EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 July 2024
EMA/323692/2024
Emergency Task Force (ETF)

EMA guidance document on the use of medicinal products for treatment in case of exposure to chemical agents used as weapons of terrorism, crime, or warfare

This guidance replaces the previous European Medicines Agency (EMA) guidance, EMEA/CPMP/1255/03.

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Introduction

In 2003, at the request of the Directorate General Enterprise of the European Commission, the EMA published a guidance document on the use of medicinal products for the treatment and prophylaxis of intoxication in patients exposed to chemical agents that might be used as weapons in terrorist or warfare actions.

The aim of the document was to give an overview of current expert opinion and recommendations on the use of medicines for the treatment of patients exposed to chemical agents. In 2024 the guidance was updated after a review of the scientific literature and existing guidelines and a consultation with a panel of European experts in toxicology, pharmacology, clinical management, and military aspects related to chemical agents and other toxic chemicals.

This document is not intended to be a comprehensive guideline on the clinical management of patients and on the public health measures that would be necessary in the case of deliberate release of the selected chemical agents. The scope of the document is confined to the description of the main aspects on decontamination and supportive treatment of affected patients, and to the listing and description of specific medicines and/or antidotes that might be useful in the case of an attack. Treatment options should always be regarded in conjunction with existing national recommendations and public health or defence plans. Moreover, reference should always be made to the labelling information included in the medicines' Summary of Product Characteristics (SmPCs) of each EU Member State.

The chemical agents, which are considered to be potential terrorist weapons and/or primarily warfare agents, have been evaluated by categories with similar effects and treatments. The list of substances is mainly derived from the one from the US Centre for Disease Control and Prevention. 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. Of note, toxins of plant origin (ricin and abrin) are not considered in this guidance but in the "EMA guidance document on the use of medicinal products for treatment and prophylaxis in case of exposure to biological agents used as weapons of terrorism, crime or warfare". (1)

Most of the experience with chemical agents is derived from military open battlefields. As the civilian population includes a large spectrum of ages including children and pregnant women as well as people who may already suffer from illnesses, a military medical management may not always apply fully to the civilian context. Victims may be exposed to different chemical agents resulting in combined injuries, such as burns and trauma. Supportive treatment of combined injuries is beyond the scope of this review, which will be limited to chemical injuries.

As far as possible, the description of the antidote treatments includes an assessment of their urgency of use. The medicinal products used for symptomatic treatments are given, in most of the cases, only as a pharmacological class (e.g. anticonvulsants, vasopressors), rather than mentioning specific products.

The availability of medicinal products, and the legal, practical, and logistic considerations that might influence the selection of products depends on the individual EU Member States. The existence of national or European stocks and of emergency plans involving both civilian and military authorities may well influence which and how medicines would actually be used in the case of an attack. Moreover, some medicines, may have to be obtained through special access mechanisms in individual EU Member States. Even in the lack of an EU centralised or national marketing authorization, medical countermeasures listed in this guidance may be made available to the population in case of need. Therefore, prescribers should always consult existing national guidance and expertise, and should

always refer to the national prescribing information and/or a poisons centre, as applicable, regarding each of the medicinal products suggested.

This guidance document will be further updated on a regular basis as appropriate.

This guidance document was adopted by the EMA Emergency Task Force (ETF) on July 12, 2024.

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Decontamination

General Principles of Decontamination

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 in the environment or to additional people. If there is a need for prioritisation between decontamination and treatment with life-saving antidote therapy, decontamination should never take precedence. In these cases, decontamination should be performed either concurrently or after treatment. If decontamination cannot be performed, appropriate personal protective equipment should be provided to health care personnel. (1-5)

Decontamination procedures partly depend on the physical state of the chemical agent involved, i.e. solid, liquid or gas. If gases are the only known sources of exposure, skin decontamination may still be necessary if vapour has contaminated the skin. 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 labelled and sealed double plastic bags. Following dermal exposure, particularly 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. Pressurising the water is necessary to ensure adequate washing of the skin and removal of the chemical agent, however excessive pressure can cause damage to the skin and exacerbate the "wash-in" effect, accelerating the amount of chemical agent that is absorbed through the skin. Unheated water may increase the risk of hypothermia especially in cold environments, heated showers will reduce this risk. 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. (1-5)

In emergency situations where no water is available, dry powders such as Fuller's earth, activated carbon, or any other available absorbent materials like flour or towels may be used for decontamination. Special decontamination solutions will only be relevant in exceptional cases, but specific products for specific chemical agents do exist, such as reactive skin decontamination lotion (RSDL) for mustards and nerve agents. 0.5% hypochlorite solution (diluted household bleach) has been recommended as a chemical decontaminant in the past, but now should be avoided as evidence suggests it has no benefit over decontamination with water alone, has a corrosive effect on skin, and can induce further dermal injury when used for wound decontamination. It is also unsuitable for use to decontaminate the eyes or mucous membranes. (1-8)

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. 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 an ophthalmologist is recommended. (1-5)

Persistent liquid chemical agents and solid chemical agents pose a risk of secondary contamination of medical personnel during both decontamination and the rest of the treatment process, meaning adequate protective equipment should be used. Highly volatile liquid agents and gaseous agents do not usually pose a secondary decontamination hazard, however there could be a risk if clothes are not removed. The patient's body fluids, urine and faeces and blister fluid usually do not present a

significant chemical warfare hazard. Decontaminated wastewater should ideally be contained, but this should never stand in the way of immediate action. (1-5)

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1. Issa F.S., Z.A. Alhussaini, 'Decontamination: Chemical and Radiation', in: Ciottone's Disaster Medicine, pp. 545–550, Elsevier, 2024.
2. Organisation for the Prohibition of Chemical Weapons (OPCW), International Cooperation and Assistance Division Assistance and Protection Branch, 'Practical Guide for Medical Management of Chemical Warfare Casualties' 2019
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Symptomatic Treatment

Following or even during decontamination, the treatment of chemically injured patients is based on supportive treatment, and when available, specific antidote treatment. 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. 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. The general approach to symptomatic treatment in case of a chemical attack is described below. Specific medicinal products will be discussed in more detail for each agent.

Chemical-induced respiratory failure

A great number of chemical agents can induce respiratory failure within a few seconds or minutes to several hours after exposure. These include lung damaging agents, cyanide, nerve agents, opioids, and tear gases used in a closed atmosphere. The first care for patients suffering from respiratory symptoms is to place them in a recovery position. Lung damaging 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 must be closely monitored over several hours. The treatment of respiratory failure is primarily based on the administration of oxygen 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. The unavailability of oxygen and proper equipment should not prevent the use of other urgent lifesaving interventions. Hypersecretion and bronchial deposits may require frequent airway suctioning. Bronchospasm should be treated symptomatically with adrenergic β2-agonists. Inhaled corticosteroids could also be used in case of bronchospasm or intense coughing, however evidence of use in the context is low. Severe irritation of the respiratory tract can be associated with secondary respiratory infection requiring antibiotic treatment.

