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Pre-authorisation Evaluation of Medicines for Human Use

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**EMEA/CPMP Guidance Document
on the Use of Medicinal Products for the Treatment of Patients Exposed to
Terrorist Attacks with Chemical Agents**

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INTRODUCTION

The European Commission has developed with its Health Security Committee, an action Programme of Cooperation on Preparedness and Response to Biological and Chemical attacks (BICHAT). The EMEA and one of its scientific committees (CPMP), was asked by the Directorate General Enterprise of the European Commission, to produce the following guidance document on the use of medicinal products for the treatment and/or prophylaxis of intoxication in patients exposed to chemical agents that might be used as weapons in terrorist actions.

The aim of this document is to give an update of current expert opinion and recommendations in selected cases. It should not be considered as an encyclopaedia of chemical warfare agents and all possible treatment and/or prophylactic measures.

The chemical agents, which are considered to be potential terrorist weapons and primarily warfare agents, have been evaluated by categories with similar effects and treatments. The list of substances is mainly derived from the one of the US Centre for Disease Control and Prevention ([CDC](#)). Although this guidance document addresses individual substances, it should be emphasised that agents used by terrorists may contain unknown amounts of impurities. Furthermore, mixtures of individual substances may be used.

Most of the experience with chemical weapons is derived from military open battlefields, whereas exposure in buildings and other confined spaces, a more likely scene of a terrorist attack, can be expected to be higher. As the civilian population includes a large spectrum of ages including children and pregnant women as well as people who may already suffer from illness, a military medical management may not always apply fully to the civilian context. Victims may be exposed to the triple threat of chemical injuries, burns and trauma. Supportive treatment of trauma and burns are beyond the scope of this review that will be limited to chemical injuries.

General public health measures that would be necessary in the case of exposure to the agents following a terrorist attack depend on the individual Member States.

Decontamination has been addressed in a separate section. In relation to the specific chemical agents, decontamination procedures have only been mentioned when methods other than the use of water and soap have documented advantages.

A specific section has also been dedicated to symptomatic treatments. It is essential to bear in mind that the lack of availability of specific antidotes does not preclude any efficient medical intervention.

The selection of pharmaceuticals discussed is restricted to medicinal products with well-documented effectiveness and/or widely used. As far as possible, the description of the antidote treatments includes also an assessment of their urgency of use. The medicinal products used for symptomatic treatments are given only as a pharmacological class (e.g. anticonvulsants, vasopressors), rather than mentioning specific products.

Information concerning 'immediate treatment' (first dose), and subsequent maintenance treatment (=24-hour) is included. This information would be useful in estimating when, and what amounts of a specific product, might be needed in the event of large-scale terrorist actions.

The availability of medicinal products or decontamination solutions, and the legal, practical and logistic considerations that might influence the selection of products depend on the individual Member States.

GENERAL PRINCIPLES OF TREATMENT

DECONTAMINATION

In order to be effective, early and thorough decontamination is very important. This serves two functions: (1) for the individual victim to reduce local effects and absorption and (2) to prevent spread of the toxic substance.

Decontamination procedures partly depend on the physical state of the chemical agent involved, i.e. liquid or gas.

If gases are the only known sources of exposure, skin decontamination will not be necessary.

In dealing with any exposures, prompt removal of the victim from the area of exposure is the first emergency measure. Thereafter, clothing should be removed and isolated in sealed double plastic bags.

Following exposure to liquids, skin decontamination should be performed with the decontamination solution available, as rapid decontamination is crucial. Water and soap or copious water alone are the first choice, since they will be readily available in sufficient amounts for most situations and since it is of the easiest use. Special attention should be paid to cleaning the hair, nails, skin creases, axilla, groin and around the genitalia and anus. Watches, jewellery and contact lenses if eyes have been exposed, should also be removed. Contaminants in particle form may be removed physically with forceps or a spatula.

In emergency situations where no water is available, dry powders such as earth, flour, and soap detergents may be used for decontamination.

Special decontamination solutions will only be relevant in exceptional cases.

After exposure to aerosols (vapour or smoke), removal from exposure, and removal and isolation of clothes, is followed by skin decontamination as described above for liquids. Usually showering with soap and water is considered adequate.

In the case of riot control agents in aerosol, special emphasis should be laid on avoiding hypochlorite solutions for decontamination, as these solutions may exacerbate skin lesions

Eye exposure should be treated in emergency. The eyes should be flushed with a gentle flow of water, saline (0.9% sodium chloride solution), or other eye-wash solutions for about 15 minutes. Care from a consultant ophthalmologist is recommended.

Secondary contamination of medical personnel is a hazard during decontamination and adequate protective equipment should be used. The patient's body fluids, urine and faeces and blister fluid do not present a chemical warfare hazard.

Decontaminated wastewater should ideally be contained, but this should never stand in the way of immediate action.

SYMPTOMATIC TREATMENT

Following or even during decontamination, the treatment of chemically injured patients is based on supportive treatment, and when available, specific antidotal treatment.

Supportive treatment of organ failure can be classified as basic life support and advanced life support. Basic life support is of utmost importance in emergency medicine.

Chemical attacks raise the major problem of immediate availability of supportive treatment to a large number of casualties.

Exposure to chemicals may induce a variety of organ injuries and failures. Several chemical agents can induce irritation and burn the skin, eyes, and the respiratory tract that may require symptomatic treatment. Biological toxins may cause severe diarrhoea. Anxiety and restlessness in a great number of patients may overwhelm medical facilities at the scene of the event. Finally, within weeks or months after the event, the follow-up of casualties may reveal a number of persons suffering sequelae related to the toxicant and to the event as such.

Chemical-induced respiratory failure

Standard treatment

A great number of chemical weapons can induce respiratory failure within a few seconds or minutes to several hours after exposure. These include choking agents, cyanide, organophosphates, opioids like fentanyl and tear gases used in a closed atmosphere.

- The first care for patients suffering from respiratory symptoms is to place them in a resting position.
- Choking agents may cause laryngeal oedema, which requires emergency endotracheal intubation as a life-saving treatment. The patency of the upper airway is a major concern in these patients and has to be closely monitored over several hours.
- The treatment of respiratory failure is primarily based on the administration of high flow of oxygen (100%) that may commonly require 12 l/min in adults. Treatment of a large number of patients at the scene requires the availability of sufficient oxygen supply and proper equipment for high flow administration to several patients simultaneously, including facial mask for mild injuries, continuous positive airway pressure in moderate injuries, while severe injuries may require mechanical ventilation after endotracheal intubation.
- Hypersecretion and bronchial deposits may require frequent airway suctioning.
- Bronchospasm should be treated symptomatically with adrenergic β_2 -agonists, if necessary supplemented with a methylxanthine according to standard protocols. While steroids are not recommended in the early phase of chemical-induced respiratory injury, severe bronchospasm may require steroids to be administered either by inhalation or by intravenous route.
- Severe irritation of the respiratory tract can be associated with secondary respiratory infection requiring antibiotic treatment.

Specific indications

- In case of organophosphate poisoning, there is a large body of knowledge supporting the immediate and repeat use of atropine together with oxygen and immediate assisted ventilation.
- Opioid poisoning causes a rapid onset of life-threatening central respiratory depression. Administration of an opioid antagonist may obviate the need for assisted ventilation.
- Significant cyanide poisoning causes bradypnoea and frequently apnoea that require immediate oxygen administration and assisted ventilation.

Chemical-induced Cardiovascular failure

Standard treatment

- Hypotension is treated by placing the patient in a supine position with elevation of the lower limbs above the level of the heart facilitating venous return. High flow of oxygen should be given and an intravenous line for fluid administration inserted. In case of drug-induced cardiovascular shock, 1 to 2 litres of intravenous isotonic fluids per patient are commonly used. Thereafter, the administration of catecholamines by an infusion pump should be considered.
- Cardiopulmonary arrest requires immediate resuscitation using cardiac life support.

