



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

EXECUTIVE SUMMARY

1. This note contains the SAB's Response to the Director-General's Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection (Paragraph 9.20 of SAB-21/1, dated 27 June 2014).
2. This report was drafted as a follow up to the Director-General's previous request for advice from the SAB. Readers are advised to refer to the previous report (SAB-21/WP.7, dated 29 April 2014) when considering the information presented herein.
3. This report contains recommendations addressed to the Technical Secretariat of the OPCW. It is made available to the public for informational purposes, but is 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's Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection



Annex

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

1. DIRECTOR-GENERAL'S REQUEST

- 1.1 At the Twentieth Session of the OPCW Scientific Advisory Board (SAB), the Director-General requested that the SAB provide further advice on assistance and protection against chemical weapons (see Annex 6 of the SAB-20/1, dated 14 June 2013). The SAB completed its work and provided the Director-General with the report of their findings (see SAB-21/WP.7, dated 29 April 2014).
- 1.2 In light of recent events and victims of chemical weapons currently undergoing medical care, there is a compelling need to have a better understanding of what can be done to mitigate the longer term effects of chemical agent exposure. Such information would be a valuable addition to the International Support Network for Victims of Chemical Weapons (C-16/ DEC.13, dated 2 December 2011).
- 1.3 At the Twenty-First Session of the SAB (Paragraph 9.20 of SAB-21/1, 27 June 2014) the Director-General requested the SAB to provide further advice, namely:
 - (a) identify best practices for preventing and treating the health effects that arise from acute, prolonged, and repeated organophosphorus nerve agent exposure; and
 - (b) identify any emerging medical countermeasures, intended for use at the point of exposure, that can reduce or eliminate longer term health effects arising from acute, prolonged, and repeated organophosphorus nerve agent exposure.
- 1.4 This report addresses these questions and reviews current and promising developments in nerve agent medical countermeasures.

2. NERVE AGENTS

- 2.1 Organophosphorus (OP) nerve agents (NAs) are 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	<i>O-ethyl N,N-dimethylphosphoramidocyanidate</i>
GB	Sarin	<i>O-isopropyl methylphosphonofluoridate</i>
GD	Soman	<i>O-pinacolyl methylphosphonofluoridate</i>
GF	Cyclosarin	<i>O-cyclohexyl methylphosphonofluoridate</i>

V agents

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

GV agents

GV	<i>2-(dimethylamino)ethyl N,N-dimethylphosphoramidofluoridate</i>
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- 2.2 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

- 2.3 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:

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

Respiratory system:

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

Cardiovascular system:

- 2.6 Initially an increase in heart rate and blood pressure can occur, followed by an increase in vagal tone, possibly resulting in bradycardia and atrioventricular block. Circulatory failure and cardiac arrest may also occur.

Nervous system:

- 2.7 Fatigue, muscle weakness, flaccid paralysis, local and/or generalised fasciculation, and seizure may occur. Exposure to low doses may cause headache, dizziness, restlessness, anxiety, mental confusion, ataxia, irritability, insomnia, depression, forgetfulness, impaired judgment and concentration. Peripheral muscle failure may result in respiratory arrest and subsequent death.

- 2.8 Skin and mucosal membrane: Although skin penetration by nerve agents differs according to the type of nerve agent, skin absorption generally increases as the surrounding temperature rises from 18 to 46 °C. In case of prolonged dermal and/or inhalation exposure, generalised sweating is common.
- 2.9 Gastrointestinal system: Increased mobility, nausea and vomiting and defecation can occur.
- 2.10 Genitourinary system: Spontaneous urination can occur after systemic exposure to nerve agents.

