OPCW

Scientific Advisory Board

Twenty-First Session
23 – 27 June 2014

SAB-21/WP.7
29 April 2014
ENGLISH only

RESPONSE TO THE DIRECTOR-GENERAL'S REQUEST TO THE SCIENTIFIC ADVISORY BOARD TO PROVIDE FURTHER ADVICE ON ASSISTANCE AND PROTECTION

EXECUTIVE SUMMARY

1. Response to the Director-General Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection.

2. This report contains recommendations addressed to the Technical Secretariat of the OPCW. It is made available to the public for informational purposes, but was not meant to be used by the public. All decisions regarding patient care must be made with a healthcare provider and consider the unique characteristics of each patient. The information contained in this publication is accurate to the best of the OPCW's knowledge; however, neither the OPCW nor the independent experts of the Scientific Advisory Board assume liability under any circumstances for the correctness or comprehensiveness of such information or for the consequences of its use.

Annex:

Response to the Director-General Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection.

CS-2014-8506(E) distributed 30/04/2014

Annex

RESPONSE TO THE DIRECTOR-GENERAL REQUEST TO THE SCIENTIFIC ADVISORY BOARD TO PROVIDE FURTHER ADVICE ON ASSISTANCE AND PROTECTION

1. EXECUTIVE SUMMARY

1.1 The Scientific Advisory Board (SAB) has provided further advice on assistance and protection, with regards to the status of currently available medical countermeasures and treatments, according to the Director-General's two specific requests (Appendix, page 22).

1.2 In reply to the first request, this report recommends to the Technical Secretariat pre-treatments, emergency care, and long-term treatments that are currently available for blister and nerve agents (pages 2-21).

1.3 In reply to the second request, to inform the Technical Secretariat of the most relevant information sources that can be monitored to keep abreast of new developments in these areas, this report included over 130 scientific references (pages 23-36), which can be used as a platform for watching future medical countermeasure developments.

1.4 No further action in response to the two specific requests of the Director-General is recommended; literature surveillance of new developments in chemical warfare agent medical countermeasures and treatments will be monitored by the SAB as routine activity, and any significant advances in this field flagged by the SAB to the Technical Secretariat.

2. BLISTER AGENTS (VESICANTS)

Blister agents can be fatal following exposure: they reduce soldiers' fighting capability through injury and force them to wear protective equipment. Their use, especially in thickened form, contaminates soil, vehicles and equipment, and presents a persistent hazard. Sulfur mustard (HD), nitrogen mustard (HN), arsenical vesicants (Lewisite, L), and halogenated oximes, are the most common. Their effects on the body include local and systemic damage (skin, eyes, lungs, mucous membranes, heart, blood, immune and endocrine system, gastrointestinal and respiratory tract), psychological disorders, and vomiting and diarrhea after inhalation.

3. TREATMENT OF MUSTARD LESIONS

3.1 Therapeutic goals are to treat symptoms, prevent infection, and aid recovery. Specific antidotes are unavailable and new strategies to optimise and expedite healing are required. Signs and symptoms appear after a delay and the time between exposure and their development can be used as a triage criterion. The earlier signs and symptoms present, the poorer the prognosis. Signs and symptoms on skin 1 h after exposure are frequently associated with lethality. In the symptom-free period, mustard may persist on clothing, posing a hazard to the patient, medical staff, and first responders.

Eye lesions

3.2 Mustard poisoning should be treated with systemic analgesics (narcotics) and not local analgesics since the latter may increase corneal damage. Infection should be prevented with antibacterial preparations and mydriatic drugs used for corneal lesions to prevent adhesion of cornea and iris. The eyes should be irrigated with sterile isotonic saline and sterile petroleum jelly (Vaseline®) smeared on the eyelids to prevent sticking. Opaque goggles can be applied, but the eyes should not be covered with bandages. The cornea can be examined for lesions once the eyelids can be separated without much pain, using a fluorescein solution and lavage, a green spot indicating a lesion. Eyelid oedema, blepharospasm, and photophobia occur in severe injuries. To assure patients that they are not blind, the eyelids should be forced open gently. Permanent blindness is rare and temporary blindness common. Treatment involves the use of artificial tears, mydriatic and antiglaucoma drops, ocular washings, topical antibiotics and corticosteroids.

Skin lesions

3.3 Contamination should be removed before treatment. Red and itching skin should be treated with water, cooling preparations (calamine lotion) and corticosteroid solutions, but not with ointments and creams, as these can aid infection. There is no agreement on whether to de-roof blisters or how best to treat them when open/covered or dry/wet. When broken, the ragged roof of a blister should be removed to reduce the chance of infection.

3.4 Therapeutic procedures for acute injury follow those for heat burns: (a) application of topical antibacterial agents (silver sulfadiazine), (b) bullae smaller than 2 cm should be left intact, while those > 2 cm should be opened and debrided, (c) blister fluid, blood and urine samples should be collected and examined forensically, (d) if infection is suspected, the affected area should be cultured, disinfected with 0.2-0.3% Chloramine-T solution, and targeted antibiotics or antimicotics given, (e) wet to dry dressings should be avoided, (f) diuretics should be prescribed (to reverse hypervolemia), topical steroids applied early, a high calorie and protein diet followed, and analgesics and antihistamines used. Frequent changes of primary dressing should be avoided unless infection is suspected.

Respiratory tract lesions

3.5 No treatment is usually required if the injury is light (sore throat). Codeine should be given for cough relief, while laryngitis and tracheitis is best treated with steam or sterile cool mist inhalations. Repetitive bronchoscopic lavage may be indicated. Pseudomembranes can form and detach and cause cardiac arrest. Hospitalisation is advised for more severe injuries. Antibiotics should be used according to antibiograms.

4. Systemic effects

4.1 Replacing loss of fluids and electrolytes and maintaining metabolic status is vital. Infection should be treated immediately. Sodium thiosulfate can prevent or reduce systemic damage when given intravenously during the first 20 min of exposure.

Burns from high doses of fluid and vapour

4.2 Nausea, vomiting and collapse usually appear before complete development of erythema. The time between exposure to high doses of vapour and appearance of signs and symptoms may indicate the severity of burns. Systemic reaction correlates with severity of burns.

Burns from low doses of vapour

4.3 The symptoms and signs are itching, irritation and erythema. Mild burns can result in more severe burns later and must be treated immediately.

Sensitisation after re-exposure

4.4 Sensitisation, manifest as "re-exposure" burns 1-3 weeks after exposure, leads to a rapid onset of symptoms such as erythema, possible oedema, and intense itching and burning sensations within 1 h of re-exposure. These symptoms subside after a few days. Morbilliform rash is a common manifestation in sensitised patients along with eczematoid dermatitis which surrounds old lesions. Severe blistering in the torso region and more localised blistering in other areas often results in casualties. High doses of vapour, which cause oedema and skin blistering, and systemic reactions (nausea, vomiting, prostration) to masked personnel (especially in tropical climates), lead to casualty-causing burns—whereas low doses of vapour, that cause only skin reactions, are usually not fatal. It is important to ascertain the lesion's stage of development in order to classify an individual as a casualty.

Distribution of blisters

4.5 Trunk and neck: Prompt evacuation is necessary. Trunk blistering is more likely to occur on the back than the front due to better covering of the latter by protective equipment. Progress of illness can be monitored by systemic symptoms (fever, nausea, vomiting). Bacterial infection complicates the clinical course. Localised trunk blistering commonly affects the natal cleft, extending forward to the scrotum and penis. Depending on severity, such blistering may or may not result in casualties. Walking is difficult as it irritates lesions and defecation is painful. Blisters in the gluteal region do not produce casualties. Protective dressing of the trunk is desirable to prevent rubbing on clothing.

4.6 Arms: Blistering of arms, with adequate treatment, leaves the patient without disability. More extensive vesication, reaching axillae, elbows, volar or dorsal aspects, affects adversely the movement of limbs at these joints, and oedema of the surrounding tissue further immobilises the extremities. Severe burns on forearms and elbows are common. If blistering is widespread, it may result in partial disability, so evacuation is advised.

4.7 Hands: Burns are common and cause more disability than assumed based on their size. Although the palms resist blistering, injury there is painful and slow to heal. If the burn is localised and singular, or the patient has multiple small blisters and limited erythema, little or no disability may result with proper treatment. However, burns on the back of the hands lead to painful oedema. If blistering started 12-24 hpost-

exposure, immediate evacuation of the casualty is necessary, as severe vesication may develop. Those affected are viewed as casualties. If exposure starts 24 h before treatment, even minor looking blisters may incapacitate the next day. Evacuation is required in cases of vapour exposure of the hands and wrists, where diffuse erythema, oedema and vesication may ensue.

4.8 Lower extremities: most often affected are the knees, with burns, oedema and lesions and the ankles leading to incapacitation due interference with movement. Walking or running worsens the oedema and irritates the lesions. Vesication can spread to the thighs and/or feet, and casualties with such injuries should be evacuated. However, burns of the thighs are less restricting that those of the legs. Less severe blisters on the lower extremities incapacitate and such casualties are to be regarded as partially disabled. The afflicted can return to their duties after being given the necessary treatment, and physical and psychological evaluation.