Specific indications

- Cardiovascular failure may result from severe respiratory injury. In these patients mechanical ventilation after endotracheal intubation in association with adrenaline infusion should be considered.
- Patients severely poisoned with cyanide who exhibit a cardiovascular collapse, should be treated with a cobalt derivative, which may rapidly correct haemodynamic compromise and even obviate the need for fluid repletion and catecholamine administration.
- In organophosphate poisoning, in addition to standard treatment, the immediate administration of atropine should be considered more especially in patients with a slow heart rate.
- Diarrhoea or vomiting-induced cardiovascular shock requires the administration of a large amount of fluids (see below).

Chemical-induced Stupor and Coma

In chemical exposure, a direct depressant effect of the toxicant on the central nervous system, as well as the low oxygenation of the brain induced by respiratory or cardiac failure, may lead to coma.

Standard treatment

- Treatment includes securing free airways and respiration, administration of oxygen, and insertion of an intravenous line. The patient should be placed in a supine right-sided position.

Chemical-induced Seizures

Standard treatment

- Initial management of seizure is the same as for coma while sustained seizures may result in brain damage and require treatment with anticonvulsants such as benzodiazepines.
- Both nerve agents and cyanide can cause seizures that are rapidly followed by respiratory arrest. In these cases basic life support should be followed by administration of the relevant antidote.

Chemical-induced diarrhoea and vomiting

Standard treatment

- Sustained and profuse diarrhoea and vomiting may cause dehydration, metabolic disturbances, renal failure, hypovolaemic cardiovascular shock, and eventually death. Administration of fluids using either the oral or the intravenous route is an efficient treatment. Rehydration of one adult patient may require volume of fluids as large as 8 litres per day.

Chemical-induced skin and eye burns

Standard treatment

- For chemicals causing burns, standard treatment of thermal burns is adequate.

CHEMICAL WARFARE AGENTS

BLISTER OR VESICANT AGENTS

Blister/vesicant agents are represented by two main categories: the mustards (nitrogen or sulphur) and the organic arsenicals such as Lewisite. Other substances include Phosgene Oxime and mixtures of mustards and arsenicals.

Mustards

Toxicity

Exposure

Sulphur mustard was used in World War I, and has been reported in several other conflicts thereafter including in Middle-East conflicts in the 1980's. Nitrogen mustards are used in medicine as chemotherapeutic drugs.

Individuals may be contaminated with liquid or inhalation of vapor in the context of chemical warfare (e.g. through explosives, aircraft spray). Sulphur mustard is absorbed via the skin, respiratory tract and gut. Sulphur mustard penetrates also rapidly through clothing.

Sulphur mustard is persistent (freeze at 14°C) and long-term ground contamination may occur especially under cold conditions. The freezing point is lower if mixed with other agents (i.e. Lewisite).

Mode of action and toxicity

Mustards are powerful electrophilic and alkylating agents. By their properties of cross-linking to nucleic acids, cell membranes and proteins, these substances are potentially cytotoxic, mutagenic and carcinogenic.

In chemical warfare, exposure of patients to the liquid or vapour of mustard agents primarily causes damage to the exposed surfaces: skin, eyes and respiratory system. Systemic effects include the gastrointestinal tract, haematopoietic and lymphoid tissues and CNS. Reported case-fatality rates are less than 5%.

Clinical symptoms

Skin: the first symptom is usually itching. An erythema appears 4 – 12 hours after exposure first in areas with thin, warm and moist skin. The lesions progress in the following hours leading to the formation of blisters, which flow together in thin-walled painful vesicles with yellow content to reach a maximum after 48-72 hours. The vesicles may be arranged around necrotic wounds after heavy exposure. The typical fully developed clinical picture will resemble first and second degree burns. Full thickness burns may occur following contact with liquid mustard. Severe and large lesions can lead to complications similar to burn patients with a particular vulnerability to secondary infections. Severe cases should be treated in specialised burn units and considered as potentially immune-suppressed patients. Healing normally takes 4 – 6 weeks and may be followed by pigmentation changes and neuropathic symptoms in the affected areas.

Eyes: Symptoms are delayed for 1 to 6 hours until the appearance of clinical signs such as photophobia, lacrimation and painful conjunctivitis, corneal lesions and rarely iritis.

Respiratory symptoms: appear after a delay of 4 to 24 hours leading to a tracheo-bronchitis with clinical signs such as coughing, bloody expectoration, dyspnoea and in severe cases, pulmonary oedema. Secondary infections are frequent.

Gastrointestinal tract: Ingestion of liquid mustard induces vomiting, severe diarrhoea and secondary dehydration.

Systemic exposure: can lead to bone marrow depression and complications related to a pancytopenia.

Treatment management

First aid measures are essential and should be carried out even if no symptoms occur. It will however, only prevent damage if performed immediately. Later decontamination may reduce severity of the lesions and prevent spread of the mustard.

- Removal from the source of contamination
- Removal of contaminated clothes, watches etc. See general section on decontamination.
- Decontamination by washing with water and soap.
- Eye rinsing with saline if available, or source water. These measures are of value when administered in the first 5 minutes of liquid mustard contamination of the eyes.

Protection of the rescue team is important due to the risk of persistent contamination from the ground, clothes or the skin of victims.

Medicinal treatment

Considerable experience in managing mustard gas injuries was obtained during World War I. More recently, their use in the Iraq-Iran war led to additional experience as patients were often transferred to European hospitals. No specific antidote is available: treatment remains supportive and symptomatic. The rapid binding of mustard to protein makes antidotal removal of mustard from the body impracticable. Work with drugs providing sulphur (or -SH) groups intended to bind to mustard has shown that to produce any benefit such compounds have to be given almost immediately after exposure. As is often the case when no specific antidote exists many substances have been recommended for use. The evidence base for nearly all suggested compounds is weak. The information provided below deals briefly with target organ damage.

Skin lesions should be treated as burns with debridement of bullae > 1 cm. Although healing may take months, skin grafting is normally not necessary.

Eye lesions are treated as other chemical injuries. Care from a consultant ophthalmologist is desirable. Petroleum jelly may be applied to prevent eyelid synechia.

Acute respiratory symptoms should be treated with standard symptomatic treatment. Antibiotics may well be needed if bronchitis or pneumonia of bacterial aetiology occurs.

Systemic toxicity

Severe bone marrow depression may require treatment with colony stimulating factors (e.g. granulocyte monocyte-colony stimulating factor GM-CSF). Advice from a consultant haematologist is considered essential.

Organic Arsenicals

These agents are represented mainly by Lewisite.

Toxicity

Exposure

Lewisite is an oily liquid, which is more volatile and less persistent in the environment than mustards. Exposure occurs by contact with liquid or vapour following spraying from aircraft or explosives. Penetration through the skin or mucosa is very rapid.

Mode of action and toxicity

Organic arsenicals like Lewisite (2-chlorovinyl-dichloroarsine) owe part of their toxicity to the liberation of inorganic arsenic. Preferential distribution of Lewisite to the lungs is also an important factor of toxicity.

Inorganic trivalent arsenic (As³⁺) has the property of binding to the sulphhydryl group of proteins. Effects are mainly due to the inhibition of the pyruvate dehydrogenase complex, preventing the

Inorganic trivalent arsenic (As^{3+}) has the property of binding to the sulphhydryl group of proteins. Effects are mainly due to the inhibition of the pyruvate dehydrogenase complex, preventing the formation of acetyl-coA, which results primarily in a decreased production of ATP due to the reduction of citric acid cycle activity (Krebs cycle). As^{5+} can also induce an uncoupling of oxidative phosphorylation due to the formation of ADP-arsine instead of ATP. Overall, major perturbations of oxidative metabolism with decreased glucose production and uptake as well as decreased levels of reduced glutathione (GSH) are responsible for cellular injuries.