TABLE 1: SIGNS AND SYMPTOMS AFTER EXPOSURE TO NERVE AGENTS AND SEVERITY OF POISONING (FROM CRITICAL CARE MEDICINE 2002;30:2346-2354)

Signs and symptoms after acute inhalation exposure to NAs	Signs and symptoms after dermal exposure to NAs
<i>Low-dose with mild effects</i>	<i>Low-dose with mild effects</i>
Runny nose	Localised sweating at exposure site
Miosis (blurred vision)	Fine muscle fasciculations at exposure site
Conjunctival infection	Miosis not an early sign and may be absent
Bronchoconstriction (chest tightness)	
Mild bronchosecretion	
<i>Medium-dose with moderate effects</i>	<i>Medium-dose with moderate effects</i>
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	
<i>High-dose with severe effects</i>	<i>High-dose with severe effects</i>
Loss of consciousness	Sudden loss of consciousness
Seizures	Seizures
Flaccid paralysis	Flaccid paralysis
Apnoea	Apnoea
Death usually within minutes	Death

3. MEDICAL TREATMENT

- 3.1 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. Carbamoylated 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.
- 3.2 When carbamates are used as pretreatments, carbamoylation of ~30% of AChE should prevent phosphorylation of the carbamoylated AChE fraction. As free G-agent is

hydrolysed/metabolised in vivo relatively quickly, AChE is released upon decarbamylation, restoring normal function.

- 3.3 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 (diarrhoea, 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 patches).
- 3.4 Prophylaxis: A dermal topical protective agent containing a 50:50 mixture of perfluoroalkyl polyether and polytetrafluoroethylene (Skin Exposure Reduction Paste Against Chemical Warfare Agents, 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 CWA through the skin. Effectiveness can only be expected when it 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 the 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 CWA exposure. However, it is no longer in the armamentarium in the USA, and other topical skin protectants, such as AG7 (UK) and IB1 (Israel) have been designed and are efficient, but have not always been fielded. Reactive skin decontamination lotion (RSDL) prevents dermal absorption of chemical contaminants in persons exposed to CWA and toxic industrial chemicals. It has better efficacy compared to water, bleach, and dry sorbents and may have a role in mass human exposure in military and civilian settings.
- 3.5 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 an 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 identify them for further follow-up. 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.

4. EMERGENCY FIELD THERAPY

- 4.1 These oxime autoinjectors appear to be available:
 - (a) Pralidoxime chloride (600 mg) and atropine (2 mg)

- (b) Pralidoxime methylsulfate (350 mg), atropine sulfate (2 mg) and avizafone chlohydrate (20 mg)
- (c) Obidoxime chloride (220 mg) and atropine (2 mg)
- (d) TMB 4 (80 mg) and atropine (2 mg)
- (e) HI-6 dimethanesulfonate (750 mg), atropine (2 mg) and diazepam (10 mg)

4.2 Strategies using these autoinjectors depend on the country in which they are licensed. No data on the tolerability of HI-6 dimethanesulfonate to humans were available to the authors. Therefore the use of this type of autoinjector cannot be recommended at present until sufficient information becomes available to permit an evidence-based assessment.

Self-aid (first/buddy aid)

- 4.3 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).
- 4.4 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 should be avoided. If the manifestations of poisoning are still present, further autoinjectors, up to a total of 3, should be administered depending on signs and symptoms e.g. every 5 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.
- 4.5 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

- 4.6 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. First responders should wear appropriate personal protective equipment (PPE). After referral of the patients to hospitals, self-protection of medical and paramedical personnel engaged in the management of casualties should be

continued. Masks with a charcoal filter, heavy rubber gloves and protective clothing should be used.

- 4.7 Atropine should be administered in doses of 1-2 mg intramuscularly (i.m according to signs and symptoms) 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. However, the damage resulting from prevention of atropine may be more severe.
- 4.8 In severe poisoning - involving bronchoconstriction, copious bronchial secretion, respiratory insufficiency and/or depression, and convulsions - assisted ventilation must be applied.

Cardiorespiratory resuscitation/stabilisation

- 4.9 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 are enforced. The standard mouth-to-mouth method with extreme caution might be used if there is no other option for ventilation. It is estimated that less than 10% of inspired sarin is expired resulting in a low hazard from exhaled air. 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 resuscitation are essential.

