon steel with an appropriate coating for piping for vents, drains and miscellaneous connections which protrude through the insulation and are subject to icing and defrosting.

Even if piping is going be insulated it is advisable to apply paint on piping prior to insulate. Corrosion under insulation (CUI) must be considered when selecting piping materials of construction, paint system and insulation standards. Inspection program must be appropriate to detect this corrosion mechanism.

It is recommended to follow standard color code for all the piping of phosgene.

When not in use it is of good practice to end blind all the open flanges of vent, drain and other specific open points. This may help to reduce leak prone points of plant.

Generally, the following systems are **not suitable for phosgene piping in service** for isocyanate or polycarbonate:

- Thermoplastic lined metallic piping such as CS/PTFE; CS/PP etc. are not recommended for phosgene services due to requirement of frequent flange joints.
- Rubber lined piping are also not advisable for phosgene services due to poor performance of rubber liner whenever organic solvent is present with phosgene.
- PVC, CPVC etc. pipe lines are also not recommended for phosgene service due to their poor strength against mechanical damage.

2.2.4.2 **Pipe routing and support**: phosgene piping should be laid down observing good engineering practices.

It is advisable to route piping that gives shortest distance between two equipments.

To avoid accumulation of condensed phosgene piping layout should be with minimum lowest points. A same criterion is also applicable for phosgene in liquid or dissolved form.

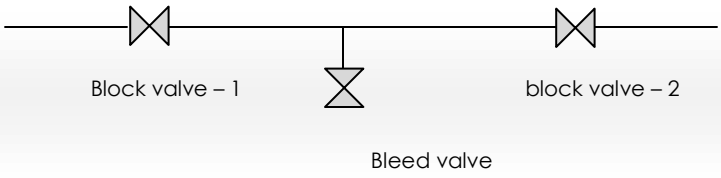
Phosgene carrying lines should be away from hot fluids or corrosive chemicals. This may help to avoid pressurization of line and external corrosion also.

Piping should be installed with proper support to avoid vibration, thermal expansion, stress etc. so as to reduce piping failure.

2.2.4.3 **Expansion joints**: to allow piping for thermal expansion it should be routed with adequate flexibility for that expansion loops may be used. But expansion joints like bellows or compensators should be avoided.

If expansion joints are unavoidable then piping should be adequately supported to lessen stresses. During installation, inspection and replacement manufacturer's guidelines should be followed.

2.2.4.4 **Double block and bleed**: The installation of double block and bleed valves allows the disconnection and opening of equipment from the live operating areas of the unit without a total shutdown of the whole unit. *D*ouble block valve with bleed valve is recommended for phosgene carrying piping. A typical example of this is illustrated below



In this example maintenance is to be done at downstream of block valve –2. For that block valve –1 and block valve –2 will be closed and trapped liquid will be drained through bleed valve provided in between block valve –1 & 2. This arrangement also ensures that line get depressurize through bleed valve.

If double block and bleed arrangement is not possible to install then care should be taken to avoid any phosgene exposure to working personnel. This may be achieved via administrative or other techno-engineering practices.

2.2.4.5 **Non-metallic piping**: Piping made of non-metallic materials is suitable for handling aqueous and liquids with organic components or other services that are corrosive to metallic materials.

When selecting non-metals such as plastics it is important that the piping system is resistant to solvents or other chemicals that may be used. Since non-metallic material applications are in a constant state of development, assessment of material for each application including testing of a representative sample under process conditions is recommended.

2.2.5 **Valves:** only routine isolation valves are discussed here keeping safety relieving and that are being used for process analyser streams a side.

Important considerations:

Minimum numbers of valves are preferable to avoid risk of leak. Valves may have flanged ends or butt welds ends.

2" NPS sized valves are recommended for process lines while 1" NPS may be used for sensors and sample collection system.

Valves should be designed for full vacuum and maximum process pressure and full vacuum and should be compatible with phosgene carrying piping also.

Welded housing for valves should be avoided instead of that housing made of ductile material is recommended.

Threaded connections in a valve body are not allowed for phosgene service

It is recommended to avoid use of three way valves as block valve.

Single body valves are preferred over split body valves

2.2.5.1 **Recommended Valve types**: *following types of valves are recommended for phosgene service*

Bellow sealed globe valve

Plug valves: Plug valves have pressure and temperature limitations. Plug valves must be of lethal service design. Vented plugs are recommended for cold service plug valves to avoid thermal expansion.

Butterfly valves – This type of valves are used whenever large diameter of valve is required. Being acceptable for phosgene carrying service required modifications are to be made to conventional butterfly valves. (2 stuffing boxes with pressure monitoring of the inner space between the stuffing boxes).

Ball valves – this type of valves are widely used for phosgene service and particularly having presence of solid. Valves having metal seat will break trapped solid and will help to maintain sealing quality of material.

It is recommended to drain ball valve completely and let trapped phosgene be released before dismantling valve body for any maintenance or inspection.

Jacketed valves (secondary containment*):* Standard jacketed valves that are providing of heating purpose are not suitable for phosgene service. Special considerations for monitoring the packing gland and bonnet joint are required for jacketed valves to be used for phosgene service.

2.2.6 **Gaskets:** some of the important considerations for use of gasket are compatibility of gasket material with process fluid, compatibility gasket material with process temperature and process conditions, type of flange where gasket is to be sandwiched.

Recommended gasket material for metallic piping system is graphite gasket with or without metal reinforcement, spiral wound gasket with PTFE, kamm profile gasket with PTFE.

Recommended gasket material for non metallic system is rubber gasket with metal inserts, restructured PTFE gasket with non asbestos fillers, PTFE gasket with memory insert, and graphite gasket without metal fillers.

Points to be considered during installation of gasket are prior to fixing gasket closely examine surface for any damage, ensure alignment of surface and centering of gasket, use torque gun to tightened bolts in incremental rounds, take leak test after installation.

2.2.7 **Relief devices**:

Vessels and piping must be protected against excessive pressure.

It is most desirable to relieve the pressure to other process equipment. In cases where this is not possible, the exhaust (outlet) of the pressure relief valve must be directed to a phosgene decomposition system designed to handle the flow rate and state of the worst credible scenario.

In general, rupture disks must not be used as the primary relief device in phosgene service because they have no mechanism to stop the release of phosgene once the excess pressure has been relieved (they are not reclosing).

Vent (test) levers are not allowed on pressure relief valves.

If closed at both ends of a pipe section, block valves in cold service systems (e.g. phosgene solution or liquid phosgene) may cause an excessive pressure increase (thermal expansion). This must be avoided by one of the following options:

- One of the valves is conspicuously identified on P&IDs and locked in the open position.
- A pressure relief valve is installed around one of the block valves.
- Provide an expansion chamber (most often with a rupture disk) and pressure indicator that alarms in the control room.

As well as physical measures organizational and strict procedural controls may be just as effective.

Pressure relief valve design details

All pressure relief valves in phosgene service must be spring-loaded with bellows. Balanced bellows are designed to eliminate the effect of back-pressure on the valve's relief setting.

Additionally, bellows protect the valve components from contact with the product to prevent corrosion, fouling, etc. If the valve has a bonnet with a vent hole, it can be the manufacturer's standard connection (tapered threads) for the monitoring requirements since the connection will not see phosgene in normal service. The bellow has to be monitored for a failure.

The inlet and outlet flanges of pressure relief valves may be the manufacturer's standard flanges as long as they are consistent with the piping system.

As a minimum, pressure relief valves in phosgene service are required to have carbon steel bodies, stainless steel seats and trim, and hydroformed bellows (description of making bellows, standard design).

Certification of the bellows material is required. The bellows connection to the valve stem must be welded.

Use of rupture discs:

It is important to ensure that the product cannot cause the pressure relief valves to stick. In locations where excessive corrosion, contamination or sticking is possible, pressure relief valves must be protected by rupture disks on the inlet and/or outlet sides. This protection is also an option in place of monitoring for bellows failure.

When rupture disks are installed, the void space between each disk and the valve seat must be monitored for disk failure

The relief valves need to be dried perfectly and installed in a way that moisture (moist air) cannot get in, otherwise they will fail in hours/days after introduction of phosgene (chlorine or HCL).

2.3 Support and auxiliary system:

2.3.1 *Segmentation:* It is practice of dividing large units into smaller sections with use of shut off valves that are remotely operated i.e. from the control room. Segmentation minimizes quantity of liquid phosgene that needs to be transferred in dump tank during leakage scenario.

Vapor space of each segmented area should connect with phosgene destruction system ensuring that no phosgene vapor goes to environment.

Segmentation practice minimizes amount of effort necessary to clean and prepare the area around leak to repair.

2.3.2 *Dump tank:* a dump tank is designed to contain the maximum quantity of the largest segment of phosgene handling system and should be connected with phosgene destruction system.

Phosgene draining to dump tank with help of gravity is ideal practice instead of using of pump. Phosgene system connected valves with that of dump tank should be remotely operated type.

It is advisable to flush phosgene draining line to dump tank with solvent once used. Dump tank should be kept empty and in ready to use condition.

2.3.3 *Blow down vessel:* It is advisable to lead discharge material of pressure relief valve to a separate vessel, known as blow down vessel where liquid and vapor phase may be separated from each other and connected with phosgene destruction system for further neutralization of phosgene vapors.

2.3.4 *Evacuation system:* It is a permanent system connected with phosgene destruction system and normally having double block and bleed valves for process side.

Evacuation system is used for clearing equipment for maintenance and to make segmented area phosgene free in case of leakage.

2.3.5 *Elephant trunk system:* It is made of flexible hose having large opening and connected with (a dedicated) phosgene destruction system. Elephant trunk system mainly used to suck any of the phosgene vapors during opening of any flange, line or equipment. The phosgene destruction system of the elephant trunk system should not be connected with other phosgene destruction systems (e. g. maintenance, vent or process gas systems) to avoid backflow of phosgene and a possible phosgene release via the open ends of the flexible hoses.

2.3.6 *Breathing air system:* A dedicated and permanent breathing air supply system is to be provided from a secure source and safe source of supply. Breathing air system should be used whenever any maintenance activity or isolation activity is to be performed in phosgene handling plant. By using of breathing air system phosgene exposure may be avoided with greater extent. If a dedicated breathing air system is not installed, all maintenance or isolation activities must be performed by using SCUBA equipment.

2.3.7 Nitrogen system: to avoid backflow of phosgene to plant general nitrogen system, a dedicated nitrogen system (with adequate reverse flow protection) should be provided for phosgene handling sections.

If dedicated nitrogen system is not facilitated and general nitrogen system is being used for phosgene handling sections then appropriate arrangements are to be done to avoid back flow of phosgene.

Sometimes check valves may not provide adequate protection against back flow so interlocks should be provided to close the various valves based upon differential pressure.

2.3.8 Backflow prevention: it is possible entering of phosgene to flushing system which is permanently connected with the phosgene handling equipments of section.

To avoid backflow of phosgene appropriate pressure differential should be maintained between phosgene handling and flushing system. Valves connected to both systems should be closed on interlock whenever sufficient pressure differential is not maintained.

2.4 *Instrument and process control systems:* this section summarizes engineering and operational considerations for phosgene handling systems. It is advisable to purchase process controlling equipments from approved vendors only and adhering to all technical, legal and other engineering standards.

2.4.1 Important considerations:

Construction principles and materials: it is important that electrical and instrument equipment meet with the requirement of the pipe line to which they are mounted. That mainly contents temperature, pressure, chemical resistance of gasket and other fitments.

Delicate components of instrument / electrical equipment should be enclosed in housing to avoid damage of component due to external force.

Instruments having active sensor systems and enhanced diagnostics are preferred such that if a sensor part is damaged a diagnostic alarm (e.g. maintenance needed, failure, etc.) is generated.

The following are general construction and material considerations for E&I equipment:

- Welds situated so that they can be easily tested after assembly of the instrument are optimal.
- Deterioration due to corrosion and/or erosion can be minimized by selecting the appropriate material of construction and by correctly sizing the device. Suitable materials of construction are carbon steel and stainless steel; however, thin components (e.g. remote seal membranes and bellows) are best made of tantalum or Hastelloy C.
- Parts in contact with the phosgene process made of titanium may not be suitable due to the potential of pitting corrosion.
- When E&I devices consist of parts fastened by bolts, a static gasket seal or a chambered o-ring seal are the best option. When selecting the gasket and sealing materials consider all aspects of the process including solvents, temperatures and possible impurities.
- Process connections welded or flanged consistent with the pipe design are preferred. The instrument mating flange and the E&I instrument flanges are most reliable when surfaces of each matched.
- Avoid using threaded connections to seal the process fluid from the environment, either when making connections or as a component of the instrument.
- When choosing the materials of construction for the fasteners used to hold the parts of the instruments together consider potential corrosion, thermal and brittle effects caused by cold process temperatures, including icing and de-icing.
- Ductile cast material (e.g. ferritic cast steel, austenitic cast steel, spheroidal graphite cast iron) are good options for phosgene services.
- Be aware that PTFE can be permeated by phosgene meaning that it cannot be completely decontaminated. Properly dispose of PTFE components (gaskets, seals, lining, etc.) before the device can be sent outside of the plant for maintenance.

Selection criteria: In general, it is best that the following PCT equipment be considered and only purchased from qualified vendors. PCT equipment, for the purpose of this section, includes:

- Level Measurement by vibration, radar, external nuclear measurement
- Flow measurement by coriolis, vortex, ultrasonic, rotameter
- Pressure measurement
- Temperature measurement(installation of welding thermos-wells into the equipment is preferred)

It is recommended that all pressure bearing butt welds, which are exposed to the phosgene medium during normal operations, be 100% radio graphed wherever practical.

If the exposed butt weld cannot be radio graphed (e.g. due to a thin wall thickness or small diameter) then the weld can be 100% tested using either a dye penetration test (for stainless steel and nickel based alloys) or magnetic particle test (for carbon steel and low alloy steel materials)

It is good practice to test 100% of pressure bearing welds, other than butt welds (e.g. fillet welds), that are exposed to the phosgene medium by either dye penetration or magnetic particle testing.

Installation considerations:

PCT field equipment is installed in a self draining position. Avoid installation of measuring equipment on vessels below the normal liquid level.

All process connections for PCT (and PAT) with a minimum of DN25 (1-inch diameter) are preferred for mechanical stability. This connection can be made in one of three possible methods:

No process block valve: This is a poor option as it requires process shut down for maintenance of PCT and is not reliable enough for PAT applications

A single process block valve: This option also requires process shut down for maintenance of PCT and is considered the minimum requirement for PAT applications.

A double block and bleed valve arrangement (either with process piping and valves, or a mono-flange valve for clean service only): This option is the best option as it allows maintenance of instrumentation to be done while the process is running.

It is good practice to include instrumentation and automated valves in piping and equipment pressure/ leak testing programs unless the testing could damage the instrument. If not included in the pressure testing, the instrumentation should be installed before leak testing of the equipment is complete.

2.4.2 ***Analyzer instrumentation***: Analyzer instrumentation for phosgene service can be classified according to its purpose for monitoring of vent gases, perimeter monitoring and leak detection, of rooms and stream composition monitoring.

2.4.2.1 ***Monitoring of vent gases***: Good options for measurement of phosgene are by infrared absorption or color reaction with reagent solution on paper tape.

2.4.2.2 ***Perimeter monitoring and leak detection***: The design of the monitoring system is based on the detection sensitivity, response time and monitor location.
The degree of monitoring is determined by the number and spatial distribution of the sample points or analyzers.

Followings are two basic designs:

- The "detector tube concept" where the gas samples are conveyed to one or more central analyzers via one or more lines, each having a number of sample points for monitoring certain areas of the unit or critical equipment. The test method is color reaction with reagent solution on paper tape.

  Note: Paper tape devices have negative cross sensitivity interference with HCl.
- The "individual analyzer concept" is one where each measurement point is an individual sensor or analyzer. Measuring method is with an electrochemical sensor.

  Cross sensitivities to other substances are possible. Details can usually be found in the manufactures documentation.

2.4.2.3 ***Air monitoring of rooms***: air monitoring of rooms are to be done for following criteria.

Room air monitoring for intermittently manned rooms: Monitoring of air in closed rooms that contain or located near phosgene bearing apparatus and where personnel are only present on an intermittent basis (e.g. analyzer rooms and decontamination rooms) can be done with phosgene analyzers, directly installed in the room.

Room air monitoring for manned rooms: for ventilation systems in rooms that are manned with personnel on a continuous basis or for extended periods of time, a

phosgene analyzer installed with the sample point in the fresh air inlet duct is advisable.

If phosgene is detected in the air intake, the safest option is to automatically shut off the air intake. And evacuate the personnel in the room to safety following the appropriate emergency procedures. The air intake system should have the possibility to flush it backwards, if phosgene had been detected in the system.

2.4.2.4 ***Design requirements for process analyzer systems***: The tubing in sampling systems consisting of stainless steel tubing (316 or higher alloy) joined by welding or double ferrule compression tube fittings (for example Swagelok) have been shown to be reliable. Threaded connections (that are not double ferrule fittings) may not be reliable enough for phosgene service.

Designing and installing sample lines that allow for flushing the tubing back into the process or to a controlled disposal system is important. Using valves with a high quality stem seal such as bellows sealed valves and diaphragm sealed valves (membrane sealed valves) is recommended.

2.4.2.5 ***Leak detection for analyzers:*** Process analyzer systems have many connections, which can develop leaks. Purging analyzer components, which use non-metallic seals and are in contact with the product (e.g. a glass window in a photometer sealed with an o-ring) continuously with a gas that is monitored for toxic substances (phosgene) and flow is a good safety practice.

It is important to design backflow prevention into the purge gas system to prevent toxic materials flowing back into the purge gas supply.

2.4.2.6 *Sample disposal requirements:* Two options for handling analyzer exhaust streams are: a) to be returned to the process or b) disposed of in a phosgene decomposition system.

Consideration should be given in the design of disposal lines to the potential for corrosion and the potential of over pressure conditions from the process or decomposition system.

2.4.2.7 Analyzer rooms: Potential leaks in the complex analyzer tubing systems could lead to a hazardous situation. These potentials can be minimized by engineering design such as the use of high quality sealing components.

Process analyzer equipment is generally not available in an explosion proof design (EEx rating). In the case of a leak, ventilation of the room is a widely used and accepted practice.

Analyzer rooms constructed away from other rooms will reduce the risk of contaminating those rooms with phosgene or other hazardous substances. Audible and visible plant alarm signals must be also present inside of the analyzer room.

It is good practice that ventilation of analyzer rooms meets the following:

- Avoid exhaust air from the analyzer room contaminating air leading to other rooms.
- The air intake is located away source of hazardous chemicals.

Analyzer rooms, which handle phosgene, should be equipped with the following items:

- Monitors for all potential hazards, e. g. phosgene, chlorine, Oxygen (low), CO and LEL (combustibility).
- An alarm panel showing alarm / status signals from each of the room air sensors and a status indicator for the ventilation system is recommended outside at the entrance to the room with these alarms transmitted to the control room. The functionality of all warning lights must be able to test from the outside before entering the room (Lights bulbs can be burned out and a toxic atmosphere would be undetected).

2.4.2.8 *Calibration:* If possible, use phosgene free gas for calibrations. When measuring phosgene as one component in a mixture, substitute methods are best used, especially if higher phosgene ranges will be calibrated. Reliable substitute methods include the use of surrogate gases or optical absorption filters.

2.5 *Electrical supply:* Two independent 100% power supply lines coming from different sources with automatic switch over are an important consideration to ensure safe, uninterrupted plant operation.

If there is only a single electrical feeder power supply for critical systems and pumps, (i.e. rotating equipment necessary to safely shut down the plant, pumps for the scrubber systems, the process control system, phosgene alarm system, critical lightning), a backup supply provided by either diesel operated generators or/and batteries is encouraged.

2.6 ***Building design***:

2.6.1 Control room and safe rooms: Some sites have their control room as the only clean-air refuge in the case of a chemical release: others have an additional safe area, which is called a "safe room" or "safe haven". The same basic design criteria could apply to both types of refuge areas.