Clinical symptoms

Arsenicals produce more rapid clinical effects compared to Mustards.

Immediately after exposure (liquid contact or inhalation of the vapour), pain in the skin and eyes occurs as well as eye irritation, coughing, sneezing, lacrimation and salivation. The effects reach a maximum after 4-8h. Exposure of the eyes can lead to necrosis of the anterior part of the eye leading to blindness. Severe exposure can lead to pulmonary oedema and respiratory failure. In case of systemic absorption, toxic effects such as liver and kidney damage, encephalopathy and neuropathy, haemolytic anaemia, rhabdomyolysis, or myocardial damage can be observed. Haemodynamic shock and acute renal failure due to capillary leak may occur.

Treatment management

Decontamination and protective measures as for mustards are needed.

Medicinal treatment

Specific ointment, injections, and eye drops with dimercaprol ('British Anti-Lewisite', BAL, 2,3-dimercapto-1-propanol) or other chelating agents may be used to chelate arsenic (see Table 1).

Table 1: Antidotes for organic arsenicals

Activity	Active substances	Treatment management and posology	
		Administration	Posology
Chelators	2,3-dimercaptosuccinic acid (DMSA)*	Oral or IV in saline	<i>Adults & Children:</i> <ul style="list-style-type: none"> • <u>First 5 days:</u> 10-30 mg/kg x3/day • <u>Next 14 days:</u> 10 mg/kg x2/day
	2,3-dimercapto-1-propane sulphonic acid (DMPS)**	Oral or IV in saline	<i>Adults & children:</i> <ul style="list-style-type: none"> • <u>First 48 hours:</u> 250mg every 3 - 4 hours • <u>Next 48 hours:</u> 250mg every 6 hours • <u>Next 14 days:</u> 250mg every 8 hours
	Dimercaprol (5%)	Ointment for skin lesions or Eye drops	N/A
	Dimercaprol (10%)***	IM	<ul style="list-style-type: none"> • Day1: 400-800mg IM • Day2: 200-400mg IM • Day3: 100-200mg IM
	D-Penicillamine****	Oral	<i>Adults:</i> 1000 – 1500 mg/day in divided doses. <i>Children:</i> 10 mg/kg/day increased to 30 mg/kg/day before meals, 2-3 doses/day

* mild and transient elevation of hepatic transaminases or gastrointestinal discomfort are possible.

** rash, nausea or leucopenia are infrequently observed

*** second choice as painful and limiting drug toxicity

**** second choice due to limiting adverse effects.

Topical treatment: For skin and eye lesions dimercaprol in the form of an ointment or as eye drops (5% dimercaprol in oil with benzyl benzoate) may be applied.

Systemic treatment: The newer products DMSA and DMPS are superior to dimercaprol (BAL) which produces severe side effects when given systemically. Recent work by NATO identified the following advantages of these drugs over dimercaprol:

- they are substantially more effective than BAL systemically;
- they are more effective than BAL in mobilising arsenic from tissues, especially from the brain;
- they are water soluble and when given orally are relatively non-toxic;

Phosgene Oxime

Toxicity

Phosgene Oxime (CX) or dichloroformoxime is very irritating to the eyes and nose mucosa.

Clinical symptoms

Phosgene oxime does not induce blisters or vesicles but lesions resembling urticaria. Severe irritation occurs within 30 seconds together with lesions at the site of contact, sometimes corrosive. Experience with exposure is limited.

Treatment management

Decontamination should start as early as possible.

The treatment is only symptomatic.

Medicinal treatment

No specific medicinal products are available.

NERVE AGENTS AND OTHER HIGHLY TOXIC ORGANOPHOSPHATES

Nerve agents are related to organophosphate (OP) pesticides. There are two groups, the so-called G-gases and V-gases. The most important G-agents are tabun (GA), sarin (GB), soman (GD), and cyclosarin (GF). The V-agents are represented mainly by VX.

Toxicity

Exposure

Nerve agents are liquids at room temperature and exposure occurs by contact with liquid or inhalation of an aerosol or vapour. The G agents are significantly volatile (GB is the most volatile) and give off a dangerous vapour, whereas the V agents, such as VX, do not.

The V-agents are oily and persistent and could remain in a contaminated area for weeks. Of the G agents, GD can be thickened by the addition of plastic substances to produce a sticky, persistent formulation.

Exposure to nerve agents is also possible by intake of contaminated water and food.

Mode of action and toxicity

Nerve agents do, like organophosphate (OP) pesticides, produce toxicity by phosphorylating and hence inactivating enzymes involved in the breakdown of the acetylcholine neurotransmitter. The accumulation of neurotransmitters causes initial signs and symptoms of poisoning. While the effects of organophosphates on cholinesterase have been extensively studied, there is a growing body of knowledge supporting the assumption that the pathophysiology of poisoning may involve other mechanisms of action that remain to be clarified, especially in the case of nerve agents.

Clinical symptoms

Exposure to nerve agents may induce clinical effects that tend to occur theoretically in three different entities:

- Acute cholinergic phase
- The intermediate syndrome
- Delayed polyneuropathy (rare)

While clinical experience is limited, the intermediate syndrome has not been reported following acute nerve agent poisoning.

Polyneuropathy following nerve agent exposure is considered to be very unlikely.

A major concern regarding the ability of nerve agents to cause cognitive dysfunction and long-term sequelae of impaired intellectual function at low doses remains to be clarified.

Poisoning with nerve agents has only rarely been observed, although some clinical experience exists due to the use of these agents in the terrorist attack in Tokyo in 1995. It is considered that qualitatively, the toxicity of OP pesticides and nerve agents is similar. However, there may be some differences which cannot be solely attributed to dose, time and potency of the agents in question. Clinical reports on the Tokyo attack showed that sarin nicotinic response dominated, while VX is known to cause bradycardia, a classical muscarinic sign. Soman, causes seizures more frequently than other OP and both nerve agents and pesticides can cause acute respiratory failure. However, nerve agents may rapidly cause central apnoea whilst this has not been commonly reported in pesticide poisoning.

The severity of clinical symptoms can be categorised as follows:

Table 2: Classification of severity of acute symptoms after nerve agents exposure

Severity	Mild	Moderate	Severe
Presentation of the patient	Able to walk	Unable to walk but spontaneous breathing	Not breathing
Clinical symptoms	Lacrimation, salivation, miosis, blurring of vision and eye pain, cough, mild bradycardia, sweating, nausea, vomiting, abdominal pain	<i>As mild</i> , + dyspnoea, wheezing, tightness of chest, tremor, diarrhoea, urination, incontinence, coma	<i>As moderate</i> , + respiratory failure, epileptic seizures, flaccid paralysis

The above classification does not exclude that a poisoning may initially appear to be mild, but progresses rather rapidly to a more severe and life threatening poisoning.

According to their pharmacological site of action, these symptoms can be also classified as follows:

Muscarinic symptoms: salivation, lacrimation, urination, diarrhoea, gastrointestinal distress, emesis, miosis, bronchorrhea, bronchoconstriction, bradycardia.

Nicotinic symptoms: muscle fasciculations, cramping, and weakness, diaphragmatic failure, paralysis, areflexia. Initially, autonomic effects as tachycardia, hypertension, and mydriasis can be observed, but usually the muscarinic symptoms take the overhand very rapidly.

CNS effects: drowsiness, confusion, ataxia, dysarthria, seizures, coma, respiratory depression.

