Piratox sheet #5: "Suffocating agents and phosphine

Indicative list of concerned agents:

Toxic compounds with suffocating action
- **Phosgene** (CAS number: 75-44-5) - **Chlorine** (CAS number: 7782-50-5) - **Methyl isocyanate** (CAS number: 624-83-9) - But also: o **Ammonia** (CAS number: 7664-41-7) o **Diphosgene or surpalite** (CAS number: 503-38-8) o **Chloropicrin** (CAS number: 76-06-2) o **Fluorine** (CAS number: 7782-41-4) o **Perfluoroisobutylene** (CAS number: 382-21-8) o **Fumigants** o Marketed industrial and domestic products - **Phosphine** or PH_3 or Hydrogen Phosphide (CAS number: 7803-51-2).

! Key points not to forget

→ The 1st emergency step is the extraction of victims from the hazard area: rescuers must possess suitable breathing and eye protection.
→ At ambient temperature (20°C) most suffocating agents are gases that penetrate the body via the respiratory route. They are thus poorly or non-persistent, frequently limiting victim decontamination needs to simple undressing.
→ Most suffocating agents are heavier than air.
→ They affect the respiratory system: glottis, bronchi, alveoli and cause eye damage.
→ In pre-hospital settings, avoid any physical exertion that could promote the onset of pulmonary oedema.
→ In general, the shorter the symptom onset time, the more serious the intoxication and the more severe the symptoms.
→ Treatment is symptomatic only.
→ All symptomatic choking gas victims must encouraged to rest, in a sitting position, under oxygen.
→ The duration of surveillance for symptomatic subjects is of at least 12 to 24 hours.
→ For Phosphine (PH_3):
  o victims must be undressed and showered;
  o toxicity is respiratory, cardiac, renal and neurological;
  o subjects having inhaled PH_3 and presenting with significant initial manifestations shall be monitored in the hospital for 48 to 72 hours, due to the risk of delayed acute pulmonary oedema.
→ For additional information concerning the risk, assistance with patient treatment and follow-up, we recommend contacting the poison control centres, referring healthcare establishments or military health service.

1. Pharmaco-toxicological class of suffocating agents

Suffocating agents are lethal agents that penetrate the body via the airways, causing tracheal and bronchial irritation, then acting on the lung tissue, creating a lesional oedema. They represent a major aspect of NRBC risk, whether in the context of terrorism, industrial accidents or for armies during external operations.

2. Main characteristics of suffocating agent intoxication

Intoxication varies according to absorbed dose and exposure time.
Suffocating agent toxicity is respiratory. It causes manifestations ranging from benign irritation to acute lesional pulmonary oedema (lesional **APO**) or even to acute respiratory distress syndrome (**ARDS**). The common denominator is hypoxia by impaired oxygen diffusion through the damaged alveolar-capillary membrane. This is an aspecific lesional affliction. In simple forms, oxygen may be sufficient, though patients must be placed under observation. More complex forms require ARDS treatment in a specialist environment. Persons with respiratory diseases such as asthma or chronic obstructive bronchitis, constitute at-risk populations.
Symptoms depend on the agent's water-solubility, atmospheric concentration and exposure duration. At low concentrations, inhalation causes **throat irritation**, or **oedema of the glottis** in the first 6 to 12 hours following intoxication, remaining one of the main causes of death, with lesional APO, causing a **cough**. Exposure to vapours also causes eye irritation, or even **severe chemical conjunctivitis**.

> The **penetration syndrome** is characterised by eye or oro-pharyngeal irritation manifestations, along with a sensation of oppression or chest pain. It may be associated with facial congestion, headaches, nausea, vomiting, bronchospasm and loss of consciousness. During this initial phase of intoxication, symptom intensity and duration varies from one individual to another. Moreover, the intensity of fits of coughing is not a sign of severity.
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> The **free interval phase**: symptoms may lessen as soon as exposure stops and a paucisymptomatic phase lasting several hours (most frequently between the 6^{th} and 24^{th} hours) precedes, in serious cases, the onset of **acute pulmonary oedema**. The victim must rest during this phase to reduce its duration. Radiological examination reveals alveolar or interstitial damage.
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> The **acute pulmonary oedema phase** set in, with the onset of coughing, dyspnoea with tachypnoea and progressive cyanosis. Symptoms are related to the establishment of an aspecific lesional oedema that can progress towards an acute respiratory distress syndrome. The major disruption is severe hypoxia. If the acute phase is overcome, the oedema resorbs progressively and the prognosis improves. Complications may nevertheless still arise: secondary infection with bronchopneumonia and, subsequently, risk of sequelae (pulmonary fibrosis, non-specific bronchial hyperreactivity).

Surveillance must be initiated according to the nature of the agent and to exposure.