4.9 Another case where the injured should be evacuated is when blisters develop near the ankles, as these are unprotected, and pain is severe because of circulatory impairment and tense oedema of the leg. Vapour burns of the legs, if mild, are associated with irritation, itching, and casualties do not require evacuation. If blisters are in the popliteal region, and caused by the higher doses of vesicant, erythema with scattered blisters can affect the entire leg; these lesions are often associated with systemic effects. In the case of feet burns, movement is impaired and injuries are manifested as local reactions like the ones on the backs of the hands. However, shoes provide decent protection to the soles.

4.10 Genitals: These are sensitive and injury causes casualties despite protective clothing - burns are likely to be caused by vapour. Symptoms include pain, itching and anxiety. If burns are mild, without blistering or oedema, the patient may be returned to duty after receiving treatment. Severely injured patients should be evacuated. Penile and scrotal oedema is characteristic. Sometimes vesication is superimposed on the oedema. Secondary infection at the prepuce can lead to ulcers. In severe cases, urine retention can occur. As for the scrotum, mild burns are likely to be unnoticed due to normal pigmentation and elasticity of the skin; onset of symptoms can be delayed for 4-10 days. More serious cases present an enlarged scrotum, with degradation of rugae and pinpoint vesication.

Systemic effects

4.11 Systemic effects include lesions of the respiratory tract and severe disabling skin lesions accompanied by nausea, vomiting, anorexia, depression and fever (more likely to occur in hot environments). Symptoms appear 4-12 h post-exposure and prior to visible skin damage, and tend to subside after 24-26 h (anorexia and nausea may last longer). Days after exposure, increased body temperature and depression may persist. Individuals in this condition are regarded as casualties and evacuated as soon as possible.

Secondary bacterial infection

4.12 Secondary infections, only apparent days after exposure, often affect the skin lesions, respiratory tract and eyes. In cases of infection of small skin lesions, evacuation is

not necessary, but if multiple lesions are infected and systemic infection has set in, or if the infection is disabling (affecting the hands, feet, genitalia or limb joints), evacuation is advised. Respiratory symptoms are almost always associated with severe eye effects—and as respiratory lesions may not develop for days, the patient should be evacuated upon presentation. In cases of mild conjunctivitis, infection is unlikely and the individual should not be evacuated. However, burns may be associated with pharyngitis, laryngitis and tracheitis, and severe respiratory infection.

Course and prognosis

4.13 Most patients with eye lesions recover 14 days after exposure. Cases with superficial skin lesions recover 2-3 weeks after exposure, whereas those with more deep and severe skin lesions recover in up to 60-90 days. It is difficult to ascertain the time course for the treatment of patients with lesions of the upper respiratory tract. If the lesions solely affect the upper respiratory tract, lung function tests reveal normal function in most cases; an abnormal pattern in patients with parenchymal damage occurs.

Long term effects of mustard poisoning

4.14 These are divided into three groups: (a) prolonged psychological manifestations, including chronic depression, anxiety and loss of libido, (b) local effects, including visual impairment, skin scars, chronic bronchitis, bronchial stenosis, and increased sensitivity to mustard, and (c) an increased lung cancer incidence. Late complications arise from damage to the respiratory system, skin, eyes, CNS, blood, and immune, gastrointestinal and endocrine systems. Although mortality induced by sulfur mustard is low, the variety and severity of toxic effects can be dramatic. Psychological complications can include anxiety, depression, personality disorders, psychosis, post-traumatic stress disorder, disorders of consciousness, attention deficit, emotional behaviour, and sleep disorders. Hematologic complications include leucopenia, decreased T cells, anaemia, thrombocytopenia, and leukaemia. Other complications include liver and kidney failure and bone marrow depression.

5. TREATMENT OF LEWISITE LESIONS

DMPS sodium salt (Unithiol™) $HSCH_2CH(SH)CH_2SO_3Na$

Day 1: 1 ampoule	DMPS-Heyl i.v.	every 3-4 h (1.5-2.0 g DMPS (Na)/day)
Day 2: 1 ampoule	DMPS-Heyl i.v.	every 4-6 h (1.0-1.5 g DMPS (Na)/day)
Day 3: 1 ampoule	DMPS-Heyl i.v./i.m.	every 6-8 h (0.75-1.0 g DMPS (Na)/day)
Day 4: 1 ampoule	DMPS-Heyl i.v./i.m.	every 8-12 h (0.5-0.75 g DMPS (Na)/day)

5.1 On following days: depending on the clinical situation one to three times 1 ampoule DMPS-Heyl i.v./i.m. per day (0.25-0.75 mg DMPS Na/day), or the oral form (Dimaval® capsules).

5.2 Lewisite is believed to cause systemic toxicity by binding to thiol groups of important proteins in the body. The primary mode of antidoting such action is to administer thiol

drugs which scavenge intact Lewisite and/or reactivate the affected proteins. Several thiol drugs can be used; the current recommended therapy is Dimercaprol.

5.3 Dimercaprol (2,3-dimercaptopropanol $HSCH_2CH(SH)CH_2OH$, British Anti-Lewisite, BAL), is a colourless water-soluble liquid. Its therapeutic effect is due to it: (a) combining with arsenic to form a water-soluble complex that is excreted, and (b) providing the organism with SH groups that displace the arsenic bound to enzymes (e.g. pyruvate dehydrogenase). The enzymes are reactivated and resume normal activity. However, the toxicity of dimercaprol itself, including local irritation, must be considered.

5.4 Eyes: The efficacy of dimercaprol eye ointment in diminishing Lewisite effects is optimal if applied 2 min after exposure. Systemic morphine for pain control may be required. Atropine sulphate ointment or eye drops to maintain mydriasis in cases with corneal erosions, iritis, cyclitis marked photophobia, or miosis, is recommended. Antibiotics to combat infection and sterile petroleum jelly (Vaseline®) to prevent eyelid sticking are advantageous. Isotonic solutions should be used for eye irrigation, but occlusive dressings or pressure on the globe must be avoided.

5.5 Skin: Dimercaprol ointment may be applied to skin exposed to Lewisite before vesication has begun. It is spread on the skin in a thin film and left for at least 5 min (occasionally it causes stinging, itching or urticarial weals, lasting ~1 h). Mild dermatitis may occur if the ointment is applied frequently to the same area. Dimercaprol is incompatible with silver sulfadiazine and the two should not be used together. Treatment of blisters, erythema, and denuded skin is identical to that for mustard lesions. Pain develops earlier than in sulfur mustard poisoning. In cases of severe third degree burns over a large area, intravenous resuscitation, to correct potential hypovolaemic shock, must be given. Morphine and splinting of affected parts may help relieve pain. Hospitalisation is indicated when the affected area is > 20% of the body surface, or even less when the depth of skin involvement is significant.

5.6 Systemic effects: Burns severe enough to cause shock and systemic poisoning can be life-threatening and if the patient survives the acute effects, the prognosis is uncertain for weeks.

Indications for systemic treatment

5.7 These include: shortness of breath, cough, dyspnoea, frothy sputum with traces of blood, a skin burn the size of the palm of the hand or larger (caused by an arsenical blister agent not decontaminated within the first 15 min, or skin contamination by a liquid arsenical over > 5% of the body surface, with skin damage (blanching)).

Types of treatment

5.8 Two types may be used: (a) Local neutralisation by application of dimercaprol ointment. Affected skin should be covered with a layer of ointment, but only after other protective ointment used before the treatment is removed, and (b) intramuscular injection of 10% BAL in oil. The maximum dosage of BAL is 3 mg/kg (200 mg for an average person) intramuscularly repeated every 4 h for 2 days, every 6 h on the

third day, and every 12 h for up to 10 days. The injection must be deep and intramuscular.

5.9 Injected Dimercaprol often produces alarming reactions including: blood pressure elevation, tachycardia, dose-related nausea and vomiting, headache, burning sensation of lips, feeling of constriction of the chest, conjunctivitis, lachrymation, rhinorrhea, sweating, anxiety and unrest. About 50% of patients experience adverse reactions if 5 mg/kg doses are given. Dimercaprol injection should not be used in iron, cadmium, selenium poisoning, or when hepatic function is impaired.

Therapy

5.10 Dimercaprol is the current therapy for Lewisite poisoning. Newer therapies include:

(a) DMSA - *meso*-2,3-dimercaptosuccinic acid $HO_2CCH(SH)CH(SH)CO_2H$

(b) DMPS - 2,3-dimercapto-1-propanesulfonic acid $HSCH_2CH(SH)CH_2SO_3H$

(c) DMPS - sodium salt $HSCH_2CH(SH)CH_2SO_3Na$ (Unithiol™)

(d) DMPA - the phthalamidic acid *o*-$(HO_2C)C_6H_4CONHCH_2CH(SH)CH_2SH$

5.11 Favourable pharmacokinetic/pharmacodynamic properties include:

(a) They are water soluble, active when given orally and relatively nontoxic.