It is advisable that control rooms and safe rooms/ safe havens be designed with the following features:

1) Location should upwind of the plant and as far as possible from sources of phosgene or other hazardous chemicals, which are toxic, flammable or explosive. Any entrance from an area with the potential for phosgene contamination having the characteristics of an air lock (two sealed doors in series in a small enclosed area) is good practice.

2) Gas-tight windows designed such that they may not be opened (except if designated as a fire escape) and preferably installed on the side of the building facing away from the unit.

3) No chemical lines, including compressed air (except breathing air) or nitrogen, running through the room, under the floor or in false ceilings.

4) Alarms and warning systems that are audible and visible in all rooms and buildings in a phosgene unit that announcement systems and alarms be operational at all times so that they are always available during emergencies.

5) It is prudent to maintain a slight positive pressure in control rooms with a reliable and safe fresh air intake monitored for toxic gases including phosgene and other applicable chemicals. Activating an automatic shut down of the ventilation system based on the toxic gas monitor output is a good practice. Control rooms can also serve as safe havens in case of a phosgene release.

6) Adequate and sufficient personal protective equipment, which has been periodically inspected and well maintained, will normally be provided for all personnel operating or shutting down the plant and for evacuation purposes.

7) Self-contained breathing apparatus or breathing air manifold supplied with compressed breathing air, sufficient for all personnel during the period of a safety shutdown of the plant and complete evacuation.

2.6.2 *Ventilation system:* It is good practice to locate the fresh air intake for the ventilation system upwind of the prevailing wind direction and away from potential sources of phosgene or other toxic and/or flammable substances.

Analyzers to detect hazardous chemicals in the air intake that can activate an automatic shut down of the ventilation system and an alarm to the control room if toxic gas is detected are advisable. Duplicate analyzers could also be considered for increased safety.

Visual indication should be provided in the control room for monitoring of the status for all unit ventilation systems with automatic shutdown. It is prudent that the control room has a manual means controlling the ventilation units to allow maintenance of the analyzers.

2.6.3 *Elevators:* It is important if elevators are used in buildings in process areas that they are equipped with:

Breathing air equipment or escape filter masl for all occupants, An alarm, which may be audible or visual, unless the external alarm can be heard or seen at all times in the elevator

External signs at all elevator levels saying "Do not use in the event of an emergency"

2.6.4 *Alarm system:* It is advisable to inform and warn all personnel inside a unit when a phosgene emission is detected and, if necessary, to evacuate the plant. It is prudent, in an emergency situation that personnel outside the unit not be allowed to enter the unit without proper PPE.

Consequently consider equipping units with acoustic and optical alarm and warning systems.

This section describes phosgene alarm systems, used to alert personnel in and around a phosgene unit of potential and immediate danger of phosgene releases. They normally consist of a visual part (lights) and an audible part (horns and/or announcements).

It is understood that there may be needs for additional warning, alarm and protection systems (fire alarms, explosion protection, etc.) but these are not specific to phosgene units and thus are not addressed here.

Ideally phosgene alarm systems will have a back-up power source (batteries, uninterrupted power supply, generators, etc.) to provide power for operating at least one hour after loss of the normal external power source.

It is prudent to have a secure method (always powered and not able to be blocked) transmit phosgene alarm signals (as required by Safety Procedures) to a central site alarm station such as the Plant Fire Brigade Control Centre, Incident Command Centre or Public Fire Department with a clear identification of the location initiating the alarm.

It is prudent that phosgene producing and consuming facilities be equipped with area alarm lights.

The location of the lights depends on the unit structure (open structure or chamber) and would be determined in consultation with safety experts.

Enough lights are positioned in such a way, that anyone approaching the phosgene containing areas from outside be able to see them before entering. This usually means lights positioned at chamber entrance doors, unit corners or stair wells and, if necessary, at appropriate distances down each side of the unit.

Installation of the same style of lights just inside exits of buildings within and directly adjacent to the phosgene unit to alert occupants of the danger outside should be considered.

The lights may be activated by automated sensors (perimeter monitors, process analyzers etc. as defined in the safety procedure), but levelcould also manually activated in the control room.

In units with open structure, alarm lights and sound could also be activated manually from the field by one of the following methods:

Activation button positioned at strategic locations throughout the unit such as entrance to stair wells and normal exit points. Activation by these buttons would also initiate an alarm in control room.

An intercom system may be positioned at strategic locations throughout the unit, which can be used to alert the control room of an alarm situation.

It is prudent that any activation of the alarm system be designed causes an audible alarm to sound in the control room.

2.6.5 ***Announcement system***: a system of speaker should be provided to allow a unit announcement from the control room to the plant about any toxic release, action to be taken etc.

This speaker system is not to be confused with any plant wide announcement system, which provides audio coverage of all plant units and facilities, including non-phosgene production units and offices.

The different announcement systems (e.g. site versus phosgene unit) could be coordinated on a site wide basis into a unified warning concept. If a phosgene unit announcement system is tied into a site announcement system covering a larger combination of units, it would be prudent to coordinate between safety systems.

Precedence in case of competing announcements would be given to the safety announcement of higher importance as defined by Safety Procedures.

It is important that the phosgene alarm announcement system provide clear audio coverage in all phosgene production areas including auxiliary areas such as tank farms, motor control centers, instrument rooms, offices and warehouses. Recorded messages are recommended to provide better understanding and consistent wording.

2.7 ***Phosgene emission control***: It is advisable to install a reliable phosgene monitoring system with multiple, strategically installed, detectors throughout the plant giving an audible and optical alarm in the control room if phosgene is detected.

It is advisable that a system is established that revokes all work permits in the event of a phosgene alarm, stopping all work immediately and providing all personnel in the plant with emergency instructions which typically includes information about predefined safe assembly points where all employees, contractors and visitors gather and be accounted for.

Since wind direction and velocity is important for proper response in the event of a release, installation of wind indicating equipment in strategic locations is advisable.

As part of evaluating your company's needs, the following considerations may be of assistance in case of a plant emergency:

- One or more safe assembly point is needed so as to ensure that at least one assembly point is not downwind from the phosgene emission point
- Emergency coordinators to direct all personnel on the plant to a safe assembly point.
- A weather vane which indicating wind's direction and velocities in the control room.
- A system to account quickly for all personnel (operations, maintenance, lab personnel, service personnel, contractors, visitors) on the plant in case of a plant emergency.

2.8 ***Phosgene destruction systems***: sometimes it is necessary to divert phosgene carrying streams to a destruction system so as to maintain plant parameters. Phosgene destruction systems should be designed considering the worst scenario of phosgene release along with the rate of release, time duration of release etc. It is important that phosgene destruction systems are functional during both normal operations and shutdown operations, as long as there is phosgene in the plant

<u>Sources of phosgene during normal operations</u>

The following phosgene-containing streams may need to be neutralized during normal operations:

- Off-gas from phosgene generation facilities
- Off-gas from phosgenation areas

- All other off-gas streams in the unit, e.g. off-gas from tanks, analyzers and other equipment
- Vacuum off-gas from distillation areas
- Other vent streams not mentioned above

Phosgene destruction systems can be located outside the secondary containment because of the low concentration of phosgene in gaseous form. The number of phosgene decomposition systems required and their distribution depends on the plant concept. For safe operation, at least one destruction system must be available as long as phosgene is in the plant.

To avoid releasing phosgene to the atmosphere even when the primary decomposition system fails, consideration of a redundant system may be necessary.

2.8.1 There are various primary safety measures are available to decompose phosgene as follows:

1) Caustic scrubber is a packed column fed with caustic soda. Concentration of circulating caustic soda should be monitored regularly for effectiveness of system.

   The reaction of the phosgene with caustic soda forms sodium carbonate, sodium chloride and water. It is advisable that the circulation pumps have redundancy and are connected to an emergency power supply and that an adequate inventory of caustic soda be available.

   A cooling system for the caustic loop to remove the heat of reaction is important.

   Caustic soda reacts with atmospheric carbon dioxide leading to a reduction in its alkalinity and thereby the scrubbing efficiency. Consequently, a system to replenish caustic soda is desirable.

   A further factor to be assessed is blockage of the system (plugging) due to the buildup of insoluble sodium carbonate formed in the reaction between caustic soda and phosgene.

2) Trickle bed towers, with activated carbon system, consist of series of towers filled with activated carbon bed and fed with trickling water.

   The phosgene is catalytically decomposed to carbon dioxide and hydrochloric acid. The reaction is exothermic; the heat generated is removed by the water or hydrochloric acid solution, which must be cooled. The distribution of water on

the activated carbon is very important to prevent hot spots. Therefore, the water distribution should be monitored through sight glasses during operations.

The circulation pumps need to have redundancy and are connected to an emergency power supply. An adequate inventory of water must be available.

Active carbon decomposition systems can be operated with slight positive pressure or under vacuum. With vacuum operation, phosgene emission is improbable. However, if air is sucked into the system at leaking flanges and blowers, explosive gas mixtures maybe formed in the decomposition system.

The risk can be reduced by monitoring oxygen. With positive pressure operation, leaks are more easily recognized and the formation of explosive gas mixtures in a decomposition system is improbable. On the other hand, phosgene and/or explosive gas mixtures in this case can be anticipated outside the decomposition system, close to the leak points.

The efficiency of the tower is affected by several factors. It is prudent to monitor the pH since the efficiency declines as the acidity of the created hydrochloric acid rises above about 5%. Further, there is a drop in efficiency if there are high loadings of solvents or inert materials.

The following general principles apply:

- In general, the activity of the carbon (e.g. to phosgene destruction) is an inverse function of mechanical stability. It is important to replace the carbon since its activity is diminished as the particle size is reduced.
- Activated carbon with high activity has good phosgene decomposition properties, but is easily oxidized by oxygen and chlorine and this is to the detriment of its chemical properties.
- Demineralized water or condensate is preferred to avoid the risk of blocking active sites on the carbon due to the deposition of minerals or suspended particles.
- Activated carbon can be contaminated by algae or bacteria, especially if ground water is used or if there is high oxygen content in the system, as could be the case with spot ventilation. This contamination can be minimized by occasionally heating the tower with steam or condensate, however without exceeding the operational temperature limits.
- A tower already contaminated with the types of biomass described above can be decontaminated by the targeted addition of hydrochloric acid.
- A particular problem may arise when the off-gas contains isocyanates, which react with water to form highly insoluble, waxy polyureas.

2.8.2 Secondary safety measures

Secondary containment is to prevent the dispersion of phosgene in the case of a failure of the primary containment. This is to protect personnel in the plant, in neighboring plants and in the community beyond the site fence line.

Phosgene destruction systems can be located outside the secondary containment because of the low concentration of phosgene in gaseous form.

Options for secondary containment are:

2.8.2.1 **A ventilated containment**, also called chamber, enclosure or dome, housing the phosgene-containing equipment.

A ventilated, completely enclosed containment chamber or enclosure housing all of the equipment containing phosgene and equipped with a phosgene detection system, which can be used to contain any release of phosgene.

In the case of a release into the containment chamber, the gases can be diverted to a phosgene destruction system. With the right equipment in place, such as analyzers for various chemicals (phosgene, carbon monoxide, etc.), cameras and safe entry procedures, the containment chamber can be made accessible for personnel.

Design and operational considerations

- Atmospheric or pressure resistant
- Air tightness or slight negative pressure
- Ventilation for temperature control, air exchange and dilution effects
- Phosgene analyzers with alarms
- Analyzers for other air contaminants, such as carbon monoxide, chlorine, flammables with alarms
- Ventilation management system in case of phosgene detection
- Functional tests at regular intervals
- Connection to a phosgene destruction system
- Fire protection
- TV monitoring
- Accessibility for personnel
- Communication system
- Access doors with alarms (consider air lock system)
- Larger opening for moving large pieces of equipment
- Procedures and permits for controlled access

- Procedures and permits for executing work inside the chamber
- Specifications for personal protective equipment (PPE)

2.8.2.2 **Fully jacketed equipment and piping**.

This is a system with an outer jacket enclosing phosgene-containing equipment, piping, flanges, valves and E&I systems. Jacketed piping, for example, is a piping system consisting of one pipe inserted within another pipe. The inner pipe (the core) is in contact with liquid or gaseous phosgene and the space between the inner and outer pipe (the annulus) is filled or purged (under pressure or vacuum) with a dry gas such as nitrogen or instrument air.

The gas in the annulus is monitored, analyzed for phosgene and connected to a destruction system. This is used to identify leaks in the entire phosgene system.

Monitoring can be achieved by purging the annulus to an analyzer system, padding the annulus with pressure and monitoring or applying a vacuum to the space and monitoring.

There are two typical jacketed systems

- Fully jacketed systems: This is a system with an outer jacket enclosing all equipment, piping, flanges, valves and PCT systems. A system typically consists of a double-wall pipe construction, flow through flanges, flow through gaskets, jacketed valves and PCT systems. This system allows for the monitoring of pipe leaks, leaks at flange connections and leaks at inline components.
- Partially jacketed systems: This is a system consisting of a double-wall pipe construction, with standard phosgene flanges, gaskets, valves and PCT items. The jacket typically ends on the hub of the flange, which will contain the pipe-to-flange weld within the jacket. This system uses flanges and valves from single-wall systems and does not allow the monitoring for leaks at flanges and valves. Partially jacketed piping systems are usually used as primary measure and are only regarded as secondary measure in combination with an additional measure like a steam-ammonia curtain.

Design and operational considerations:

- Phosgene-containing equipment that needs to be enclosed
- Outer jacket should have same pressure rating as equipment enclosed
- Monitoring of the jacketed space, as the inner pipe wall can no longer be inspected visually

- The annulus should be purgeable
- The gas in the annulus should be dry (consider inert gas rather than air)
- The annulus is pressurized or under vacuum at all times
- Analyzed for phosgene
- Functional tests at regular intervals
- Able to divert automatically to a destruction system in case of phosgene detection

2.8.2.3 **Steam–ammonia curtain**

This is a system designed to destroy phosgene released from the primary containment in open air structures. Proper design and operational measures are important so that in the case of an unintended release of phosgene, existing regulatory value limits of ammonia are not exceeded. **(Not recommended now a days as it has its own health hazards)**

Design and operational considerations

- A piping ring system surrounding the phosgene containing area at one or multiple elevations depending on the height of the structures
- Phosgene analyzers with alarms
- Possibility to inject ammonia into the steam
- Activation procedure, automatic or manual
- Functional tests at regular intervals
- Procedures for protecting personnel from ammonia exposure
- Availability of the steam source has to be evaluated
- Size of ammonia storage

Phosgene decomposition systems: These can be located outside the steam-ammonia containment because of the low concentration of phosgene in gaseous form.

2.8.2.4 Combinations of the three options above

2.9 Completion check and acceptance:

Prior to the introduction of phosgene into a unit after new construction, any modification of an existing unit or any maintenance work with opening of flanges or changes in the DCS system, the following checks have to be performed:

- Tightness check of all flanges with a soap bubble test or helium leakage test
- Installation is according the documentation (P&ID, pipe and E&I specifications)
- All drain or flush connections are closed with blind flanges
- E&I installation and DCS programming is loop check and tested with media (i.e. solvent or nitrogen)
- All interlocks are checked for correct action
- Secondary containment is checked and in operation
- Alarm and announcement system is working

All the checks have to be performed by owner personal.

3. Operational requirements:

3.1 ***Safe Operating Procedures***: it is of basic requirement to develop a Safe Operating Procedure (SOP) both for normal and abnormal working condition of plant by management. During preparation of S.O.P. other national and international safety standards, safety philosophy etc. also should be taken in to consideration. Safety procedures, instructions and methods should be prepared in co-operation with the people who are required to follow them.

Operating procedures should always be kept up to date and must be revised periodically (good practice: on an annual basis). Operating procedures can be divided into

- Standard operating procedures
- Safety procedures
- Work instructions

3.1.1 Standard Operating Procedures (SOPs):

Standard operating procedures are the operating instructions for a phosgene unit and should include procedures for:

- Start-up (e. g. after turnarounds or maintenance shutdowns)
- Shutdown (prior to turnarounds or maintenance activities)
- Rate changes
- Process upsets
- Response to process deviations
- Definition of key process parameters (including alarm and interlock settings)

3.1.2 Safety Procedures:

Safety procedures should be in place for activities which are not covered by standard operating procedures. Special attention **should be decided on** all activities which must be performed in the phosgene work area of a plant.

Management must ensure that all the laid down S.O.P. are being followed by each and every concerned personnel.

3.2 Work instructions

It is important that instructions for working in phosgene service / phosgene work areas consider the following main elements:

- Appropriate personnel protection equipment (PPE) needed with respect to the hazard of the work
- Adequate instructions about the work to be performed, including risk evaluation
- Attendance of operating personnel for all line openings in order to respond to an unexpected situation or opening of wrong piping
- Attendance of a **safety guard during line breaking work** (It is recommended that the safety guard shall not be allowed to actively participate in the job!)
- **Warning announcements for the hazardous area before, during and after the work**

Scheduled work on phosgene systems must only be performed following the additional issue of a valid **phosgene work permit**

Standard procedure for de-Phosgenation, clearing and cleaning of phosgene containing equipment:

If equipment that has contained phosgene needs to be opened for maintenance, cleaning or inspection, proper preparation and decontamination is important to avoid phosgene emissions and unacceptable risk for the working personnel.

Standard detailed procedures for shutdown, de phosgenation and cleaning equipment in phosgene service are recommended and could include the following for each type of equipment:

- Segregate the equipment from the rest of the process
- Flush equipment with an appropriate solvent
- Purge equipment with nitrogen
- Pull vacuum on the equipment to evaporate liquid residues
- Purge with steam
- Purge with ammonia or caustic soda
- Flood equipment with water, caustic soda or ammonia water

- Empty and purge with nitrogen or another inert gas
- Connect equipment to a decomposition system during de Phosgenation and / or opening
- Carefully decontaminate catalyst used for generating phosgene prior to disposal
- Gaskets or solid residues may contain trapped phosgene
- Enter equipment after clearing, i.e. for removing tower internals, only with proper PPE including breathing air

3.3 ***Permit to work System***:

It is important that a work permit be issued for all work where a primary barrier in the phosgene unit is opened. A work permit will normally contain detailed instructions for the preparation and performance of the work to be done, as well as the technical and organizational precautionary measures for the work area and its surroundings.

It is important that only authorized personnel issue work permits. In accordance with the dual-control principle, work permits should not be completed and signed by the same person.

Work permits (focus on phosgene) must be prepared and signed at a time close to the date when the work is to be performed. Prior to the start the work, the operating supervisor must determine that the situation on which the work permit is based and the steps to be taken have not changed since the time the permit was signed.

Work permits (focus on phosgene) should assess the actual risk situation, especially in situations with increased risks:

- An unforeseen upset has occurred.
- The unit had to be shut down quickly in a manner not conforming to normal procedure.
- The unit section cannot be adequately flushed and / or drained.
- Problems have been encountered during similar work in the past.
- The effectiveness of preparatory steps cannot be adequately assessed.

Avoid deviations from the work sequence as they can be dangerous. If the permitted work cannot be completed as planned, it is important to stop the work and secure the area until a new plan can be approved with a new work permit issued as per the new plan.

In the event of a phosgene emission to the atmosphere, unit personnel are expected to respond according to emergency response procedures.

3.4 ***Personnel training and qualification***:

It is important that the operation and maintenance of phosgene-generating and processing units be assigned only to well-trained and experienced operations and maintenance personnel.

People entering the units can be divided into four groups: 1) operating staff 2) company service and contract personnel who regularly work in phosgene area 3) company service and contract personnel who infrequently work in phosgene area 4) visitors

It is advisable that personnel using breathing air get a medical check-up and a physician's approval prior to working and that these check-ups are repeated at regular intervals.

It is strictly recommended that personnel are admitted to phosgene-producing or using plant only after receiving safety instruction and then only with the prescribed personal protective equipment (PPE). Phosgene badges are part of PPE and should be made readily available. Correct storage and usage is important.