Treatment management

First aid measures

- Patients should be removed to an uncontaminated atmosphere
- Removal of clothes and thorough washing of skin with soap in case of dermal exposure is necessary

Protective measures

Gas masks and protective clothes for rescuers at the scene of the event are recommended.

The treatment of organophosphate-induced acute respiratory failure, coma, and seizures is based on adapted supportive treatment in association with atropine. Initially, endotracheal intubation may be required to allow frequent airway suctioning and a secure airway (see section on symptomatic treatment).

Medicinal treatment

The most efficient treatment results from a combination of drugs.

Atropine effectively ameliorates most muscarinic effects by itself, but has little effect on the nicotinic effects (muscle twitching, flaccidity). The oximes are useful as an aid in countering the nicotinic effects. They potentiate the effects of atropine, and oximes are considered to possess an atropine sparing effect.

Benzodiazepines are used in ameliorating central nervous system irritation (convulsions).

Antidotal therapy is essentially the same in nerve agents and insecticide toxicity. Nevertheless, there are specific differences regarding the dose and duration of treatment. The rather limited clinical experience regarding human poisoning with nerve agents should be borne in mind.

Atropine

Atropine should be considered the basic treatment of organophosphate poisoning that has to be immediately available. Atropine should be administered in patients receiving oxygen. Atropine will alleviate most of the muscarinic signs, little of the central nervous system symptoms, and almost none of the nicotinic symptoms. Atropine should be administered to obtain dryness of mouth and airway secretion and/or correction of severe bradycardia. Miosis is not easily reversed by injectable atropine and must not be used as a therapeutic measure as it may result in atropine overdose.

In adults, the initial recommended dose is 2 mg IM or IV. Further dosing is recommended in case of persistent bronchial hypersecretion and bradycardia.

Thereafter, the dosage regimen depends on the course of poisoning (consider - worst case scenario).

- Only a limited number of moderately to severely poisoned patients with sarin in the Tokyo attack required more than 2 mg of atropine sulphate. However, all authors observed that sarin induced more nicotinic than muscarinic signs and symptoms that may have limited the usefulness of atropine in sarin poisoning. These findings cannot be extrapolated to other nerve agents. Some patients may require initial repeated doses of up to 15 to 20 mg.
- In insecticide poisonings, the cumulative dose of atropine found in the literature appears to be more important, requiring repeated IV administration every 3 to 10 min to relieve muscarinic symptoms. Indeed, the cumulative dose of atropine may be more than 100 mg per patient in 24 hours.

Local atropine eye drops (0.25% to 1 %) may be considered to relieve ocular symptoms and eye pain relief. Indeed, G agents having a high volatility may cause eye pain and visual disturbances. In Tokyo sarin attack, patients with mild poisoning, complaining only of visual disturbances, were treated with atropine eye drops which improved visual disturbances. However, atropine was discontinued by the patients due to its side-effects (dryness of mouth, photophobia or difficulty in reading).

Oximes

In Europe, several oximes are presently available including various salts of pralidoxime as well as obidoxime. The different oximes do not have the same efficacy regarding the different nerve agents as well as the various insecticides. Thus, the efficacy of oximes remains a matter of debate. The efficacy of oximes depends on (1) the chemical structure of the organophosphate, (2) the delay in treatment due to the ageing of the phosphorylated enzyme, (3) the endpoints used to assess their efficacy.

Experimental and clinical studies suggest that the plasma concentration of oxime would be a key parameter to determine its efficacy. However, the measurement of plasma oxime concentration is limited to a small number of laboratories and is thus not generally available in an emergency.

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Regarding the controversial results in the literature, the group suggests that, while atropine should be immediately available at the scene of the event, oximes should be available as soon as possible. Administration of oximes should be considered in moderate to severe casualties at the recommended dose. The duration of treatment depends on the type of organophosphate. In nerve agents, the treatment is usually needed for approximately 24 hours and may be prolonged on a case-by-case basis. Several days of treatment are generally needed for organophosphate pesticides.

The choice of oxime is crucial in the case of nerve agent intoxication. The experience from nerve agent intoxication in man is limited but a large body of experimental data in guinea pigs and primates shows that pralidoxime and obidoxime are inferior to the so called H-oximes. This is the case not only in soman intoxication, where acetylcholine esterase is irreversibly changed within minutes, but also in poisoning caused by other nerve agents. In the future pralidoxime and obidoxime could be replaced by an H-oxime. The most likely candidate drug is HI-6 and the dimethansulphonate salt of this oxime. Unfortunately HI-6 is not stable in aqueous solution and has to be delivered by a two-compartment wet-dry injector device and at present only a limited number of countries have authorised this type of device with HI-6.

Unfortunately HI-6 is not an effective oxime against some organophosphate pesticides. Therefore oximes like obidoxime will still be needed in general health care. This, in combination with the lack of safety and efficacy data in humans, does not presently allow for an objective assessment of the value of HI-6 in an unidentified or mixed organophosphate poisoning in the context of a terrorist action.

Table 3: Medicinal treatment recommendations for nerve agents and other highly toxic organophosphates

Activity	Active substances	Treatment management and posology		
		Initiation	= 24h	Continuation**
Anticholinergics	Atropine citrate or sulphate*	Urgent (1 st minutes)	<i>Adults:</i> 2mg IM or IV every 5 to 60 mn according to severity <i>Children:</i> 0.002-0.08 mg/kg I.M. or I.V.	Up to 24h ≈ 50 mg max (adults)
Oximes	Pralidoxime chloride or methanesulphonate	As soon as possible	<i>Adults:</i> slow IV injection or IM, 1 to 2g. Repeat up to a total of 30mg/kg. <i>Children</i> slow IV injection, 25-40 mg/kg (max 1g)	Up to 24h ≈ 2000 to 4000 mg max (adults)
	Pralidoxime methylsulphate		Infusion of 10-20 mg/kg.h for 18h or longer	
	Obidoxime		<i>Adults:</i> slow IV or IM, 250mg. Repeat after 2 h. <i>Children:</i> slow IV or IM, 4-8 mg/kg (max 250 mg)	Up to 24h 750-1250 mg
	HI 6 dichloride monohydrate or dimethane sulphonate		<i>Adults:</i> 500 mg slow IV Repeat after 2h	Up to 24h 1500-2000 mg

* Multidose preparations containing preservatives should be avoided in order to prevent the potential toxicity related to the preservatives.

** Treatment may be needed for several days, especially for highly toxic OP.

BLOOD AGENTS (CYANIDES/CYANOGENS)

Cyanide Sources

The most toxic cyanide forms are: Hydrogen Cyanide (HCN, hydrocyanic acid, prussic acid) and its sodium and potassium salts (NaCN, KCN), cyanogen or dicyanogen (CN)₂ and its halides (e.g. CNCl, CNBr). Cyanogens are more of an irritant than cyanides.

Toxicity

Exposure

The main exposure route is by inhalation of volatile cyanides. A bitter almond odour is not always recognized since 20 to 40 % of the population are unable to perceive the smell.

After dermal or oral exposure, the absorption through intact skin or mucous membranes is good and systemic toxicity can be expected.

Mechanisms of Action

Cyanides and cyanogens are cellular poisons binding to metallo-enzymes e.g. with high affinity for Fe^{3+} and consequent cytochrome oxidase inhibition, thus blocking the aerobic respiration in the mitochondrial oxidative phosphorylation of the respiratory chain, and leading to lactic acid accumulation. Other enzymes are inhibited to a lesser degree.

Clinical symptoms

Symptoms appear within seconds to minutes after inhalation and a number of immediate fatalities may be expected. In these severe cases, clinical signs of hyperventilation, via direct stimulation of the respiratory centre and metabolic acidosis, are followed by loss of consciousness with convulsions and ultimately cardiovascular collapse and/or respiratory arrest. Other clinical signs include dizziness, weakness, palpitations, and anxiety, followed by dyspnoea, pulmonary oedema, confusion, ataxia, and paralysis.