(b) They are more effective in terms of therapeutic index.

(c) BAL binds arsenic in most tissues but less effectively than DMSA, DMPS or DMPA.

(d) Unlike DMPA or DMPS, BAL given to rabbits poisoned by sodium arsenite increased brain arsenic levels.

(e) DMPS is the most potent and BAL the least potent in reversing or preventing pyruvate dehydrogenase inhibition by sodium arsenite.

(f) A body of evidence indicates that the new chelating agents should be considered as alternatives to dimercaprol in the treatment of systemic Lewisite poisoning.

(e) Course and prognosis

(f) Long term effects of Lewisite exposure are unknown.

6. HALOGENATED OXIMES

6.1 These include diiodoformoxime, dibromoformoxime, monochloroformoxime and dichloro-formoxime. The latter is the most irritant and is phosgene oxime (codename CX). Ordinary clothing affords little or no protection against it; a respirator, NBC suit, gloves and over-boots are required. Chlorination is an ineffective decontaminant

- inactivation by alkalis is recommended. Adsorbent powders, e.g. fullers' earth, are used for physical decontamination. Eyes should be flushed immediately with water or isotonic aqueous sodium bicarbonate.

Clinical effects

6.2 Phosgene oxime causes corneal lesions and blindness; respiratory damage (with pulmonary oedema) and skin irritation (the affected area turns white within 1 min, fringed by erythema, oedema occurs within 1 h, and the lesion yellows and blisters within 24 h). After several days the area shows desquamation and necrosis, crusting and purulent secretion.

Treatment

6.3 Treat as any other ulcerated necrotic skin lesion (e.g. thermal burn) with supportive measures. Consider appropriate treatment of pulmonary oedema. Recovery takes 1 to 3 months.

7. NERVE AGENTS

7.1 Organophosphorus (OP) nerve agents (NAs) are stable organophosphorus compounds. They are easily dispersed and highly toxic when inhaled or absorbed through skin. They are classified into G and V agents, but some are hybrid in structure, and are called GV agents.

G agents

GA	Tabun	*O-ethyl N,N-dimethylphosphoramidocyanidate*
GB	Sarin	*O-isopropyl methylphosphonofluoridate*
GD	Soman	*O-pinacolyl methylphosphonofluoridate*
GF	Cyclosarin	*O-cyclohexyl methylphosphonofluoridate*

V agents

VE	*O-ethyl S-2-(diethylamino)ethyl ethylphosphonothiolate*
VM	*O-ethyl S-2-(diethylamino)ethyl methylphosphonothiolate*
VG	*O,O-diethyl S-2-(diethylamino) ethyl phosphorothiolate*
VR	*O-isobutyl S-2-(diethylamino)ethyl methylphosphonothiolate*
VX	*O-ethyl S-(diisopropylamino)ethyl methylphosphonothiolate*

GV agents

GV	*2-(dimethylamino)ethyl N,N-dimethylphosphoramidofluoridate*

7.2 Nerve agents (NAs) are potent acetylcholinesterase (AChE) inhibitors. The development of signs and symptoms varies depending on the dose and route of exposure, and clinical manifestations include: runny nose (rhinorrhea), chest tightness, shortness of breath, excessive salivation and sweating, nausea, vomiting, abdominal cramps, involuntary defecation and urination, muscle twitching, confusion, seizures, flaccid paralysis, miosis/mydriasis (“tunnel vision”), bradycardia/tachycardia and hypotension/hypertension (depending on the phases of muscarinic or nicotinic receptor hyperstimulation), coma, respiratory failure, and death (Table 1).

Acute effects

7.3 Depression of respiratory and vasomotor centres in the brain may result in respiratory failure. Hypoxia can cause cerebral oedema, convulsions, and brain damage. Acetylcholine build-up at muscarinic and nicotinic receptors causes systemic complications.

Ocular system:

7.4 The most common sign is miosis that may continue for several days to 9 weeks post exposure. Impaired vision, tearing and bloodshot appearance are common.

Respiratory system:

7.5 Rhinorrhea is common followed by bronchorrhea, wheezing, bronchiolar smooth muscle constriction, and breathing failure.

Cardiovascular system:

7.6 The increase in vagal tone usually results in bradycardia and atrioventricular block. Cardiac arrest and myocarditis may also occur.

Nervous system:

7.7 Fatigue, muscle weakness, flaccid paralysis, generalised fasciculation, and seizure may occur. Apnoea responding only to antidotal therapy may occur. Exposure to low doses may cause headache, dizziness, restlessness, anxiety, mental confusion, ataxia, irritability, insomnia, depression, forgetfulness, impaired judgment and concentration.

7.8 Skin and mucosal membrane: Although skin penetration by nerve agents differ, skin absorption increases as the surrounding temperature rises from 18 to 46 °C.

7.9 Gastrointestinal system: Increased mobility, nausea and vomiting can occur.

7.10 Genitourinary system: Micturition can occur after dermal contact or inhalation of vapour.

TABLE 1: SIGNS AND SYMPTOMS AFTER EXPOSURE TO NAS (FROM CRIT. CARE MED. 30 (2002))

Signs and Symptoms after acute inhalation exposure to NA	**Signs and symptoms after dermal exposure to NA**
Low-dose with mild effects	Low-dose with mild effects
Runny nose	Localised sweating at exposure site
Miosis (blurred vision)	Fine muscle fasciculations at exposure site
Conjuctival injection	Miosis not an early sign and may be absent
Bronchoconstriction (chest tightness)	
Mild bronchosecretion	
Medium-dose with moderate effects	Medium-dose with moderate effects
Shortness of breath	Nausea and vomiting

Coughing	Severe headache
Wheezing	Generalised fasciculation
Nausea and vomiting	Feelings of weakness
Fasciculation	BEWARE: No respiratory signs present yet
Generalised feelings of weakness	
High-dose with severe effects	High-dose with severe effects
Loss of consciousness	Sudden loss of consciousness
Seizures	Seizures
Flaccid paralysis	Flaccid paralysis
Apnea	Apnea
Death usually within minutes	Death

8. MEDICAL TREATMENT

8.1 Pretreatment and prophylaxis: Pretreatment is the administration of drugs before poisoning, to increase the efficacy of treatment post-exposure, while prophylaxis is the administration of drugs before poisoning, designed to prevent poisoning. Carbamates, e.g. pyridostigmine, may be used as pretreatments against NA poisoning due to their ability to carbamoylate AChE, preventing the OP inhibitor from binding. Carbomoylated AChE conjugates breakdown rapidly, while OP-AChE conjugates are particularly stable. Aging of OP-AChE conjugates results in stable OP-AChE-complexes that cannot be reactivated.

8.2 When carbamates are used as pretreatments, carbamoylation of ~30% of AChE should prevent phosphylation of the carbamoylated AChE fraction. As free G-agent is cleaved quite fast from the tissue, AChE is released upon decarbamoylation, restoring normal function.

8.3 Pyridostigmine (30 mg every 8 h) is used as a pretreatment. In conjunction with post exposure therapy, good protection against lethality is obtained within 2 h of the first dose, but is not optimal until the third dose. Pyridostigmine pretreatment should be stopped upon observation of NA poisoning symptoms and post exposure therapy started. If the recommended dose is exceeded, symptoms of carbamate poisoning occur (diarrhea, gastrointestinal cramps, tight chest, nausea, rhinorrhea, headache and miosis). Pretreatment for soman poisoning is in a form usable by non-medical personnel (tablets, sublingual or transcutaneous patch).

8.4 Prophylaxis: Recently, a dermal topical protective agent containing a 50:50 mixture of perfluoroalkylpolyether and polytetrafluoroethylene (SERPACWA) has been used by military personnel wearing personal protective equipment (PPE) when chemical warfare is deemed possible. Its purpose is to reduce or delay the absorption of chemical weapons agents through the skin. However, effectiveness can only be expected when SERPACWA is applied prior to exposure (to the skin until a barely visible white layer is evident). Before application, a dry towel should be used to remove perspiration, insect repellents, camouflage paint, or dirt from skin. Decreased toxicity of sulfur mustard, VX, soman, T-2 mycotoxins, and CS has been confirmed experimentally. SERPACWA's duration of action has not been evaluated for > 6 h. Its major side effect is an occasional mild flu-like syndrome. No systemic absorption

occurs through intact skin (not studied in children). Standard decontamination methods should be followed after NA or other chemical weapons agent exposure.

8.5 Post-exposure therapy: A therapeutic scheme for nerve agent poisoning includes early decontamination, supportive measures and specific pharmacological treatment to achieve muscarinic cholinergic blockade (atropine), enzyme reactivation (oximes), and anticonvulsant effect (benzodiazepines). Post acute exposure effects may appear as an intermediate syndrome and delayed polyneuropathy. Examining the patients by electromyography for nerve conduction velocity is helpful to diagnose such cases and triage them. The neuropathy after acute or low-level prolonged exposures develops without preceding cholinergic toxicity. Persistent inhibition of AChE is responsible for muscle weakness, but this is not the only factor involved in the neuropathy.