Chemical-induced cardiovascular failure

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. Cardiovascular failure may result from severe respiratory injury. In these patients, mechanical ventilation after endotracheal intubation in association with vasopressors should be considered. Diarrhoea or vomiting-induced cardiovascular shock requires the administration of a large amount of fluids.

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. Treatment includes securing free airways, administration of oxygen, and insertion of an intravenous line.

Chemical-induced seizures

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. In the case seizures are rapidly followed by respiratory arrest basic life support should be followed by administration of the relevant antidote.

Chemical-induced diarrhoea and vomiting

Sustained and profuse diarrhoea and vomiting may cause dehydration, metabolic disturbances, renal failure, hypovolemia, cardiovascular shock, and eventually death. A large amount of crystalloids could be needed for IV fluid replacement.

Chemical-induced skin and eye burns

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

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Blister or Vesicant Agents

A blister or vesicant agent may cause or induce blisters and vesicles to the exposed tissues. Blister/vesicant agents are represented by two main categories: the mustards (nitrogen or sulfur) and the organic arsenicals such as lewisite. Other substances include phosgene oxime and mixtures of mustards and arsenicals. (1)

Mustards

Toxicity, disease characteristics, and general points on decontamination and treatment

The mustard agents include sulfur-, nitrogen- and oxygen-based compounds. Nitrogen mustards (or their derivatives) are known for their medicinal uses as chemotherapeutics and have not been used as chemical weapons. However, the nitrogen mustards HN1, HN2 and HN3 may be used for chemical warfare purposes. Sulfur mustards (H, HD, and HT) are only known as possible weapons. Sulfur mustard was used in World War I and has been reported in several other conflicts thereafter including Middle East conflicts in the 1980's and in 2016. Individuals may be contaminated with liquid or through inhalation of vapor in the context of chemical warfare (e.g. through explosives, aircraft spray). Sulfur mustard is absorbed via the skin, eyes, respiratory tract, and gut. Sulfur mustard penetrates also rapidly through clothing. Sulfur mustard is persistent (freezes 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 as in HL, a blend of distilled mustard (HD) and lewisite (L)). 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. (1-4)

In chemical warfare, exposure of patients to the liquid or vapour of mustard agents primarily causes damage to the exposed surfaces: eyes, skin, and respiratory system. Secondary infections of damaged tissues can also occur and represent serious complications. Other systems commonly affected are the gastrointestinal, hematopoietic, lymphoid, and central nervous systems. Reported case-fatality rates are less than 5%. Initial eye symptoms are likely to be observed first, especially in case of exposure to high concentrations of sulfur mustard. Photophobia, lacrimation and painful conjunctivitis, corneal lesions and rarely iritis can appear within a range of 30 minutes to 6 hours. The first skin symptom is usually itching. An erythema appears 4 to 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 to 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 like 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 to 6 weeks and may be followed by pigmentation changes and neuropathic symptoms in the affected areas. Respiratory system 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 and/or mechanical asphyxia due to due to fragments of necrotic tissue obstructing the trachea or bronchi. Secondary infections are frequent. Ingestion of liquid mustard induces vomiting, severe diarrhoea, and secondary dehydration. Systemic high dose exposure can lead to bone marrow depression and complications related to a pancytopenia up to 3 to 5 days after

exposure. CNS excitation (including convulsions) followed by depression and cardiac irregularities can also occur. Long term effects include chronic lung disorders, pruritus, and corneal abnormalities. (1-3)

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

Main measures include removal from the source of contamination, removal of contaminated clothes, watches etc., washing with water and soap, and eye rinsing with saline solution if available, or water otherwise. These measures are of value when administered in the first 5 minutes of liquid mustard contamination of the eyes. Skin decontamination could also be performed with reactive skin decontamination lotion (RSDL). Protection of the rescue team is important due to the risk of persistent contamination from the ground, clothes, or the skin of victims. (1-3)

Considerable experience in managing mustard gas injuries was obtained during World War I. Their use in the Iraq-Iran war (1980-1988) 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. Studies with drugs providing sulfur (or -SH) groups intended to bind to mustard have shown that to produce any benefit such compounds must be given almost immediately after exposure. Skin lesions should be treated as burns with debridement of bullae >1 cm. Although healing may take months, skin grafting is normally not necessary. Calamine lotion, corticosteroids in solution and even water can decrease the pain of lesions. Topical antibiotics should be used as for routine burns care to avoid secondary infections. Eye lesions are treated as other chemical injuries. Care from a consultant ophthalmologist is desirable. Sterile petroleum jelly may be applied to prevent eyelid synechia. Acute respiratory symptoms should be treated with standard symptomatic treatment. Antibiotics may be needed if bronchitis or pneumonia of bacterial aetiology occurs. Severe bone marrow depression may require treatment with colony stimulating factors (e.g. granulocyte monocyte-colony stimulating factor GM-CSF) and antibiotics. Advice from a consultant haematologist is considered essential. (1-3)

Organic Arsenicals

Toxicity, disease characteristics, and general points on decontamination and treatment

These agents are mainly represented by lewisite (L; 2-chlorovinyldichloroarsine). 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. Organic arsenicals like lewisite 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. Lewisite is corrosive to steel and in non-alkaline conditions may also decompose to trisodium arsenate. Inorganic trivalent arsenic (As^{3+}) has the property of binding to the sulfhydryl 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. (1, 2, 5)

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 to 8 hours. Exposure of the eyes can lead to necrosis of the anterior part of the eye leading to blindness. Severe inhalation 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. Cutaneous manifestations can be also expected. (1, 6)

Decontamination and protective measures as for mustards are needed. (1, 6)

Various chelating agents are available for therapy after poisoning with arsenicals and heavy metals. The chelating agents 2,3-dimercapto-1-propane sulphonic acid (DMPS, Unithiol) and 2,3-dimercaptosuccinic acid (DMSA, succimer) should be regarded as first choice. Dimercaprol ('British Anti-Lewisite', BAL, 2,3-dimercapto-1-propanol) is available as ointment, eye drops and for systemic administration. However, systemic administration of dimercaprol is considered obsolete because of the limited success rate, the multiple side effects, and possible accumulation of arsenic in the brain. Systemic treatment should be started in case of severe clinical conditions (dyspnoea, bloody sputum), large skin burn, skin contamination >5% of the body surface, delayed decontamination. (6, 7)

These guidelines do not address the treatment of chronic poisoning.