A plasma concentration of lactate = 10 mmol/l can be used as a sensitive but non-specific marker of cyanide poisoning.

Cyanogens are also respiratory irritants, and may cause pulmonary effects if the victim survives asphyxia.

After oral administration, symptoms may be delayed for about 30 minutes, sometimes more.

Treatment management

First aid measures:

Remove the patient to an uncontaminated environment and atmosphere.

Decontamination

Generally, decontamination is not necessary, as dispersion of the gas is very rapid.

In case of dermal exposure, careful removing of clothes and thorough washing of the skin with water and soap is necessary.

With oral poisoning, if the patient is stabilised and in the rare cases when almost immediate measures can be applied, the administration of activated charcoal is recommended as a primary method of gastrointestinal decontamination.

Protective Measures

Gas masks and protective clothes are necessary for rescuers.

Symptomatic Treatment

- Supportive care including oxygenation with 100% O_2 , and if necessary, mechanical ventilation (mask or/and intubation)
- Management of seizures by anticonvulsants according to standard protocols.
- Arrhythmias management according to standard protocols
- Hypotension management by vasopressors as by standard protocols
- Metabolic acidosis management as by standard protocols

Medicinal treatment

Several antidotes are available. Controversial opinions on efficiency are common, due to the lack of reliable clinical studies.

Frequently the simultaneous or successive administration of different antidotes has been recommended. Dicobalt edetate is an efficient complexation antidote to cyanide. Its use should be restricted to cases when the diagnosis of cyanide poisoning is certain and only for severe poisoning, since it has serious adverse cardio-vascular adverse effects in the absence of cyanide.

Hydroxocobalamin is considered to be the best choice, if available. It is an experimentally well-documented antidote, with clear advantages in situations such as fires with concomitant exposure to agents that reduce oxygen transport, such as carbon monoxide.

Thiosulphate should be considered together with the other cyanide antidotes in sequential treatment but should not be administered as a mixture at the same time as hydroxocobalamin.

In case of non-availability of hydroxocobalamin or dicobalt edetate, alternative antidotes which act by indirect complexation of cyanide to methaemoglobin, should be considered. The methaemoglobin forming antidotes include sodium nitrite, amyl nitrite and 4-dimethylaminophenol.

Table 4: Summary of Cyanide Intoxication Antidote Treatments

Mechanisms of Action	Active Substances and Formulations	Management and Dosing Recovery within 4h or death			Adverse Effects
		Indications	Initial posology	Continuation	
Complexation agents	Hydroxocobalamin 2,5 % * (VitaminB _{12a}) in 0,9 % NaCl or 25 mg/ml in 100 ml vials	First choice , when cyanide poisoning is suspected.	<i>Adults:</i> 200 ml = 5 g dose IV or 70 mg/kg over 25 to 30 min <i>Children:</i> same initial dose or 70 mg/kg over 25 to 30 min	Repeat if necessary	-Hypersensitivity (extremely rare) -Deep red discoloration of urine lasting about 8 days
	Dicobalt edetate 1,5 % or 15mg/ml in 20 ml vials	Alternative choice , and only when cyanide poisoning is certain.	<i>Adults:</i> 20 ml = 300 mg dose IV over 1 min followed by 50 ml hypertonic glucose <i>Children:</i> 20 ml = 300 mg dose IV followed by 2 ml/kg of hypertonic glucose	Repeat 5 min later max 3 times	Hypo- or hypertension Cardiotoxicity in case of uncertain diagnosis
Methaemoglobin inducers	Amyl Nitrite in 0.2 ml vials	Second choice when complexation agents are unavailable.	One vial inhaled over 0.5 to 3 min while an IV-line is established	Repeat if necessary	Hypotension
	Sodium Nitrite 3 % or 30 mg/ml in 10 ml vials		<i>Adults:</i> 10 ml = 300 mg dose IV at an infusion rate of 2.5 ml/min <i>Children:</i> 0.3 ml/kg = 10 mg/kg at an infusion rate of 2.5 ml/min to max of 10 ml**	Additional half-sized dose, if no response in 30 to 60 min	Hypotension
	4-Dimethylaminophenol-HCl 5% or 50 mg/ml in 5 ml vials		<i>Adults:</i> 5 ml = 250 mg dose IV or 3 to 4 mg/kg followed by thiosulphate <i>Children:</i> 3 mg/kg		Excessive MetHb
Sulphur Supplier to promote Thiocyanate Conversion. Very slow action onset	Sodium Thiosulphate 25 % or 250 mg/ml in 50 ml vials	Sequential treatment following MetHb inducers	<i>Adults:</i> 50 ml = 12.5 g dose IV or 180 mg/kg over at an infusion rate of 2.5 ml/min. <i>Children:</i> 1.6 ml/kg or 400 mg/kg, up to 50 ml at an infusion rate of 2.5 ml/min	Additional half-sized dose, if no response in 30 to 60 min	

* Other commercially available solutions of 1 mg/ml are not adequate (highly diluted)

** Based on haemoglobin concentration

LUNG-DAMAGING AGENTS (CHOKING AGENTS)

The only lung damaging agents that have been used on a large scale in chemical warfare are phosgene and chlorine. During World War I, phosgene was responsible for approximately 80 – 90 % of fatalities from gas attacks in, and chlorine was the first chemical warfare agent used. With respect to toxic effects, these agents are respiratory irritants like the other warfare agents diphosgene and chloropicrin. Respiratory irritants include gases, aerosols and a mixture of these as in smoke.

Examples of respiratory irritants and some relevant toxicological characteristics are given below. Toxicity is expressed as the concentration considered Immediately Dangerous to Life and Health (IDLH) according to NIOSH classification (<http://www.cdc.gov/niosh/idlh/intrid14.html>).

Table 5: Selected list of respiratory irritants and their characteristics

Substance	Examples of use	Water solubility	Odour threshold (ppm)	IDLH (ppm)
Ammonia	Refrigerators, Polymer industry	High	5	300
Formaldehyde	Chemical industry, Disinfection	High	0.1-1	20
Hydrogen chloride	Chemical industry, Food industry	High	1-5	50
Chlorine	Polymer industry, Paper production	Moderate	0.3	10
Hydrogen sulphide	Petroleum industry, Manure	Moderate	0.025*	100
Methyl Isocyanate	Chemical industry	Moderate	-	3
Nitrogen Dioxide	Combustion	Low	0.12	20
Ozone	Disinfection	Low	0.05	5
PFIB (Perfluoroisobutylene)	Thermal decomposition of Teflon (possible warfare agent)	n.a.	n.a.	n.a. (LC50=17 ppm/10min)
Phosgene	Chemical industry, Warfare agent	Low	0.5	2
Sulphur Dioxide	Combustion and industrial use	Moderate	1	100
Zinc chloride	Military smoke granates (hexite)	Particles	-	50 mg/m ³

Toxicity

Respiratory irritants include acids, bases and substances with oxidizing and alkylating properties which all have a potential to induce an inflammatory response and tissue destruction in the airways. The effects are induced through oxidation, production of free radicals, combination of these and other mechanisms including physiologic defence mechanisms to injury.

The location of the effect largely depends on the water solubility of the substance. Highly water-soluble substances like acids, SO₂ and ammonia primarily exert their action in the upper airways. Lipid-soluble substances such as phosgene, ozone and oxides of nitrogen have their prime effect on the lower airways and alveoli. Chlorine, phenol and isocyanates have an intermediate position. However, at high concentrations, irritants induce diffuse injury to the respiratory system. For aerosols, deposition in the lung depends on the "aerodynamic diameter" of the particles. If water-soluble substances are adsorbed to respirable particles or droplets in an aerosol their effect may be shifted to more peripheral parts of the lung.