3.4.1 **Basic qualification**:

Once a **new employee** has finished any general technician training (e.g. basic knowledge of rotating equipment, PCT instrumentation and functionality of other typical equipment of chemical units) *, unit-specific training is required, which should involve details of the various physical, chemical and hazardous characteristics of phosgene as well as standard operating procedures of the phosgene equipment and processes. This training should include the following:

- Start-up procedures
- Shutdown procedures
- Normal operating parameters and procedures
- Consequences of operating outside normal operating parameters
- Emergency procedures / actions

It is important that the training plan include on-the-job training, consisting of specific unit operations for which competency should be demonstrated by the trainee.

Since units may operate for long periods between major shutdowns, it may be possible that employees who have passed the initial training period may still not have firsthand experience with some basic unit operations (e.g. start-up,

shutdown, upset conditions, etc.). To provide this experience, special training in the form of tabletop drills, discussions with experienced operators, emergency drills or other means may be required.

When a scheduled shutdown is planned, consideration should be given to ensuring that employees with experience of certain operations (start-up, shutdown and preparation of maintenance work) are available.

* Proof of general technical knowledge should be documented with a certificate before unit-specific training can be started.

3.4.2 Ongoing training for employees who operate phosgene-containing equipment

Once an employee has been certified to operate phosgene-containing equipment, tabletop exercises that pertain to unit operations and upset conditions for phosgene-containing portions of the unit should be performed to enhance operating skills on a regular basis.

Refresher training and training in additional topics should also be common practice.

Additionally, regular unit evacuation drills (with attention given to ensuring all shifts participate in these drills) are advisable. (At least one drill per shift and year is recommended.)

3.4.3 Training for employees (company or long-term contractors) who maintain phosgene-containing equipment

It is important that the maintenance of phosgene-generating and processing units be assigned to well-trained, experienced and certified maintenance personnel.

Prior to beginning work in the phosgene unit, it is important that all personnel have been instructed about:

- The potential hazards of working in a phosgene area
- Aspects of the work planned
- The planned response in the event of a release or other emergency

They must also be issued with the proper PPE and ensure that their escape device is in proper working condition.

It is advisable that contract employees, who are used in the same role as company technicians, should obtain the same training as company employees.

3,4,4 Visitors training

Important considerations for visitors to phosgene-operating areas prior to entering the area:

- Inform visitors of the basic characteristics of phosgene (smell, gas density, etc.).
- Issue phosgene indicator badges to visitors and inform them about the proper use and care of them.
- Instruct visitors about the general alarm plan for the area they are visiting as well as exit/evacuation procedures. This can be accomplished by means of a safety video or a safety briefing.
- Instruct visitors on the use of the escape device used by the area being visited.
- Assign unit personnel to accompany visitors and take responsibility for their safety.

3.4.5 ***Laboratory technicians***: Only personnel with at least 2.5 years training (normally 3.5 years) in the laboratory and 1 year training on the job are allowed to handle phosgene, diphosgene or tri phosgene.

- Before using the compounds in a laboratory, additional training is required. Any person handling phosgene must demonstrate the necessary competence. Training and competence must be documented. The status of training and competence must be checked at appropriate intervals thereafter.
- The instructor for training/qualification must have long experience in the laboratory and expert knowledge in handling very toxic compounds. Typically, the instructor is a laboratory leader with a higher academic degree (master or PhD).

3.4.6 Training documentation:

It is important that participation at instructions, training courses and other qualification activities be controlled and documented.

It is advisable that if training occurs for an entire operating shift, this is documented for all personnel who participated in the training and that a shift member who is unavailable to participate should be required to make up the missed training, which must also be documented.

3.5 Incident / accident management:

A thorough incident /accident investigation may identify previously overlooked physical, environmental, or process hazards, the need for new or more extensive safety training, or unsafe work practices.

The primary focus of any accident investigation should be the determination of the facts surrounding the incident and the lessons that can be learned to prevent future similar occurrences.

Most accidents in the workplace result from unsafe work behaviors (more than 90% based on statistics) and may indicate safety management system weaknesses.

Incident investigation reports and other information must be included in the company's incident information and management system. Lessons learned must be shared as applicable through established procedures.

3.5.1 **Incident investigation**:

The investigation of incidents and accidents, even if minor (i. e. near-misses), by knowledgeable experts with corrective action defined and implemented in a timely fashion is important to the continuous improvement of safety systems. Incident investigations are best conducted by knowledgeable, operationally long-term experienced engineering or plant management personnel. Following a documented Management of Change (MOC) process is useful to review, authorize and validate the success of the proposed changes.

3.5.2 ***Root Cause Analysis***:

Root cause investigations using established methods should be carried out for all serious and potentially serious events. The investigation is only useful when its objective is to identify root causes.

Root cause analysis (RCA) is a systematic approach to get to the true root causes of problems and incidents.

The objectives of the RCA process are:

- Determine the causes of failures and successes
- Identify the contributing factors
- Develop corrective actions to prevent the recurrence of failures and ensure the recurrence of successes

The following categories should lead to an RCA:

- Personal safety and health incidents / accidents
- Process safety incidents

- Loss of primary containment, leaks and spills
- Potentially serious events (near misses/near incidents)
- Environmental incidents
- Blowing of process safety valves / rupture disks
- Frequent equipment failures (e.g. corrosion or mechanical failures)
- Security events

A successful accident investigation determines not only what happened, but also finds how and why the accident occurred.

3.6 ***Emergency Preparedness and Response***: management should have prepared an Emergency Preparedness and Response (EPR) plan for un-fortunate event of phosgene releases and any emergency situations arising post release of it. A comprehensive EPR should contain all the information and what to do instruction in case of on-site or off site emergency. Effectiveness of EPR should be checked by carrying out mock drills at regular interval of time. Management should submit a copy of EPR to local authorities including disaster management cell.

Table top drills also used to train company and contract employees to create awareness about emergency preparedness and response

Recommend to develop the scenario of effect of leakage by dispersion modelling and consider the responses in case of emergency preparedness.

3.7 ***Medical assistance***: phosgene producing facilities should have adequate numbers of First Aid centers or Occupational Health Center. Timely administered first aid to victim of phosgene exposure is of much importance. Management should also focus to train as much as possible first aider.

For detailed information refer chapter 6

3.8 ***Sampling***:

3.8.1 General requirements: Reduced sampling will minimize the potential for releasing phosgene to the environment. It is very important that when phosgene-containing samples are taken, appropriate safety systems are in operation and that written procedures are available and followed.

Proper PPE including supplied air is required for personnel taking any phosgene-containing sample, not only in production units but also in laboratories and pilot

plants. Safety is increased when sample points are easily accessible, ergonomically sound and when spot ventilation is used to remove any escaping vapors.

3.8.2 *Routine sample*: Samples from the production units that are included in a sample plan are considered routine, even though the frequency of sampling may be monthly, quarterly, etc.
For routine liquid samples, such as phosgene solutions, the best option for a sampling station is an enclosure (box) that is equipped with a venting system, connected to a phosgene destruction system, and a means to ensure that the venting system is working prior to taking any samples.

It is important that enclosures be of an approved design that permits their use in explosive atmospheres. It is good practice that the valves inside the enclosure are operable from the outside and that the dead volume inside the sampler is minimized.

To avoid purging before taking a sample, valves with a "zero" clearance space should be used. It is recommended that samplers with a defined sample volume be used to prevent uncontrolled amounts of the product from entering the collection vessel.

It can be dangerous if samples are taken using open sample containers outside the enclosure (i.e. open to the atmosphere). However, the use of threaded jars in an approved sampling station is permissible even though the cap is applied after the sample has been taken. The cap is to be tightened prior to transport. A basket is normally used for carrying.

Self-contained sample stations with fixed volume samplers, have been used successfully and are considered excellent examples of a contained sampling station. If other supplied stations are to be used, specifications equal to or exceeding those of the two sampling stations mentioned above are recommended.

Cold phosgene samples should be transported on ice and with appropriate secondary containment. Phosgene samples should never be carried ina vehice with a closed cabin.

It is important that the sampling process follows a written procedure that has been reviewed and approved for safety.

3.8.3 ***Non-routine samples:*** Any sample that is not in the production unit's sample plan is considered non-routine.

If liquid samples are obtained from phosgene-containing streams on a non-routine basis, it is important that appropriate sampling stations be designed and utilized.

Stainless steel sample cylinders (bombs) or other contained methods can be used when taking non-routine samples, but open sample containers should not be used.

It is important that the non-routine sampling process also follows a written procedure that has been reviewed and approved for safety.

3.8.4 ***Gas sampling***: Sampling of gas streams is performed but is uncommon. When sampling gas streams, stainless steel cylinders are the usual vessel of choice and the sampling method is designed to prevent a phosgene release. (It is better to analyze gas streams using online analysis and fixed pipe connections).

Sampling designs can make use of process bypasses and maintenance decomposition/spot vent systems for clearing lines before detaching the sample cylinder.

It is important that the gas sampling process follows a written procedure that has been reviewed and approved for safety.

3.8.5 ***Phosgene solutions:*** Minimize sampling of pure phosgene solutions (i.e. phosgene and solvent only) by using on-line analysis. If a phosgene solution must be sampled, the best way to obtain the sample is with a sampler that neutralizes the phosgene at the source.

This may be accomplished by using a fixed-volume sampler containing a pre-weighed amount of sodium hydroxide that will react with the phosgene. The phosgene concentration is then calculated after back titration with HCl. A colorimetric indication should be added to show if the phosgene is in excess of the neutralizing solution. If the solution is acidic, phosgene must be assumed as present.

This neutralization method alleviates the need for secondary containment of the sample while in transport because the sample no longer contains phosgene.

An alternative to neutralization is to dilute the phosgene solution using pre-weighed solvent in the container with the fixed-volume sampler. However, this sample still contains phosgene, which requires secondary containment during transportation.

4. Maintenance and Inspection:

Maintenance: It is necessary to have a documented maintenance process describing how to maintain, repair and inspect equipment which has been in phosgene service. All activities can be done by either company or contractor personnel.

It is important to have a contractor qualification process to select the appropriate contractor meeting the company requirements and to utilize only qualified contact personnel who have been thoroughly trained, know plant safety guidelines and who actively participate in plant emergency drills.

It is important that, prior to working on phosgene-containing equipment, the equipment be flushed with solvent, purged with nitrogen and evacuated. It is recommended to use an elephant trunk / spot ventilation system to remove residual fumes during opening of flanges.

For safety reasons it is important that equipment leaving the phosgene plant for repair or disposal be free of phosgene and residual solids as phosgene can be trapped in solids. Equipment may have to be partially disassembled and gaskets removed to verify the absence of phosgene. Documentation by the plant personnel is necessary.

4.1 ***Inspection****:*

4.1.1 ***General:*** In service equipments are advisable for all technical equipment in phosgene units. Equipment inspections are regulated by codes, standards, rules, statutory regulations and company specific requirements.

In-service inspections can be performed using the time-based methodology or the risk-based methodology (RBI). Both methodologies are commonly used.

Inspection intervals are generally defined by the local regulations, but inspection intervals and the extent of inspection for the RBI methodology may vary for any item depending on the associated likelihood of failure/criticality.

4.1.2 ***Time based inspection:*** There are different inspection types:

- Internal inspection for pressure vessels,
- External inspection,
- Shop test of relief devices and inspection of rupture discs and
- Testing of piping.

The testing of piping may be a pressure test or adequate non-destructive inspection methods such as radiographic examination, ultrasonic wall thickness measurement, a leak test and an external inspection.

It is recommended that a wall thickness program be in place with special attention given to exterior corrosion under insulation.

The inspection interval is defined in local or other applicable regulations.

4.1.3 ***Risk based inspection:*** The risk based inspection is a systematic and integrated use of expertise from the different disciplines that impact plant integrity. These include design, material selection, operating parameters and understanding of future degradation mechanism and risks involved.

Risk based inspection enable the assessment of the likelihood and potential consequences of equipment failure. RBI provides the opportunity to prioritize equipments for inspection, optimize inspection methods and frequencies, to develop specific inspection plans and the most suitable non-destructive test methods.

4.2 Equipment preparation for repair, maintenance or disposal outside unit:

4.2.1 ***General:*** Equipment referenced in this section is defined as any apparatus that has been in contact with phosgene such as centrifugal pumps, vacuum pumps, reactors, heat exchangers, piping/piping components, as well as E&I equipment, such as control valves, pressure gauges, mass flow meters and PAT analyzers, among other things.

This section also applies to all equipment that will be discarded or scrapped. It is important that any apparatus leaving the unit be decontaminated and certified as phosgene-free.

It is best if complete decontamination can occur within the plant unit boundaries or inside a special decontamination facility. Decontamination of equipment in situ is preferred.

Consider the use of phosgene indicator paper or portable detection devices. Decontamination will usually consist of using ammonia/water (or similar) to wash the individual components and be specified in a written procedure.

All equipment must be dissembled to its component parts before being removed from the phosgene area. This may require the opening of components that appear to be intact, but where there are no means to verify that the component is phosgene-free. Parts that may be included in this category are canned motor pump stators and bellows portions of manual or control valves, gaskets, among other things. Breathing air equipment, elephant trunks system and neutralizing solution must be available at the location of disassembly. Other PPE such as chemical suits, gloves, shoe covers should be worn as appropriate.

It is important that plant personnel critically evaluate all parts to be sent out to ensure that even intact components do not contain phosgene.

If in doubt, equipment or equipment components may have to be disassembled to gain access to areas that may be contaminated with phosgene.

4.2.2 ***Work description:*** The following specific area decontamination steps to consider based on previous experience or best practices.

It is best to remove soft parts like gasket, packing etc. from equipment to ensure that no pocket of phosgene exists.

Pay special attention to bellows and multiple bellows to ensure that they are phosgene free

5. Phosgene: Science, Toxicology and regulatory standards

5.1 *Properties:*

- Phosgene (carbonyl chloride) is a highly reactive, acylating colorless gas at ambient temperature and pressure and a colorless, fuming liquid below 45.7 ^{0}F (7.6 ^{0}C)
- At low concentrations, its odor is similar to that of new-mown hay.
- It is 3.4-times heavier than air.
- It is manufactured from a reaction of carbon monoxide and chlorine gas in the presence of activated charcoal.
- Phosgene is slightly soluble in water and is hydrolyzed slowly by moisture to form hydrochloric acid.
- These properties make phosgene amenable to an 'on-demand production strategy', i.e. phosgenation reactions are executed at low stationary levels and transportation and storage is abandoned at chemical plants.
- It is used as an intermediate in the manufacture of building blocks of various types of plastics and numerous industrial materials, such as polyurethanes, polycarbonates, and in the production of dyestuffs, pharmaceuticals and agrochemicals.

5.2 *Toxic effects:*

- The low solubility and rate of hydrolysis of phosgene in aqueous media favors its deep penetration into the gas exchange region of lungs without causing subjective signs of irritation. The odor threshold concentration has been reported to be 1.6 mg/m³ (PPM).
- Due to its low water solubility, phosgene is not scrubbed in the upper respiratory tract or conducting airways to any appreciable extent so that phosgene gas penetrates effectively into the lower airways, including the alveolar region.
- However, very high concentrations can cause irritation of the eyes and the airways of the entire respiratory tract.

- Typically, phosgene causes pulmonary toxicity as a result of acute lung edema and lymph-drainage overflow which reach their climax 10-20 hours post-exposure.
- Survivors gain full reconstitution within weeks post-exposure.
- In more recent experimental studies on rats and dogs delayed, long-lasting or irreversible effects were not found following exposure to phosgene gas but were observed when exposed to the vapor phase of triphosgene.
- Prevailing experimental evidence suggests that phosgene gas acts preferentially at the alveolar level in a concentration x exposure duration (C x t)-dependent manner.

5.3 History of phosgene as chemical warfare agent

- The first use of chemicals in terms of weapons of mass destruction goes back to World War (WW) I (first use in Belgium, 1915) when large amounts of chlorine were released by German military forces.
- The first chemical agents used in WW I were respiratory irritants, such as chlorine, phosgene, and diphosgene.
- Chlorine was then replaced by more effective agents, e.g. phosgene, diphosgene, and chloropicrin.
- Phosgene and phosgene/chlorine mixtures generated the highest mortality rates in comparison to other chemical agents used during World War I.

5.4 Occupational hygiene standards (Occupational exposure limits):

Occupational exposure limits represent the time-weighted average (TWA) concentration for a conventional 8-hour workday and a 40-hour work week to which healthy, adult workers are exposed day-by-day.

- ❖ In the US, the legally binding limit is the PEL (Permissible Exposure Limit, OSHA).
- ❖ Short-term exposures are regulated by STELs (Short-Term Exposure Limits) which are usually defined as a 15-minute TWA exposure which should not be exceeded any time during a workday even if the 8-hour TWA is within the PEL-TWA.

- There should be at least one hour between successive exposures in this range with maximal four excursions per shift. Workplace limits for China, the US, the EU and Germany are summarized in Table below. In the People's Republic of China, the documentation Health Standards for the Design of Industrial Premises (Standard TJ 36-79) is regarded as the backbone for setting occupational health standards. It was jointly promulgated by the Ministry of Health, the State Capital Construction Commission, the State Planning Commission, the State Economic Commission, and the Ministry of Labour (Ministry of Health, 1979).

Summary of Occupational Exposure Limits

(all concentrations are in ppm; the conversion factor from ppm to mg/m³ is 4)

Organization	Designation	Value
ACGIH	TLV (TWA)	0.1
EU-SCOEL	IOELV (TWA)	0.1
EU-SCOEL	IOELV (STEL)	0.2
DFG-MAK	MAK (TWA)	0.1
DFG-MAK	MAK (STEL)	0.2
BAuA	TRGS 900	0,1
China TJ 36-79	MAC (TWA)	0.125
NIOSH	REL (TWA)	0.1
NIOSH	REL (C)	0.2
OSHA	PEL (TWA)	0.1
OSHA	PEL (STEL)	NA
UK-HSE	WEL-LTEL	0.02
UK-HSE	WEL-STEL	0.06

Abbreviations / Acronyms

ACGIH = American Conference of Governmental Industrial Hygienists

DFG-MAK: Deutsche Forschungsgemeinschaft (DFG) – Maximal Workplace Concentrations, List of MAK and BAT values; phosgene was reevaluated and adopted in 2006 (no published information currently available)

IOELV = Indicative Occupational Exposure Limit Values. IOELVs are European legal limits which are set to protect workers in the European Union. For phosgene the IOELV was published in Directive 2000/39/EEC (98/24/EEC) of June 8, 2000 but revised in 2009 (not published yet).

PEL = Permissible Exposure Level

REL = Recommended Exposure Level

SCOEL = Scientific Committee on Occupational Exposure Limits

STEL or C = Short-Term Exposure Limit or Ceiling is specified as follows: the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency. A STEL is defined as a 15-minute TWA exposure which should not be exceeded any time during a workday, even if the 8-hour TWA is within the TLV-TWA. There should be at least 1 hour between successive exposures in this range with maximal 4 excursions per shift.

TLV (TWA) = Threshold Limit Value Time - Weighted Average are specified as follows: the time-weighted-average concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect.

China-MAC: Maximum Allowable Concentration for Chemical Substances in the air of Workplaces (Standard TJ 36-79, see Liang et al., 1995). Value given in 0.5 mg/m³ and converted to 0.125 ppm.

UK-HSE WEL = Health & Safety Executive. EH40/2005 Workplace exposure limits. The Stationery Office, London, 2005; LTEL = Long-term exposure limit; STEL = Short-term exposure limit

Summary of Community Exposure Limits (all concentrations are in ppm)

Community exposure limits (Inhalation Reference Concentrations, RfCs) have been derived for phosgene for continuous, lifetime exposure of the general public (US-EPA, 2005). Permissible intermittent exposure excursions for a maximum of 1 hour have been defined by the Acute Reference Level (Acute REL) (Collins et al., 2004).

Organization	Exposure Limit	Value
US-EPA IRIS	RfC	7.5×10^{-5}
CalEPA-OEHHA	Acute REL	1×10^{-3}

Abbreviations / acronyms:

US-EPA IRIS = US Environmental Protection Agency (EPA) – Integrated Risk Information System (IRIS) (last update January 31, 2006).