9. EMERGENCY FIELD THERAPY

9.1 These oxime autoinjectors appear to be available:

(a) Pralidoxime chloride (600 mg) and atropine (2 mg)

(b) Obidoxime chloride (220 mg) and atropine (2 mg)

(c) TMB 4 (80 mg) and atropine (2 mg)

(d) HI-6 dimethanesulfonate (750 mg), atropine (2 mg) and diazepam (10 mg)

9.2 Strategies using these autoinjectors depend on the country in which they are used. No data on the tolerability of HI-6 dimethansulfonate to humans were available to the authors. Therefore the use of this type of autoinjector cannot be recommended at present.

Self aid (first/buddy aid)

9.3 The rapid effects of NAs require immediate intramuscular injection of atropine (2 mg) combined if possible with an oxime (available oxime in adequate dose). Each soldier carries 1 to 3 autoinjectors, each containing atropine (2 mg) or a mixture of atropine, oxime and/or anticonvulsant (diazepam).

9.4 One autoinjector should be administered immediately after development of symptoms and/or signs of NA poisoning by the soldier or a helper; the injection site depends on the drug loaded - typically perpendicularly through the clothing into the thigh. The design of the autoinjector provides maximum safety and accidental injection is avoided. If the manifestations of poisoning are still present, further autoinjectors, up to a total of 3, should be administered during the next 30 min. The timing of these further injections and whether each drug is given singly or as a mixture varies between nations and depends on the condition of the casualty.

9.5 Note that symptoms and signs of atropinisation may occur if autoinjectors are used in the absence of NA exposure: dry mouth and skin, increased heart rate (> 90 beats/min), dilated pupils, urine retention, and central nervous system disturbance.

Susceptibility to heat exhaustion or heat stroke is increased, particularly in closed spaces or while wearing PPE.

First aid by first responders

9.6 The aim is to restore or maintain vital bodily functions. If the casualty is not wearing a mask, the respirator must be adjusted by the nearest person, and decontamination initiated. Afterwards, atropine should be injected at intervals until clear signs of atropinisation are evident (drying of bronchial, salivary and skin secretions and an increase in heart rate to > 90 beats/min). Systemic atropine does not affect miosis from vapour exposure.

9.7 Atropine should be administered in doses of 1-2 mg intramuscularly (i.m) every 30 min to 4 h, as required (with individual adjustment), or ideally infused (20% of a loading dose) for at least 24 h. Atropinisation carries the risk of ventricular arrhythmia if the casualty is anoxic. Therefore, anoxia must be corrected prior to atropinisation (by cleaning the airways by suction etc).

9.8 In severe poisoning - involving bronchoconstriction, copious bronchial secretion, respiratory insufficiency and/or depression, and convulsions - assisted ventilation must be applied.

Cardiorespiratory resuscitation/stabilisation

9.9 This preserves brain function until the necessary measures can be taken to restore other vital functions. If the atmosphere is uncontaminated, the casualty's face and mouth are decontaminated and assisted ventilation and chest compression is enforced by the standard mouth-to-mouth method. In a contaminated atmosphere, if resuscitation is needed, a portable resuscitator with an NBC filter may help ventilate the casualty. Decontamination of the casualty and resuscitator is obligatory.

10. PHARMACOLOGICAL TREATMENT OF NA POISONING

10.1 This involves the use of:

(a) Anticholinergics (atropine) to antagonise the muscarinic effects.

(b) Oximes to reactivate the inhibited enzyme and antagonise the nicotinic effects.

(c) Anticonvulsants to prevent CNS damage.

10.2 Atropine: Atropine sulfate remains essential for treatment of NA poisoning. It is a competitive antagonist at muscarinic receptors and blocks the effects of acetylcholine (ACh) at muscarinic receptors in the peripheral (PNS) and central nervous system (CNS). Atropine cannot counteract ACh’s effects at nicotinic receptors in the PNS or CNS.

10.3 After emergency field treatment, it is necessary to continue atropinisation for at least 24 h by repeated intramuscular injections or ideally by intravenous infusion of 1 to 10 mg of atropine per hour as required (depending on the severity of intoxication).

Intervals of 5 to 15 min are acceptable for adjusting the atropine dose based on the therapeutic effects. Administration of a double dose (4 mg) may be required. Electrocardiographic (ECG) monitoring should be undertaken in all patients if possible.

10.4 Atropine overdose may induce CNS signs: blurred vision, dry mouth, decreased sweating, mydriasis, tachycardia, euphoria, hallucinations, anxiety, fever and delirium. Observation of patients is necessary to avoid these and bladder dysfunction may necessitate catheterisation.

10.5 By inhibiting sweat production, atropine increases heat stress and care must be taken to avoid hyperthermia in warm or hot weather. Atropine given parenterally has comparatively little effect on NA-induced miosis. Application of cycloplegics (atropine eye drops) to the eye reduces the degree of miosis, eye pain and headache. The effects of atropine are fairly prolonged, lasting 3-5 h after one or two injections of 2 mg, and 12-24 h after over-atropinisation. In severe cases of NA poisoning, atropine can be given as an initial dose up to 6 mg intravenously (i.v) or i.m, and then 2 mg i.v or i.m, every 5-10 min until ventilation is regular and secretions have dried. Intravenous administration followed by infusion is preferred.

10.6 Oximes: These remove the organophosphorus group from the OP-inhibited AChE, restoring the normal function of AChE. Their use with atropine in the early stages of poisoning alleviates the clinically-important symptoms and signs of skeletal neuromuscular blockade, and reduces the amount of atropine needed, if administered on time. As oximes penetrate the CNS poorly, and cannot reverse the muscarinic effects (particularly hypersecretions), simultaneous administration of atropine is always required. Relative potencies of oximes in reactivating AChE inhibited by four NAs appear in Table 2, dosing schemes for intravenous administration of oximes, applied to poisoning of humans by OP insecticides, appear in Table 3.

TABLE 2: EFFECTIVENESS OF VARIOUS OXIMES IN THE TREATMENT OF NA POISONING

Oxime	GA	GB	GD	GF
P2S	-	+	-	-
Obidoxime	+	+	-	+/-
+ effective, - ineffective, and +/- sometimes effective				

TABLE 3: DOSING SCHEME FOR INTRAVENOUS ADMINISTRATION OF OXIMES

Oxime	Loading dose	Continuous infusion
Obidoxime	250 mg	750 mg/24 h
2-PAM or P2S	1-2 g	500 mg/h

10.7 Obidoxime chloride: 250 mg bolus then 750 mg/24 h for an adult. Pralidoxime (2-PAM; molecular weight 173 and mesylate P2S; molecular weight 232): 1-2 g/h loading dose, then 8 mg/kg/h continuously infused (1-2 g loading dose over 20-30 min, then 500 mg/h). The recommended plasma concentration of 3.6 mg/l of

obidoxime chloride and pralidoxime of ~13.8 mg/l should suffice to antagonise the toxic effects of OP compounds. Similar doses can be given intramuscularly in the field, avoiding accidental intra-arterial injection.

TABLE 4: OXIME DOSING

Oxime	Route of administration	Dose
Pralidoxime chloride (2-PAM)	Individual autoinjector dose Total adult loading dose	600 mg 1-2 g (30 mg/kg)
Pralidoxime mesylate (P2S)	Individual autoinjector dose Total adult loading dose	500 mg 2 g (30 mg/kg)
Obidoxime chloride	Individual autoinjector dose Total adult loading dose	220 mg *
HI-6	Individual autoinjector dose Total adult loading dose	

* Autoinjector ATOX II (220 mg obidoxime and 2 mg atropine).

10.8 Results of studies of human poisoning by OP insecticides have shown that oxime treatment should be continued for 12 h after reactivation has been achieved and the patient has recovered (e.g. no need for further atropine). If enzyme reactivation has not occurred after 24-48 h and the patient has not recovered, it should be accepted that the inhibited enzyme is resistant to reactivation by the oxime, and administration should be stopped. There is only limited experience with human poisoning by NAs, but experimental data suggest that NAs will persist in the body for a shorter time than OP insecticides. Thus, administration of oximes should be continued for 24-48 h or more until recovery of the patient. To assess this, a commercial laboratory test system of AChE status should be used.

11. SIDE EFFECTS/ADVERSE EFFECTS OF OXIMES

Rapid injections of 2-PAM or P2S can cause nausea, drowsiness, headache, disturbance of vision, increased blood pressure, tachycardia, hyperventilation and muscular weakness. Hypotension and facial warmth, and sensations similar to those caused by menthol, occur during obidoxime treatment; i.m application can cause pain at the injection site and hepatic dysfunction after multiple doses. HI-6 can have similar effects but has a better tolerance profile. Adverse effects reported for HI-6 in healthy volunteers are nausea and headache only.