Clinical symptoms

Gases with high water solubility induce immediate symptoms from the upper airways, eyes and even from the skin. They have good warning properties and if escape is possible exposure will usually be limited. With higher exposure, more severe manifestations and effects including laryngeal oedema, injury to mucous membranes, bronchospasm and even Acute Respiratory Distress Syndrome (ARDS) may occur.

Less water-soluble gases, in particular phosgene and oxides of nitrogen, may induce injury to the lungs even when initial symptoms have been moderate. In the most severe cases the alveolar-capillary integrity is disrupted with fluid moving into the alveolar lumen, i.e. acute lung injury or in most severe cases acute respiratory distress syndrome (ALI/ARDS). The effects may be delayed for up to 24 (48) hours but can occur a few hours after intensive exposure.

Long-term effects may include Reactive Airway Dysfunction Syndrome (RADS), fibrosis, and bronchiectasis.

Treatment management

The only option for decontamination is to end exposure.

Treatment is basically supportive according to the clinical manifestations. It includes support of vital functions with focus on free airways, supplemental oxygen and broncho-dilators. Victims should be kept at rest and fluid intake restricted. Due to the role of oxidative stress in pathogenesis, treatment with 100% oxygen should only continue as long as required to keep sufficient oxygenation. Ventilation support may be required and is recommended with positive end expiratory pressure (PEEP) and a low tidal volume.

Unless exposure is clearly non-significant, victims exposed to phosgene or other gases with low water solubility should be kept under medical observation for 24 hours due to the risk of late pulmonary injury.

Medicinal treatment

No specific antidote exists for any of the pulmonary irritants.

INCAPACITATING AGENTS

Used in this context, incapacitation means the inability to perform any task effectively and implies that the condition was achieved via deliberate use of a non-lethal chemical agent. However, exposure to high doses of these agents may be lethal. Substances mostly used are those with effects predominantly on the central nervous system, especially those impairing the higher functions of the brain. They can be classified in four categories: stimulants, depressants, psychedelics, and deliriants. Although many compounds fall into these categories, only a few chemical agents are considered to be incapacitating agents in this sense.

Possible agents are:

- BZ (3-quinuclidinyl benzilate; Agent 15 is an (almost) identical compound),
- LSD (D-Lysergic acid diethylamide), and
- Fentanyl and other potent opioids.

BZ

Toxicity

BZ (3-quinuclidinyl benzilate) and its analogues are glycolic acid esters that cause a long lasting anticholinergic syndrome. BZ's clinical profile closely resembles that of atropine, although differing significantly in duration of action and potency.

Exposure to this compound is most likely as an aerosol or in smoke-producing munitions. Therefore, the respiratory system is the primary route of absorption. After inhalation, the onset of symptoms is seen in about one hour and symptoms peak in approximately 8-10 hours. After skin exposure (often dissolved in propylene glycol), absorption is 5-10% and symptoms may be delayed up to 24-36 hours. After ingestion, although this may be rare, absorption is estimated to be about 80%. After an incapacitating dose, recovery is gradual, starting after approximately 48 hours and taking up to 96 hours.

Clinical symptoms

Prominent peripheral antimuscarinic symptoms are mydriasis, dry, flushed skin and drying mucous membranes, hyperthermia, tachycardia, decreased intestinal motility, and urinary retention.

Important central nervous system symptoms are confusion, agitation, tremor, poor coordination, disturbances in perception, cognition and memory functions, hallucinations (usually visual), and delirium. Seizures and coma with respiratory depression may occur in severe poisoning.

Treatment management

Contaminated patients may cause secondary exposure to others. Contaminated clothing should be removed and isolated. Showering with water or washing with water and soap is adequate.

Treatment is symptomatic and supportive. Safe surroundings and close supervision are necessary. If these are not possible, separation of affected individuals into small groups is preferable to large groups.

Intravenous benzodiazepines may be used to control agitation or seizures.

Hyperthermia should be treated by external cooling.

Medicinal treatment

The use of the antidote physostigmine is generally not recommended because of its short duration of action (only 20-60 minutes). Furthermore, physostigmine may precipitate seizures and dysrhythmia.

LSD

Toxicity

LSD (D-Lysergic acid diethylamide) is a synthetic derivative of an ergot alkaloid and belongs to the classic hallucinogens. When administered by the aerosol route, the onset of symptoms is within minutes. After ingestion, symptoms start after 30-60 minutes. Peak effects are reached within 2-5 hours. The duration of action is 8-12 hours.

Clinical symptoms

The hallucinogenic effects are often preceded by nausea and sympathetic effects such as mydriasis, tachycardia, hypertension, tachypnoea, hyperthermia, and diaphoresis. The psychological effects include changes in arousal, emotion, perception (perceptual distortions), thought process, and self-image. Depersonalization with "out-of-body experiences" and sensory misperceptions are frequent. Hallucinations can be visual (most common), auditory, tactile, or olfactory. Panic reactions and psychosis including prolonged psychotic reactions can occur.

Treatment management

Gastrointestinal decontamination with activated charcoal may be considered for asymptomatic patients with recent ingestions, but it is not helpful once clinical symptoms are present.

Medicinal treatment

Treatment is symptomatic and supportive.

A quiet surrounding with minimal stimuli may be of benefit.

Benzodiazepines may be used to control agitation and hyperthermia. Severe psychotic reactions may require antipsychotic medication.

Fentanyl and other Potent Opioids

All fentanyls are synthetic opiates used clinically to produce surgical and/or postoperative analgesia. Fentanyls used clinically are in general 100 times more potent than morphine. Medical use of fentanyls is usually safe because these products are generally administered at low dose levels for a short time and under medical observation.

Various fentanyl analogues, not currently used in medicine, have also been synthesized and are approximately 10-50 times more potent than fentanyls. Other opioids from the thebaine group (e.g. ethorphine, acetorphine), used in veterinary medicine, are also very potent opioid agents and could be potentially used in a chemical attack.

Toxicity

Exposure

In normal medical practice, fentanyls are usually injected or administered as a transdermal patch.

Fentanyls easily pass biological membranes and rapidly reach the brain.

Delivery of fentanyls as an aerosol or a smoke with exposure by inhalation is the most probable route in a terror attack. Adding fentanyls to bulk water sources is another possible route of poisoning to consider.

Mechanism of action

Like morphine, all fentanyls are potent μ -opioid receptor agonists. Their toxicity is principally caused by a dose-related respiratory depression.

Clinical symptoms

The main life-threatening effect is a respiratory depression with bradypnoea, cyanosis, unconsciousness, and respiratory arrest. Other clinical signs include analgesia, miosis, seizure-like activity (unusual), and muscular rigidity (of chest wall, trunk and extremities). Injection or inhalation of very high doses may result within minutes in unconsciousness and respiratory arrest. The outcome will generally be fatal without rapid medical intervention.

Treatment management

First aid measures: secure the airway, administer oxygen and initiate assisted or controlled ventilation

Protection: a respiratory mask with particle and charcoal filters will protect against inhalation of fentanyl and its analogues. Body protection may be required if one of the more potent fentanyls is being used.

Medicinal treatment

Parenteral administration of naloxone (IM or IV) or nalmefene (IV) is recommended, if necessary as repeated doses until effective antagonism of symptoms and signs is achieved. Significantly higher doses (more than 10 times higher) of these antidotes compared to the standard medication may be required. In severe intoxication intravenous infusion of either antidotes may be needed. Due to the short half-life of naloxone repeated administration is necessary. Myorelaxant agents may be required in cases of pronounced muscular rigidity and concurrent respiratory depression to facilitate assisted or controlled ventilation. Possibly occurring haemodynamic instability should be treated with intravenous fluids and vasoactive agents.