RfC = Inhalation Reference Concentration (lifetime continuous exposure of the general public)

OEHHA = California Environmental Protection Agency / Office of Environmental Health Hazard Assessment – Air-Hot Spots-Acute Reference Levels (Acute REL) (last update March 1999). The acute REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed to that concentration for one hour on an intermittent basis. The health-based acute REL is applicable to risk characterization of air releases, defined in Health and Safety Code 44303.

- **For further scientific and medical details (with case study) refer Appendix 1 & 2 attached to this guide.**

6. Occupational Health

Management of occupational hazards must be based on the so-called hierarchy of controls.

Considering that avoidance and substitution of phosgene is not an option, technical solutions are the first step (engineering controls like enclosure, general and local exhaust ventilation).

If an exposure cannot fully be ruled out, personal protective equipment (PPE) must be used in addition to administrative/organizational measures.

It has to be kept in mind, that PPE will always be regarded as being only a bridging solution until measures higher up in the hierarchy can be implemented.

For emergency situations, escape masks, filter masks and self-contained breathing apparatus (SCBA) must be available for certain groups of employees (and escape masks also for visitors) and cannot be abolished.

Administrative measures:

- Only plant staff trained in handling phosgene and dealing with emergencies and contractors informed in detail about phosgene and supervised by a plant employee may be in the plant. It must be ensured that no unaccompanied persons not belonging to the plant can enter.
- Respiratory protection (filter mask) must be immediately available for each and every worker.
- In case of an alarm/phosgene leakage, everyone must immediately leave the plant wearing the filter mask.
- In the event of a leakage, re-entry is only permitted for trained emergency staff wearing SCBA until the source of the emission has been closed, and the plant has been well ventilated.
- Work involving opening lines and vessels may only be done either wearing SCBA or a filter mask with breathing air supply from a hose connected to a fixed installed breathing air system.
- If external visitors are admitted, they must always carry an escape mask. They must have been informed/trained in its use.

Operating staff:

All employees must put on the company-specified protective clothing and equipment before entering the unit, including a phosgene indicator badge (with the employee's name and date) affixed near the breathing zone. It is also good practice that each employee carries an escape device at all times.

Escape devices are meant to be used only in an emergency when it is necessary to evacuate the unit. These devices are not a substitute for breathing air systems which are used when performing work in the units.

It can be dangerous to perform any operation on phosgene-containing equipment if there is a possibility of phosgene being released, unless an independent breathing air supply is used and additional safety measures are applied, as described in detail in standard operating and safety procedures and phosgene work permits.

It is important to provide training on the use of personal protective equipment for unit personnel. This must be refreshed on a regular basis and bear in mind local regulations and restrictions.

Operating staff must always check that their escape device is in good condition (e.g. the expiration dates of the filter cartridges) before entering the unit.

Service and contractor personnel who regularly work in phosgene areas:

It is important that service and contractor personnel regularly working in phosgene service areas are provided with the same training as operating staff and that it is documented and refreshed.

Service and contractor personnel who infrequently work in phosgene areas*:*

It is important that personnel from the service departments and contractor companies working for the first time or only occasionally in phosgene service areas receive extensive safety training concerning the hazards of the unit and the proper PPE required before starting any work. The work permit must specify whether a contractor can work without supervision.

Visitors:

Visitors are persons entering phosgene service areas who are not involved in working activities.

Visitors must be provided with basic information and training about what to do in an emergency and be equipped with the appropriate personal protective equipment before entering phosgene-containing units. Training in the practical use of the escape device is especially important.

Personal protection

Besides the usual protective equipment (e.g. safety shoes, adequate gloves, safety glasses or goggles, work suits, in some situations coveralls), respiratory protection in 4 levels is key for personal protection.

- Level 1: Escape masks

  It can be considered that each worker carry an escape mask, although the strong recommendation is for filter masks. Visitors to a phosgene plant must always carry an escape mask.

- Level 2: Filter masks

  Each worker should have a personal filter mask with a cartridge giving protection from phosgene for the time required to escape from a contaminated area, at least for 5 minutes. This filter mask can be carried by the worker in a box, or the filter masks can be stored throughout the plant in a sufficient number of locations to ensure that each worker can reach a filter mask within 5 (absolute maximum 10) seconds. The storage boxes must be clearly marked (preferably bright yellow or orange). The filter masks and cartridges must be regularly checked and replaced if necessary.

- Level 3: Breathing air lines

  For routine work potentially involving opening lines, flanges or vessels, a breathing air system for use with full-face masks can be installed throughout the plant. There must be sufficiently well signposted outlets to ensure that the hoses between the outlet and the full-face mask are not too long. Such a breathing air system must be checked at least weekly, and clean breathing air must be used exclusively.

- Level 4: SCBA.

  For emergencies, and also for routine work potentially involving breaking containment if no breathing air system has been installed, SCBA is mandatory. A risk assessment must define whether 1 or 2 air bottles are required. SCBA equipment must be routinely tested. Bottles must be replaced after emergency use.

Workers who have to use SCBA must be regularly trained and medically examined for fitness to work with SCBA (considering the weight of the equipment and the cardiovascular fitness of the employee as assessed by stress ECG).

Workplace measurements and badges

Air measurements

Measurements of phosgene in workplace air, both as stationary and personal sampling, underlie country-specific regulations. These must be followed.

Phosgene monitoring

Continuous air monitoring in phosgene plant

- Various sniffers / phosgene detectors at strategic locations connected to DCS with plant tripping interlock
- Portable phosgene detector
- Ammonia torch for better detection

Phosgene badges

Specifically for phosgene there are medical badges available that show the dose of exposure. Dose is the product of concentration and time, thus ppm x min (parts per million times minutes)

There are several makes of badges available on the market. They all rely on a color reaction.

When choosing a badge it is important to make sure that the badge covers the medically important range. The dose levels required by a physician for his decisions on monitoring and treatment are

- 50 ppm x min below this does there is no need for monitoring or therapy, above 50 ppm x min monitoring is necessary
- 100 ppm x min above this dose early treatment may be considered (this level is not really required)
- 150 ppm x min above this dose admission to a hospital with ICU and mechanical ventilation equipment is strongly advised
- 300 ppm x min above this dose ICU treatment is mandatory

In order to have a safety factor the badges should start to discolor slightly at 5-10 ppm x min. However, the first reading needed and desirable is 50 ppm x min.

There are badges on the market that start discoloring as low as 0.3 ppm x min. This is of no value at all for medical decisions and will only confuse patients and physicians. Such badges also often have a maximum reading of 150 ppm x min, which is insufficient for medical decisions.

The badges need to be fixed openly as close to the breathing zone as possible, preferable on the shirt or jacket collar.

Reading of the badge as the basis for medical decisions may only be done by a medical expert (physician or nurse). It must be kept in mind that the **exposure dose as shown by the badge may differ from the inhalation dose**, e.g. because respiratory protection has been worn, because the worker held his breath and escaped, because the badge might have been misused for leakage detection, or because the badge was not worn correctly but kept in a pocket, for example. The estimation of the inhaled dose – higher or lower than the exposure dose according to the badge - is also the task of the medical expert.

Badges must be worn at least by all workers in and everyone entering a phosgene area, including contractors or visitors. The badges must be replaced according to the manufacturer's recommendations.

It is preferable to make badge use mandatory for everyone working in or entering a phosgene plant (not only for the immediate phosgene work area).

Some companies require badges for everyone entering a site where phosgene is used somewhere. This can be done, but is not really convincingly necessary.

Emergency medicine

Under all circumstances, the attending medical practitioner must take into account the actual situation of the emergency and the patient, the available resources on site and off site, and thus decide treatment on a case-by-case basis.

Clinical course of phosgene poisoning (latency period)

Background

Exposure to phosgene for practical reasons is only via the airways, i.e. by inhalation. There is virtually no uptake through the skin; however, phosgene can cause irritation on moist skin. In contact with the skin, liquid phosgene can cause burns. Ingestion is no real possibility.

Phosgene is often handled dissolved in solvents (e.g., monochlorobenzene). Contamination of the skin and/or clothing with such solutions can cause further or continuous inhalation of phosgene by the victim due to off-gassing, as can contamination with liquid phosgene. This can lead to secondary exposure of others, e.g. rescue or medical personnel.

The odor of phosgene, comparable to hay or freshly cut grass, which is detectable at 0.5 ppm recognizable at a concentration of about 1.5 ppm, is not a sufficient warning. Poisoning can occur at lower, undetectable concentrations, if the exposure time is long enough (see below).

Additionally, olfactory fatigue can occur quickly and may result in prolonged and unnoticed exposures with delayed pulmonary effects.

Irritation of the eye/upper airways can also not serve as a warning as it will not occur at low concentrations.

As phosgene is heavier than air, it will accumulate near the floor, in low lying or enclosed areas, especially if ventilation is insufficient.

Mechanism of action of phosgene

There are two mechanisms of action of phosgene in the organism:

- Phosgene can hydrolyze with moisture on mucous membranes to HCl (hydrogen chloride). The resulting HCl may be irritating to the eyes and the upper airways. Signs and symptoms would be irritation, a burning feeling, lacrimation, coughing, eventually chest oppression, quite similar to the signs and symptoms resulting from inhalation of water-soluble irritant gases.

  However, these signs are rarely observed in phosgene inhalation cases. The process of hydrolysis would be slow and symptoms can only be expected after exposure to higher concentrations. The symptoms will abate within a few hours so this mechanism cannot be expected to play a role in the damage to the lower airways and formation of pulmonary edema.

  Phosgene can also react in this way with humidity in air. This means that exposure would be to a mixture of phosgene and HCl gas. This can also explain irritation symptoms.

- The reactivity of phosgene allows for acylation of nucleophilic cell structures and products in the lower airways/alveoli. This will destroy the blood-air barrier and fluid will be excreted first 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 edema formation, fluid will be excreted into the alveoli, thus flooding these ("pulmonary edema").

These mechanisms activate the inflammatory cascade, resulting in the formation of reactive oxygen species that adversely impact alveolar and capillary integrity and lead to a further compromised blood-air barrier and a dose-dependent pulmonary edema.

Whilst the whole process of lung edema formation starts immediately with phosgene inhalation, clinically obvious signs and symptoms will not appear before a critical volume of extravascular fluid has accumulated. This leads to a **latency period**, during which fluids accumulate in the interstitial space and no overt clinical symptoms will be obvious. The higher the phosgene dose, the faster the pulmonary edema will appear. The pulmonary edema may persist for up to several days; however, it will usually peak at about 24-32 hours after exposure.

It is of the utmost importance to be aware of this symptom-free latency time. **Treatment in significant poisoning cases must always start during this latency phase,** even though the patient is not symptomatic. Failure to do this will put the patient at high risk of severe complications or death, as a full-blown lung edema is difficult to treat successfully.

Correlations between exposure and effect

The clinical effects of phosgene depend to some degree on the inhaled concentration, yet mainly on the inhaled dose (concentration x time). Concentration is given in ppm (parts per million), dose in ppm x min (product of concentration and exposure time in minutes).

Only two effects relate to concentration:

- Odor recognition > 1.5 ppm
- Irritation of eyes and upper airways > 3.0 ppm

Relations between dose and effect are far more important:

- < 25 ppm x min : No clinical effect
- 25-<50 ppm x min : Subclinical (biochemical) lung effects
- 50-150 ppm x min : Subclinical pulmonary reactions
- > 150 ppm x min : Overt alveolar pulmonary edema
- > 300 ppm x min : Possibly fatal

- ~ 500 ppm x min : Approx. 50% mortality

Note: The doses have to be established by a critical assessment of all circumstances, not only by badge reading (see below).

Clinical presentation

As explained above, the signs and symptoms after phosgene inhalation may vary considerably depending mainly on the dose inhaled. To elaborate on this:

A dose of **60 ppm x min** may result from:

- 1 ppm during 1 hour: No odor recognition, no irritation
- 3 ppm during 20 minutes: Odor recognition, no irritation
- 5 ppm during 12 minutes: Odor recognition and eye/upper airway irritation

A lung edema can result e.g. from any of the following exposures, all resulting in 180 ppm x min:

- 1 ppm during 180 minutes (3 hours): No odor recognition, no irritation, latency e.g. 12 hours
- 3 ppm during 60 minutes (1 hour): Odor recognition, no irritation, latency e.g. 8 hours
- 10 ppm during 18 minutes: Odor recognition, irritation, latency e.g. 6 hours
- 60 ppm during 3 minutes: Strong irritation, rapid appearance of overt pulmonary edema

In addition, a fatal case is conceivable from inhalation of 1 ppm (below the odor threshold) during 6 hours, resulting in a dose of 360 ppm x min, rapidly developing pulmonary edema after exposure and death, e.g. after 24 hours.

These examples show why the dose and not the concentration inhaled is of the utmost importance for any medical decision.

It also shows that odor recognition, irritation, and lung edema may be completely independent from one another. Again, the absence of odor and/or irritation does not mean the patient is not in danger.

While the latency period may give some indication of the prognosis (the shorter the latency period, the more dangerous the poisoning), there are no clinical tests that reliably indicate the development of pulmonary edema.

The following examinations and tests may give some indication:

- Auscultation: Wheezing, asthma-like symptoms
- Pulse oximetry: Decreased oxygen saturation
- Blood-gas analysis: Decrease in pO2
- Airway resistance: Increase
- Chest X-ray: Blurred hili/perihilar edema

Phosgene badges and evaluation

All persons entering plants/units handling phosgene have to wear a phosgene badge at all times (see above). The badge must be located close to the mouth/nose (e.g. shirt collar) to ensure reliable readings correlating to the actually inhaled dose. The frequency for changing the badge is given in the manufacturer's recommendations.

The badge needs to show medically important dose levels – 50 ppm x min (start of monitoring), 150 ppm x min (hospital treatment) and 300 ppm x min (ICU treatment).

The badge readings must be assessed by trained medical personnel regarding the reliability of the dose reading (correct badge position, heavy work with increased breathing volume, respiratory protection) to estimate the "inhaled dose".

Procedures:

<50 ppm x min	- if no symptoms occurring, no treatment necessary
>50 and < 150 ppm x min	- monitoring, in the higher range treatment
>150 ppm x min	- hospital treatment
>300 ppm x min	- ICU treatment

If there is no badge (not used or thrown away), an inhalation exposure of 150 ppm x min should be assumed and treated accordingly.

Rescue and first aid

Rescue

If at all possible, exposed persons should leave the contaminated atmosphere as quickly as possible – against the wind or at a 90-degree angle to the wind. As soon as they are out of the exposure area, physical rest becomes mandatory.

Rescue of victims from contaminated atmospheres may only be done using respiratory protection – at least filter masks, preferably SCBA. It may be necessary to supply the victim(s) with filter masks for the rescue.

Decontamination

If patients have been exposed to phosgene gas only, they will not pose a significant risk of secondary contamination. If, however, **clothing or skin is contaminated with liquid or gaseous phosgene or solvents containing phosgene, both patient(s) and rescue personnel are at risk from inhalation of the off-gassing phosgene. Therefore, the patients' clothing should be completely removed and double-bagged**. The absence of phosgene gassing off can be shown by phosgene detectors or indicator paper held close to the patient ('s clothing).

Exposed patients should be put under an emergency or preferably a lukewarm shower. The shower duration should be adapted to exposure: short, if at all, for transient gas exposures; longer, up to 15 minutes, for skin/clothing contamination.

In case of eye involvement, the eyes should be flushed thoroughly with water or eye irrigation solutions. The usual procedures apply, e.g. regarding contact lenses.

It is important that the necessary treatment measures indicated by the inhaled dose are rapidly implemented. If decontamination is deemed necessary, it should not delay the start of therapy. In cases of severe exposure, severe symptoms or suspicion of imminent or manifest pulmonary edema, the decontamination period can be shortened to 3 to 5 minutes to allow for prompt initiation of medical treatment and transport to a higher level of care. However, protecting the victim(s), emergency responders and ambulance personnel from contamination with phosgene and other potential compounds like solvents must not be compromised.

It is critical that any physical stress or exercise be avoided after significant phosgene exposure, as animal experiments have shown that physical activity increases both the speed of development and the severity of lung edema. Psychological stress should also be avoided as far as possible.

First aid

The key measure to be taken is absolute physical rest. Victims should be carried to the ambulance/emergency room on a stretcher if possible. If decontamination is required, this should preferably be done passively, i.e. the first aiders shower the victim down, again on a stretcher if possible.

If available, first aiders can give corticosteroid aerosol (5 puffs or the highest dose as recommended by the manufacturer).

Transport (ambulance)

Transport must be by ambulance accompanied by a nurse or similar. If the victim is suffering from dyspnea or decreased oxygen saturation (< 92-94%), oxygen should be given during transport.

The patient should lie flat on a stretcher or with slightly raised chest (max. 45 degrees). The patient must avoid any exertion (walking etc.) and must be carried on a stretcher to and from the ambulance.

Corticosteroid aerosol application may be continued. If available, positive pressure breathing (EPAP = expiratory positive airway pressure, or CPAP = continuous positive airway pressure) is advisable.

Medical policy (development) and communication

Sites handling phosgene must cooperate with nearby hospital(s) to develop a medical policy that takes into account the available medical provisions like ambulance and hospital equipment, travel time to hospital(s).

If there is no fully equipped ICU in the nearby hospital(s), the policy must include advice on transportation to higher level medical care. This must be done quickly. Attempts to treat phosgene inhalation cases with inadequate technical equipment are to be avoided.

It is recommended that written processes or standard operating procedures (SOP) are defined with this goal, always in cooperation with the local medical emergency service and hospital(s).

Use, hazards and company provisions for phosgene exposures, e.g. the use and assessment of badges, must be clearly communicated to the local medical community, including hospital(s).

Likewise, current treatment recommendations must be very clearly communicated, preferably also in the form of an SOP. It must be kept in mind,

however, that physicians may deviate from recommendations and cannot be obliged to follow a recommended treatment regimen.

This makes good communication, support and relations even more important. This should be done both orally and in writing.

Personal protection and tasks of the medical personnel must be clearly defined, too. For example, in most countries, rescue is not the task of the medical team but of the firefighters.

Regular (annual) documented training on all these aspects is strongly recommended.

Monitoring

Inhalation dose below 50 ppm x min

If inhalation exposure has definitely been below 50 ppm x min, the patient can be discharged quickly.

Inhalation doses above 50 and below 150 ppm x min

Medical monitoring is required for inhalation doses higher than 50 ppm x min.

This can only be done in a well-equipped medical facility on site or in a hospital. Some measures can already be implemented during transport.

Medical monitoring shall include:

- History of exposure
- Badge reading and assessment of inhaled dose
- Medical history, especially regarding cardiovascular and respiratory diseases
- Clinical examination with a focus on the respiratory function (auscultation)
- Pulse oximetry and vital signs (heart and respiratory rate, blood pressure) at least every 30 minutes or continuously
- Repeated lung auscultation, at least every 30 minutes
- Chest X-ray as deemed appropriate, e.g. in the case of an unusual auscultation result or after 8 hours

  Note: A lung edema is not expected to occur if the lung X-ray is clear 8 hours after inhalation. The early signs of lung edema in X-ray are enlarged and blurred hili and ill-defined patches or strip shadows in central parts of the lung.

Monitoring for exposure between 50 and 150 ppm x min should be done for 8 hours. A longer observation is not deemed necessary. However, many hospitals will keep patients for 24 hours.

Inhalation dose above 150 ppm x min

For such inhalation doses, monitoring must be longer (24 hours) and more intense. The following should be implemented:

- Continuous pulse oximetry
- Baseline arterial blood gases and repetition if oxygen saturation drops
- Check of vital signs (heart and respiratory rate, blood pressure) every 15 minutes or continuously
- Frequent chest auscultation
- Lung X-ray, possibly repeated

  The early signs of lung edema in X-ray are enlarged and blurred hili and ill-defined patches or strip shadows in central parts of the lung.

This monitoring should be done in a hospital with an ICU in order not to lose time by transport from hospital to hospital.

Inhalation dose above 300 ppm x min

In such cases, continuous monitoring is part of standard ICU treatment.