5. PHARMACOLOGICAL TREATMENT OF NA POISONING

- 5.1 This involves the use of:
- (a) **Anticholinergics** (atropine) to antagonise the muscarinic effects.
 - (b) **Oximes** to reactivate inhibited AChE and antagonise the nicotinic effects.
- 5.2 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 nervous system (PNS) and central nervous system (CNS). Atropine cannot counteract the effect of ACh at nicotinic receptors in the PNS or CNS.
- 5.3 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. 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

- 5.4 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. Children are more susceptible to atropine over-dosage with sometimes severe occurrence of arrhythmia.
- 5.5 By inhibiting sweat production, atropine increases heat stress and care must be taken to avoid hyperthermia in warm or hot weather. Atropine given by the parenteral route 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.
- 5.6 Atropine dosage after transfer to hospital: Atropine dosage after transfer to hospital: Clinical experience in the treatment of NA toxicity indicates that lower atropine doses are needed than for severe OP pesticide poisoning. There is no established atropine dosage protocol, and numerous variations of dosing schedules are used in clinical practice. However, the general agreement is that atropine dose should be individually titrated to achieve clinical effect. For easier handling a high concentration atropine solution (100 mg/ml) or large volume (10 to 20 ml) ampules of 2 mg/ml atropine solutions are recommended for stockpiling. After initial atropinisation, 10-20% of a loading dose of atropine should be used in 5% dextrose solution as a continuous therapy that should be gradually decreased according to the clinical findings.
- 5.7 Oximes: These remove the organophosphorus group from the OP-inhibited AChE, restoring 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, and dosing schemes for intravenous administration of oximes, applied to poisoning of humans by OP insecticides, appear in Table 3.
- 5.8 Obidoxime chloride: 250 mg bolus then 750 mg/24 h for an adult. Pralidoxime (2-PAM chloride; 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) (Table 4). The recommended plasma concentration of 3.6 mg/l of obidoxime chloride and pralidoxime chloride 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 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

TABLE 4: OXIME DOSING

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

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

- 5.9 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 might be cases where the net-reactivation is approximately zero due to the high amount of NA circulating in the body. Nevertheless continuous reactivation even if followed by immediate re-inhibition prevents AChE from “ageing”. There is only limited experience with human poisoning by NAs, but experimental data suggest that NAs (G-, but not V-type) will persist in the body for a shorter time than OP insecticides. Thus, administration of oximes should be continued for 24-48 h or longer until recovery of the patient. To assess this, a commercial laboratory test system of AChE status should be used.
- 5.10 Unequal efficacy of bispyridinium oximes is well known. During the last five decades, five pyridinium oximes have been found to be worthy of use as antidotes against nerve agents in humans: pralidoxime chloride (PAM-2 Cl) and mesylate (P2S) against sarin, cyclosarin and VX; trimedoxime (TMB-4) and obidoxime (LüH-6) against tabun, sarin and VX; HI-6 against sarin, soman, cyclosarin and VX; and HLö-7

against all the five nerve agents. Only HLö-7 can reactivate AChE inhibited by all the nerve agents mentioned *in vitro* and *in vivo*. Yet, the synthesis is laborious and HLö-7 is pretty unstable with a short shelf-life complicating stockpiling. Next in efficacy follows HI-6, which can reactivate AChE inhibited by 4 of the agents, but not that inhibited by tabun.

Oxime treatment after transfer from the first line to hospitals

5.11 Although numerous oximes are available, the clinical experience refers mainly to the use of pralidoxime and obidoxime. Until a sufficient level of clinical evidence is provided, although there are authors who disagree and insist on flexible dosing schemes, the therapeutic scheme recommended by the World Health Organization should be used:

- (a) Pralidoxime administered by intravenous (i.v) at a dose of 30 mg/kg in 5% glucose solution (30 min duration), followed by 8 mg/kg/h continuously, until clinical recovery, or 12 h after the last dose of atropine was given. In countries relying solely on pralidoxime, a significant antidotal gap exists. Obidoxime is a much potent reactivator in case of VX, sarin and common pesticides such as dimethoxy- or diethoxy-OPs.
- (b) Obidoxime i.v at a dose of 8 mg/kg initially, followed by 3 mg/kg/h (500 mg loading dose, followed by 750-1000 mg in a continuous infusion).