Recommended medicinal products for treatment in case of exposure to organic arsenicals and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of poisoning with lewisite and other organic arsenicals	**First line regimens**[6-14]		
	2,3-dimercapto-1-propane sulphonic acid (DMPS, Unithiol)		Dimaval® ampoules and Dimaval® capsules are authorised in Germany for different indications.
	Adults and children	Mild-moderate poisoning: 12 to 24 100 mg sodium salt capsules PO evenly spaced throughout the day, depending on the severity of poisoning. Duration of treatment depends on clinical condition and laboratory findings. Severe poisoning: Day 1: 3-5 mg sodium salt/kg (approx. 1 ampoule) IV/IM q3-4h Day 2: 3-5 mg/kg (approx. 1 ampoule) IV/IM q4-6h Day 3: 3-5 mg/kg (approx. 1 ampoule) IV/IM q6-8h Day 4: 3-5 mg/kg (approx. 1 ampoule) IV/IM q8-12h Subsequent days: depending on clinical condition 3-5 mg/kg (approx. 1 ampoule) IV/IM q8-24h. In alternative the patient can switch to PO treatment (1 capsule q6-8h).	
	Pregnancy and lactation	DMPS should be administered only in life-threatening conditions. Breastfeeding should be discontinued, if possible.	
	Notes	IV administration is reserved for severe acute intoxication or in cases where oral or gastric tube administration is not possible. IV injections should be administered slowly over 15-20 minutes since rapid intravenous administration is associated with vasodilation and transient hypotension.	

	2,3-dimercaptosuccinic acid (DMSA, Succimer)		Succicaptal® is authorised in France for a different indication.
	Adults and children	Day 1-5: 10 mg/kg PO q8h (max 1.8 g/day). Subsequent 14 days: 10 mg/kg PO q12h (max 1.8 gm/day).	
	Pregnancy and lactation	DMSA should be administered in case of unavailability of other treatments, and only in life-threatening conditions.	
	Notes	As capsules cannot be split, dose should be rounded up or down.	
	Alternative regimens[15]		
	Dimercaprol (BAL) for systemic treatment (use only in case of unavailability of other treatments)		Authorised in France.
	Adults and children	Day 1-2: 3 mg/kg IM q4h. Day 3: 3 mg/kg q6h. Day 4-10: 3 mg/kg q12h.	
	Pregnancy and lactation	Dimercaprol (BAL) should be administered to pregnant women only in life-threatening conditions. Breastfeeding should be discontinued, if possible.	
	Notes	Systemic use of dimercaprol (especially at doses of 5 mg/kg) often causes elevation of blood pressure, tachycardia, nausea, vomiting, headache, chest constriction and anxiety. Patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk of haemolysis. Dimercaprol is contraindicated in patients treated with medicinal iron.	
	Dimercaprol (BAL) eye/skin ointment 5% (use only in case of unavailability of other treatments)		Not authorised in the EU.
	Adults and children	Apply on eye 2 min after exposure. Apply on skin in a thin layer before vesication has begun for at least 5 minutes.	
	Pregnancy and lactation	Dimercaprol (BAL) should be administered to pregnant women only in life-threatening conditions. Breastfeeding should be discontinued, if possible.	
	Notes	B.A.L. eye/skin ointment may be available as galenic preparations. Patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk of haemolysis. Dimercaprol is contraindicated in patients treated with medicinal iron.	

Phosgene Oxime

Toxicity, disease characteristics, and general points on decontamination and treatment

Phosgene Oxime (CX or dichloroformoxime) is very irritating to the skin, eyes, and nose mucosa. It is not a true vesicant as it does not cause blistering. It can be better classified as an urticariant. The mechanism of action has not been determined. It has the ability to penetrate fast, cause tissue destruction, and immediate pain. Experience with exposure is limited. (1)

Individuals exposed to phosgene oxime experience skin blanching and burning, eye pain and respiratory distress. Severe irritation occurs within 30 seconds together with lesions at the site of contact, sometimes corrosive. Corneal lesions, blindness and pulmonary oedema can occur. (1, 2)

Decontamination should start as early as possible.

No specific medicinal products or antidotes are available. Treatment is only symptomatic. (1, 2)

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Nerve Agents

Nerve agents are related to organophosphate (OP) insecticides. There are three groups, the so-called G agents, V agents, and A agents. The most important G agents are tabun (GA), sarin (GB), soman (GD), and cyclosarin (GF). The V agents are represented mainly by VX. The A agents, also called "Novichok" agents, are the newest class of nerve agents which include A-230, A-232, A-234, A-242, and A-262. Very little is known about this class of nerve agent. (1, 2)

Toxicity, disease characteristics, and general points on decontamination and treatment

Nerve agents are generally 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. Data on the physicochemical properties of A agents is scarce, meaning their volatility and persistency can only be estimated. A-230, A-232, and A-234 are low volatile liquids, with A-232 being more volatile than A-230. A-242 and A-262 are thought to be solids at room temperature. 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. If not decontaminated, A agents could persist in the environment due to their low vapour pressure. Exposure to nerve agents is also possible by intake of contaminated water and food. Much of our knowledge on the mechanism of action and treatment of nerve agents stems from the treatment of OP insecticide intoxication, which is a far more common occurrence. Nerve agents do, like OP insecticides, produce toxicity by phosphorylating and hence inactivating enzymes involved in the breakdown of the acetylcholine (ACh) neurotransmitter, most notably acetylcholinesterase (AChE). 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. (1-13)

In contrast to OP insecticides which may induce clinical effects that occur theoretically in three different entities (the acute cholinergic phase, the intermediate syndrome, and delayed polyneuropathy), nerve agents are believed to produce clinical effects occurring in only a single entity – the acute cholinergic phase. In this phase, nerve agents inactivate AChE and other enzymes involved in regulating the flow of ACh by phosphorylation. This results in a build-up of ACh in peripheral and central cholinergic synapses, precipitating a cholinergic crisis and the nicotinic and muscarinic symptoms associated with it. Poisoning with nerve agents has only rarely been observed, although some clinical experience exists due to the use of these agents in the Iran-Iraq war, the Tokyo terrorist attack in 1995, in Syria in 2013, as well as more recent isolated incidents such as in Kuala Lumpur in 2017, Salisbury and Amesbury in 2018, and Omsk in 2020. It is considered that qualitatively, the toxicity of OP insecticides 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 OPs and both nerve agents and insecticides can cause acute respiratory failure. However, nerve agents may rapidly cause central apnoea whilst this has not been commonly reported in pesticide poisoning. (1-15)