Medical treatment

Note: None of the following treatment recommendations has been evaluated in randomized studies. They are not evidence-based but have been derived from animal experiments, most often with rodents, and/or are based on anecdotal reports of physicians with more or less experience in the treatment of phosgene inhalation cases.

In 2004/5 an international group of physicians with such experience gave recommendations. This advice is largely based on that work.

As none of the therapeutic approaches is evidence-based and most have been criticized by other authors, no physician can be obliged to follow these recommendations. Each case must be assessed and managed individually.

It is clear from clinical experience and animal experiments that physical rest is mandatory. This must be ensured at all stages.

Emergency room

Initial treatment

- Cough may require a non-narcotic anti-tussive.
- Wheezing/bronchospasm may respond to aerosolized β2-selective adrenergic agonists, e.g. terbutaline, salbutamol or isoproterenol, as per standard treatment for asthma.
- Oxygen addition to inspired air (by mask or nasal catheter): only for dyspnea, wheezing or pulse oximetry <92% - humidified oxygen should be given if available. 100% oxygen should not be used.

  The reason for this is the probable involvement of free oxygen radicals in the pathophysiology of the pulmonary edema.
- As in all chemical accidents, patients will react with anxiety, especially as phosgene exposure may involve dramatic circumstances and is known by workers to be dangerous.

  Such an anxiety reaction is absolutely normal but can evoke symptoms of toxicopy. This means that symptoms occur due to the "knowledge" or perception of being "poisoned", without real exposure having occurred or symptoms attributable to specific poisoning (e.g. headaches and dizziness are typical symptoms, even though it is very unlikely that phosgene could exert cerebral effects). This should be explained to the patient in a reassuring way. Sometimes, a light sedative may be required but care must be taken not to cause respiratory depression.

Early treatment

Clinical experience clearly indicates that early treatment of suspected pulmonary injury during the latency phase is more effective than the treatment of clinically overt pulmonary edema. If treatment is started once edema has manifested, it is difficult or even impossible to save the patient.

Therefore, treatment should be started as early as possible. Again, like for monitoring requirements, therapy should be adapted to the inhalation dose.

For doses above 100 ppm x min, early treatment with steroids only can be considered.

Unfortunately, no dose level at which treatment is definitely warranted can be determined. These recommendations are thus opinion-based.

- An inhaled steroid at its maximum dose as recommended by the manufacturer (one such regimen calls for initial administration of 8 puffs of aerosolized beclomethasone initially, followed by 4 puffs every 2 hours), as soon as available, should be given.

  Alternatively: 125 mg prednisolone or equivalent IV once

Hospital

After inhalation of a larger phosgene dose (> 150 ppm x min) or the suspicion thereof, the development of a pulmonary edema has to be expected. As explained, treatment must be initiated as early as possible, even in the absence of signs and symptoms. Here, all available therapeutic approaches should be considered.

- Positive airway pressure ventilation by mask (EPAP = expiratory positive airway pressure, or CPAP = continuous positive airway pressure) could probably reverse or prevent alveolar collapse and arteriovenous shunts and should be started forthwith

- Steroids: Though there is no evidence-based medicine proof, the early use of corticosteroids via the most readily available route, inhaled, oral and/or intravenous, according to some experts may provide the best chance to directly reach the alveolar epithelium as well as the pulmonary capillary endothelium. If the intravenous route is readily available, then an IV dose of 125 mg methylprednisolone or equivalent can be given. Additionally and/or if the IV route is not available, an inhaled steroid at the maximum dose recommended by the manufacturer is an initial option until IV treatment can be applied (one such regimen calls for initial administration of 8 puffs of aerosolized beclomethasone initially, followed by 4 puffs every 2 hours). Oral prednisone (80mg) may be given if the inhaled and/or IV steroid is not yet available. It must be kept in mind that the application of steroids is probably the most intensely discussed approach and is regarded as ineffective by some experts.

- N-acetyl cysteine (NAC) (20 ml of a 20% NAC solution by nebulizer) restores the glutathione lung antioxidant defense system. Bronchoconstriction and allergies have been reported as a side effect prompted by inhaled NAC, so care should be taken. Some experts even advise against the use of NAC.

- The formerly recommended Terbutaline (0.25 mg SC or as an aerosol) or other ß2-selective sympathomimetic as per treatment protocol for asthma are no longer recommended as they increase cardiac output.

- Option only: Leukotriene receptor antagonists (PO, also available as aerosol combined with steroids): Varieties of agents with a high safety profile are currently available for the treatment of asthma and may be considered in moderate to severe phosgene exposures. Animal toxicology studies have indicated that leukotriene-mediated capillary permeability is a factor in phosgene-induced pulmonary edema. These medications are suggested for consideration based on their pharmacological effects.

Experience with their use in treatment of phosgene exposures is very limited and has not been compiled.

Intensive care unit (ICU)

For cases with imminent or manifest lung edema or with an inhalation of 300 ppm x min or more, or 150 ppm x min and lung symptoms, referral to a hospital intensive care unit with adequate mechanical ventilation facilities is absolutely mandatory. If at all available, transport should initially and without time loss be done to a hospital with long-term ECMO capability. Transport must be done under CPAP or similar and with the option to start mechanical ventilation after intubation ihn the ambulance car.

Treatment is basically similar to acute respiratory distress syndrome (ARDS). ref: Tiered Ventilation Approach, This is a recommendation, the ultimate decision needs to be taken by the attending specialist.

The patient is supposed to be on CPAP/EPAP. Positive airway pressure ventilation by mask (EPAP = expiratory positive airway pressure, or CPAP = continuous positive airway pressure) could probably reverse or prevent alveolar collapse and arteriovenous shunts. Efficacy for prevention of lung edema has been shown in animal experiments.

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. Efficacy has been shown in animal experiments. 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 FiO2 of 100% O2 , or if the PaO2 is below 60 mm Hg, either of which for more than 1 hour, and if there are no contraindications

⇓

ECMO (extracorporeal membrane oxygenation) can be considered. 4 successful cases of ECMO use have been reported in literature in phosgene poisonings. This should only be used by centers experienced in long/term ECMO for days or weeks, e.g. for H1N1 influenza, if feasible not by cardiac surgery departments with short-term ECMO experience.

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

Medication approaches must be regarded as unproven.

Steroids: Methylprednisolone 125mg IV or equivalent, may be repeated every 8 – 12 hours, if needed. Application via inhalation or the oral route is not an option here.

Further treatment options, though unproven in humans except for single desperate cases are not recommended, but mentioned here::

- **N-acetyl cysteine 4-7 g as IV infusion:** There is one single anecdotal case report of a phosgene-induced pulmonary edema refractory to steroid and ventilation treatment but dissipating after the application of NAC as above. Such high doses of NAC can have significant unwanted side-effects, from nausea to allergic reactions. A flush reaction developing during application should prompt immediate discontinuation of the infusions.

- **Ibuprofen:** Various animal studies have been conducted, which indicate that ibuprofen at very high doses may have a beneficial effect on treating phosgene induced lung injury. However, since there are no reports to indicate that ibuprofen is beneficial in the treatment of phosgene exposures of humans and since it is not useful in the treatment or prevention of ARDS, ibuprofen is not routinely recommended. Repeated administration of 10 mg/kg bw (maximum of 800 mg three times/day, total dose 2400 mg/day) may be considered in severe phosgene exposure.

- **Diuretics** have not been recommended or have even been regarded as contraindicated in toxic lung edema until recently. However, recent casuistics have reported their use in surviving patients.

Obsolete treatments

Some historical treatment approaches are no longer recommended or are advised against. This may change, however, as the example of diuretics shows (see above).

- **Overinfusion must be avoided.** Experience indicates that it is advantageous to manage fluids and electrolytes very restrictively (especially if pulmonary edema is present or imminent) and to avoid use

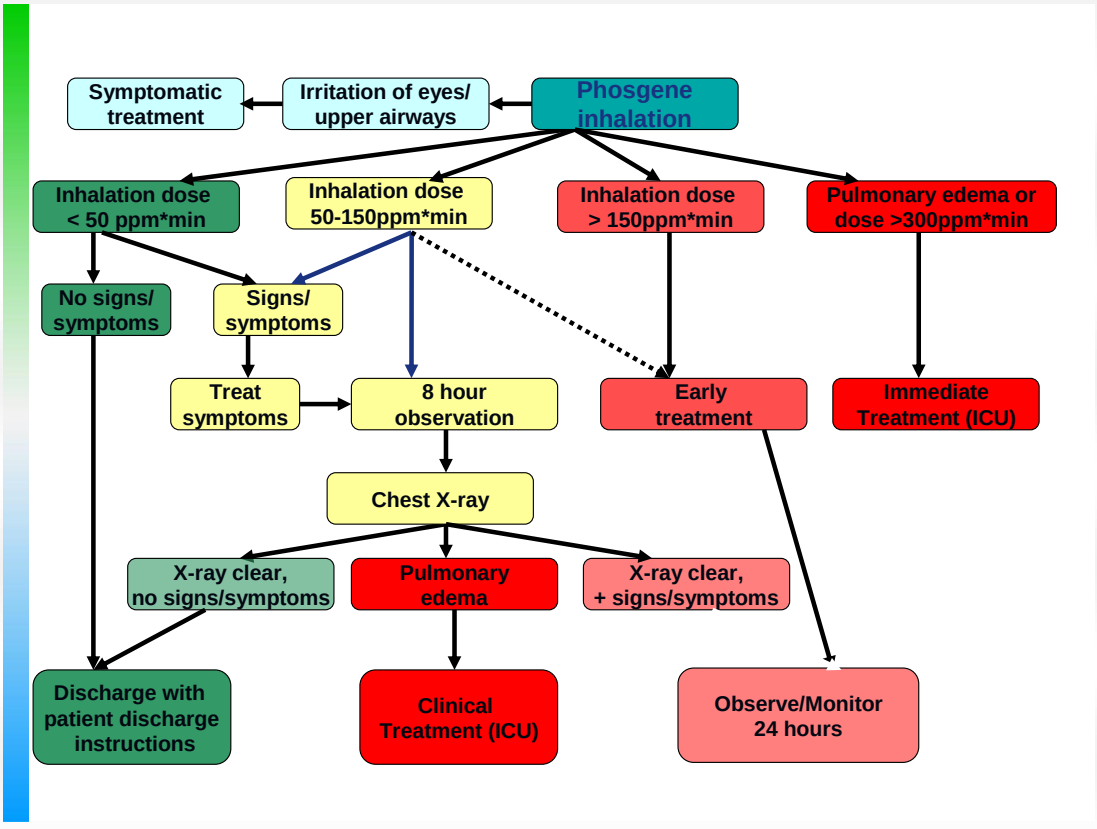
of crystalloid IV fluids. If volume expansion is deemed necessary in rare cases, colloid solutions have been used with some success.

- **Antibiotics:** Though pulmonary superinfection may occur in very rare cases, the prophylactic administration of antibiotics is not recommended. It is advisable to withhold antibiotics until signs of infection become manifest (sputum culture, C-reactive protein increase).
- **Phlebotomy** (also referred to as venesection or bloodletting) is not justified, though it was reported to have been successful in World War I gassing victims. Later animal experiments have failed to show a benefit.
- Other medications, e.g. hexamethylentetramine, have not been shown to be useful. Even they have a prophylactic effect if given before phosgene exposure in experiments, their application after phosgene inhalation is not successful.

Medical plan, medical decision tree

As mentioned above, a medical treatment plan should be worked out in cooperation with the local hospital(s).

To make decisions easier, a decision tree has been developed:



Re-evaluation after phosgene inhalation incidents

Patients with inhalation doses below 50 ppm x min can be discharged quickly.

Patients with inhalation doses between 50 and 150 ppm x min can be discharged after 8 hours if a lung X-ray is clear and after 24 hours if no X-ray can be taken.

Patients with inhalation doses between 150 and 300 ppm x min can be discharged after 24 - 48 hours if no pulmonary edema develops.

At discharge, a written note on what to do in case of problems or symptoms must be handed over and explained. An emergency phone number must be provided in writing.

On the next (working) day after discharge, the patients should be re-evaluated by a physician. This re-evaluation must include,

- History, signs and symptoms after discharge, if any
- Clinical examination
- Pulse oximetry
- Lung function testing, at least vital capacity and Tiffeneau test, if possible airway resistance testing

A similar re-evaluation is recommended after 3-4 weeks.

Training of medical personnel

Both internal and external medical personnel must be trained regarding badge assessment, decisions (decision tree), trigger levels, monitoring, therapeutic recommendations and options, patient discharge and re-evaluation. Training in personal protection must also be provided.

Such training should be done annually, bearing in mind the frequent fluctuation of hospital physicians especially.

Training should include:

- Personal protection (e.g. filter masks until patient is decontaminated)
- Type of badges used, limitations of the specific badges
- Badge reading with original color comparators
- Questions to be asked to assess the inhalation dose
    - Location of the badge
    - Use time of the badge

  - Respiratory protection used
  - Abuse of badges, e.g. leakage detection
- Trigger levels
  - Below 50 ppm x min
  - Between 50 and 150 ppm x min
  - Above 150 ppm x min
  - Above 300 ppm x min
- Monitoring to be done at different levels of exposure
- X-ray necessity and evaluation
- Treatment recommendations and further options at different levels of exposure, including Tiered Ventilation Approach
- Obsolete treatments
- Patient discharge at different exposure levels
- Re-evaluation timing and content

Incident notification and documentation (database)

In order to learn from experience both with regard to symptoms, course and treatment, a database for case collection and documentation may be useful. Such a database, however, must account for certain limitations:

- A clear and defined protocol has to be established and agreed upon in advance.
- All cases defined by the protocol must be entered. It is not acceptable to select cases for entry based on any criteria.
- It is possible to enter all cases, but a classification must then be made as to the triggering levels as above:
  - Below 50 ppm x min
  - Between 50 and 150 ppm x min, possibly divided into 2 groups without and with treatment
  - Between 150 and 300 ppm x min
  - Above 300 ppm x min

The alternative would be to enter only treatment cases (treatment between 50 and 150 ppm x min and all cases above 150 ppm x min).

- Medical history, especially regarding respiratory conditions and smoking, needs to be documented.
- Signs and symptoms must be recorded after admission and for any change of signs and symptoms.
- Results of technical measurements, e.g. oxygen saturation, must be recorded.
- Treatment approaches should be defined and recommended in advance; deviations from recommended treatment need single-case evaluation.

- Re-examination results/data (after 24 hours and 3-4 weeks) should be entered.

7. Transportation:

Transportation and supply of phosgene on- or off-site by rail, waterways or road is not advisable for any reason.

A phosgene production (generation) unit integrated to the phosgenation unit of phosgene-consuming plants will reduce the likelihood of a release. When transporting small laboratory scale quantities of phosgene or phosgene solutions for R&D or analytical purposes, special precautions may need to be taken.

---End of the report---

Phosgene: Toxicology, Regulatory Standards, and Countermeasures

Properties affecting toxicity and hazard:

Phosgene (carbonyl chloride) is a highly reactive, colorless gas at ambient temperature and pressure and a colorless, fuming liquid below 47 ^{0}F (8.2 ^{0}C). Its gas phase is 3.4-times heavier than air. It is an acylating agent, and as such reacts covalently with nucleophilic moieties. Biomolecules (e.g., proteins, cell membranes) containing amino, hydroxyl, and sulfhydryl functionalities may become potential scavengers of phosgene. Their increased denaturation at the alveolar level of the lung causes cardiopulmonary disturbances. If severe enough, the ensuing acute cardiogenic lung edema is the cause of death [1-4].

The congeners of phosgene trichloromethyl chloroformate (diphosgene) and bis(trichloromethyl) carbonate (triphosgene) are liquid and solid, respectively. Systematic toxicological studies with the gas phase of phosgene and congeners demonstrate that one mole of diphosgene behaves like two moles of phosgene. However, this idealized stoichiometry cannot be applied to triphosgene (for details see Pauluhn, 2011)[5]. The median lethal concentrations (LC_{50}) following 4-hour exposure of rats was 7.2, 13.9, and 41.5 mg/m³ or 1.8, 1.7, and 3.4 ppm for phosgene, di- and triphosgene, respectively. Somewhat similar mortality patterns were observed in rats exposed to phosgene and diphosgene whereas triphosgene caused biphasic mortality patterns. Triphosgene caused unique additional delayed mortality pattern typical of central airway injury (bronchiolitis obliterans). Solid triphosgene sublimates so that lethal concentrations of vapor may occur at the head-space of containers containing crystalline triphosgene. Hence, due to its tendency to sublimate and re-crystallize and the absence of any robust analytical method to quantify airborne triphosgene (and by-products), the hazards and risks associated with triphosgene appear to be markedly more complex and difficult to characterize as compared to phosgene. Although the solid physical state of triphosgene conveys the erroneous and equally insidious perception of insignificant exposure. The toxicity of phosgene has been examined in bioassays following harmonized OECD testing guidelines which served as basis for setting Occupational Exposure Values (OELs). Triphosgene lacks from even basic data allowing any robust regulatory classification or setting of OELs. Suffice it to say, this also mandates a clear analytical distinction of triphosgene (vapor and sublimated solid phase combined) from phosgene gas [5-8].

2 Mechanisms of Toxicity

The inhalation toxicity of phosgene gas has received extensive toxicological attention with focus on its acute mode of action which is the induction of a potentially life-threatening acute cardiogenic pulmonary edema in both experimental animals and humans. The inhaled dose-mortality-relationship is very steep and suggestive of an acute inhaled dose dependent mode of acute lung injury (ALI). In this context inhaled dose is defined as concentration x continuous exposure duration (time) (Cxt) relationship. Single and repeated subchronic exposure studies on rats demonstrate that chronic effects appear to be contingent upon an 'acute-on-chronic' localized effects resulting in essentially identical no-observed-adverse-effect levels (NOAELs) independent whether the duration of study was acute (1x6-hours) or subchronic (6-hours/day on 5 days/week for 3-month. Based on the physicochemical properties of phosgene 'lipophilicity' and 'electrophilicity', phosgene retained in the alveolus titrates out pulmonary surfactant inhaled dose-dependently followed by cardiogenic lung edema, changes in lung mechanics due to decreased elastic recoil and mechanical compression of smaller airways and vessels. Dysfunctional surfactant increases surface tension followed by alveolar collapse and atelectasis [1-4,9,10].

Thus, phosgene-induced ALI is characterized by a Cxt-dependent increased pulmonary vascular permeability, phenotypically manifested as potentially life-threatening acute lung edema. In contemporary animal bioassays, the quantification of protein in bronchoalveolar lavage fluid (BAL) is taken as an unequivocal endpoint suggestive of disruption of alveolar barrier function. However, extravasated protein can only be a surrogate endpoint for assessing the extravascular fluid dynamics of the lung. This pathophysiological hallmark of ALI is diagnosed and quantified *in vivo* in humans by assessing the accumulation of excess extravascular lung water (EVLW) [11-17]. The Point of Departure (POD) of the Cxt relationship of this adverse outcome pathway constitutes the basis for setting safe occupational and emergency response values. Unlike the EVLW approach, toxicology-based animal models often utilize postmortem analyses of total protein in BAL and lung weights as the basis for human risk assessment. With either approach, it remains difficult to unequivocally evaluate pulmonary edema in terms of etiopathology and specificity, i.e., cardiogenic and hydrostatic versus increased permeability edema. The clinical scoring of the severity grades of *in vivo* EVLWs from humans inflicted with ARDS (Acute Respiratory Distress Syndrome) was compared with the respective postmortem biomarkers BAL protein and collagen versus wet lung weights in rats and dogs exposed by inhalation to phosgene gas.