12. ANTICONVULSANTS

Atropine protects only partially against convulsions and the resulting brain damage in severe poisoning. Anticonvulsants (e.g. diazepam, lorazepam or midazolam) having a neuroprotective effect, should be applied as necessary. Experimental soman poisoning shows that adding diazepam to the basic treatment works by antagonising the convulsions, as well as by decreasing the morbidity and mortality rate. Diazepam should be injected i.m starting with a 10 mg dose and the frequency of later injections adjusted to control the convulsions. When seizures occur, up to 40 mg diazepam given by medical personnel may be used.

13. SUPPORTIVE CARE

Supportive treatment includes general measures like i.v feeding, restoration of electrolyte balance and treatment of respiratory failure and/or convulsions. In some cases, treating the infection and symptoms is necessary. OP casualties often remain incapacitated for days after exposure, despite initial therapy which reduces mortality. Care using muscle relaxants must be taken. Intensive care and assisted ventilation is often required for several hours or even days, watching whether the patient is comatose or suffering brain damage due to hypoxia.

14. PREHOSPITAL MANAGEMENT

Casualties whose skin or clothing is contaminated with liquid NA can contaminate rescuers by contact or off-gassing vapour. NAs can cause loss of consciousness and convulsions within seconds and death from respiratory failure within minutes of exposure. Atropine and pralidoxime chloride (2-PAM Cl) are antidotes; however, 2-PAM has to be administered within minutes to a few hours following exposure (depending on the NA) to be effective. Treatment consists of supportive measures and repeated administration of antidotes.

15. HOT ZONE

Responders should have received training and wear protective clothing before entering a Hot Zone. If PPE is unavailable, or rescuers have not been trained, a call for assistance should be made according to local Emergency Operational Guides (EOG) (Figure 1).

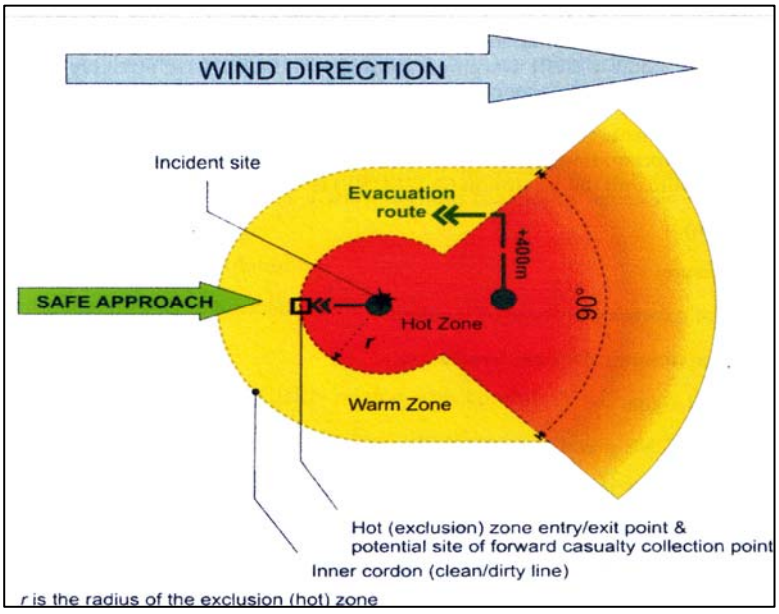

FIGURE 1: INCIDENT MANAGEMENT AND DOWNWIND HAZARD (NATO STANAG 2103)

16. RESCUER PROTECTION

16.1 Rapid local and systemic effects are induced when NA vapour is readily absorbed by inhalation and eye contact. Absorption of liquid thorough the skin is prompt but the effects may be delayed for several minutes up to 18 h.

16.2 Respiratory protection: First responders must wear pressure-demand self-contained breathing apparatus (SCBA) to respond to casualties poisoned by NA vapour or liquid.

16.3 Skin protection: To prevent skin absorption of liquid NA, chemical-protective clothing and butyl rubber gloves are recommended.

Triage

16.4 Chemical casualty triage is based on walking feasibility, respiratory status, age, and additional conventional injuries. The triage officer must know the course of a given injury, the medical resources available, the current and likely casualty flow, and medical evacuation capabilities. There are three triage categories: T1 immediate-severe (unconscious, convulsions, respiratory distress or arrest, profound bradycardia, cyanosis), T2 urgent/moderate (non-ambulatory, excessive secretions, confusion, not obeying commands), T3 delayed/mild (walking, pinpoint pupils only). Triage is repeated in mass-casualty circumstances.

17. SUMMARY

17.1 First aid recommendations under field conditions

17.2 Casualties from NA exposure should be extracted from the contaminated area by first responders wearing PPE. The responders should place the unconscious patients in a position preventing aspiration (left lateral decubitus) and attend to ABC (Airway-Breathing-Circulation). In severe cases of exposure, treatment should be commenced immediately: decontamination should be started and the casualty given an antidote by self or buddy aid via autoinjectors:

(a) MARK I kit: Atropine (2 mg, 0.7 ml) and 2-PAM (600 mg)

(b) ATOX II: Atropine (2 mg, 0.7 ml) and obidoxime (220 mg)

(c) ATNAA: Atropine (2 mg/0.7 ml) and 2-PAM (600 mg/2 ml); 1 needle injects both drugs

(d) ATROPEN: Atropine (2 mg, 0.7 ml). Each soldier must have 3 kits and 1 auto-injector with diazepam (10 mg) (if warned of NA attacks). Based on the severity of poisoning, one to three MARK I kits are applied:

(i) miosis, severe rhinorrhea (1 × MARK I kit)
(ii) severe respiratory distress (2 × MARK I kits)
(iii) severe breathing difficulties, apnea, cyanosis, muscle twitching, seizures and unconsciousness (3x MARK I kits and diazepam)

17.3 The atropine dose in the MARK I kit is between the therapeutically desirable and safely administrable dose to a non-intoxicated person. Absorption of antidotes administered with autoinjectors is more rapid than by i.m injection (autoinjectors spray the liquid throughout the muscle as the needle enters, while classical needle-and-syringe cause the liquid to pool in the muscle). Following administration, the patient should be monitored and medical action taken accordingly. Emergency treatment under field conditions is summarised in Table 5.

TABLE 5: EMERGENCY MEDICAL TREATMENT OF NA POISONING

Symptoms and signs	Mark-1 Kit	Repeat dosing
Severe difficulties with breathing, apnoea, cyanosis, muscle fasciculation or twitching, seizure, loss of consciousness	ABC (Maintain patent airway; assist breathing as needed, give oxygen, provide suction, restore normal cardiac rhythm) Administer Mark I Kit (3 times at 10-15 min intervals)	Diazepam autoinjector may be repeated 3 times every 10-15 min
Severe respiratory distress	Administer Mark I Kit (2 doses)	
Sweating, miosis, rhinorrhea, nausea, vomiting, anxiety	Administer Mark I Kit (1 dose)	
NOTE:	Monitor for symptoms every 10 min. Repeat atropine if needed	

Appendix

DIRECTOR-GENERAL'S REQUEST TO THE SCIENTIFIC ADVISORY BOARD

1. Article X establishes the obligations and rights of a State Party concerning the assistance and protection against chemical weapons, and accords each State Party the right to request and to receive assistance and protection against the use or threat of use of chemical weapons. It is anticipated that, in most cases, the main assistance needed from the OPCW would be provision of medical countermeasures and treatment for chemical weapons casualties.

2. At its Sixteenth Session (in 2012) the Conference of States Parties to the Chemical Weapons Convention established the international support network for the victims of chemical weapons. This decision requires the establishment of a webpage and a databank to include information on offers by Member States relevant to the victims of chemical weapons and information on needs of the victims of chemical weapons. In order to be in a position to fully meet the expectations of the Convention States Parties with regard to the victims' network, it is necessary for the Technical Secretariat to compile information on relevant scientific advances with respect to new medical countermeasures and treatments of victims of nerve and blister agents.

3. In its report on developments in science and technology to the Third Review Conference (cf. paragraphs 120-123 in RC-3/DG.1, dated 29 October 2012), the Scientific Advisory Board informed the Technical Secretariat on the status of currently available countermeasures and treatments. As a follow up to this information, the Director-General requests the Scientific Advisory Board to:

   (a) recommend to the Technical Secretariat pre-treatments, vaccines, emergency care, and long term treatments that are currently available for blister and nerve agents; and

   (b) To inform the Technical Secretariat of the most relevant information sources that can be monitored to keep abreast of new developments in these areas.

Technical Secretariat

June 2013

REFERENCES ON BLISTER AGENTS

1. A Aasted, E Darre, H C Wulf. Mustard gas: clinical, toxicological, and mutagenic aspects based on modern experience. *Ann. Plast. Surg*. **19** (1987) 330-333.

2. M Balali-Mood, M Hefazi. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. *Basic Clin. Pharmacol. Toxicol*. **99** (2006) 273-282.

3. M Balali-Mood, M Hefazi. The pharmacology, toxicology, and medical treatment of sulphur mustard poisoning. *Fundam. Clin. Pharmacol*. **19** (2005) 297-315.