<u>Specifically concerning Phosphine</u>:
Acute intoxication may occur after direct gas inhalation from storage containers, or after release, when a metal phosphide is placed in contact with water. After lung penetration, the PH_3 distributes mainly to the heart, lungs and kidneys, but also to the central nervous system.

Main characteristics of intoxication with agent:

▪ Phosgene (CG)

This agent penetrates the body almost exclusively by inhalation. In the upper airways, a fraction of the agent is hydrolysed by water to hydrochloric acid and carbon dioxide. Due to its very poor water-solubility, phosgene rapidly reaches the alveoli. It causes the denaturation of proteins and lipoproteins, irreversible structural membrane damage and causes enzymatic and cell metabolic alterations.
In general terms, liquid phosgene (temperature below 8.2°C) can cause burns to skin and eyes. In vapour form, if its atmospheric concentration rises above 3 ppm (12 mg/m³), irritation and eye and mucosal pain appear immediately, caused by the product's contact action.
Inhalation can lead to inflammation of the bronchi and alveolar structures. The onset of effects may be delayed by up to 24-48 hours. The severity of symptoms is dictated by the concentration of phosgene in the air breathed.
If the product ([C] x t) is high: the phosgene rapidly penetrates the airways, causing apnoea and bronchostenosis. Diffusion into pulmonary circulation causes haemolysis. The red blood cell membrane fragments can obstruct blood flow, leading to death in a few minutes. In animals, broncho-alveolar lavage is a good market of the predictable progression of pulmonary lesions, with maximum protein concentration at 24 hours, before a latency period that can last up to 15 hours.

Phosgene toxicity in humans during acute intoxication:

If the product ([C] x t) is greater than AEGL 3 (Acute Exposure Guideline Levels), the symptoms comprise three phases:

- Penetration phases, characterised by lacrimation caused by eye irritation, oro-pharyngeal pain or pruritus, irritative cough, chest pains and a sensation of oppression. The intensity of fits of coughing is not a sign of severity.
- Free interval phase, during which symptoms may disappear rapidly after exposure and a silent period of 2 to 36 hours precedes the onset of acute pulmonary oedema.
- Pulmonary oedema phase, this is a lesional oedema that can progress to ARDS. It is accompanied by low blood pressure, bradycardia and arrhythmia. Death results from respiratory distress or right heart failure.

In all cases, the victims of phosgene exposure must be kept under observation for at least 24 hours.

One-hour exposure at a concentration of: mg/m^3	**AEGL 1**	**AEGL 2**	**AEGL 3**
Phosgene	-	1.2 mg/m^3	3 mg/m^3

▪ Chlorine

Lesions are dictated by concentration and affect the eyes, skin and airways.

One-hour exposure at a concentration of: mg/m^3	**AEGL 1**	**AEGL 2**	**AEGL 3**
Chlorine	1.5 mg/m^3	5.8 mg/m^3	58 mg/m^3

Acute exposure at low concentration (< 45 mg/m³) causes irritation to nasal, ocular and pharyngeal mucosa, with no clinical consequences. If the atmospheric concentration is > 90 mg/m³, immediate burning sensations appear, along with ocular mucosa pain, airway pain (cough, rhinorrhoea) and mouth pain (ptyalism). General signs of intoxication also appear: sensation of suffocation with anxiety, tachypnoea and tachycardia, retrosternal pain, headaches and abdominal pain, accompanied by nausea and vomiting. In severe cases, respiratory distress, cyanosis and haemoptoic sputum are observed. Cases of respiratory and cardiac arrest have been described at the highest concentrations.
In the event of higher acute exposure, ocular burns (corneal ulceration) and skin burns may appear (in the event of direct contact); the main respiratory complications are 1) oedema of the glottis causing dysphonia or laryngeal (inspiratory) dyspnoea, along with 2) acute pulmonary oedema, the first sign of which is polypnea.
The main sequelae encountered are chemical asthma (Brooks syndrome) and emphysema.
Highly exposed patients should be observed for 24 to 48 hours.

- **Methyl isocyanate**

This agent is irritant to the skin and to ocular, respiratory and digestive mucosa. Skin projections can cause severe burns. At low doses, it is a lacrimating agent; at higher concentrations, it causes serious ocular burns (significant irritation, corneal and palpebral oedema, blurred vision, corneal ulcer). There is a risk of amaurosis. Inhalation at low concentrations causes nose and throat irritation with secretions. At higher concentrations, it causes coughing, chest pains, dyspnoea, an asthmatiform reaction, or lesional APO. Abdominal pains accompanied by diarrhoea and vomiting may appear.

One-hour exposure at a concentration of: mg/m^3	**AEGL 1**	**AEGL 2**	**AEGL 3**
Methyl isocyanate	-	0.067 mg/m^3	0.20 mg/m^3

- **Ammonia**

This agent causes irritations to the respiratory mucosa (cough, asthmatiform dyspnoea, ulceration, respiratory distress with lesional APO) and to the ocular mucosa (lacrimation, conjunctival congestion, ulceration). High blood pressure and tachycardia may also be observed.