Despite the different methodological approaches taken in humans and animals, the EVLW-based predicted thresholds for the onset of pulmonary edema and potentially life-threatening severe pulmonary edema were in remarkable agreement. Data from dogs appear to more aptly reflect the human etiopathology and should be given preference over data from rodents. Especially in rats, elevations in BAL protein may lead to a marked overestimation of the edematous potency of phosgene due to actively secreted protein into airways serving protection. Collectively, increased lung weight in rats and dogs scaled favorably with the human-EVLW and was shown to be the biomarker of choice for the scaling lung edema. The EVLW-value from patients presenting 9 mL/kg, the lung edema was judged "borderline". From that matching evidence it was concluded that an increased EVLW of ≈20% above normal in lung weight fulfills the criterion of the human-equivalent POD for alveolar edema. Thus, any rat lung weight-based threshold is implicitly more conservative than the borderline EVLW-based human threshold. This outcome hardly justifies additional intra-/interspecies adjustments for the lung weight-based assessment of this human-equivalent threshold in rats for the setting of occupational exposure levels (for details see Li & Pauluhn, 2019 [13]).

Additional factors must also be considered: Alveolar macrophages receive their nutrients via pulmonary surfactant. Any substantial deterioration of these cells either by surfactant depletion or direct exposure may trigger the release of vasoactive factors contributing further to hemodynamic disturbances in the pulmonary circulation. Overarching sensors controlling pH, oxygenation or restrict the vascular perfusion to inadequately ventilated regions of the lung (HPO, hypoxic pulmonary vasoconstriction), tend to defeat some of these disturbances; however, instead of defeating these disturbances, even more blood is shifted from the systemic circulation to that of the lung [4]. In concert with depleted lung surfactant, the increased fluid flux through the pulmonary endothelium may promote alveolar flooding (lung edema). Thus, the alveolar blood-barrier can be breached just by affecting the physicochemical forces keeping this barrier functional as conceptualized by Starling's equation [18-21. All these events may become already operative during the clinically asymptomatic interval between exposure and the onset of lung edema and hemodynamic disturbances. Depending on the inhaled dose (Cxt) of phosgene, these events may be downregulated by self-repair at low Cxt's or accentuated further until severe enough to become a lung edema refractory to conventional treatment.

In summary, the mechanism involved in the acute inhalation toxicity of phosgene

are not stereotypical of irritant gases, rather, they depend on the somewhat unique physicochemical properties of phosgene. Especially during the yet clinically occult period, complex and inter-concatenated changes in cardiopulmonary hemodynamics occur and call for degree-of-dysfunction-adjusted physiological countermeasures rather than pharmacological counter-measures. Mechanical ventilation with personalized titration positive end-expiratory pressure mechanical ventilation (PEEP), supplemented by extracorporeal membrane oxygenation (ECMO) at conditions where PEEP cannot maintain any longer adequate oxygenation without ventilator-induced-lung injury, appears to be the treatment strategy of choice [14, 22-25]. Thus, any preventive measures should be given preference to curative measures, if clinically indicated and manageable. However, suffice it to say, titration hemostasis, conventional fluid resuscitation, antibiotics, and shock-preventing measures need to be observed as well. Recalling that phosgene is produced from carbon monoxide and the airway irritant gas chlorine, production-related incidences must consider two possibly different profiles of ALI, one may be caused by the alveolar irritant phosgene, the other by the airway irritant chlorine. Each type of injury requires specialized countermeasures and diagnostic tools to guide clinicians for optimal treatment. In this context it is particularly important to recall that phosgene-induced ALI, opposite to chlorine-induced ALI, is not caused by inflammatory mechanisms. Accordingly, with regard to phosgene, corticoids may not only without any beneficial effect they may even aggravate the phosgene-induced ALI [4,24-26].

3 Prognosis, Triage, and Treatment

Prognosis & triage: A wealth of published evidence supports the prognostic relevance of measurements of physiological dead space (V_D) relative to tidal volume (V_T) for patients inflicted with ALI [16-22]. Its ratio V_D/V_T is taken as an indirect but early marker of dysfunctional endothelium of pulmonary capillaries as a reflection of the status of blood flow through the lung (perfusion) relative to the ventilation of the pulmonary gas-exchange region. Endothelial dysfunction may even precede that of the pulmonary epithelium due to the instant devastation of alveolar macrophages. These mobile cells contain vasoactive and other factors known to initiate and orchestrate pulmonary inflammation. In humans, volumetric capnography and ventilation dead space calculations were shown to further elucidate the relative contributions of venous admixture ("shunt", alveolus perfused but not ventilated) and dead space ventilation alveolus not perfused but ventilated) in ALI. Increased exhaled nitric oxide (NO) increased during the

asymptomatic phase and the development of lung edema in experimental models of phosgene-induced ALI [4,26-28]. Consistent with human data, CO_2 in exhaled air decreased by more than 50% post-exposure to phosgene (rats) and can be judged to be a readily available biomarker of early ALI.

Hemoconcentration (hypovolemia) was shown to be a biomarker of ALI in blood paralleling the time-related aggravation of the phosgene-induced ALI [4]. Unlike increased hemoglobin in blood (hematocrit), CO_2 and NO measured in the expired gas deliver the advantage of being sensitive and direct biomarkers amenable for monitoring real-time the progression of the lung edema. Re-triage by time-course measurements of CO_2 and NO in exhaled breath may increase the diagnostic power of this assay [4,27-38]. Bedside quantification of dead space ventilation could be used to titrate countermeasures at the yet asymptomatic stage of injury. In cases of exposure to mixtures of irritant gases, late complications cannot be entirely excluded. Therefore, prior to discharge of patients or before changing treatment strategies from anti-edema to anti-inflammatory, these readily available analyses may deliver important information to the clinician regarding which course to take. These methods appear to be easy to manage and suitable for both triage and re-triage.

Treatment: Systematic research on countermeasures to mitigate the phosgene-induced acute lung injury (ALI) focused on either pharmacological curative principles [4,14,29,33-36] or personalized, protective principles of intervention. The latter approach is aiming at the protection from life-threatening conditions to occur, e.g., PEEP initiated shortly after exposure to phosgene. Management of phosgene-induced ALI with PEEP and monitoring its effects by measuring chest mechanics have been inextricably linked as detailed in the seminal papers on ARDS [39-41]. In brief, respiratory system compliance (C_{RS}) measured in a dynamic state was "strikingly" reduced and that "stiff lungs had marked difficulties with oxygenation". The underlying lesion etiopathological of this particular illness was described as increased alveolar surface tension and alveolar collapse and that PEEP exhibited salutary effects on oxygenation.

In clinical practice, assessing the mechanical effects of PEEP is done indirectly through the measurement of C_{RS} by dividing the difference between end-inspiratory plateau pressure (P_{plat}) and PEEP into tidal volume (V_T). The physiologic studies of PEEP in patients with various forms of acute respiratory failure clearly demonstrated a linear relationship between incremental increases in PEEP with increased functional residual capacity (FRC), dynamic and quasi-static C_{RS}, and

oxygenation. However, the heterogeneity of ventilated lung units and increased FRC require titration PEEP and low V_T not to exceed TLC. The adverse effects of PEEP on lung overdistention and hemodynamic compromise precipitously when C_{RS} deteriorated as either PEEP or the driving pressure delivered by V_T used with its application exceeded the normal total lung capacity (TLC). Pneumomediastinum, also known as mediastinal emphysema, is pneumatosis (abnormal presence of air or other gas) in the mediastinum. Such injury pattern was observed following PEEP ventilation [14]; however, seems to be related to transpulmonary pressures above TLC. As demonstrated by He and coworkers [14], EVLW water is amongst the most useful feed-back biomarkers for titration PEEP on patients with otherwise lethal lung edema. Successful treatment of phosgene-ALI with an EVLW higher than 30 mL/kg (potentially lethal threshold 15 mL/kg) was demonstrated when using a combination of titration PEEP supplemented by ECMO to prevent barotrauma. Such approach can be taken as robust evidence that end-stage improvement of oxygenation can better be achieved by ECMO at PEEP levels preventing barotrauma-related aggravation of lung injury [14]. Thus, from a practical standpoint, it appears that a hemodynamics, oxygenation- and lung mechanics-guided course of treatment using a combination of titration PEEP with ECMO has greater impact on any clinical outcome than any meticulous assessment of chest mechanics in severely affected patients. In this context, a titration approach should observe EVLW and volumetric capnography in addition to the conventionally recorded physiological biomarkers. However, when reproducing some of the published conclusions from multiple authors [29,33-36,39-41], "The 'best PEEP' does not exist". It remains a wishful dream that has nothing to do with the reality message that any best compliance, best oxygenation and lowest dead space without causing hyperinflation and affecting hemodynamics can be achieved by any best PEEP setting. With regard to infrequently or rarely occurring incidences with phosgene, this conclusion calls for an instant translocation of exposed workers to highly specialized and experienced ICU centers. The seminal course taken by He et al. (2019)[14] give directions to treatments of highly exposed workers (Fig. 1). Accordingly, physicians must take decisions well ahead before clinical evidence of potentially lethal lung edema is apparent. This requires a dicision making process relying upon the readings from the mandatorily worn "phosgene badges". Exposures in the range and above 300 ppm x min cannot be handled by any trial-and-error approaches at local hospitals not familiar with the phosgene-specific titration PEEP and ECMO.

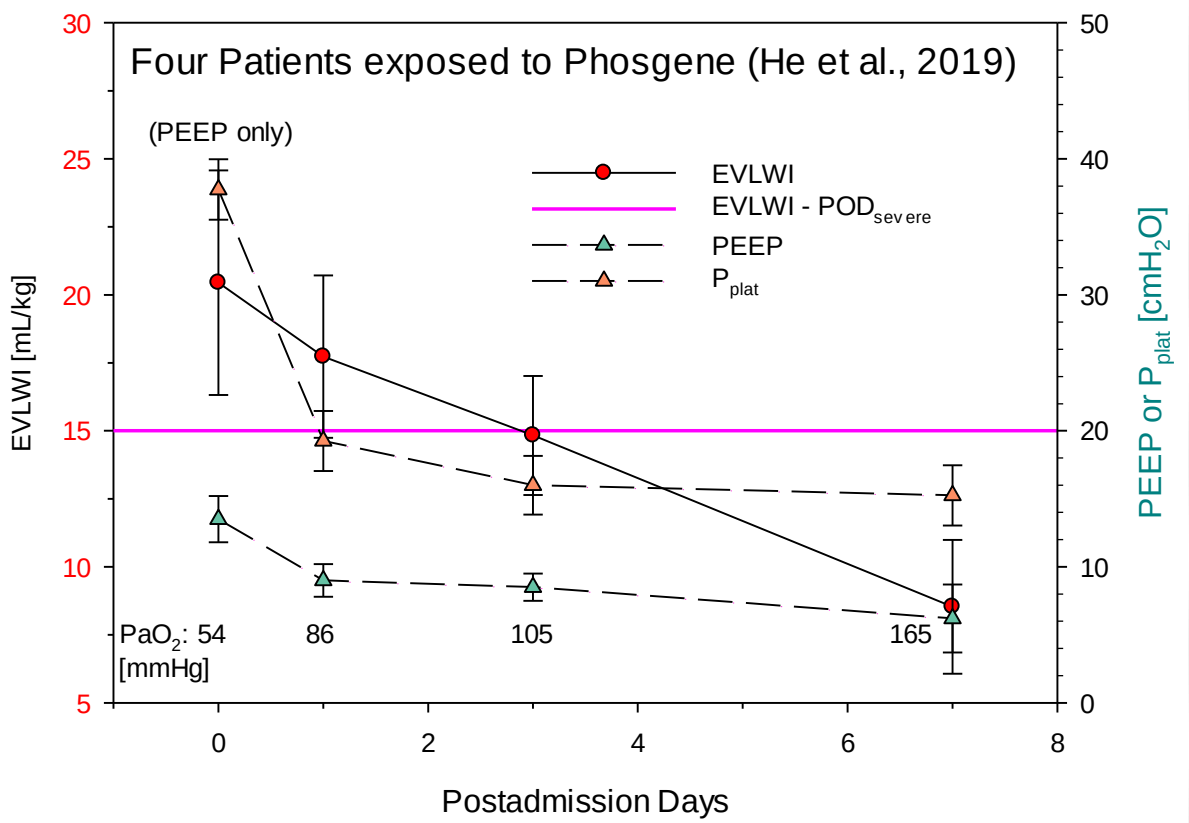


Figure 1 (data duplicated from ref. [14])**:** Four cases of lethal phosgene exposures to phosgene, admission to ICU after evidence of lung edema (visible foam). PEEP complication: mediastinal emphysema & pneumothorax, oxygenation difficult to maintain. VV-ECMO day one post-admission at V_T: 6-3 mL/kg, titration PEEP/P_{plat}: 14-6/36-15 cmH_2O, FiO_2: 0.3. Pharmacological support: antibiotics, titration anti-coagulation (Heparin), cumulative fluid balance (CFB) conser-vative (≤ 80 mL fluid/kg/day). Methylprednisolone 80 mg i.v. infusion 2x/day, bronchodilator, norepinephrine to maintain blood pressure, propofol, atracurium. All 4 patients discharged after 6-20 ECMO days and 8-27 ICU days.

Putative early mechanisms of phosgene-induced ALI include direct interaction and deterioration of lung surfactant and associated changes in lung mechanics [1,42-44]. Pulmonary irritation and pathology incident to phosgene poisoning may produce marked circulatory disturbances not unlike that seen in shock. If the acute stage of pulmonary edema with its attendant hypoxemia is survived, circulatory failure may become a more important factor in the ultimate outcome. While past approaches focused on trial-end-error pharmacological interventions during the more refractory symptomatic period, the more current approaches focus on preventive countermeasures controlling the early physiological dysregulations during the yet clinically "occult" period. In terminally anesthetized dogs and pigs preemptive, early protective ventilation (PEEP) proved to be adjustable to time-course changes in disease development and as promising countermeasure to avert life-threating conditions. Concurrent with the change in paradigms for treatment, the emphasis of more recent research has shifted from

treating to preventing ALI using triage-based preemptive, personalized ventilator strategies applied to maintain normal lung function in patients at high risk [4,30-36,39-41]. Supportive treatment commonly includes moderately increased fractional concentrations of inspired oxygen (FiO_2), the use of protective PEEP, and physical rest. Fluid resuscitation must be conservative to prevent any superimposed aggravation of lung edema due to dysregulated nervous control of the cardiopulmonary system. Published evidence suggests that fluid overload by infusion may precipitately aggravate lung edema. Thus, clinical experts have to manage a balancing act between the improvement of lung function vs. jeopardizing extrapulmonary organ perfusion and shock. Anti-inflammatory pharmacological principles must be considered when mitigating injuries caused by airway irritants, such as chlorine. However, corticoids were ineffective for mitigating the progression of edema in phosgene-exposed rats [25,37,38]. Accordingly, the premise of successful treatment requires knowledge on the toxic gases and inhaled dose involved and cannot be considered as a "one-size-fits-all" approach.

In summary, phosgene as an alveolar irritant with negligible scrubbing of the gas within the conducting airways. It penetrates the lower respiratory tract independent on the concentration, and injury becomes solely dependent on the inhaled Cxt but not C alone (opposite to the irritant chlorine). High-risk patients from accidental occupational exposure to phosgene can readily be identified by the mandatorily worn Cxt-based dosimeter ("Phosgene Badges"). The badge-reading is amongst the most decisive endpoint for guiding treatment strategies during the asymptomatic period.

4 Occupational Standards and Emergency Response Values

National Agencies take responsibility for organizing independent, multidisciplinary, collective scientific expert appraisal for setting occupational exposure limits (OELs). Commonly, a dedicated expert committee is set up to support the Agency in this mission under the umbrella of the national Ministry of Labor to develop structures that support consultation with all involved stakeholders. Once promulgated, OELs are subject to cyclic re-appraisals depending on the availability of new scientific and workplace evidence as well as mechanistic understanding. For phosgene, new published evidence on toxicology became available for review in 2007 [1,42-44]. Numerous mechanistic studies on countermeasures followed [2,13,23,26-28]. As summarized in Table 1 [45], OELs either remained at 0.1 ppm or if lower, were raised from 0.02 to 0.1 ppm (time-weighted average, TWA). Not all OELs given in Table 1 underwent re-appraisal yet. The reasons for these differences are detailed in section "5.5 Background for Differences in Occupational Standards of Phosgene".

Table 1: Summary of Occupational Exposure Limits (all concentrations are in ppm; a factor of 4 must be applied to convert ppm to mg/m³) [45] https://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx

Substance	Phosgene			
CAS No.	75-44-5			
	Limit value - Eight hours		Limit value - Short term	
	ppm	mg/m³	ppm	mg/m³
Australia	0,02	0,08	0,06	0,25
Austria	0,02	0,08	0,1	0,4
Belgium	0,02	0,08	0,1 (1)	0,4 (1)
Canada - Ontario	0,1			
Canada - Québec	0,1	0,40		
Denmark	0,02	0,08	0,04	0,16
European Union	**0,02**	**0,08**	**0,1 (1)**	**0,4 (1)**
Finland	0,02	0,08	0,05 (1)	0,2 (1)
France	**0,02**	**0,08**	**0,1**	**0,4**
Germany (AGS)	0,1	0,41	0,2 (1)	0,82 (1)
Germany (DFG)	0,1	0,41	0,2	0,82
Hungary		0,08		0,4
Ireland	0,02	0,08	0,1 (1)	0,4 (1)
Italy	0,02	0,08	0,1	0,4
Japan (JSOH)	0,1	0,4		
Latvia	0,02	0,08	0,1 (1)	0,4 (1)
New Zealand	0,02	0,08	0,06	0,25
People's Republic of China				0,5 (1)
Poland		0,08		0,16
Romania	0,02	0,08	0,1 (1)	0,4 (1)
Singapore	0,1	0,40		
South Korea	0,1	0,4		
Spain	0,02	0,08	0,1	0,4
Sweden			0,05 (1)	0,2 (1)
Switzerland	0,1	0,41	0,2	0,82
The Netherlands		0,08		0,4
Turkey	0,02	0,08	0,1 (1)	0,4 (1)
USA - NIOSH	0,1	0,4	0,2 (1)	0,8 (1)
USA - OSHA	0,1	0,4		
United Kingdom	0,02	0,08	0,06	0,25

Note: The TLV-TWA of phosgene for India is 0.1 ppm. For further details see next page.

	Remarks
Belgium	(1) 15 minutes average value
European Union	(1) 15 minutes average value Bold-type: Indicative Occupational Exposure Limit Value (IOELV) ~ (for references see bibliography)
Finland	(1) Ceiling limit value
France	Bold type: Restrictive statutory limit values
Germany (AGS)	(1) 15 minutes average value
Germany (DFG)	STV 15 minutes average value
Ireland	(1) 15 minutes reference period
Latvia	(1) 15 minutes average value
People's Republic of China	(1) Ceiling limit value
Romania	(1) 15 minutes average value
Sweden	(1) Short-term value, 15 minutes average value
Turkey	(1) 15 minutes average value
USA - NIOSH	(1) Ceiling limit value (15 min)

Occupational exposure limits represent TWA concentrations for a conventional 8-hour workday and a 40-hour work week to which healthy, adult workers are exposed day-by-day. In the US the respective limits are the PEL (OSHA) and REL (NIOSH). The National Institute for Occupational Safety and Health (NIOSH) establishes Recommended Exposure Limits (RELs) whereas the Occupational Safety and Health Administration (OSHA) issues Permissible Exposure Limits (PELs). The legally binding level is that what is "permissible". Short-term exposures are regulated by STELs (Short-Term Exposure Limits) which are usually defined as a 15-minute average or a Ceiling limit values which should not be exceeded any time during a workday even if the 8-hour TWA is not exceeded. There should be at least one hour between successive STEL exposures with maximal four excursions per shift. A published summary of the workplace limits of phosgene is given in Table 1.