4. M Balali-Mood, M Hefazi, M Mahmoudi, E Jalali, D Attaran, *et al*. Long-term complications of sulphur mustard poisoning in severely intoxicated Iranian veterans. *Fundam. Clin. Pharmacol*. **19** (2005) 713-721.

5. J Borak, F R Sidell. Agents of chemical warfare: sulfur mustard. *Ann. Emerg. Med.* **21** (1992) 303-308.

6. E H Braue, C R Nalls, R A Way, J E Zallnick, R G Rieder, L W Mitcheltree. Nikolsky's sign: a novel way to evaluate damage at the dermal-epidermal junction. *Skin Res. Technol*. **3** (1997) 245-251.

7. K G Davis, G Aspera. Exposure to liquid sulfur mustard. *Ann. Emerg. Med*. **37** (2001) 653-656.

8. M Emad. The diversity of the effects of sulfur mustard gas inhalation on the respiratory system 10 years after a single exposure; analysis of 197 cases. Chest 112 (1997) 734-738.

9. S N Emadi, J Aslani, Z Poursaleh, M Izadi, M Soroush, M Kafashi, *et al*. Comparison late cutaneous complications between exposure to sulfur mustard and nerve agents. *Cutan. Ocul. Toxicol*. **31** (2012) 214-219.

10. M Etezad-Razavi, M Mahmoudi, M Hefazi, M Balali-Mood. Delayed ocular complications of mustard gas poisoning and the relationship with respiratory and cutaneous complications. *Clin. Experim. Ophthamol*. **34** (2006) 342-346.

11. M Ghanei, S Akhlaghpoor, M M Moahammad, J Aslani. Tracheobronchial stenosis following sulfur mustard inhalation. *Inhalation Toxicology* **16** (2004) 845-849.

12. M Ghanei, Z Poursaleh, A A Harandi, S E Emadi, S N Emadi. Acute and chronic effects of sulfur mustard on the skin: a comprehensive review. *Cutan. Ocul. Toxicol*. **29** (2010) 269-277.

13. J S Graham, R P Chilcott, P Rice, S M Milner, C G Hurst, B I Maliner. Wound healing of cutaneous sulfur mustard injuries: strategies for the development of improved therapies. *J. Burns Wounds* **4** (2005) 1-45.

14. J S Graham, K T Schomacker, R D Glatter, C M Briscoe, E H Braue, K S Squibb. Efficacy of laser debridement with autologous split-thickness skin grafting in

promoting improved healing of deep cutaneous sulfur mustard burns. *Burns* **28** (2002) 719-730.

15. J S Graham, R S Stevenson, L W Mitcheltree, T A Hamilton, R R Deckert, R B Lee, A M Schiavetta. Medical management of cutaneous sulfur mustard injuries. *Toxicology* **263** (2009) 47-58.

16. M Hefazi, M Maleki, M Mahmoudi, A Tabatabaee, M Balali-Mood. Delayed complications of sulfur mustard poisoning in the skin and the immune system of Iranian veterans 16-20 years after exposure. *Int. J. Dermatol.* **45** (2006) 1025-1031.

17. U R Hengge, T Ruzicka, R A Schwartz, M J Cork. Adverse effects of topical glucocorticosteroids. *J. Am. Acad. Dermatol*. **54** (2006) 1-15.

18. A Hosseini-Khalili, D D Haines, E Modirian, M Sroush, S Khateri, R Joshi, *et al*. Mustard gas exposure and carcinogenesis of lung. *Mutation Res.* **678** (2009) 1-6.

19. W F Hughes. Mustard gas injuries to the eyes. *Arch Ophthalmol*. **27** (1942) 582-601.

20. C G Hurst, J P Petrali, D J Barillo, J S Graham, W J Smith, F R Sidell. Vesicants, in: M. Lenhart (Ed.), *Textbook of Military Medicine, Part I: Warfare, Weaponry and the Casualty - Medical Aspects of Chemical Warfare*, Washington DC: Borden Institute, Walter Reed Army Medical Center, 2008, pp. 259-309.

21. K Kehe, L Szinicz. Medical aspects of sulphur mustard poisoning. *Toxicology* **214** (2005) 198-209.

22. K Kehe, H Thiermann, F Balszuweit, F Eyer, D Steinritz, T Zilker. Acute effects of sulfur mustard injury - Munich experiences. *Toxicology* **263** (2009) 3-8.

23. P C Livingston, H M Walker. A study of the effects of liquid mustard gas upon the eyes of rabbits and of certain methods of treatment. *Br. J. Ophthalmol.* **24** (1940) 67-73.

24. S Mansour Razavi, P Salamati, M Saghafinia, M Abdollahi. A review on delayed toxic effects of sulfur mustard in Iranian veterans. *Daru* **20** (2012) 51.

25. A Z Momeni, S Enshaeih, M Meghdadi, M Amindjavaheri. Skin manifestations of mustard gas: a clinical study of 535 patients exposed to mustard gas. *Arch. Dermatol*. **128** (1992) 775-780.

26. J Newmark, J M Langer, B Capacio, J Barr, R G McIntosh. Liquid sulfur mustard exposure. *Mil. Med*. **172** (2007) 196-198.

27. Y Panahi, S M Davoodi, H Khalili, S Dashti-Khavidaki, M Bigdeli. Phenol and menthol in the treatment of chronic skin lesions following mustard gas exposure. *Singapore Med. J.* **48** (2007) 392-395.

28. Y Panahi, S M Davoudi, F Beiraghdar, M Amiri. Doxepin cream versus betamethasone cream for treatment of chronic skin lesions due to sulfur mustard, *Skinmed*. **9** (2011) 152-158.

29. Y Panahi, S M Davoudi, A Sahebkar, F Beiraghdar, Y Dadjo, I Feizi, *et al*. Efficacy of Aloe vera/olive oil cream versus betamethasone cream for chronic skin lesions following sulfur mustard exposure: a randomized double-blind clinical trial. *Cutan. Ocul. Toxicol*. **31** (2012) 95-103.

30. Y Panahi, Y Moharamzad, F Beiraghdar, M M Naghizadeh. Comparison of clinical efficacy of topical pimecrolimus with betamethasone in chronic skin lesions due to sulfur mustard exposure: a randomized, investigator-blind study. *Basic Clin. Pharmacol. Toxicol.* **104** (2009) 171-175.

31. Y Panahi, A Sarayani, F Beiraghdar, M. Amiri, S M Davoudi, A Sahebkar. Management of sulfur mustard-induced chronic pruritus: a review of clinical trials, *Cutan. Ocul. Toxicol*. **31** (2012) 220-225.

32. B Papirmeister, A J Feister, S I Robinson, R D Ford. *Medical Defense against Mustard Gas: Toxic Mechanisms and Pharmacological Implications*, Boston: CRC Press, 1991. pp. 2, 22-26.

33. P Rice, R F Brown, D G Lam, R P Chilcott, N J Bennett. Dermabrasion - a novel concept in the surgical management of sulphur mustard injuries. *Burns* **26** (2000) 34-40.

34. R Roshan, P Rahnama, Z Ghazanfari, A Montazeri, M R Soroush, M M Naghizadeh, *et al*. Long-term effects of sulfur mustard on civilians' mental health 20 years after exposure (The Sardasht-Iran Cohort Study). *Health Qual. Life Outcomes* **11** (2013) 69.

35. M Rowell, K Kehe, F Balszuweit, H Thiermann. The chronic effects of sulfur mustard exposure. *Toxicology* **263** (2009) 9-11.

36. J A D Settle. Principles of replacement fluid therapy, in: J A D Settle (Ed.), *Principles and Practice of Burns Management,* New York: Churchill Livingstone, 1996. pp. 83-94.

37. M Shohrati, J Aslani, M Eshraghi, F Alaedini, M Ghanei. Therapeutic effect of N-acetyl cysteine on mustard gas exposed patients: evaluating clinical aspect in patients with impaired pulmonary function test. *Respiratory Medicine* **102** (2008) 443-448.

38. M Shohrati, M Davoudi, M Ghanei. Cutaneous and ocular late complications of sulfur mustard in Iranian veterans. *Cutan. Ocul. Toxicol*. **26** (2007) 73-81.

39. M Shohrati, A Tajik, A A Harandi, S M Davoodi, M Almasi. Comparison of hydrazine and doxepin in treatment of pruritis due to sulfur mustard. *Skinmed.* **6** (2007) 70-72.

40. F R Sidell. Nerve agents, in: Textbook on *Medical Response to Chemical Casualties (Course Manual)*, Aberdeen Proving Ground, Maryland: US Army Medical Research Institute of Chemical Defense, 1990.

41. H D Somani, S R Babu. Toxicodynamics of sulfur mustard. Int. *J. Clin. Pharmacol. Ther. Toxicol.* **27** (1989) 419-435.

42. T Kadar, S Dachir, L Cohen, R Sahar, E Fishbeine, M Cohen, *et al*. Ocular injuries following sulfur mustard exposure – pathological mechanisms and potential therapy, *Toxicology* **263** (2009) 59-69.