The different muscarinic, nicotinic, and CNS symptoms that can occur upon exposure to nerve agents are classified by severity in the following table:

Severity	Mild	Moderate	Severe
Presentation of the patient	Able to walk	Unable to walk but spontaneous breathing	Not breathing
Clinical Symptoms	Lacrimation, salivation, miosis, rhinorrhoea, blurring of vision and eye pain, cough, mild bradycardia, sweating, nausea, vomiting, abdominal pain	*As mild* + dyspnoea, wheezing, tightness of chest, tremor, diarrhoea, urination, incontinence, coma	*As moderate* + 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. It also does not exclude the development of other symptoms. The order in which symptoms may appear will depend on the route of exposure. Respiratory symptoms would likely be seen first in cases of inhalation exposure, before potentially progressing to more systemic symptoms. Other causes might produce similar signs and symptoms e.g. small pupils due to bright sunlight, decreased level of consciousness due to opioid exposure, etc. (1-14)

As first aid, patients should be moved to an uncontaminated atmosphere, clothes should be removed, and decontamination with thorough washing of skin with soap and water or a reactive skin decontamination lotion kit (RSDL) is necessary in case of dermal exposure. In the absence of soap and water, dry removal of nerve agent from the skin using any available absorbent material is the last option. (1-6, 12, 13, 15, 16)

The treatment of organophosphate-induced acute respiratory failure, coma, and seizures is based on adapted supportive treatment in association with atropine and an oxime. A benzodiazepine may also be required in severe exposures or if seizures are observed. Ventilatory support may be needed in severe exposures, or in cases where patients do not respond to oxime treatment. 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, usually diazepam or midazolam, are used to treat convulsions. Avizafone, the water-soluble prodrug of diazepam is also used as standard by some countries, usually as part of combination autoinjector preparations containing atropine and an oxime. 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. (1-6, 12, 13, 15-17)

Atropine competitively blocks the action of acetylcholine at muscarinic receptors and should be considered the basic treatment of organophosphate poisoning that has to be immediately available. In an emergency involving many patients poisoned with nerve agents, it is likely that large quantities of atropine will be required. Atropine should be administered in all patients regardless of the need of oxygen supplementation. 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 unless administered in very large doses and must not be used as an indicator of atropine effectiveness as it may result in atropine overdose. Local atropine eye drops (0.25% to 1%) may be considered to relieve ocular symptoms, such as miosis

and/or eye or head pain, however, its use will cause blurred vision. Indeed, G agents, having a high volatility, may cause eye pain and visual disturbances in the absence of systemic features of poisoning. In the 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). In the case of atropine hypersensitivity, scopolamine could be used in its place. However, no clinical data is available to support this. (1-6, 12, 13, 15, 16, 18, 19)

Oximes reverse acetylcholinesterase inhibition by reactivating the phosphorylated acetylcholinesterase and preventing further inhibition, which reverses cholinergic excess at both muscarinic and nicotinic receptors. In Europe, two types of oximes are presently available, including various salts of pralidoxime as well as obidoxime. The two different oximes do not seem to have the same efficacy regarding the different nerve agents as well as the various insecticides. Nerve agents and organophosphorus insecticides can induce a conformational change in acetylcholinesterase called "aging", in which an alkoxy group leaves the phosphorylated acetylcholinesterase. Once this occurs, oximes are no longer able to reactivate the enzyme and are thus ineffective. Treatment with oximes is most efficacious when they are administered before aging occurs. Different agents induce aging at different speeds, meaning that oximes have varying effectiveness depending on the nerve agent used. Soman, for example, ages acetylcholinesterase quickly, between 5 to 8 minutes of administration, while VX takes around 24 hours to age acetylcholinesterase. The efficacy of oximes therefore depends on many criteria: (1) the chemical structure of the acetylcholinesterase inhibitors, (2) the delay in treatment due to the ageing of the phosphorylated enzyme, (3) the oxime dose, (4) the endpoints used to assess their efficacy, and (5) the aging half-life and the blood concentration of nerve agent. (1-6, 12, 13, 15, 16)

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.

The duration of treatment depends on the type of organophosphate. For nerve agents the treatment may be needed for up to 24 hours and could be prolonged on a case-by-case basis. Several days of treatment are generally needed for organophosphate insecticides (1-6, 12, 13, 15, 16).

Benzodiazepines can be neuroprotective in case of severe nerve agent exposure. They may not be needed in the treatment of mild to moderate OP nerve agent exposure but should be given if convulsions are observed. In severe exposures, flaccid paralysis can mask convulsions. The most common benzodiazepines used for seizure control in OP nerve agents are diazepam, midazolam, or the water-soluble prodrug of diazepam named avizafone. Dosing of these benzodiazepines should be done in line with established procedures for seizure control. (1-6, 12, 13, 15, 16)

Recommended medicinal products for treatment in case of exposure to nerve agents and their EU marketing authorisation status

<table>
<tr><th>Clinical indication</th><th colspan="2">Medicinal products</th><th>EU MA status</th></tr>
<tr><td rowspan="5">Treatment of exposure to nerve agents and other highly toxic organophosphates</td><td colspan="3">First line regimen[1-6, 12, 13, 15-17, 20-23]</td></tr>
<tr><td colspan="2">Atropine and one oxime</td><td>Atropine, pralidoxime, and obidoxime are authorised at national level in MSs.</td></tr>
<tr><td>Adults (≥18 years, > 40kg)</td><td colspan="2">Atropine: 2 mg IM/IV, doubling dose every 5-10 minutes until clear chest on auscultation, adequate heart rate (80 bpm), and adequate systolic blood pressure (80 mmHg) are achieved. Then, 1-2 mg/hour IV continuous infusion adjusted as required for up to 24 hours.

And one of the following oximes:

Pralidoxime chloride: 600 mg, 1200 mg, or 1800 mg IM/IV according to severity of exposure, then 10-20 mg/kg in 0.9% normal saline IV infusion after initial dose and continue until atropine has not been needed for 12-24h and the patient has been extubated.

Obidoxime: 250 mg bolus slow IM/IV infusion, then 750 mg/24 hours IV infusion and continue until atropine has not been needed for 12-24h and the patient has been extubated.</td></tr>
<tr><td>Children (>1 month to 18 years)</td><td colspan="2">Atropine: 0.05-0.1 mg/kg IM/IV, doubling dose every 5-10 minutes until clear chest on auscultation, adequate heart rate (80 bpm), and adequate systolic blood pressure (80 mmHg) are achieved. Then 0.025 mg/kg/hour IV continuous infusion adjusted as required for up to 24 hours.
**Do not exceed adult dose.