Table 6: Antidotes to opioid poisoning

Activity	Active substances	Treatment management and posology		
		Initiation	=24h	Duration
μ-opioid receptor antagonists	Naloxone IM or IV	<ul style="list-style-type: none"> 0.2-0.4mg repeated until effect observed up to 2-4 mg for fentanyl 	<i>Adults:</i> 10-20 mg <i>Children:</i> 0.1mg/kg	<24 hours
	Nalmefene	<i>Adults:</i> 0.5-1.5 mg IV <i>Children:</i> 0.25-1 μg/kg IV	<i>Adults:</i> 5-10 mg or higher. <i>Children:</i> 40μg	<24 hours

TEAR/LACHRYMATORS/VOMITING AGENTS

Lachrymatory chemical agents (also referred to as “tear gas”) are used in riot control and other law-enforcement situations. Although they are solid chemicals and not true gases. They are, administered as a fine dust or aerosol spray. Only chloropicrin is a gas. Most lachrymators are relatively benign compared to many other chemical agents of terrorism.

Toxicity and Symptoms

Immediately after exposure, ocular burning, blepharospasm, lachrymation, rhinorrhoea, coughing, sneezing, and pain appear. Usually, this does not result in permanent tissue damage. Later, chest tightness and coughing, shortness of breath, burning of tongue and mouth, salivation and vomiting may develop. Exposure to high concentrations may lead to chemical burns of the eye. A burning sensation of the skin, followed by erythema and bullous dermatitis, although rare may develop following exposure to CS or CN. Individuals with pre-existing pulmonary disease may infrequently develop bronchospasm, which may be delayed up to 48 h post-exposure. Extremely rare cases of pulmonary oedema have been reported up to 24 hours post-exposure.

Treatment management

The treatment is symptomatic (see also section on symptomatic treatment).

Eyes: Depending on exposure, the eyes may not require external irrigation, self irrigation may be adequate. If necessary, irrigate with lukewarm water for up to 15 minutes. If irritation, pain, swelling lacrimation or photophobia persists after 15 min, refer to ophthalmologic examination and treatment.

Skin: Treat as chemical burns. Remove all contaminated clothing (Put in sealed polyethylene bag. If clothing is washed, use cold water, as hot water will cause residual CS gas to vaporize.). Wash exposed area with soap and water (see general section on decontamination). Contaminated hair may lead to re-exposure of the patient on showering or bathing.

Inhalation exposure: Move to fresh air. The treatment is symptomatic.

Medicinal treatment

There are no specific medicinal product recommendations, apart from those required by the symptomatic treatment.

TOXINS

Botulinum Toxin

The following recommendations are made in complement to the existing CPMP guidance document on treatments to be used in the case of terrorist attacks with biological agents. (EMEA/CPMP/4048/01).

Source: Botulinum toxin is produced by a common, rod-shaped earth bacteria *Clostridium botulinum*. *Clostridium botulinum* will form spores in an environment hostile to it and thus considerably increase its ability to survive and resist for example a high temperature.

Different types of toxins are produced (A-G). The most common in bacterial infections are A, B and E. The type A toxin is used medically and injected locally as therapy in a variety of neurologic and ophthalmologic disorders.

In terrorism, a mixture of cultured *Clostridium botulinum* and its spores can be expected but probably not a purified toxin.

Toxicity

Exposure: Probably by ingestion of water and food contaminated by the toxin or/and bacteria and spores. The toxin appears to be absorbed, degraded or eliminated 3 days after ingestion but the effects of the toxin can last for several weeks or months. Inhalation of the toxin is a possible route of exposure, but the effects are not well documented. Wound botulism and infant botulism are out of the scope of this document.

Mode of action and toxicity: Botulinum toxin impairs the presynaptic release of the neurotransmitter acetylcholine. Even if there is some evidence for additional mechanisms of action, almost all signs and symptoms observed can be explained by the effects of botulinum toxin on the cholinergic neurons.

The purified toxin is probably the most potent toxin known. The mean lethal dose after injection into mice is 0.03 ng/kg. Inhalation of the toxin, if effective, could also be highly toxic. However, it can be expected that toxicity will vary considerably depending on the purity of the toxin preparation and on the quality of the pharmaceutical product.

Clinical symptoms and signs

After an infection caused by *Clostridium botulinum*, the incubation time is 0-7 days before onset of any symptoms and signs. These ought to appear without delay after poisoning with a purified botulinum toxin.

The following symptoms are likely to appear: shortness of breath, dysphagia or dysphonia, dysarthria, diplopia, poor accommodation and dry or sore throat.

On physical examination the following signs will be observed: flaccid, descending and symmetric paralysis, and respiratory insufficiency without any specific laboratory findings.

Treatment management

Protection: respiratory protection with masks will effectively protect against inhalation of toxin or spores.

Treatment: gastric decontamination should be performed primarily by administration of activated charcoal or alternatively by gastric lavage in case of suspicion of oral exposure and before the onset of symptoms.

Prophylaxis: intoxication can be prevented by boiling food and water at 100°C for 10 minutes in order to destroy the spores of *Clostridium botulinum*. To destroy the spores of *Clostridium botulinum*, heating at temperature higher than 100°C are needed.

Medicinal treatment

Besides the supportive treatment, the only other treatment is human-derived botulism immunoglobulins (BIG), but clinical investigations to show efficacy are still ongoing.

Antitoxins of equine origin could be effective but have serious side effects such as serum disease in 10-15 % of treated patients. Antibiotics are only useful when there is evidence of bacterial growth.

Ricin and abrin

Source: Ricin is a lectin, a toxic glycoprotein, found in the fibrous portion of the seeds of the ordeal or ornamental plant, Castor bean (*Ricinus communis L.*). The Jequirity bean (*Abrus precatorius*) also has a lectin, abrin, similar to ricin and also very toxic. For both the Castor bean and the Jequirity bean, the toxins are present in the seeds or in water-soluble extracts.

Toxicity

Exposure: Ricin and abrin do not penetrate intact skin. There is an extensive degradation of ricin in the stomach so that less than 10% is absorbed after oral consumption. Some cases of intentional or unintentional ricin poisoning have also been reported. Spreading of ricin or abrin as particles or as aerosol of droplets of toxins in solution, are other possible routes of exposure.

Mode of action: There are two lectins in the fibrous part of the seed of the Castor bean – Ricin I and Ricin II. Ricin II is the most toxic lectin. It contains two chains of amino acids A and B linked together by disulphide bonds. The B chain (MW 33 000 Daltons) binds to the cell membrane and facilitates the endocytosis of the A chain (MW 30 000 Daltons) into the cell. In the cytosol, the A chain is a powerful inactivator of ribosomes, and blocks irreversibly the protein synthesis.

The seeds of the Jequirity bean contain four lectins called isoabrin. They consist also of two amino acids A and B chains linked together by disulphide bonds. One of the four isoabrin, isoabrin-a, has the highest inhibitory effect on the protein synthesis.

Toxicity: The estimated oral lethal dose in humans is 1mg/kg but could probably vary considerably. If seeds are swallowed as a whole, symptoms are much less likely to develop than if seeds are chewed or broken thoroughly. The majority of people poisoned after oral intake of ricin survived after proper medical handling and supportive treatment. As the Castor bean contains also allergenic glycoproteins there is a risk of anaphylactic or other allergic reactions in sensitised persons. The toxicity of abrin after oral intake is not well documented, but it is probably at least as toxic as ricin.

In humans, the minimum estimated lethal dose of ricin is 1 mg/kg orally, and 10-30 µg/kg by IM injection.