6. 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; intramuscular (i.m) application can cause pain at the injection site and hepatic dysfunction after multiple doses. HI-6 has a better tolerance profile. Adverse effects reported for HI-6 in healthy volunteers are nausea and headache only. HI-6 dimethanesulfonate has better solubility in aqueous media than HI-6 dichloride for application in dry/wet autoinjectors.

7. ANTICONVULSANTS

7.1 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. Lorazepam and midazolam are also effective in treatment of NA-induced seizures. Midazolam is even more potent than diazepam in antidoting seizures owing to its fast penetration and distribution following i.m. injection and may replace diazepam in cases requiring urgent treatment.

- 7.2 Anticholinergic drugs such as scopolamine, caramiphen, benactyzine, procyclidine trihexyphenidyl were investigated for anticonvulsive effect in comparison with diazepam. It was demonstrated that seizures are caused by glutamergic and cholinergic receptors, which raises the question of whether benzodiazepines are sufficient as they express their anticonvulsive effect only through the gabaergic mechanism. Several studies elucidated the effect of centrally active antigitamergic and anticholinergic compounds. A promising candidate in addition to benzodiazepines is scopolamine. A review of the current literature shows that scopolamine could be administered in a single dose in addition to atropine, an oxime and benzodiazepine. The best results were obtained 40 min after seizure onset with diazepam as the most potent, and then scopolamine, benactyzine and biperiden. In experimental studies in guinea pigs it was shown that benactyzine could stop seizures more effectively than diazepam. Israel and the USA from 1975-1980 used TAB – a mixture of the oxime TMB-4, atropine and the lipid soluble anticholinergic drug benactyzine - for immediate nerve agent treatment. Benactyzine was found to produce less sweating than atropine, so it might be a preferable treatment compared to atropine for soldiers operating in a warm environment.

8. SUPPORTIVE CARE

Supportive treatment includes general measures like i.v infusions, restoration of electrolyte and pH balance and treatment of respiratory failure and/or convulsions. In some cases, treating the infection and symptoms are 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.

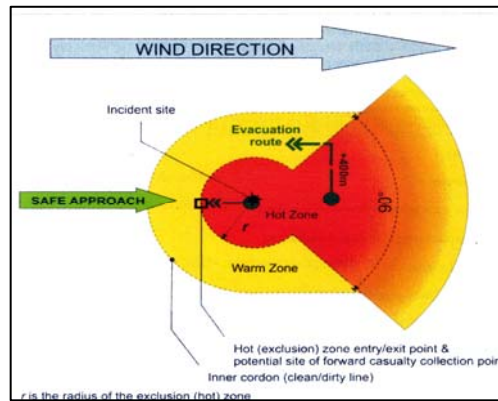
9. PREHOSPITAL MANAGEMENT

- 9.1 Casualties whose skin or clothing is contaminated with liquid NA can contaminate rescuers by contact or intoxicate them with 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,
- 9.2 2-PAM or obidoxime have 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.

10. HOT ZONE

Entering the hot zone requires PPE and trained personnel. 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 Guidelines (EOG) (Figure 1).

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



11. RESCUER PROTECTION

- 11.1 Rapid local and systemic effects are induced when NA vapour is readily absorbed by inhalation and eye contact. Absorption of liquid through the skin is prompt but the effects may be delayed for several minutes up to 18 h depending on the dose and the nature of the agent.
- 11.2 Respiratory protection using an appropriate charcoal filter is sufficient. First responders must wear pressure-demand self-contained breathing apparatus (SCBA) to respond to casualties poisoned by NA vapour or liquid.
- 11.3 Skin protection: To prevent skin absorption of liquid NA, chemical-protective clothing and butyl rubber gloves are recommended.

Triage

- 11.4 Chemical casualty triage is based on walking feasibility, respiratory status, age, and 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.