And one of the following oximes:

Pralidoxime chloride: 15-25 mg/kg slow IM/IV according to severity of exposure. Then 10-20 mg/kg in 0.9% normal saline IV infusion after initial dose and continue until atropine has not been needed for 12-24h and the patient has been extubated.
**Do not exceed adult dose.

Obidoxime: 4-8 mg/kg bolus slow IM/IV infusion. Then 10 mg/kg per 24 hours IV infusion and continue until atropine has not been needed for 12-24h and the patient has been extubated.
**Do not exceed adult dose.</td></tr>
<tr><td>Pregnancy and lactation</td><td colspan="2">Atropine crosses the placenta. Animal studies did not show teratogenic effects of atropine. Limited clinical data did not show adverse effects on foetus and neonates. The use of atropine in pregnant women should not be withheld if there is a clear indication. Dosage as for adults.
Atropine is present in breast milk. The decision to breastfeed during therapy should consider the risk and benefit of infants.

The safety of pralidoxime or obidoxime during pregnancy has not been established. Oximes should be administered to pregnant women if there is a clear indication for use. It is not known if oximes are excreted in breast milk.</td></tr>
</table>

	Notes	Pralidoxime chloride and obidoxime are either authorised as a single agent or as part of a combination with atropine and a benzodiazepine.

Autoinjectors

Autoinjectors are used by military personnel and in civil defense to rapidly deliver antidotes for nerve agent poisoning to themselves or to a buddy in a single injection. Autoinjectors can contain atropine, an oxime, and a benzodiazepine in a single injector which are all concurrently administered upon injection, or they may separate the benzodiazepine in a second injector which is only injected if convulsions are observed or in severe exposures. Usually up to three total autoinjectors can be administered to a patient depending on the severity of exposure, with one autoinjector being administered every 15 minutes until three have been given. Involving a separate benzodiazepine autoinjector avoids unnecessary benzodiazepine dosing in patients requiring one or more autoinjector administrations but complicates administration with a second autoinjector. (1-6, 12, 13, 15-17)

Some autoinjectors are approved for use in some countries within the EU: Ineurope®, containing atropine sulfate, avizafone, and pralidoxime metilsulfate licensed in France, Trobigard®, containing atropine sulfate and obidoxime chloride licensed in Belgium, Rafaject®, containing atropine licensed in Denmark and Germany, and IZAS-05®, which is a kit of three autoinjectors, licensed in Poland; one autoinjector contains atropine sulfate, a second autoinjector contains both pralidoxime and atropine, and a third autoinjector contains diazepam. In the US, the FDA has approved the Duodote® autoinjector, containing atropine and pralidoxime chloride for civilian use. Other autoinjectors and treatments exist in certain countries but are not approved for use outside of military personnel, and as such are not listed here. In severe emergencies, such as cases where many patients require immediate rapid treatment, relevant national competent authorities may assess the risk-benefit balance of treatment with these products against alternative treatments and decide to use these products in civilian populations. In these scenarios, patients should receive whatever treatment is available if it would improve patient outcomes. Transport of such products from military stockpiles may take too long to arrive at civilian hospitals, and as such considerations on the location of stockpiles are important for relevant national competent authorities. (1-6, 12, 17, 24-29)

While autoinjectors can provide crucial rapid antidote delivery at appropriate doses to adults, their lack of adjustable doses means their use in children is restricted to those above a specific weight, e.g. 41kg for the Duodote® autoinjector. Autoinjectors should not be the only dosing method available because of this restriction. (29)

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Cyanides

Toxicity, disease characteristics, and general points on decontamination and treatment

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. cyanogen chloride CNCl; cyanogen bromide CNBr). Cyanogens are more of an irritant than cyanides. The main exposure route is by inhalation of volatile cyanides. Exposure through food or water with cyanide salts or solutions is also possible. The bitter almond odour associated with cyanides 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. 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. (1-9)

Symptoms appear within seconds to minutes after inhalation. Mild cases may present with headache, nausea, drowsiness, mucous membrane irritation, and/or a metallic taste if the cyanide was ingested. In 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. In these severe cases, a number of immediate fatalities may be expected. 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. (1-9)

Decontamination consists of removing the patient to an uncontaminated environment and atmosphere. First aid should be aimed at stabilizing the patient's airway, breathing and circulation. Supplemental oxygen should be administered. (1-9)

Several antidotes are available. Controversial opinions on efficiency are common, due to the lack of reliable clinical studies. Treatment can be based on three strategies or combination thereof: binding of cyanide, induction of methemoglobinemia, use of sulfur donors. Direct cyanide binding can be achieved with the use of hydroxocobalamin or dicobalt edetate. Hydroxocobalamin is an experimentally well-documented antidote with a good safety profile. It is the best choice in situations such as fires with concomitant exposure to agents that reduce oxygen transport, such as carbon monoxide. However, large doses of hydroxocobalamin are required to be effective in cyanide treatment, the cost of which may make it prohibitively expensive to stockpile on a large scale. In addition, reconstitution of the required vials is time-consuming, even more so in scenarios where there are many patients requiring treatment. Dicobalt edetate is an efficient complexation antidote to cyanide. However, 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 cardiovascular adverse effects. Alternative antidotes which act by the induction of methaemoglobin and by the indirect complexation of cyanide to methaemoglobin should also be considered. The methaemoglobin forming antidotes include sodium nitrite and 4-dimethylaminophenol (4-DMAP). Both sodium nitrite and 4-DMAP may cause severe methaemoglobinaemia. In addition, nitrite antidotes produce nitric oxide which causes hypotension, a serious side effect in patients who may have hypovolaemia after trauma or haemorrhage. Administration of IV sodium nitrite is only recommended in hospital care to manage these side effects

should they occur. Victims of smoke inhalation, and with concurrent carbon monoxide toxicity, often present with carboxyhaemoglobinaemia alongside cyanide poisoning, meaning oxygen transport within the blood is at a decreased level. As methaemoglobin cannot carry oxygen and will worsen oxygen transport, nitrite antidotes and 4-DMAP are contraindicated in the treatment of cyanide poisoning in smoke-exposed patients. Thiosulphate is a sulfur donor for rhodanese, an enzyme that detoxifies cyanide by transforming it to thiocyanate, which is finally renally excreted. Since the onset of action is slow, up to 30 minutes, thiosulfate should be considered together with nitrite or other cyanide antidotes in sequential treatment but should not be administered as a mixture at the same time as hydroxocobalamin. Dimethyl trisulfide (DMTS) is a novel sulfur donor that is being investigated in animal studies. Among its advantages, it has shown to have minimal side effects, to be effective when administered intramuscularly, and to penetrate the blood-brain barrier conferring protection against CNS damage. In general, none of the above antidotes are an ideal antidote for the treatment of cyanide poisoning due to their administration requirements, cost, side effect profiles, contraindications, and varying time to onset of action. Selection of a preferred antidote depends on the specific attack scenario and the availability of antidotes for use. Supportive care includes oxygenation with 100% O_2, and if necessary, mechanical ventilation. The use of hyperbaric oxygen is still controversial. Management of seizures, arrhythmias, hypotension and metabolic acidosis should follow standard protocols. (1-11)