43. United Nations Centre for Disarmament Affairs. *Disarmament: the Chemical Weapons Convention with Selective Index*, New York: United Nations Publication Number E.95.IX.2, 1994.

44. J L Willems. Clinical management of mustard gas casualties. *Ann. Belg. Med*. Mil. **3** (1989) 1–61.

45. T Zilker, N Felgenhauer. S-Mustard gas poisoning – experience with 12 victims. *Clin Toxicol.* **40** (2002) 251 (abstract).

46. R Zojaji, M Balali-Mood, M Mirzadeh, A Saffari, M Maleki. Delayed head and neck complications of sulphur mustard poisoning in Iranian veterans. J. *Laryngol*. Otol. **123** (2009) 1150-1154.

REFERENCES ON NERVE AGENTS

1. C Aaron, M A Howland, Insecticides: Organophosphates and Carbamates, Goldfrank's Toxicologic Emergencies, L R Goldfrank, R S Weisman, N E Flomenbaum *et al*. (Eds.), Norwalk CT, Appleton & Lange, 1994, pp. 1105-1116.

2. M Abdollahi, T K Rajnbar, S Shadnia, S Nikfar, A Rezaiee. Pesticides and oxidative stress: a review. *Medical Science Monitor* **10** (2004) RA 141-147.

3. M Abdollahi, S Mostafalou, S Pournourmohammadi, S Shadnia. Oxidative stress and cholinesterase inhibition in saliva and plasma of rats following subchronic exposure to malathion, *Comparative Biochemistry and Physiology. Part C. Toxicology and Pharmacology,* **137**, 2004, pp. 29-34.

4. M B Abou-Donia. Organophosphorus ester-induced chronic neurotoxicity. *Arch. Environmental Health* **58** (2003) 484-497.

5. A W Abu-Qare, M B Abou-Donia. Sarin: health effects, metabolism, and methods of analysis. *Food & Chemical Toxicology* **40** (2002) 1327-1333.

6. American Heart Association. Management of Cardiac Arrest. *Circulation* **112** (2005) 58-66.

7. B Antonijević, S Vučinić, V Ćupić. Protective effect of HI-6 and trimedoxime combination in mice acutely poisoned with tabun, dichlorvos or heptenophos. *Acta Veterinaria (Beograd)* **62** (2012) 123-135.

8. E Auf der Heide. Principles of hospital disaster planning. Disaster medicine, D. Hogan and J. L. Burstein, Lippincott Williams & Wilkins, Philadelphia USA, 2002, 57-89.

9. M Balali-Mood, M Shariat. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *Journal of Physiology, Paris* **92** (1998) 375-378.

10. D Bateman. Are there long-term sequelae from repeated low dose organophosphorus insecticide exposures? *Clinical Toxicology* **37** (1999) 368-369.

11. H P Benschop, L P A de Jong. Toxicokinetics of nerve agents, in: S M Somani, J A Romano (Eds.), *Chemical Warfare Agents: Toxicity at Low Levels*, CRC Press: Boca Raton USA, 2001, pp. 25-81.

12. B Benson, D Tolo, *et al*. Is the intermediate syndrome in organophosphate poisoning the result of insufficient oxime therapy? *J. Clin. Toxicol*. **30** (1992): 347-349.

13. N Buckley, A L Karalliedde, *et al*. Where is the evidence for treatments used in pesticide poisoning? Is clinical toxicology fiddling while the developing world burns? *J. Toxicol. Clin. Toxicol*. **42** (2004) 113-116.

14. R F Clark (2002). Insecticides: organic phosphorus compounds and carbamates, in: *Goldfrank's Toxicological Emergencies*, L R Goldfrank, N E Flomenbaum, N A Lewin *et al*. (Eds.), McGraw-Hill, New York USA, 2002, 1346-1360.

15. C Colosio, M Tiramani, *et al*. Neurobehavioral effects of pesticides: state of the art. *Neurotoxicology* **24** (2003) 577-591.

16. J L Daniels, A F Olshan, *et al*. Residential pesticide exposure and neuroblastoma. *Epidemiology* 12 (2001) 20-27.

17. R C Dart, Y Stark, *et al*. Insufficient stocking of poisoning antidotes in hospital pharmacies. *J. Am. Med. Assoc*. **276** (1996) 1508-1510.

18. J De Bleecker, J K Van Den Neucker, *et al*. Intermediate syndrome in organophosphorus poisoning: a prospective study. *Critical Care Medicine* **21** (1993) 1706-1711.

19. J De Bleecker, J Willems, *et al*. Prolonged toxicity with intermediate syndrome after combined parathion and methyl parathion poisoning. *J. Clin. Toxicol*. **30** (1992) 333-345.

20. H J de Silva, R Wijewickrema, *et al*. Does pralidoxime affect outcome of management in acute organophosphorus poisoning? *Lancet* **339** (1992) 1136-1138.

21. D J Ecobichon. Toxic effects of pesticides, in: *Casarett and Doull's Toxicology*: *The Basic Science of Poisons,* C D Klaassen, M O Amdur and J Doull (Eds.), McGraw-Hill: New York USA, 1996, pp. 643-689.

22. M. Eddleston, L Szinicz, *et al*. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. *QJM* **95** (2002) 275-283.

23. A R Erdman. Pesticides. Medical Toxicology, R C Dart (Ed.), Lippincott Williams & Wilkins: Philadelphia USA, 2004, pp. 1475-1496.

24. P Eyer. Optimal oxime dosage regimen, a pharmacokinetic approach, in: L Szinicz, P Eyer, R Klimmek (Eds.), *Role of Oximes in the Treatment of Anticholinesterase Agent Poisoning*, Spektrum Akademischer Verlag: Berlin, Germany, 1996, pp. 33-51.

25. P Eyer. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev*. **22** (2003) 165-190.

26. M Fernández, M. (2004). *Atropine. Medical Toxicology*, R C Dart (Ed.), Lippincott Williams & Wilkins: Philadelphia USA, 2004, pp. 163-165.

27. Food and Drug Administration (FDA) Talk Paper: FDA Approves Pediatric Doses of Atropine, 20 June 2003; accessed on 4 November 2005, from http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01232.html

28. T Galloway, R Handy. Immunotoxicity of organophosphorus pesticides. *Ecotoxicology* **12** (2003) 345-363.

29. R Geller. Antidote availability: reformulation of bulk atropine for nerve agent casualties, National Disaster Medical System Conference, Atlanta, Georgia Poison Center, Grady Health System, and Emory University Department of Pediatrics, 1999.

30. R J Geller, G P Lopez, *et al*. Atropine availability as an antidote for nerve agent casualties: validated rapid reformulation of high-concentration atropine from bulk powder. *Ann. Emerg. Med*. **41** (2003) 453-456.

31. H Golsousidis, V Kokkas. Use of 19,590 mg of atropine during 24 days of treatment after a case of unusually severe parathion poisoning. *Human Toxicology* **4** (1985) 339-340.

32. R Goswamy, A Chaudhuri, *et al*. Study of respiratory failure in organophosphate and carbamate poisoning. *Heart and Lung* **23** (1994) 466-472.

33. J B Hack, R S Hoffman. General management of poisoned patients, in: *Emergency Medicine: A Comprehensive Study Guide*, J E Tintinalli, G D Kelen and J S Stapczynski (Eds.), McGraw-Hill: New York USA, 2004, pp. 1015-1022.

34. L W Harris, B G Talbot, *et al*. The relationship between oxime-induced reactivation of carbamylated acetylcholinesterase and antidotal efficacy against carbamate intoxication. *Toxicol. Appl. Pharmacol*. **98** (1989) 128-133.

35. A L Hayes, R A Wise, *et al*. Assessment of occupational exposure to organophosphates in pest control operators. *Am. Ind. Hyg. Assoc. J*. **41** (1980) 568-575.

36. W J Hayes, E R Laws. Diagnosis and treatment of poisoning, in: *Handbook of Pesticide Toxicology*, Academic Press: San Diego USA, 1991, pp. 388-403.

37. D K Horton, Z Berkowitz, *et al*. Secondary contamination of ED personnel from hazardous materials events, 1995-2001. *Am. J. Emerg. Med*. **21** (2003) 199-204.

38. M A Howland. Antidotes in depth: pralidoxime, in: *Goldfrank's Toxicological Emergencies,* L R Goldfrank, N E Flomenbaum, N A Lewin *et al*. (Eds.), McGraw-Hill, New York USA, 2002, pp. 1361-1365.

39. M A Howland, C Aaron. Antidotes in depth: pralidoxime, in: *Goldfrank's Toxicological Emergencies*, L R Goldfrank, R S Weisman, N E Flomenbaum *et al*. (Eds.), Appleton and Lange, Norwalk CT, USA, 1994, pp. 1117-1119.

40. C G Hurst. Decontamination, in: Medical Aspects of *Chemical and Biological Warfare*, F R Sidell, E T Takafuji and D R Franz (Eds.), Office of The Surgeon General, United States Army, Falls Church VA, USA, 1997, pp. 351-359.