12. SUMMARY OF CURRENT NERVE AGENT TREATMENTS

- 12.1 First aid recommendations under field conditions: 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) AIBC: Atropine (2 mg), pralidoxime methylsulfate (350 mg), avizafone chlorhydrate (20 mg)
- (c) ATOX II: Atropine (2 mg, 0.7 ml) and obidoxime (220 mg)
- (d) ATNAA: Atropine (2 mg/0.7 ml) and 2-PAM (600 mg/2 ml); 1 needle inject both drugs ATROPEN:
- (e) 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 rhinorrhoea (1 × MARK I kit)
 - (ii) severe respiratory distress (2 × MARK I kits)
 - (iii) severe breathing difficulties, apnoea, cyanosis, muscle twitching, seizures and unconsciousness (3 × MARK I kits and diazepam)

12.2 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, taking as an example the current US army doctrine. Other countries may have slightly different approaches, especially when using an autoinjector combining the three drugs.

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	

13. ADJUNCT AGENTS AND NEW TRENDS IN THE TREATMENT OF NERVE AGENT POISONING

Neuroprotective agents

- 13.1 **Gacyclidine:** Gacyclidine was studied in experimental and clinical trials for different neuroprotective indications. It is a new fencyclidine derivative that binds to *N*-methyl-D-aspartate (NMDA) receptors, and also to non-NMDA binding sites located in the cerebellum and on the dendritic tree of Purkinje cells, and unrelated to known neurotransmitters. Gacyclidine prevents glutamate-induced neuronal death, reduces the size of lesions after traumatic brain injury, and enhances the neuroprotective activity of atropine, pralidoxime and diazepam in soman poisoning. The clinical findings and EEG recording revealed that convulsions could be prevented in soman experiments using primates. Optimal effects were achieved within 30 min of poisoning. Gacyclidine was useful in inhibiting neuropathologic changes occurring 3 weeks after a soman challenge. Unfortunately, gacyclidine production had been stopped several years ago. Ketamine, a weaker NMDA antagonist, with a large clinical use worldwide should be considered for the treatment of nerve agent-induced refractory status epilepticus (see 13.3).
- 13.2 **Tezampanel:** Tezampanel is an anti-glutamatergic agent with a specific affinity for kainate sub-type receptors. In experimental animals it reduced the length of status epilepticus and neuropathy induced by soman. The best results were achieved if it was administered within 1 h after exposure.
- 13.3 **Ketamine:** Ketamine is a cyclohexanone derivative that blocks NMDA receptors non-competitively. A study with soman-poisoned guinea pigs showed that ketamine effectively stopped seizures and reduced related brain damage when administered 1 h after exposure. Co-administration of benzodiazepines provided a synergistic effect, and when used with atropine, an additional neuroprotective effect (suppression of neutrophil granulocyte infiltration and partial suppression of glial activity). The additional benefit of ketamine and atropine was explained by NMDA antagonism, possibly reduction of glutamate release and the anticholinergic effect of atropine. Similar benefits have been observed on mice and rats.
- 13.4 **Huperzine A:** Huperzine A is an alkaloid purified from the Chinese club moss, that is used to treat Alzheimer's disease and myasthenia gravis. It inhibits AChE reversibly, similar to donepezil, rivastigmine or galantamine. A beneficial effect of reducing the severity of seizures and prevention of status epilepticus by blocking the NMDA receptors has been shown in animal experiments.
- 13.5 **Caramiphen:** Caramiphen is an antimuscarinic drug with antiglutamergic and gabaergic properties. Its therapeutic efficacy against OP-poisoning as a prophylactic and post-exposure treatment has been confirmed in several experimental studies.
- 13.6 **Galantamine:** Galantamine (GAL) inhibits AChE and potentiates ACh-induced currents in brain neurons. It also potentiates the activity of NMDA receptors, an action which is partially responsible for the improvement of neurocognitive function in patients with Alzheimer's disease. In contrast to pyridostigmine and physostigmine that also inhibit BuChE, it should help preserve the scavenger capacity of plasma

BuChE for OP compounds. It crosses the blood-brain barrier, protecting the brain AChE from OP-induced irreversible inhibition. Magnetic resonance imaging revealed that galantamine, administered 30 min prior to exposure of guinea pigs to a lethal dose of soman, prevented brain damage. Galantamine is absorbed rapidly with absolute oral bioavailability between 80% and 100%. It has a half-life of 7 h. Peak inhibition of AChE was achieved ~1 h after a single oral dose of 8 mg in some healthy volunteers. In one study, performed in guinea pigs, challenged with 16.8 µg/kg VX ($2 \times LD_{50}$), GAL hydrobromide antagonised VX-induced lethality, impairment of muscle tension, and EEG changes. Optimal clinical effect was found with 10 mg/kg GAL. It did not alter seizure onset induced by VX, but produced a significant decrease in seizure duration when administered as a post-exposure treatment against $2 \times LD_{50}$ VX.