One-hour exposure at a concentration of: mg/m^3	**AEGL 1**	**AEGL 2**	**AEGL 3**
Ammonia	21 mg/m^3	112 mg/m^3	770 mg/m^3

- **Phosphine**

Inhalation of low concentrations leads, in just a few minutes, to signs of respiratory mucosal irritation: cough, epistaxis, chest pains.

If exposure is prolonged, or on inhalation of high concentrations, the following appear rapidly:

- headaches, dizziness, paraesthesia, coma, convulsions,
- digestive pains, choleriform diarrhoea,
- low blood pressure, or state of shock frequently refractory to pressor amines,
- heart rhythm and conduction disorders,
- metabolic acidosis, hypomagnesaemia, hyperkalaemia,
- acute respiratory distress syndrome that may develop in a delayed manner,
- cytolytic hepatitis and jaundice occur more rarely,
- kidney failure due to tube impairment.

Eye and skin lesions, outside of direct contact with liquid phosphine, have not been described.

One-hour exposure at a concentration of: mg/m^3	**AEGL 1**	**AEGL 2**	**AEGL 3**
PH_3	-	2.78 mg/m^3	5 mg/m^3

The symptoms appear within a few minutes to a few hours. Death may occur in a presentation of multi-organ failure, within 4 to 14 days.

3. Physicochemical properties of suffocating agents and phosphine

List of properties used to assess exposure and to modulate treatment:

- **Phosgene** occurs, at ambient temperature (20°C) and at atmospheric pressure, as a colourless, heavier than air gas, its vapour density relative to air is of 3.4 (air = 1). Its smell is suggestive of freshly cut hay.

- Chlorine occurs, at ambient temperature (20°C) and at atmospheric pressure, as a greenish heavier than air gas, with a sharp and suffocating smell that is perceptible at concentrations of less than 1 ppm (at 25°C, 1 atm, 1 ppm = 2.9 mg/m^3).

- **Methyl isocyanate** occurs, at ambient temperature (20°C) and at atmospheric pressure, as a colourless, volatile and bitter smelling liquid. It is usually stored in stainless steel containers. It is a highly flammable product (flash point = -7°C). Its vapours are heavier than air and, when mixed with air, it rapidly becomes explosive. It is an intermediate product used for the production of carbamate pesticides.

- **Ammonia** occurs, at ambient temperature (20°C) and at atmospheric pressure, as a colourless lighter than air gas with an acrid smell.

- **Phosphine** occurs, at ambient temperature (20°C) and at atmospheric pressure, as a gas. It can spontaneously ignite in the presence of moisture. It reacts violently with oxidizers such as chlorine, bromine and their respective aqueous solutions.

4. Antidotes (specific treatments)

There are no approved antidotes to date.

5. Symptomatic treatment

Treatment is essentially symptomatic and is aimed at maintaining vital functions.

- **First aid:**

Remove victims from the contaminated atmosphere and undress them if they have potentially been exposed to a concentrated cloud.
If ocular symptoms are present, rinse the eyes abundantly for at least 15 minutes.
Avoid any physical exertion that could increase the probability of lesional APO onset. Victims must be evacuated in a semi-sitting position.
The usual airway freeing and oxygen therapy measures should be taken.
"Fragile" individuals (asthma, COPD, children) should be monitored closely.

- **Suffocating agent-specific measures:**

Skin:
- Burn-like skin lesions should be treated in the same manner as heat burns.

Respiratory:
- Seated rest and oxygen therapy.
- Treatment of severe oedema of the glottis.
- The administration of β2 mimetics and corticosteroids should be considered if there is a spastic components, particularly in subjects with a history of spastic bronchial disease.
- There are no specificities in the treatment of ARDS of toxic origin relative to ARDS of other origins, in particular concerning the prescription of corticosteroids.

- **Phosphine-specific measures:**

In the event of acute kidney failure, haemodialysis is necessary. This is not, however, a suitable method for toxic compound elimination.

Intravenous hydrocortisone (400 mg every 4-6h) or dexamethasone (4 mg every 4h) have been proposed.

The administration of corticosteroids in cases of severe low blood pressure failing to respond to catecholamines would appear justified in theory, as there is a depletion of corticosteroids by direct impairment of the adrenal glands and that these potentiate the response of sympathetic receptors to catecholamines.

Subjects having inhaled PH_3 and presenting with significant initial manifestations shall be monitored in the hospital for 48 to 72 hours, due to the risk of delayed acute pulmonary oedema.

In the event of convulsions, administer clonazepam (due to its efficacy and low consciousness and respiratory depressor effect); if the seizures persist, switch to phenobarbital or propofol.