Recommended medicinal products for treatment in case of exposure to cyanides and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of cyanide intoxication	**First line regimens**[1-9, 12-17]		
	Hydroxocobalamin (in suspected or confirmed cyanide poisoning)		Cyanokit® is authorised at EU level.
	Adults (≥18 years)	5 g IV given over 15 minutes, then if no rapid clinical improvement 10-15 minutes after completion of the first dose, 5 g IV (for a total of 10g), given over 15 minutes to 2 hours.	
	Children (>1 month to 18 years)	70 mg/kg IV given over 15 minutes, then if no rapid clinical improvement 10-15 minutes after completion of the first dose, 70 mg/kg IV given over 15 minutes to 2 hours **Do not exceed adult dose	
	Pregnancy and lactation	Hydroxocobalamin crosses the placenta. Animal reproduction studies have shown teratogenic effects following daily exposures. There are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Dosage as for adults. Hydroxocobalamin is present in breast milk. Breast-feeding discontinuation is recommended after receiving the drug.	
	Notes	None.	
	Combination of sodium nitrite 3% solution and sodium thiosulfate 25% solution.		Sodium nitrite and sodium thiosulfate are authorised at national level in MSs, some for different indications. A combination product is

			authorised in Ireland. Sodium thiosulfate (Pedmarqsi®) is authorised at EU level for an indication that differs from cyanide poisoning.
	Adults	**Sodium nitrite 3% solution:** 300 mg IV given at 75 mg/minute, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given. **Sodium thiosulfate 25% solution (to be given immediately following sodium nitrite administration):** 12.5 g IV infusion given over 10 minutes, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given.	
	Children	**Sodium nitrite 3% solution:** 6 mg/kg IV infusion given at 2.5 ml/min, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given. **Do not exceed adult dose **Sodium thiosulfate 25% solution (to be given immediately following sodium nitrite administration):** 412.5 mg/kg IV infusion given at 2.5 mL/min, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given. **Do not exceed adult dose	
	Pregnancy and lactation	Sodium nitrite should be avoided in pregnant and lactating women. Animal reproduction studies with sodium thiosulfate have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Dosage as for adults. Breastfeeding is not recommended.	
	Notes	Sodium nitrite dosing may need adjusting in patients unable to tolerate significant methemoglobinemia because of comorbidities (anaemia, hearth disease, lung disease). Caution when administering sodium nitrite in out-of-hospital settings due to challenges in managing occurrences of excess methaemoglobinaemia and hypotension.	
	Combination of 4-dimethylaminophenol (4-DMAP) and sodium thiosulfate 25% solution.		4-DMAP is authorised in Germany. Sodium thiosulfate is authorised at national level in MSs.
	Adults	**4-dimethylaminophenol (4-DMAP)** 250 mg or 3-4 mg/kg IV over one minute infusion. **Sodium thiosulfate 25% solution (to be given immediately following 4-DMAP administration):** 12.5 g IV infusion given over 10 minutes, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given.	

	Children	**4-Dimethylaminophenol (4-DMAP) 5% solution:** 3.25 mg/kg IV. **Do not exceed adult dose. **Sodium Thiosulfate 25% solution (to be given immediately following 4-DMAP administration):** 412.5 mg/kg IV infusion given at 2.5 mL/min, then if physical findings persist after 30-60 minutes, an additional dose of half of the initial dose is given. **Do not exceed adult dose	
	Pregnancy and lactation	There is no published data available on the risks of use of 4-DMAP in pregnancy. In severe cyanide poisoning where 4-DMAP is required, treatment should not be withheld at any stage of the pregnancy. Dosage as for adults The decision to breastfeed during therapy should consider the risk and benefit of infants. Animal reproduction studies with sodium thiosulfate have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Dosage as for adults. Breastfeeding is not recommended.	
	Notes	None.	
	Dicobalt edetate 1.5% solution (only in confirmed cyanide poisoning)		Kelocyanor® is authorised in France.
	Adults	300 mg IV given over 1 minute and immediately followed by 50 mL of glucose 50% intravenous infusion. Then, if no clinical improvement after 5 minutes, half of the initial dose may be repeated followed by 50 mL of glucose 50% intravenous infusion.	
	Children	There is no clinical experience with the use of dicobalt edetate in children. Paediatric dose has not been established. A possible initial dose of 7.5 mg/kg has been suggested.	
	Pregnancy and lactation	There is no published data available on the risks of use of dicobalt edetate in pregnancy and during breastfeeding. In severe cyanide poisoning where dicobalt edetate is required, treatment should not be withheld at any stage of the pregnancy. Dosage as for adults.	
	Notes	None.	

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Lung-damaging 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% to 90% of fatalities from gas attacks, and chlorine was the first chemical agent used as a weapon.

Toxicity, disease characteristics, and general points on decontamination and treatment

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: (1, 2)

Substance	**Water solubility**	**Odour threshold (ppm)**	**IDLH (ppm)**
Ammonia	High	5	300
Formaldehyde	High	0.1-1	20
Hydrogen chloride	High	1-5	50
Chlorine	Moderate	0.3	10
Hydrogen sulphide	Moderate	0.025*	100
Methyl Isocyanate	Moderate	-	3
Nitrogen Dioxide	Low	0.12	20
Ozone	Low	0.05	5
PFIB (Perfluoroisobutylene)	n.a.	n.a.	n.a. (LC50=17 ppm/10min)
Phosgene	Low	0.5	2
Sulphur Dioxide	Moderate	1	100
Zinc chloride	Particles	-	50 mg/m^3

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, a combination of these factors, 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, SO_2, 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. Phosgene can lead to a cascade of inflammatory cytokines and mediators that can cause vascular permeability, alveolar leakage, and pulmonary oedema. Phosgene dissolves slowly in water, eventually hydrolysing to form carbon dioxide and hydrochloric acid. Chlorine, phenol and isocyanates have an intermediate position. However, at high concentrations, irritants induce diffuse injury to the respiratory system due to the formation of free radicals and other molecules that can eventually lead to pulmonary oedema. (1, 3, 4)

Gases with high water solubility induce immediate symptoms from the upper airways (cough, hoarseness, inspiratory stridor, wheezing), 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 or absent. In the most severe cases acute lung injury and acute respiratory distress syndrome (ALI/ARDS) can develop after a latent period of several hours with symptom of tightness or shortness of breath, typically in the absence of coughing or rhonchi. The effects may be delayed for up to 24 to 48 hours but can occur a few hours after intensive exposure. Long-term effects may include reactive airway dysfunction syndrome (RADS), fibrosis, and bronchiectasis. (1, 3, 4)

The main option for decontamination is to end exposure. Moreover, exposed individuals should always be undressed. Washing with water should be performed if skin and eye symptoms occur.