- 13.7 **Penehyclidine hydrochloride:** The anticholinergic agent penehyclidine hydrochloride has been used clinically for treating poisoning by organophosphorus pesticides. Previous studies confirmed its ability to cross the blood-brain barrier and antagonise muscarinic and nicotinic receptors in the brain. Penehyclidine hydrochloride was able to pause ongoing seizures and had a better neuroprotective effect if administered soon after seizure onset in soman poisonin in experimental animals.
- 13.8 **Sodium hydrogencarbonate and blood alkalinisation:** To increase the hydrolysis of OP molecules *in vivo*, the effects of higher doses of sodium hydrogencarbonate (5 milli-equivalent/kg (mEq/kg) in 1 h, followed by 5 mEq/kg/day) were assessed. Adjustment of the dose according to the arterial blood gas analysis was necessary. Increasing one unit of pH was accompanied by a 10-fold increase in OP hydrolysis, and alkalinisation products of NAs such as those from soman were less toxic. Hence, blood alkalinisation may be beneficial in NA poisoning. The proposed mechanism involves better control of cardiotoxicity, increased bio-availability of oximes, increased atropine activity, and/or a direct effect of sodium hydrogencarbonate on neuromuscular function. The administration of sodium hydrogencarbonate is not yet established as a standardised procedure.
- 13.9 **Magnesium sulfate:** The mechanism of action of magnesium sulfate is inhibition of ACh release through blocking calcium channels in the central nervous system and at peripheral sympathetic and parasympathetic synapses. Its efficacy in acute OP poisoning has been evaluated in several studies that have shown decreased mortality and reduced overstimulation of the CNS due to NMDA receptor activation. Doses of 4-16 g of magnesium sulfate were assessed and no side effects were observed. However, there is still insufficient evidence to recommend the routine use of magnesium sulfate in NA casualties.
- 13.10 **Antioxidants:** Besides the inhibition of AChE, the mechanism of OP compound poisoning possibly includes induction of oxidative stress and generation of free oxygen radicals, indicated by the increased activity of catalase, superoxide dismutase (SOD), glutathione peroxidase, and the concentration of malondialdehyde in red blood cells and liver as a biomarker of oxidative stress. Chronic toxicity studies have revealed an increased level of oxidative stress biomarkers as well as increased DNA damage. A beneficial effect of vitamin E and *N*-acetyl-L-cysteine has been shown in experimental studies. However, there is still insufficient evidence to recommend the routine use of drugs fighting the oxidative stress in NA casualties.

Protective bioscavengers

- 13.11 New medical treatment of NA exposure should provide reduced lethality, reverse toxicity following exposure, and help eliminate the need for further treatment. The need to start treatment within 1 min after exposure to be effective against poisoning by all OP compounds has prompted the development of pretreatment therapy, such as bioscavengers of different profile.
- 13.12 **Bioscavengers** are enzymes or antibodies that sequester and neutralise toxic OP compounds before they reach their biological targets.
- 13.13 If enzymes are to be used as therapeutic agents they must fulfill the following:
- have a large spectrum of activity versus different NAs and rapid activity;
 - have a suitable retention time in circulation (ideally 11-15 days);
 - be available in sufficient concentration to be effective;
 - be without antigenic potential (i.e. have no immunogenic properties); and
 - they should be available at a reasonable cost.
- 13.14 The classes of available bioscavengers available are:
- Stoichiometric bioscavengers** - cholinesterases (ChEs), especially butyrylcholinesterase (BChE), and carboxylesterases (CaEs) which react stoichiometrically with OP compounds (1 mole of enzyme neutralises 1 mole of OP compound, inactivating it). A major drawback is that since stoichiometric scavengers bind OP compounds irreversibly in a 1:1 ratio, high doses are required for efficient protection against OP poisoning.
 - “Pseudo catalytic bioscavengers”** that combine AChE (that has scavenging properties and binds NA) and oxime (that acts as a pseudocatalytic bioscavenger reactivating ChE) and thus restores AChE function;
 - Catalytic bioscavengers** (OP hydrolase, OP anhydrase, and paraoxonase (PON) that trap and degrade neurotoxic OP compounds rendering them non- toxic.