Clinical symptoms and signs

After ingestion of ricin or seeds of the Castor bean there will be a delay of 4-6 hours up to several days until symptoms appear. The symptoms start with a loss of appetite, nausea, vomiting and diarrhoea followed by signs of severe gastroenteritis, with persistent vomiting, hemorrhagic diarrhoea and dehydration. Icterus, and eventually circulatory collapse might occur within 6-8 days in fatal cases.

Few human data are available on symptoms and signs after inhalation of ricin or abrin (Kacnelson IB et al). Local irritation of the respiratory tract may appear after hours, and may lead to more serious lung damage with haemoptysis and severe or fatal circulatory changes.

Treatment management

Protection: respiratory masks will protect against inhalation of ricin and abrin.

Treatment: after ingestion of ricin or abrin, gastric decontamination should be performed primarily by administration of activated charcoal or alternatively by gastric lavage. An observation period of at least 8 h following any substantial exposure is required for a non-symptomatic patient. In more severe cases, intensive treatment (usually in hospital) may be required such as intravenous fluids, supportive care, electrolyte replacement, monitoring for hypoglycaemia, haemolysis and complications of hypovolaemia. Haemodialysis and forced diuresis are of no value, since abrin and ricin are not dialysable.

Medicinal treatment

Experimentally there appears to be a possibility to develop a vaccine against ricin but at present, a vaccine or other effective antidote is not available.

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- EMEA/CPMP/1100/02 Note for Guidance on the Development of Vaccinia Virus Based Vaccines against Smallpox (<http://www.emea.eu.int/pdfs/human/veg/110002en.pdf>)
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Toxins

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ANNEX 1

List of Chemical Compounds that might be used by a Terrorist Organisation

<u>Blister/Vesicants</u>	CAS Registry Number
<ul style="list-style-type: none">• Mustard gas, distilled sulphur mustard (or Yperite) (H/HD)• Nitrogen mustard (HN-1)• Nitrogen mustard (HN-2)• Nitrogen mustard (HN-3)• Lewisite 1 (L1)• Lewisite 2 (L2)• Lewisite 3 (L3)• Phosgene oxime (CX)• Mustard/Lewisite mixture (HL):• Sesqui mustard (Q)• Methyl dichlorarsine (MD)• Ethyl dichlorarsine (ED)• Phenyl dichlorarsine (PD)	<ul style="list-style-type: none">• 505-60-2 (H/HD)• 538-07-8 (HN-1)• 51-75-2 (HN-2)• 555-77-1 (HN-3)• 541-25-3 (L1)• 40334-69-8 (L2)• 40334-70-1 (L3)• 1794-86-1 (CX)• n/a• 3563-36-8 (Q)• 593-89-5 (MD)• 598-14-1 (ED)• 696-28-6 (PD)
<u>Nerve agents</u>	
<ul style="list-style-type: none">• Sarin (GB)• Tabun (GA)• Soman (GD)• Cyclohexyl Sarin (GF)• Isopropyl ethylphosphonofluoridate (GE)• VX (V-gas)• VM• VE• VG• VR (Russian VX or RVX)• VS	<ul style="list-style-type: none">• 107-44-8 (GB)• 77-81-6 (GA)• 96-64-0 (GD)• 2992-95-2 (GF)• 1189-87-3 (GE)• 50782-69-9 (VX)• 21770-86-5 (VM)• 21738-25-0 (VE)• 78-53-5 (VG)• 159939-87-4 (VR)• 73835-17-3 (VS)
<u>Blood agents (cyanides/cyanogens)</u>	
<ul style="list-style-type: none">• Arsine (SA)• Hydrogen Cyanide (AC)• Cyanogen Chloride (CK)• Cyanogen Bromide	<ul style="list-style-type: none">• 7784-42-1 (SA)• 74-90-8 (AC)• 506-77-4 (CK)• 506-68-3
<u>Lung-Damaging Agents (Choking agents)</u>	
<ul style="list-style-type: none">• Chlorine (Cl₂)• Phosgene (CG)• Diphosgene (DP)• Perfluoroisobutylene PFIB	<ul style="list-style-type: none">• 7782-50-5 (Cl₂)• 75-44-5 (CG)• 503-38-8 (DP)• 382-21-8 (PFIB)

Incapacitating agents

- | | |
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| <ul style="list-style-type: none">• 3-quinuclidinyle benzilate (BZ) and Agent15• LSD• Fentanyl• Ethorphine• Acetorphine | <ul style="list-style-type: none">• 6581-06-2 (BZ)• 50-37-3 (LSD)• 437-38-7 (Fentanyl)• 14521-96-1 (ethorphine)• 25333-77-1 (acetorphine) |
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Tear/Lachrymators/Vomiting agents

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| <ul style="list-style-type: none">• a-Chloroacetophenone (CN)• 2-Chlorobenzylidene malononitrile (CS)• Dibenz(b.f.)-1:4-oxazepine (CR)• Bromobenzylcyanide (CA)• Chloropicrin (PS)• CNB - (CN in Benzene and Carbon Tetrachloride)• CNC - (CN in Chloroform)• CNS - (CN and Chloropicrin in Chloroform)• Ethyl iodoacetate (SK)• Adamsite or chlorodihydrophenarsine (DM)• Diphenylchloroarsine or Clark I (DA)• Diphenylcyanoarsine or Clark II (DC)• Capsaicin (E) | <ul style="list-style-type: none">• 532-27-4 (CN)• 2698-41-1 (CS)• 257-07-8 (CR)• 5798-79-8 (CA)• 76-06-2 (PS)• 532-27-4 (CN)• 532-27-4 (CN)• 532-27-4 (CN)• 623-48-3 (SK)• 578-94-9 (DM)• 712-48-1 (DA)• 23525-22-6 (DC)• 404-86-4 (E) |
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Toxins

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| <ul style="list-style-type: none">• Botulinum toxin• Ricin• Abrin | <ul style="list-style-type: none">• 93384-43-1 (botulinum)• 9009-86-3 (ricin)• 1393-62-0 (abrin) |
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ANNEX 2

Summary table of recommended medicinal products

Product	Exposure	Administration	Category*	Approx. Amount needed /24h/adult
DMSA	Organic arsenicals	Oral, Parenteral (IV)	B2	5-20 g
DMPS	Organic arsenicals	Oral, Parenteral (IV)	B2	2 g
Dimercaprol 5%	Organic arsenicals	Oinment, eye drops	B3	N/A
Dimercaprol 10%	Organic arsenicals	Parenteral (IM)	B3	1-2 g
D-Penicillamine	Organic arsenicals	Oral	C3	1-5 g
Atropine	Organophosphates	Parenteral (IV, IM)	A1	150mg -1-(3) g
Pralidoxime	Organophosphates	Parenteral (IV, IM)	B2	10 g
Obidoxime	Organophosphates	Parenteral (IV, IM)	B2	1-2 g
HI-6	Organophosphates	Parenteral (IV)	B2	2-3 g
Hydroxocobalamin 2.5%	Cyanide	Parenteral (IV)	A1	10-15 g
Dicobalt-EDTA	Cyanide	Parenteral (IV)	A1	900 mg
Amyl Nitrite	Cyanide	Parenteral (IV)	A2	1 vial
Sodium Nitrite 3%	Cyanide	Parenteral (IV)	A1	500 mg
4-DMAP-HCl 5%	Cyanide	Parenteral (IV)	A1	250 mg
Na-Thiosulphate	Cyanide	Parenteral (IV)	A1	25 g
Naloxone	Opioids	Parenteral (IV,IM)	A1	10 -100 mg
Nalmefene	Opioids	Parenteral (IV)	A1	1-5 mg

*Category of decreasing urgency (A to C), and proven effectiveness (1 to 3), according to Pronczuk de Garbino J &al, 1997