Given the potential for serious and large-scale health effects resulting from accidental exposure to phosgene, there is a need for the provision of scientifically based risk assessments for determining appropriate on-site control measures, as well as off-site emergency contingency plans and land-use development decisions where phosgene is produced or utilized. In this context, Acute Exposure Guideline Levels (AEGLs) or Emergency Response Planning Guideline (ERPG) values must be considered in case of an accidental chemical release [46-49]. The final AEGL of phosgene relied upon experimental data generated between 1965 and 1990 (for details see NRC, 2002 [46,48]). Unlike AEGLs, ERPG values are cyclically re-appraised for keeping abreast with scientific progress. The ERPG values published for phosgene in 2009 [47], are as follows: ERPG-1 not be defined, ERPG-2 and ERPG-3 were 0.5 and 1.5 ppm, respectively. Conceptually, both committees defined three severity tiers as follows; Tier I: the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects. These effects are not disabling and are transient and reversible upon cessation of exposure; Tier II defines the condition above which the respective population could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; Tier III predicts the condition above which this population could experience life-threatening health effects or death. While AEGL-values are derived for 10 minutes, 30 minutes, 60 minutes, 4 hours, and 8 hours, the ERPG-values predict these tiers for a one 1-hour period [47,49].

5.5 Background for Differences in Occupational Standards of Phosgene

The OEL promulgated by DFG-MAK Germany was lowered from 0.1 ppm to 0.02 ppm in 1996 (DFG-MAK: Deutsche Forschungsgemeinschaft (DFG)–Maximal Workplace Concentrations, List of MAK and BAT values). The findings from a 4-hour rat inhalation studies were considered: Rats exposed to 0.05 – 0.1 ppm were subjected to BAL 0, 4, 20, or 44 hrs. At 0.1 ppm and above arachidonic acid related eicosanoids and alveolar macrophages in BAL were decreased and neutrophilic granulocytes were increased at 0.1 ppm and above after exposure and on the first post-exposure day. Animals from all groups were indistinguishable 44 hours post exposure. The ATP content of lung tissue was different from the control. Increased lung weights were not observed. The MAK expert committee concluded that these findings provide evidence of unclear toxicological significance. This prompted a provisional decrease from 0.1 ppm to 0.02 ppm **until verifying studies with longer durations become available.** After the availability of a series of mechanistic acute studies, including a 3-month inhalation study from US-EPA [50,51] or Bayer AG (Covestro AG) [1,42-44], the MAK commission abandoned the interim value of 0.02 ppm and confirmed the previous value of 0.1 ppm in 2007. SCOEL (EU) reviewed all published evidence and promulged an IOELV (Indicative Occupational Exposure Limit Value) of 0.1 ppm and STEL of 0.5 ppm (2011) [52]. The IOELV is a European legal limit set to protect workers in the European Union. However, the EU changed the SCOEL process so that this published value was never formally legalized by the EU-specific bureaucratic processes to become an official OEL but was officially taken as a DNEL (derived no-effect level). As indicated in the ECHA information requirement R.8., DNELs are threshold endpoints derived following a procedure consisting of the following steps: (i) selection of relevant dose-descriptor(s) for the endpoint concerned, (ii) modification, when necessary, of relevant dose descriptor(s) per endpoint to the correct starting point, and (iii) application, when necessary, of assessment factors to the correct starting point to obtain endpoint-specific DNEL(s) for the relevant exposure pattern (duration, frequency, route and exposed human population). From that the SCOEL derived OEL became a DNEL.

Despite the rich data base and mechanistic understanding available, many national expert groups have adopted the interim provisionally lowered OEL of phosgene about two decades ago but did not re-adjust this value after closing the specified data gaps. One reason appears to be that within the time elapsed modified regulations concerning inter-/intra-species extrapolation and time-adjustment factors came into place. As detailed below, it must be recalled that

phosgene is destined to interact with pulmonary surfactant followed by a series of compensatory events not necessarily fulfilling the criterion "adverse" as long as any pulmonary edema is not attained. If present, the extravascular lung water content (EVLW) increases as a reflection of a transition from homeostasis to adversity. Consistent with the mechanistic pathways delineated above, chemical reactions leading to dysfunctional surfactant increases its phagocytosis and recycling by alveolar macrophages accompanied by increased discharge of storage surfactant from pneumocytes type II. As shown in experimental studies, neutrophilic granulocytes (PMNs) may temporarily be present in BAL; however, their kinetics of invasion and evasion from the lung resemble that of total protein [1,43]. Thus, exposed alveolar macrophages may discharge chemokines attracting PMNs; however, additional priming of this cells was not observed. This is consistent with findings that anti-inflammatory countermeasures had no beneficial impact [1,4,25,37,38].

EVLW is the amount of water contained in the lungs outside the pulmonary vasculature. It corresponds to the sum of interstitial, intracellular, alveolar and lymphatic fluid, not including pleural effusions. An increase in EVLW is the pathophysiological hallmark of hydrostatic pulmonary edema and acute respiratory distress syndrome (ARDS). In humans, transpulmonary thermodilution, which can be considered as the in vivo gold standard for EVLW measurement, has been developed and validated versus gravimetry. Tagami and coworkers reported an EVLW value of 7.3±2.8 mL/kg bw for the normal population. EVLW values above 10 mL/kg were reported to represent higher than normal EVLW, and 15 mL/kg bw was concluded to be the criterion for severe pulmonary edema [11,12]. Accordingly, for the human-to-rat/dog comparisons made by Li & Pauluhn [13], the PODs suggestive of increased EVLW of 10 and 15 mL/kg bw were taken to scale bioassay data to the respective human-equivalent PODs. Lung weights and BAL-endpoints were scaled by normalization to the species- and time-matched controls (100%).

The sigmoidal increase in BAL protein in the rat was much shallower in the more human-like dog. When defining the lower 95% confidence interval of the BAL protein vs. lung weight relationship in rats, an increase of at least 20% above normal in lung weight fulfilled also the criterion of possibly "biologically significant" (I). This increase matches the human-equivalent EVLW of 8.8 mL/kg bracketing that range published elsewhere [11,12,53]. The EVLW-value from patients presenting 9 mL/kg the lung edema was judged "borderline" by Hammon et al. (2014)[53]. From that matching evidence it is concluded that an increased EVLW of 20% above normal in lung weight fulfills the criterion of the human-equivalent POD for alveolar edema. Thus,

the rat lung weight-based threshold is implicitly more conservative than the borderline EVLW human-based threshold. This outcome hardly justifies additional intra-/interspecies adjustments for the lung weight-based assessment of this human-equivalent threshold in rats.

The BAL protein vs. lung weight data compared in Fig. 2-left (rats) scaled a range from normal (100%) to the threshold above which clinically significant pulmonary edema was expected to occur at an the borderline EVLW(II) of 37% above normal up to a level severe enough to represent the transition from nonlethal to potentially lethal edema at and above an EVLW(III) of 113% above normal. Dogs exposed at 495 mg/m³ x min phosgene elaborated increased BAL protein but neither increased lung weights above the EVLW(II) (Fig. 2-right) or BAL collagen. Following exposure to 1050 mg/m³ x min all of these endpoints were markedly increased; however, due to the irregular breathing of dogs were accompanied by high variability. Two dogs exposed at this Cxt showed increased lung weights close to the severe EVLW(III) which translates to a potentially life-threatening lung edema. A one-order of magnitude higher increase in BAL protein occurred in rats exposed at a similar Cxt. The respective relationships from dogs demonstrate a 70- and 9-fold difference from normal to maximal levels of BAL protein in rats and dogs, respectively. Unlike BAL protein, the analysis of lung weights revealed an almost similar relative increase in both rats and dogs. These findings suggest that extravasated protein typical of an increased loss of the alveolar barrier function seems to be better reflected by probing high(er) molecular weight proteins as compared to total protein; however, the lowest degree of uncertainty prevails when using lung weight-based PODs.

In rats, the precipitous sigmoidal increase in BAL protein was not accompanied by any proportionally increased lung weights (Fig. 1-left), corroborating the notion that most of the protein retrieved by BAL was from the airways rather than alveoli. The POD of BAL-protein/collagen from rats at 20% increased lung weights was mathematically derived by the transition towards increased lung weights. Under this condition, the respective PODs in both rats and dogs converge favorably (for details see Li and Pauluhn, 2019). The unobtrusive physiological changes in blood gases, acid-base status and histopathology observed in dogs at this Cxt support this interpretation (for details see [44]). Unlike dogs, the rodent-specific mucosal defense system might favor a reflexively (Paintal reflex)-induced secretion of proteins into the lumen of airways contributing substantially to the retrieved protein by BAL. These rat-specific nociceptive factors (related to their small lumen of airways) may be the reason for the disproportionally increased level of plasma proteins measured in the BAL of rats relative to dogs.

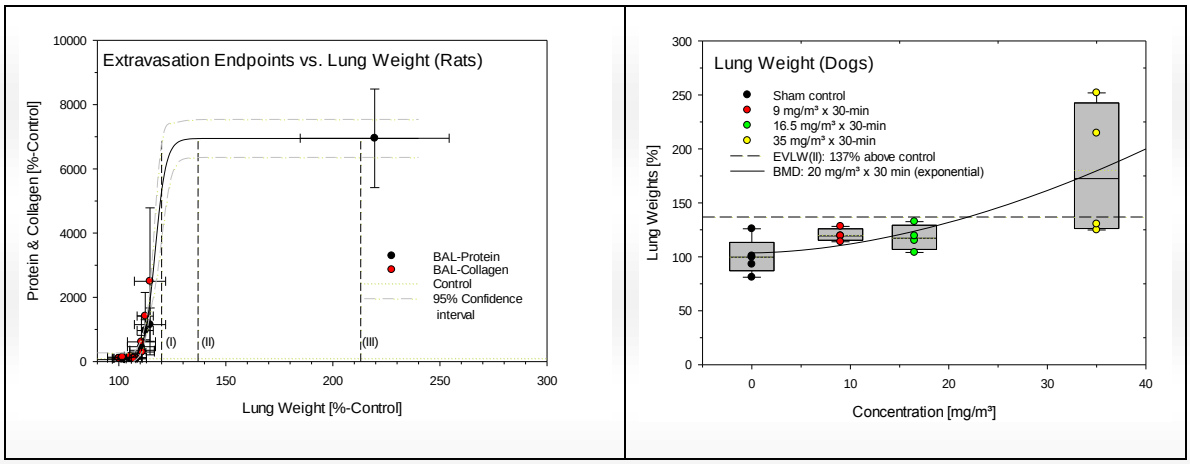


Figure 2 - left: Interrelationship of protein/soluble collagen in BAL with wet lung weights in rats exposed nose only to Cxt products of phosgene at durations of 30 and 240 min. Endpoints were determined 1-day post-phosgene exposure. Data points represent means±SD (n = 6). The curve and lower 95% confidence interval (I, 120% increased lung weight relative to control) of the combined endpoints in BAL were calculated using Sigma Plot software (Hill model). The magnitude of the relative increase in lung weights was scaled to the human EVLW as defined by Tagami & Ong [12]: II: onset of pulmonary edema (II, 137% increased lung weight relative to control) and severe edema (III, 213% increased lung weight relative to control). **Figure 2 - right:** Normalized relative lung weight to body weight ratios of four dogs per group exposed head-only for 30 min to 0, 9, 16.5 or 35 mg phosgene/m³. Non-exposed dogs (n = 5) served as concurrent time-matched control (normalized to 100%). Dashed line: Extravascular lung water (EVLW) content 37% above control (II) which characterizes the POD of the onset of pulmonary edema in humans as defined by Tagami & Ong [12]. Two hyperventilating dogs exposed at 35 mg/m³ elaborated EVLW(III) equivalent increased lung weights of ≥113% above control which scales to severe pulmonary edema. The curve and the BMD were calculated from the data shown and fitted to the polynomial model using the US-EPA benchmark software. The lower and upper boundaries of the boxes represent the 25th and 75th percentiles, respectively. Medians and means are represented by solid and doted lines, respectively. Data points represent individual dogs [44].

This data suggests that increased lung weight up to 20% above that of the matching control is a conservative rat- and dog-data based POD which is coherent with the EVLW(II)-threshold in humans. Collectively, the equivalence of the EVLW-based surrogates of phosgene-induced pulmonary edema in animal models with the human ARDS-related generic scale of pulmonary edema is remarkable as long as increased lung weights rather than BAL protein is selected. Such biological significance should outweigh statistical significance from surrogate endpoints believed to be causally related to lung edema, e.g., BAL protein and collagen.

In summary, the outcome of this *post hoc* analysis of commonly applied biomarkers suggestive of acute pulmonary edema met its intended objectives, namely that increased lung weights from bioassays scale more favorably with human-based EVLWs than protein or collagen in BAL. The derived threshold of 500 mg/m³ x min (125 ppm x min) or 8-hour adjusted occupational exposure

level of 1 mg/m³ (0.25 ppm) is 2.5-times above the current 8-hour time-weighted average TLV/MAK occupational standard of phosgene which is 0.4 mg/m³ (STEL 0.8 mg/m³) (Table 1). It could be argued that an additional adjustment factor for hyperventilating or sensitive populations needs also to be considered. However, with regard to inhalation dosimetry, the respiratory minute volumes of rats and dogs (at non-panting conditions) is about 4- and 2-times higher than those of humans, respectively. Hence, additional dosimetric adjustments appear not to be justified. Unlike many other irritant gases, phosgene is essentially insoluble in water resulting in little, if any, interactions within the airways. Therefore, it does not elicit chemosensations typically observed following exposure to the more water-soluble irritants. However, solubility and interactions occur in the more amphiphilic milieu of the lower respiratory tract. From that perspective, the past and current OELs of 0.1 ppm (STEL 0.4 ppm) from MAK and many other expert panels can be judged safe under any given occupational exposure conditions.

References

[1] Pauluhn J, Carson A, Costa DL, Gordon T, Kodavanti U, Last JA et al. (2007) Workshop Summary - Phosgene-induced Pulmonary Toxicity Revisited: Appraisal of Early and Late Markers of Pulmonary Injury from Animals Models with Emphasis on Human Significance. *Inhal. Toxicol.* 19: 789-810.

[2] Li, W.L., Pauluhn, J. (2015). Chapter 19: Mechanisms Involved in the Inhalation Toxicity of Phosgene. *Inhalation Toxicology*, 3rd Edition (Editors Harry Salem, Sidney A. Katz).CRC Press, New York pp. 459-478.

[3] United States Environmental Protection Agency (EPA) (1986) Health assessment document for phosgene. Draft. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-86/022A.

[4] Li, WenLi, Pauluhn J. (2017). Phosgene-induced acute lung injury (ALI): differences from chlorine-induced ALI and attempts to translate toxicology to clinical medicine. *Clin Transl Med*. 6:19. Review.

[5] Pauluhn, J. (2011). Acute Nose-only Inhalation Exposure of Rats to Di- and Triphosgene relative to Phosgene. *Inhal Toxicol.* 23:65-73.

[6] Damle, S.B., 1993. Safe handling of diphosgene and triphosgene. Chemical & Engineering News 71, 4.

[7] Cotarca, L., Delogu, P., Nardelli, A., and Sunjic, V., 1996. Bis(trichloromethyl) carbonate in organic synthesis. Synthesis 5, 553-576.

[8] Cotarca, L., Geller, Th., József Répási, 2017. Bis(trichloromethyl)carbonate (BTC, Triphosgene): A Safer Alternative to Phosgene? *Org. Process Res. Dev*. 21: 1439-1447.

[9] Li WL, Pauluhn J (2015) Chapter 19: Mechanisms Involved in the Inhalation Toxicity of Phosgene. Inhalation Toxicology, 3rd Edition (Editors Harry Salem, Sidney A. Katz).CRC Press, New York pp. 459-488.

[10] Pauluhn J (2015) Chapter 6: Time Scaling of Dose and Time to Response: The Toxic Load Exponent. Inhalation Toxicology, 3rd Edition (Editors Harry Salem, Sidney A. Katz).CRC Press, New York pp. 121-136.

[11] Tagami T, Kushimoto S, Yokota H. Vincent J-L, 2014. Quantitative evaluation of pulmonary edema. Annual Update in Intensive Care and Emergency Medicine 2014. Switzerland, Springer International Publishing pp. 257–267.

[12] Tagami, T., Ong MEH, 2018. Extravascular lung water measurements in acute respiratory distress syndrome, why, how, and when? Curr Opin Crit Care. 24, 209-215.

[13] WenLi Li, Pauluhn J, 2019. Phosgene-induced lung edema: Comparison of clinical criteria for increased extravascular lung water content with postmortem lung gravimetry and lavage-protein in rats and dogs. Toxicol Lett. 305, 332-339.

[14] He Z, Yang X, Yang C. [Extracorporeal membrane oxygenation for acute respiratory distress syndrome caused by acute phosgene poisoning: a report of 4 cases].Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019 Feb;31(2):232-235. doi: 10.3760/cma.j.issn.2095-4352.2019.02.022

[15] Berthiaume Y, Folkesson HG, Matthay MA, 2002. Lung Edema Clearance, 20 Years of progress – Invited Review, Alveolar edema fluid clearance in the injured lung. J. Appl. Physiol. 93, 2207-2213.

[16] Berthiaume Y, Lesur O, Dagenais A, 1999. Treatment of adult respiratory distress syndrome, plea for rescue therapy of the alveolar epithelium. Thorax. 54, 150-160.

[17] Berthiaume Y, Matthay MA, 2007. Alveolar edema fluid clearance and acute lung injury. Respir. Physiol. Neurobiol 159, 350-359.

[18] Straub NC, 1974. Pulmonary edema. Physiol. Rev. 54, 678–811.

[19] Sartori C, Matthay MA., 2002. Alveolar epithelial fluid transport in acute lung injury, new insights. Eur Respir J 20, 1299–1313.

[20] Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med. 342:1334–1349.

[21] Matthay MA, Zimmerman GA (2005) Acute Lung Injury and the Acute Respiratory Distress Syndrome: Four Decades of Inquiry into Pathogenesis and Rational Management. Am J Respir Cell Mol Biol. 33:319–327.

[22] Kallet RH, Alonso JA, Pittet JF, Matthay MA (2004) Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. *Respir Care*. 49:1008–1014.

[23] Li W., Rosenbruch M, Pauluhn J, (2015). Effect of PEEP on Phosgene-Induced Lung Edema: Pilot Study on Dogs using Protective Ventilation Strategies. Exp Toxicol Pathol. 67:109-116.

[24] Grainge C, Rice P (2010) Management of phosgene-induced acute lung injury.*Clin Toxicol Phila*. 48:497–508.

[25] Parkhouse DA, Brown RF, Jugg BJ, Harban FM, Platt J, Kenward CE, Jenner J, Rice P, Smith AJ. 2007. Protective ventilation strategies in the management of phosgene-induced acute lung injury. *Mil Med*. 172, 295–300.

[26] Luo S, Trübel H, Wang C, Pauluhn J, 2014. Phosgene- and Chlorine-induced Acute Lung Injury in Rats: Comparison of Cardiopulmonary Function and Biomarkers in Exhaled Breath. Toxicology. 326:109-118.

[27] Li WL, Liu FF, Wang C, Truebel H, Pauluhn J, 2013. Novel insights into phosgene induced acute lung injury in rats: role of dysregulated cardiopulmonary reflexes and nitric oxide in lung edema pathogenesis. Toxicol Sci 131:612–628.

[28] Luo S, Pauluhn J, Trübel H, Wang C, 2014. Corticosteroids Found Ineffective for Phosgene-induced Acute Lung Injury in Rats. Toxicology Letters 229: 85-92.

[29] Verscheure S, Massion PB, Verschuren F, Damas P. Magder S, 2016. Volumetric capnography: lessons from the past and current clinical applications. Crit Care. 20:184.

[30] Tusman G, Sipmann FS, Bohm SH, 2012 Rationale of deadspace measurement by volumetric capnography. Anesth Analg 114:866-874.

[31] Raurich JM, Vilar M, Colomar A, Ibáñez J, Ayestarán I, Pérez-Bárcena J, Llompart-Pou JA, 2010. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care. 55:282-287.

[32] Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA, 2002 Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 347:1281-1286.

[33] Fengmei G, Jin C, Songqiao L, Congshan Y, Yi Y, 2012. Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. Respir Care. 57:1578–85.

[34] Cepkova M, Kapur V, Ren X, Quinn T, Zhuo H, Foster E, et al., 2007. Pulmonary dead-space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. Chest 132:836-842.

[35] Lucangelo U, Bernable F, Vatua S, Degrassi G, Villagra A, Fernandez R, et al., 2008. Prognostic value of different deadspace indices in mechanically ventilated patients with acute lung injury and ARDS. Chest 133:62-71.