Stoichiometric bioscavengers

- 13.15 When used as a pretreatment in mice, fetal bovine serum AChE provided complete protection against VX, lower protection against soman, and in conjunction with atropine and 2-PAM in-post exposure treatment, protection against VX and soman. In one study on rhesus monkeys, equine serum BChE protected against $2 \times LD_{50}$ of soman, and $4 \times LD_{50}$ when atropine was used in the post-exposure treatment.
- 13.16 Plasma-derived human BuChE (pHuBChE) scavenging properties against different NAs were evaluated in mice, rats, and rhesus monkeys, and showed linear correlation between the concentration of pHuBChE and the level of protection against soman,

sarin and VX. Prophylactic pHuBChE has several advantages for human use such as: rapid reaction with a broad spectrum of OP compounds, a good retention time in circulation, and no immunogenic activity. After extrapolation of data from animal experiments to humans, a dose of 200 mg of pHuBChE has been estimated as a prophylaxis for humans in the case of exposure to 2 to 5 × LD₅₀ of soman. For mass production of pHuBChE two methods are currently available: purification of the enzyme from human plasma (Cohn Fraction IV) developed by Baxter Health Care Corporation, or the use of recombinant human enzyme produced in the milk of transgenic goats ('Protexia') developed by Nexia. Recently an investigation focused on identifying a safer source of HuBChE. Possible sources of recombinant HuBChE (rHuBChE) are transgenic plants, transgenic animals, transfected larvae, adenovirus or algae, and also rHuBChE can be derived in cell-lines.

- 13.17 CaE is synthesised in the liver and afterwards is present in the circulation in different concentrations in mammals. However, humans do not express CaE in their circulation and further studies are needed before considering CaE for use as a bioscavenger.
- 13.18 Fresh frozen plasma (FFP) is a blood fraction prepared by removing the cellular components by apheresis. It contains clotting factors, proteins, and enzymes and it is used when these components are deficient or lost. It is hypothesised that in OP insecticide poisoning BChE from FFP will sequester the poison present in blood and remove it from circulation. However, the results of limited studies are controversial and there is no general agreement that it can be recommended for routine use for the treatment of exposure to OP compounds.

Polysialylation of human rHuBuChE for long-acting NA bioscavengers

- 13.19 Chemical polysialylation of rHuBuChE has been used to produce bioscavengers that are stable in the bloodstream. The CHO-based expression system for rHuBuChE resulted in a significant increase of the levels of functional bioscavenger that was stable in blood, with better pharmacokinetic properties, and protection against 4.2 × LD₅₀ of *O*-isobutyl *S*-2-(diethylamino)ethyl methylphosphothiolate (VR).

14. METHODS FOR DECONTAMINATION OF NERVE AGENTS

- 14.1 Decontamination of CW agents is generally based on three methods: (i) mechanical, (ii) physical, and (iii) chemical decontamination. It was presented in a separate report by SAB members (*OPCW Today* Vol. 3 No. 1 Aug 2014).

Oxidiser gels

- 14.2 To detoxify NA, a formulation with a gelling agent (e.g. silica, alumina or aluminosilicate clays) and oxidising agent (aqueous sodium hypochlorite) can be prepared at the site of decontamination, and applied to a contaminated area. This approach is suitable for field implementation.