41. K Jaga, C Dharmani. Sources of exposure to and public health implications of organophosphate pesticides. *Pan Am. J. Public Health* **14** (2003) 171-185.

42. G A Jamal. Neurological syndromes of organophosphorus compounds. *Adverse Drug React. Toxicol. Rev*. **16** (1997) 133-170.

43. M K Johnson, A Vale, *et al*. (1992). Pralidoxime for organophosphorus poisoning. *Lancet* **340** (1992) 64.

44. M Jokanović, B Antonijević, S Vučinić. Epidemiological studies of anticholinesterase pesticide poisoning in Serbia, in: T Satoh, R Gupta (Eds.), *Anticholinesterse Pesticides. Metabolism, Neurotoxicity and Epidemiology*, John Wiley & Sons Inc., ISBN 978-0-470-41030-1, 2010, pp. 481-494.

45. M P V Jokanovic, *et al*. (2002). Organophosphate induced delayed polyneuropathy. *Current Drug Targets - CNS & Neurological Disorders* **1** (2002) 593-602.

46. A H Kaji, R J Lewis. Hospital disaster preparedness in Los Angeles County, California. *Ann. Emerg. Med*. **44** (2004) S33.

47. L Karalliedde. Organophosphorus poisoning and anaesthesia. *Anaesthesia* **54** (1999) 1073-1088.

48. L Karalliedde. Cholinesterase estimations revisited: the clinical relevance. *Eur. J. Anaesth.* **19** (2002) 313-316.

49. L Karalliedde, H Wheeler, *et al*. Possible immediate and long-term health effects following exposure to chemical warfare agents. *Public Health* **114** (2000) 238-248.

50. J Kassa. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J. Toxicol. Clin. Toxicol*. **40** (2002) 803-816.

51. S Khan, R Hemalatha, *et al*. Neuroparalysis and oxime efficacy in organophosphate poisoning: a study of butyrylcholinesterase. *Human Exp. Toxicol*. **20** (2001) 169-174.

52. R Kušić, D Jovanović, S Ranđelović, D Joksović, V Todorović, B Bošković, M Jokanović, V Vojvodić. HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Human Exp. Toxicol*. **10** (1991) 113-118.

53. T C Kwong. Organophosphate pesticides: biochemistry and clinical toxicology. *Therap. Drug Monitoring* **24** (2002) 144-149.

54. F LeBlanc, B Bensen, *et al*. A severe organophosphate poisoning requiring the use of an atropine drip. *J. Clin. Toxicol*. **24** (1986) 69-76.

55. J B Leikin, R G Thomas, F G Walter, R Klein, H W Meisin (2002). A review of nerve agent exposure for the critical care physician. *Crit. Care Med*. **30** (2002) 2346-2354.

56. S F Leon, A G Pradilla, *et al*. Multiple system organ failure, intermediate syndrome, congenital myasthenic syndrome, and anticholinesterase treatment: the linkage is puzzling. *J. Toxicol. Clin. Toxicol*. **34** (1996) 245-247.

57. H W Levitin, H J Siegelson, *et al*. Decontamination of mass casualties - re-evaluating existing dogma. *Prehospital Disaster Med*. **18** (2003) 200-207.

58. M Lotti (1992). Central neurotoxicity and behavioral effects of anticholinesterases, in: Clinical *and Experimental Toxicology of Organophosphates and Carbamates*, B Ballantyne and T C Marrs (Eds.), Butterworths: London UK, 1992, pp. 75-83.

59. T C Marrs, I Dewhurst. Toxicology of pesticides - general and applied toxicology, in: B Ballantyne, T C Marrs, T Syversen (Eds.), London, Macmillan Reference, Ltd: 2000, pp. 1993-2012.

60. M Moshiri, E Darchini-Maragheh, M Balali-Mood. Advances in toxicology and medical treatment of chemical warfare nerve agents. *Daru* **20** (2012) 81.

61. T Namba. Cholinesterase inhibition by organophosphorus compounds and its clinical effects. *Bull. World Health Organization* **44** (1971) 289-307.

62. T Namba, C T Nolte, *et al*. (1971). Poisoning due to organophosphate insecticides: acute and chronic manifestations. *Am. J. Med*. **50** (1971) 475-492.

63. J Newmark. Therapy for nerve agent poisoning. *Arch. Neurology* **61** (2004) 649-652.

64. H Okudera, H Morita, *et al*. Unexpected nerve gas exposure in the city of Matsumoto: Report of rescue activity in the first sarin gas terrorism. *Am. J. Em. Med.* **15** (1997) 527-528.

65. H Okudera. Clinical features on nerve gas terrorism in Matsumoto. *J. Clin. Neuroscience* **9** (2002) 17-21.

66. T Okumura, K Suzuki, *et al*. Lessons learned from the Tokyo Subway sarin attack. *Prehospital Disaster Med*. **5** (2000) S32.

67. T Okumura, N Takasu, *et al*. Report on 640 victims of the Tokyo Subway sarin attack. *Ann. Emerg. Med*. **28** (1996) 129-135.

68. J A J Romano, J H McDonough, *et al*. (2001). Health effects of low-level exposure to nerve agents, in: *Chemical Warfare Agents: Toxicity at Low Levels*, S M Somani and J A J Romano (Eds.), CRC Press: Boca Raton FL, USA, 2001, pp. 1-24.

69. J G Schier, P R Ravikumar, *et al*. Preparing for chemical terrorism: stability of injectable atropine sulfate. *Acad. Emerg. Med*. **11** (2004) 329-334.

70. F R Sidell. Soman and sarin: clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin. Toxicol*. **7** (1974) 1-17.

71. F R Sidell. Nerve agents: medical aspects of chemical and biological warfare, in: F R Sidell, E T Takafuji and D R Franz (Eds.), Office of The Surgeon General, United States Army: Falls Church VA, USA, 1997, pp. 129-179.

72. S Singh, Y Batra, *et al*. Is atropine alone sufficient in acute severe organophosphorus poisoning? Experience of a North West Indian Hospital. *Int. J. Clin. Pharmacol. Ther.* **33** (1995) 628-630.

73. S M Somani, K Husain. Low-level nerve agent toxicity under normal and stressful conditions, in: *Chemical Warfare Agents: Toxicity at Low Levels*, S M Somani and J A J Romano (Eds.), CRC Press Boca Raton FL, USA, 2001, pp. 83-120.

74. J Suzuki, T Kohno, *et al*. Eighteen cases exposed to sarin in Matsumoto, Japan. Internal Medicine 36 (1997) 466-470.

75. P Taylor. Agents acting at the neuromuscular junction and autonomic ganglia, in: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, L S Goodman, A Gilman, T W Rall, A S Nies and P Taylor (Eds.), McGraw-Hill: New York, USA, 2001, pp. 193-213.

76. P Taylor. Anticholinesterase agents, in: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, J G Hardman, L E Limbird and A G Gilman (Eds.), McGraw-Hill, New York, USA, 2001, pp. 175-191.

77. H Thierman, L Szinicz, P Eyer, N Felgenhauer, T Zilker, F Worek. Lessons to be learnt from organophosphorus pesticide poisoning for the treatment of nerve agent poisoning. *Toxicology* **233** (2007) 145-154.

78. K N Treat, J M Williams, *et al*. Hospital preparedness for weapons of mass destruction incidents: an initial assessment. *Ann. Emerg. Med*. *38* (2001) 562-565.

79. US Occupational Safety and Health Administration (January 2005). OSHA *Best Practices for Hospital-Based First Receivers of Victims from Mass Casualty Incidents Involving the Release of Hazardous Substances*, retrieved 18 August 2005 from www.osha.gov/dts/osta/bestpractices/html/hospital_firstreceivers.html

80. J Vale. Are there long-term sequelae from a single acute organophosphorus insecticide exposure? *Clin. Toxicol*. **37** (1999) 367-368.

81. S Vučinić, B Antonijević, N Ilić, T Ilić. Oxime and atropine failure to prevent intermediate syndrome in acute organophosphate poisoning. *Vojnosanit pregl* **70** (2013) 420-424.

82. S Vučinić, G Ercegović, D Đorđević, M Jovanović, N Vukčević-Perković, O Potrebić, M Zlatković. What are the clinical significance of oxime and sodium bicarbonate therapy for acute organophosphate poisoning? *Medical Management of Chemical and Biological Casualties,* S Tonev, K Kanev, C Dishovsky (Eds.), Publishing House, IRITA ISBN 978-954-993-91-2, Chapter 18, 2009, pp. 128-136.

83. D Wess, D B Barr, *et al*. Use of biomarkers to indicate exposure of children to organophosphate pesticides: implications for a longitudinal study of children's environmental health. *Environ. Health Perspect*. **111** (2003) 1939-1946.

84. S W Wiener, R S Hoffman. Nerve agents: a comprehensive review. *J. Intensive Care Med.* **19** (2004) 22-37.

85. F Worek, M Backer, *et al*. Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. *Human Exp. Toxicol*. **16** (1997) 466-472.

- - - o - - -