[36] Robertson HT, 2015. Dead space: the physiology of wasted ventilation. Eur Respir J. 45:1704-1716.

[37] Liu F, Pauluhn J, Trübel H, Wang C, 2014). Single High-dose Dexamethasone and Sodium Salicylate failed to attenuate Phosgene-induced Acute Lung Injury in Rats. Toxicology. 315:17-23.

[38] Luo S, Pauluhn J, Trübel H, Wang C, 2014. Corticosteroids Found Ineffective for Phosgene-induced Acute Lung Injury in Rats. Toxicology Letters 229: 85-92.

[39] Hubmayr RD, Kallet RH., 2018. Understanding Pulmonary Stress-Strain Relationships in Severe ARDS and Its Implications for Designing a Safer Approach to Setting the Ventilator. Respir Care. 63, 219-226.

[40] Chatburn RL, Kallet RH, Sasidhar M., 2016. Airway Pressure Release Ventilation May Result in Occult Atelectrauma in Severe ARDS. Respir Care. 61, 1278-1280.

[41] Kallet RH., 2016. Should PEEP Titration Be Based on Chest Mechanics in Patients With ARDS? Respir Care. 61, 876-890.

[42] Pauluhn J, 2006. Acute nose-only Exposure of Rats to Phosgene. Part I: Concentration x Time Dependence of LC_{50}s and Non-Lethal-Threshold Concentrations and Analysis of Breathing Patterns. *Inhal. Toxicol.* 18: 423-435.

[43] Pauluhn J, 2006. Acute nose-only Exposure of Rats to Phosgene. Part II: Concentration x Time Dependence of Changes in Bronchoalveolar Lavage during a follow-up Period of 3 Months. *Inhal. Toxicol.* 18: 595-607.

[44] Pauluhn J, 2006. Acute Head-Only Exposure of Dogs to Phosgene. Part III. Comparison of Indicators of Lung Injury in Dogs and Rats. Inhal. Toxicol. 18, 609–621

[45] IFA, 2019. GESTIS International Limit Values – Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung. Available at: http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx

[46] National Research Council (NRC) 2002. Phosgene: Acute Exposure Guideline Levels, Appendix 1 in Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 2. Committee on Acute Exposure Guideline Levels, Committee on Toxicology, National Research Council. ISBN: 0-309-56773-4. National Academies Press, Washington. D.C. pp. 15-70, 2002.

[47] ERPG, 2009. Phosgene. Emergency Response Planning Guideline (ERPG) and Workplace Environmental Exposure Level (WEEL) Handbook. American Industrial Hygiene Association AIHA), Falls Church, VA, USA.

[48] National Research Council (NRC) 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals Subcommittee on Acute Exposure Guideline Levels, Committee on Toxicology, Board on Environmental Studies and Toxicology Commission on Life Sciences National Research Council. Available at http://www.nap.edu.

[49] ERPG, 20014, AIHA Guideline Foundation Emergency Response Planning (ERP), Committee Procedures and Responsibilities of the AIHA Guideline Foundation ERP Committee are always open to comments, changes and revisions March 2014. American Industrial Hygiene Association AIHA), Falls Church, VA, USA.

[50] Hatch G., Kodavanti U., Crissman K., Slade R., Costa D., 2001. An 'injury-time integral' model for extrapolating from acute to chronic effects of phosgene. Toxicol Ind Health. 17(5-10), 285-293

[51] Kodavanti, U. P., Costa, D. L., Giri, S. N., Starcher, B., and Hatch, G.E., 1997. Pulmonary structural and extracellular matrix alterations in Fischer 344 rats following subchronic exposure. Fundam. Appl. Toxicol. 37, 54–63.

[52] SCOEL, 2011. Recommendation from the Scientific Committee on Occupational Exposure Limits for phosgene. European Commission - Employment, Social Affairs and Inclusion, SCOEL/SUM/004adopted September 2011.

53. Hammon M., Dankerl P., Voit-Höhne H.L., Sandmair M., Kammerer .FJ., Uder M., Janka R., 1014. Improving diagnostic accuracy in assessing pulmonary edema on bedside chest radiographs using a standardized scoring approach. BMC Anesthesiol. 18;14:94. doi: 10.1186/1471-2253-14-94. eCollection 2014.

Appendix 2

Case Study: acute phosgene poisoning

[Extracorporeal membrane oxygenation for acute respiratory distress syndrome caused by acute phosgene poisoning: a report of 4 cases]

【Abstract】 Objective To evaluate the protective effect and early efficacy of early extracorporeal membrane oxygenation (ECMO) in the treatment of acute respiratory distress syndrome (ARDS) patients with acute phosgene poisoning. Methods A retrospective analysis of 4 patients with acute phosgene poisoning-induced ARDS was performed in the Department of Critical Care Medicine (ICU) of Jiangxi Provincial People's Hospital in April 2018. The treatment parameters of patients with ECMO before and after 1, 3, and 7 days after treatment were collected, including arterial blood pressure pH, partial pressure of carbon dioxide (PaCO2), partial pressure of oxygen (PaO2), blood lactate (Lac), and peripheral vascular resistance index (SVRI), cardiac output index (CI), blood stasis extrapulmonary index (ELWI), platform pressure (Pplat), positive end expiratory pressure (PEEP), driving pressure (ΔP), and acute physiology and chronic health status Evaluation of Part II (APACHE II), ICU hospital stay, ECMO treatment days, and mechanical ventilation time. RESULTS: Four patients with severe cases underwent tracheal fistula intubation and ventilator-assisted ventilation. However, the ventilator support conditions were high, and the oxygenation and internal environment were difficult to stabilize. Therefore, ECMO treatment was performed on the next day, and the oxygenation was obvious after treatment. Improvement, ventilator support conditions can be significantly reduced, including 3 ~ 6 mL / kg small tidal volume, 8 ~ 10 cmH2O (1 cmH2O = 0.098 kPa) PE PEEP, 0.30 inhaled oxygen concentration (FiO2) and other lung protection rest strategy. After ECMO treatment, the parameters were significantly improved. Compared with before treatment, PaO2 and SVRI increased significantly at 1 day after ECMO treatment, and Lac, ELWI, Pplat, PEEP, ΔP, and APACHE II scores decreased significantly (PaO2 (mmHg, 1 mmHg=0.133 kPa): 85.5±10.7 vs. 54.2±4.5, SVRI (kPa·s·L-1·m-2): 153.6±9.4 vs. 118.0±12.6, Lac (mmol/L):
2.15±0.19 4.93±0.96, ELWI (mL/kg): 17.73±2.99 vs. 20.45±4.13, Pplat(cmH2O): 19.25±2.21 vs. 35.75± 2.22, PEEP(cmH2O): 9.0±1.2 vs. 13.5±1.7, ΔP(cmH2O) :10.25±1.26 vs 22.25±3.86, APACHE II (min): 17.25±
2.22 vs 26.50±2.08, both P<0.05]; pH value, CI increased significantly, PaCO2 decreased significantly at 3 d after treatment. Value: 7.43±0.05
Ratio 7.21±0.13, CI(mL·s-1·m-2): 64.35±3.17 vs. 59.51±3.17, PaCO2(mmHg): 42.0±2.2 vs. 55.0±8.5, both P<
0.05]. All 4 patients were successfully treated and discharged. ICU stayed in hospital for 8 to 27 days, with an average of (13.5±9.0) days; ECMO treatment time was 6 to 12 days,
average was (8.0±2.7) days; mechanical ventilation time was 6 to 20 days. , average (10.75 ± 6.19) d. Conclusion 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.

【Key words】 Extracorporeal membrane oxygenation; Acute phosgene poisoning; Acute respiratory distress syndrome 基金 Fund project: Jiangxi Provincial Health and Family Planning Commission Chinese Medicine Project (2017A324)

The phosgene chemical name is carbonyl chloride (COCl2). In some chemical plants, phosgene leakage in the production process can cause workers to inhale poisoning, which mainly damages the respiratory tract, can cause sputum, chemical bronchitis, pneumonia, pulmonary edema, and often severe patients. Death due to refractory acute respiratory distress syndrome (ARDS) [1]. Extracorporeal membrane oxygenation (ECMO) can significantly improve oxygenation in patients and remove excess CO2 from the body, thus replacing the sputum gas exchange function of the lungs; while reducing ventilator support conditions during treatment, the lungs are “rested” Can accelerate the recovery of lung function.

Four cases of acute phosgene poisoning caused by ECMO were successfully reported in the hospital as follows.

1 Materials and Methods

1.1 **Subjects**: In April 2018, a total of 13 patients were poisoned during a phosgene leak in a chemical plant, and 5 critically ill patients were transferred to the Department of Critical Care Medicine (ICU). A retrospective study was conducted to select four patients who met the diagnosis of acute phosgene poisoning [2] and the 2012 new definition of ARDS diagnostic criteria in Berlin [3], and included cardiogenic pulmonary edema.

1.2 **Ethics**: This study met the medical ethics standards and was approved by the Hospital Ethics Committee (approval number: 2018051). All treatments received informed consent from the patient's family and signed informed consent.

1.3 **Basic information of patients**: 4 patients were male; aged 34-54 years old, average (46.25±8.58) years old; acute physiology and chronic health status score II (APACHE II) 24-29 within 24 hours after admission Points, average (26.50 ± 2.08) points; 既 no previous history of special chronic diseases. Four patients were sent to the local hospital for treatment within 1 to 2 hours after inhalation of phosgene. The symptoms were mild cough and chest tightness. Symptoms after oxygen inhalation were not obvious. The breathing was fast and the pulse oxygen saturation (SpO2) was around 0.85. And interrupted coughing yellow foam 痰, the condition is critical, after the consultation on April 1 was transferred to our hospital for treatment. After entering the ICU, the tracheal intubation ventilator assisted the treatment; a large amount of yellow watery sputum was aspirated from the airway sputum, and the body was audible and widely wet and dry. Among them, 1 case had subcutaneous emphysema, and the sense of snow was obvious. Side breathing is significantly weakened. In 4 cases of patients with sputum, chest CT showed that the lungs were "hairy glass" and had flaky infiltration, and the two lungs were flaky, and one of them was complicated by subcutaneous and mediastinal emphysema, and the right side was pneumothorax. After admission, due to high ventilator support conditions, oxygenation was difficult to maintain, and ECMO was treated within 24 hours.

1.4 **Treatment**

1.4.1 **General treatment**: 4 patients underwent ECG monitoring, endotracheal intubation, and snoring assisted ventilation; placement of subclavian venous catheter and femoral artery catheter, pulse sputum showed continuous cardiac output (PiCCO) monitoring; piperacillin tazobactam against infection;

hydroxypropyl theophylline asthma; methylprednisolone 80 mg intravenous infusion, 2 times a day, gradually decreasing, and active rehydration; continued Pumping norepinephrine to maintain blood pressure, sputum sufentanil analgesia, propofol sedation, atracurium amylose and other drugs.

1.4.2 **Ventilator treatment**: 4 patients underwent invasive ventilation with orotracheal intubation treatment, volume control ventilation (VCV) mode. The parameters of the ventilator parameters before ECMO treatment were: ventilation frequency 20-22 times/min, tidal volume 6-8 mL/kg, and end-expiratory positive pressure (PEEP) 10-15 cmH2O (1 cmH2O=0.098 kPa). ECMO was used to monitor patient drive pressure (ΔP), ΔP-oriented, adjusted tidal volume 3 to

6 mL/kg, ventilation frequency 10 times/min, PEEP 8 to 10 cmH2O, inhaled oxygen concentration (FiO2) 0.30. After the condition improved and the ECMO was removed, the pressure support ventilation (PSV) mode was used, and the tube was extracted in time, and the mask was used for oxygen.

1.4.3 **ECMO treatment**: 4 patients were treated with ECMO, using the Cameda heparin-coated ECMO kit and puncture sputum tubing and accessories from Medtronic. The venous-venous (VV) ECMO transfer was used, and the bypass route was: femoral vein-centrifugal pump-membranous lung-intracervical vein. Persistence during treatment

Application of heparin to maintain activated clotting time (ACT) at 140-160 s, flow rate 2.5 ~ 3.6 3.6 L / min, using a water temperature tank to maintain blood temperature of 36.5 ~ 37.0 °C. The gas flow and blood flow were adjusted according to the results of blood gas sputum analysis, and the total flow was 6 to 12 days.

1.4.4 **Monitoring indicators**: arterial blood stasis pH value, carbon dioxide partial pressure (PaCO2), oxygen partial pressure (PaO2), blood lactate (Lac)

and peripheral vascular resistance before ECMO treatment and 1, 3, 7 days after treatment Index (SVRI), cardiac output index (CI), extravascular pulmonary sputum index (ELWI), platform pressure (Pplat), PEEP, ΔP, and APACHE II,

ECMO treatment days, mechanical ventilation time, and ICU hospitalization time.

1.5 **Statistical analysis**: Data analysis was performed using SPSS 19.0 software. The data were expressed as mean ± standard deviation (x ± s). Before and after treatment, one-way ANOVA was used for comparison, and Dunnett-t test was used for pairwise comparison. $P < 0.05$ was considered statistically significant.

2 **Results**

2.1 **Laboratory indicators** (Table 1): Compared with before treatment, the number of sputum increased gradually after ECMO treatment, PaO2, SVRI increased significantly from 1 day after ECMO treatment,

Lac, ELWI, Pplat, PEEP The ΔP and APACHE II scores decreased significantly. pH The pH value and CI

increased significantly at 3 days after treatment, PaCO2 decreased significantly, and the difference was statistically significant (P<0.05).

2.2 **Radiographic changes in the lungs** (Fig. 1): In one of the severely ill patients, X-ray chest X-ray and chest CT changes were taken as an example. On the 8th day after ECMO treatment, the patient's lung sputum exudation was significantly absorbed due to the course of the disease. The right pneumothorax was combined with closed thoracic drainage. On the 25th day after ECMO treatment, the patient's right pneumothorax was absorbed, and the lung exudation was significantly better than before treatment. After tracheotomy, the patient was able to go offline and the condition improved. Into the general ward to continue treatment.

2.3 **Prognosis**: All 4 patients were successfully treated. After being transferred to our hospital for respiratory therapy, they were discharged and discharged. No complications occurred during follow-up. Four patients underwent ECMO treatment for 6-12 days, mean (8.0±2.7) days; mechanical ventilation time 6-20 days, mean sputum (10.75±6.19) days; ICU hospitalization time 8 to 27 days, mean (13.5± 9.0)d.

3 Discussion

3.1 **Characteristics of phosgene poisoning** – pulmonary ARDS: phosgene is a highly toxic stimulating gas. The clinical manifestations of patients with acute phosgene poisoning are positively related to the concentration and time of inhaling the irritating gas. Related, 100 ~ 300 mg / m3, contact sputum 15 ~ 30 min can cause severe poisoning, and even death [4]. The lung is the target organ of phosgene poisoning, and there is often delayed toxic pulmonary edema and even ARDS. Toxic Pulmonary edema has many hypothesis mechanisms, including acylated, alveolar surface active substance damage, lung cell apoptosis and related gene expression abnormalities, oxidative damage, etc. [5]. In addition, hydrochloric acid produced by phosgene poisoning can dissolve alveolar and tracheal surface active substances, alveolar is prone to structural damage, forming a soluble "cavity",

clinical manifestations of subcutaneous, mediastinal emphysema, and even pneumothorax [6]. In this case, 4 patients with sputum developed chest tightness, dyspnea, cough, yellow foam sputum, sensation of both lungs and obvious wet sputum, blood gas analysis showed PaO2 ≤ 60 mmHg (1 mmHg=0.133 kPa)), oxygenation index (PaO2/FiO2) ≤ mm 100 mmHg, in line with ARDS diagnosis, and is pulmonary-derived ARDS. One patient with sputum developed subcutaneous, mediastinal emphysema, and right pneumothorax, which was consistent with the above characteristics.

3.2 **Status of treatment of ARDS**: The heterogeneity of ARDS patients is large, and the coexistence of multiple diseases can lead to pulmonary inflammation. The molecular mechanism of mediating lung injury is still not clear, and there is no target for ARDS. The specificity of the disease mechanism treatment. Pulmonary protective ventilation, lung recruitment, PEEP, prone position ventilation, etc. are based on the pathophysiological mechanism of ARDS to maximize the improvement of the disease.

Oxygenation, and reduction of ventilator-associated lung injury (VILI), allows the lungs to fully "rest" and accelerate the recovery of lung cells and pulmonary vessels. Although the previous research of our group showed that endothelial progenitor cell transplantation can regulate the inflammatory

response and immune function in ARDS animals, thus improving the prognosis [7], but it is still more challenging to apply it to clinical research. At present, the patients are still mainly treated with respiratory support. The small tidal volume and moderate PEEP ventilation in patients with severe sputum can improve the prognosis. However, the platform pressure is often higher than 30 cmH2O, and there is obvious CO2 retention. ECMO and CO2 clearance therapy can further reduce tidal volume and mean airway pressure while improving oxygenation and CO2 removal, thereby reducing ΔP and helping to reduce VILI. Therefore, in future clinical work, ECMO support therapy may become a routine treatment for patients with severe ARDS.

3.3 **ECMO clinical treatment experience**: The core of ECMO's work includes membrane, lung and blood pump, which function as artificial lung and artificial heart. When ECMO is running, blood is drawn from the vein, oxygen is passed through the membrane, and CO2 is excreted. The blood exchanged through the above-mentioned gas is returned to the vein (VV pathway) or arterial fistula (VA pathway) by the blood pump. In 2009, Peek et al [8] conducted a randomized controlled trial of 180 patients with ARDS. The results showed that the survival rate of patients treated with ECMO after traditional treatment was significantly higher than that of traditional treatment (63% vs. 47%).. With the improvement of VV ECMO technology and the application of percutaneous cannulation, ECMO is widely used for ARDS caused by various causes, especially to significantly improve the prognosis of patients with severe ARDS caused by H1N1 [9]. Xu Lei et al [10] showed that the use of VV

ECMO respiratory support for lung protection ventilation can significantly improve the prognosis of patients with severe pneumonia who have no mechanical ventilation. Wang Chuanhai et al [11] treated with ECMO in 6 patients with ARDS who had no significant improvement in disease after mechanical ventilation, SpO2

was significantly elevated, and PEEP and FiO2 were significantly decreased. At present, the application of ECMO technology is becoming more and more mature, and ECMO has relevant recommendations when it comes to the machine and the machine. The criteria for starting ECMO treatment are: 1 under pure oxygen, PaO2/FiO2<

100 mmHg, or alveolar-arterial oxygen pressure difference >600 mmHg, Murray lung injury score ≥3; 2 pH <7.2; Age <65 years; 4 traditional

mechanical ventilation time <7 d; 5 no anticoagulant contraindications; 6 contraindications to continue active mechanical ventilation. It is recommended that patients with severe ARDS be treated with EMCO as early as possible within 7 days of high-level mechanical ventilation [12]. In vitro membrane life support management guidelines recommend,

When the ventilator parameters can be steadily decreased, the oxygenator will gradually reduce the blood flow velocity to 1 L/min under 100% oxygen supply, or gradually reduce the blood flow velocity to 2 L/min.

Reduce the oxygen concentration, maintain arterial oxygen saturation (SaO2)>0.95; after stabilization, start the weaning test, that is, close the oxygenator, adjust the ventilator parameters (FiO2, Pplat,

PEEP, ventilation frequency), maintain The blood flow velocity and anticoagulant can be withdrawn if SaO2>0.95 and

PaCO2<50 mmHg last for more than 1 h. If PaCO2>50 mmHg

is changed to CO2 removal mode [13]. 3.4 3.4 Treatment experience and summary: For patients with ARDS caused by acute phosgene poisoning, when the treatment with conventional mechanical ventilation is still not good, early ECMO 呼吸 respiratory support treatment can significantly improve oxygenation and remove excessively high body CO2, obviously
Lowering the ventilator support parameters, allowing the lungs to fully “rest”, reduce VILI, and improve patient prognosis.
All conflicts of interest states that there is no conflict of interest