No specific antidote exists for any of the pulmonary irritants. Treatment is basically supportive according to the clinical manifestations. It includes support of vital functions with focus on patent airways and supplemental oxygen. 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 (SpO2 in the range of 92% to 98%). Airway patency and signs of respiratory insufficiency should be re-assessed frequently. Non-invasive or invasive ventilation may be required, 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. The use of inhaled corticosteroids has been proven successful in animal models and should be considered if the patient has severe initial irritating symptoms and signs (intense cough, signs of bronchospasm or lung obstruction, respiratory failure) and to prevent lung oedema. The use of intravenous high dose corticosteroids is still under debate. Inhaled bicarbonate has been safely used anecdotally, but its clinical efficacy remains uncertain, especially in the context of high exposure after deliberate use. Nebulised n-acetylcysteine showed benefit in animal models, but no clinical data are available. The efficacy of grow factors (keratinocyte growth factor, epithelial growth factor and basic fibroblast growth factor) in preventing pulmonary oedema when administered early after exposure is currently under investigation. (1, 3-11)

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Pharmaceutically-Based Agents (PBAs)

Pharmaceutically-based agents (PBAs) can be defined as a broad range of substances that are mainly intended to produce an incapacitating effect, that is an effect that impedes the ability of an individual to make decisions, undertake actions, or to perform to an acceptable or desirable standard. The use of these agents, or parent compounds, can be considered in medicine at appropriate doses. However, exposure to high doses of these agents can 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. (1-4)

Possible PBAs are:

- Fentanyls and other potent opioids.
- BZ (3-quinuclidinyl benzilate; Agent 15 is an almost identical compound)
- Indoleamines: D-Lysergic acid diethylamide (LSD), n,n-dimethyltryptamine (DMT), psilocybin
- Phenylalkylamines: mescaline, 2C derivatives

In addition, NBOMes (N-methoxybenzyl) are a group psychedelic drugs also referred to as new psychoactive substances (NPS). They can mimic or produce similar effects to common psychedelics, such as LSD or mescaline. However, there is no documented use of these agents in warfare or terrorist attacks. This chapter will limit its focus to BZ, LSD, and fentanyls and other potent opioids. (1-5)

3-Quinuclidinyl Benzilate (BZ)

Toxicity, disease characteristics, and general points on decontamination and treatment

3-quinuclidinyl benzilate (BZ) 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. 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 to 10 hours. After skin exposure (often dissolved in propylene glycol), absorption is 5% to 10% and symptoms may be delayed up to 24 to 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. (1)

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. (1)

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. Physostigmine IV should be considered for the treatment of patient with both peripheral and moderate central (agitation, delirium, or seizures) anticholinergic

toxicity and without contraindications to the drug (widened QRS on electrocardiogram). However, physostigmine acts mainly at central level and its efficacy is limited in comatose, stuporous, and ataxic patients earlier than 4 hours after exposure. The dose is 0.5 to 2 mg (0.02 mg/Kg, up to a maximum of 0.5 mg per dose in paediatric patients) by slow IV infusion that can be repeated in case on unsatisfactory clinical response. Thereafter, patients should be maintained on oral doses of 2 to 5 mg every 1 to 2 hours as necessary. Frequency of treatment and dosage can be reduced 2 to 4 days after exposure. (1, 6)

D-Lysergic Acid Diethylamide (LSD)

Toxicity, disease characteristics, and general points on decontamination and treatment

D-lysergic acid diethylamide (LSD) is a synthetic derivative of an ergot alkaloid and belongs to the classic hallucinogens. It can be disseminated with food and water or as an inhalable aerosol. LSD is an agonist of the 5-hydroxytryptamine (5-HT2) receptor that binds serotonin and mediates excitatory transmission. Therefore, LSD effects resulting in release of serotonin are excitatory. When administered by the aerosol route, the onset of symptoms is within minutes. After ingestion, symptoms start after 30 to 60 minutes. Peak effects are reached within 2 to 5 hours. The duration of action is 8 to 12 hours. (1)

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 and are dose proportional. 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. (1, 6)

Gastrointestinal decontamination with activated charcoal may be considered for asymptomatic patients with recent ingestions, but it is not helpful once clinical symptoms are present. A quiet surrounding with minimal stimuli may be of benefit. (1, 6)

Treatment is symptomatic and supportive. Benzodiazepines may be used to control agitation and hyperthermia. In cases of severe hyperthermia (core temperature >41º C) neuromuscular blockade may be necessary. (1, 6)

Fentanyls and Other Potent Opioids

All fentanyls are synthetic opioids 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. Fentanyls and other opioids are also used as recreational drugs. Various fentanyl analogues, not currently used in medicine, have also been synthesized and are approximately 10 to 50 times more potent than fentanyls. Carfentanil, a potent opioid used in veterinary medicine, and remifentanil, an ultra-short acting agent typically used for quick surgical procedures, are suspected to have been used during the siege at the Dubrovka Theatre, Moscow in 2002. Other opioids from the thebaine group (e.g. etorphine [M99], acetorphine), used in veterinary medicine, are also very potent opioid agents and could be potentially used in a chemical attack. (1-3, 6, 7)

Toxicity, disease characteristics, and general points on decontamination and treatment

Fentanyls easily pass biological membranes and rapidly reach the brain. In normal medical practice, fentanyls are usually injected or administered as a transdermal patch. Like morphine, all fentanyls are potent μ-opioid receptor agonists. Their toxicity is principally caused by a dose-related respiratory depression. (1-3)

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. (1-3)

Ventilation and/or evacuation are the first measures to put in place to prevent further exposure of victims. First aid measures include securing the airway, administer oxygen and initiate assisted or controlled ventilation.

The use of intranasal naloxone can be considered as first aid treatment. Naloxone and nalmefene are the antidotes for opioid intoxication indicated in case of respiratory failure. Repeated administration of those drugs may be necessary due to a longer residence time of fentanyls in blood. Significantly higher doses (more than 10 times higher) of these antidotes compared to the standard medication may be required in case intoxication with high potency opioids. Neuromuscular blocking 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. (1, 6-10)

Recommended medicinal products for treatment in case of exposure to fentanyls and other potent opioids and their EU marketing authorisation status

Clinical indication	**Medicinal products**		**EU MA status**
Treatment of opioid intoxication with respiratory failure	**First line regimens**[1, 6-12]		
	Naloxone		Authorised at national level in MSs.
	Adults	IV/IM/SC: 0.2-0.4 mg per dose, depending on clinical severity. Doses can be repeated*. IN: 1.8 mg administered into one nostril (one nasal spray). A second dose can be administered 2-3 minutes after if no clinical response.	
	Children (≥14 years)	IV/IM/SC: Same as adult regimen. IN: Same as adult regimen.	
	Children (≥12 years)	IV/IM/SC: Same as adult regimen. IN: Safety and efficacy have not been established.	
	Children (<12 years)	IV/IM/SC: 0.01-0.1 mg/kg (preferably IV) according to clinical presentation. Doses can be repeated*. IN: Safety and efficacy have not been established.	
	Pregnancy and lactation	Insufficient clinical data on exposed pregnancies are available. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Potential benefits may warrant	

		use of the drug in pregnant women despite potential risks. Dosage as for adults. It is not known whether naloxone hydrochloride passes into breast milk, and it has not been established whether infants who are breast-fed are affected by naloxone hydrochloride. Therefore, breast-feeding should be avoided for 24 hours after treatment with IV/IM/SC naloxone where possible. Caution should be exercised when IN naloxone is administered to a breast-feeding mother but there is no need to discontinue breast-feeding. Breast-fed babies from mothers who have been treated with IN naloxone should be monitored to check for sedation or irritability.
	Notes	*Escalating IV/IM/SC doses may be needed every 2-3 minutes. Large IV/IM/SC doses (more than 4mg) may be required in patients exposed to highly potent opioids and those who are severely poisoned. After reversal of opioid intoxication, re-administration of doses may be needed at longer intervals (20-60 minutes). Naloxone pre-filled autoinjectors (0.4-10 mg) for IM or SC use are available but are not authorised in the EU.
	Alternative regimen[1, 6-12]	
	Nalmefene	Not authorised in the EU.
	Adults	2.7 mg IN administered into one nostril (one nasal spray). If patient does not clinically respond or relapses into respiratory depression, additional doses may be administered every 2-5 minutes.
	Children (≥12 years)	Same as adult regimen.
	Children (<12 years)	Safety and efficacy have not been established.
	Pregnancy and lactation	Insufficient clinical data on exposed pregnancies are available. Animal studies have not shown reproductive toxicity. The potential risk for humans is unknown. Potential benefits may warrant use of the drug in pregnant women despite potential risks, and life-sustaining therapy for opioid overdose should not be withheld. Dosage as for adults. It is not known whether nalmefene passes into breast milk, and it has not been established whether infants who are breast-fed are affected by nalmefene. Caution should be exercised when nalmefene is administered to breastfeeding women.
	Notes	None.

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Crowd-Control Agents

Crowd-control agents, also referred to as "tear gas" or lachrymatory chemical agents, are used to manage potentially dangerous gatherings of people and other law-enforcement situations. In the case of deliberate use in a context of warfare or terrorism, the infliction of permanent injury or death may not be the intended outcome of use. The agents include 1-chloroacetophenone (CN), o-chlorobenzylidene malononitrile (CS), bromobenzylcyanide (CA), and dibenz(b,f)-1,4-oxazepine (CR), and the "skunk" malodorant. Oleoresin capsicum (OC), an oily extract of the capsaicin found in pepper plants, is also used. (1-3)

Toxicity, disease characteristics, and general points on decontamination and treatment

Most agents belonging to this group are relatively benign compared to many other chemical agents. If properly used, they can cause extreme discomfort and temporarily disable their victims, but they are not meant to cause death or to produce serious injury. However, their misuse can lead to more serious consequences and toxicity. These agents are mostly solid chemicals and not true gases; they are administered as a fine dust or aerosol spray. (1-3)

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 hours post-exposure. Extremely rare cases of pulmonary oedema have been reported up to 24 hours post-exposure. (1-3)

Since crowd-control agents are denser than environmental air, evacuation of victims to higher ground can prevent further exposure. Remove all contaminated clothing and put in sealed polyethylene bags. If clothing is washed, use cold water, as hot water will cause residual CS gas to vaporize. Depending on exposure, the eyes may not require external irrigation; self-irrigation may be adequate. If necessary, remove any contact lenses if present with clean fingers and irrigate with lukewarm water for up to 15 minutes. If irritation, pain, swelling lacrimation or photophobia persists after 15 minutes, refer to ophthalmologic examination and treatment. Diphoterine is listed as an effective ophthalmic decontaminant by the manufacturers in exposure to CN, CS, CR, and OC spray or gas. Skin should be treated as for chemical burns. Wash exposed areas with soap and water. Contaminated hair may lead to re-exposure of the patient on showering or bathing. (1-4)

Treatment is symptomatic. There are no specific antidotes recommended. Clinically relevant bronchospasm may occur in patients with pre-existing respiratory conditions such as asthma or COPD, and treatment with short-term inhaled β2-agonists, steroids, ipratropium, and/or aminophylline as appropriate in accordance with established procedures can be considered. Oxygen therapy may also be needed in these cases. (1, 5-8)

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Abbreviations

SmPC - Summary of Product Characteristics

ETF - Emergency Task Force

RSDL - Reactive Skin Decontamination Lotion

IV - Intravenous

CNS - Central Nervous System

GM-CSF - Granulocyte Monocyte-Colony Stimulating Factor

ATP - Adenosine Triphosphate

GSH – Glutathione

MA – Marketing authorisation

DMPS - 2,3-dimercapto-1-propane sulphonic acid/Unithiol

IM - Intramuscular

DMSA - 2,3-dimercaptosuccinic acid, succimer

BAL - British Anti-Lewisite/2,3-dimercapto-1-propanol

OP - Organophosphate

ACh - Acetylcholine

AChE – Acetylcholinesterase

MS – Member state

FDA - Food and Drug Administration

4-DMAP - 4-dimethylaminophenol

DMTS - Dimethyl trisulfide

IDLH - Immediately Dangerous to Life and Health

NIOSH - National Institute for Occupational Safety & Health

PFIB - Perfluoroisobutylene

ARDS - Acute Respiratory Distress Syndrome

ALI – Acute Lung Injury

RADS - Reactive Airway Dysfunction Syndrome

PBAs - Pharmaceutically-Based Agents

5-HT2 - 5-hydroxytryptamine

SC – Subcutaneously

IN - Intranasally

COPD - Chronic obstructive pulmonary disorder