Bacterial phosphotriesterase

- 14.3 Phosphotriesterase (PTE) is an enzyme isolated from the bacterium *Pseudomonas diminuta*. Modified by biotechnological processes, with redesign of the active site, engineered PTE enzymes are useful for detoxification of OP nerve agents *in vivo*.

Nano-structured solids and heterogenous catalysts

- 14.4 Administration of reactive sorbent materials as oxidation promoters or photocatalysts that are activated by sunlight may be considered as a new strategy for individual protection and decontamination in CBRN exposure. Oxides from Zn, Ti, Fe, Mn, Mg, Al, Zr or Cu have a very high specific surface area and defective crystalline edges, corners and sites that are far more reactive than the bulk material. This property is used to decompose NA into non-toxic by-products. Nanomaterials (in particular ZnO-TiO₂ nanofibers obtained by electrospinning technology) are suitable for incorporation into textiles and clothes. Catalytically-active sites on the surface of zinc titanate fibres enable the slow hydrolysis of the NA agent.

Nanosized metal oxides as CWA decontaminants

- 14.5 Having a high surface area, potent adsorbent properties and reactivity towards many CWAs, nanosized particles of MgO, Al₂O₃ and CaO are considered to be promising sorbent materials for removing NAs from contaminated surfaces and degrading them *in situ*, leading to formation of non-toxic end products.

Nanomaterials as active components in barrier creams

- 14.6 Identification of nanomaterials that can be used as reactive components of an active destructive material to treat a chemically contaminated area is of central importance for military operations. Topical skin protectants have been investigated since 1917, when different soaps and ointments were first used, and after significant research in the modern era (since 2000) approved by the FDA as SERPACWA (see Section 2.4). Excellent barrier properties are provided for protection from GD and VX due to the presence of fine PTFE solid dispersed in a fluorinated polyether. However, improvement of SERPACWA, achieved by adjusting the amount of active nanomaterials, perfluorinated polyether oil, PTFE resin and other additives, increases the resistance against sulfur mustard as well.

15. SUMMARY OF RESPONSE TO THE DIRECTOR GENERAL'S REQUEST

- 15.1 Identify best practices for preventing and treating the health effects that arise from acute, prolonged and repeated organophosphorus nerve agent exposure
- (a) In the case of prolonged nerve agent exposure, it is necessary to administer the adequate antidotal treatment consisting of the reactivator of nerve agent-inhibited acetylcholinesterase (AChE), the anticholinergic drug to counteract the overstimulation of peripheral and central cholinergic muscarinic receptors, and the anticonvulsive drug to prevent centrally mediated seizures and subsequent tonic-clonic convulsions until the exposure to nerve agent ceases. It must continue as long as NA-induced clinical and laboratory signs

and symptoms are visible. The oximes should be administered at a dose regimen that allows the clinical improvement and the normalisation of AChE activity or until no further improvement is achieved.

- (b) To regulate repeated administration of reactivators of nerve agent-inhibited AChE, it is important to measure the activity of cholinesterases in the blood (erythrocyte AChE and plasma BChE) including the test of reactivation to evaluate the reactivating efficacy of the chosen oxime. The anticholinergic drugs should be administered until the signs and symptoms of atropinisation appear. Atropinisation should be visible for a longer time (within days). The anticonvulsive drugs should be given until the signs and symptoms of disturbed neuromuscular transmission and centrally-mediated seizures are visible. To regulate the repeated administration of anticonvulsive drugs, it is important to monitor the function of the central and peripheral nervous system, including EEG examination and muscle electromyography. Antidotal treatment should be supported by symptomatic treatment including oxygenation, assisted ventilation, and the prevention of acidosis and infection, according to the severity of nerve agent poisoning.
- (c) In the case of repeated nerve agent exposure, each exposure must be treated the same way as the first exposure using adequate antidotes and supportive symptomatic drugs. It is necessary to note that humans can be more sensitive to the acute toxicity of nerve agents in the case of repeated exposure because of the lower activity of AChE in the peripheral and central nervous system due to previous NA exposures (although changes of the activity of blood ChEs have not to be very pronounced, the monitoring of their activity is necessary). The prognosis of repeated exposure to NA is more severe and the antidotal and supportive treatment must be as intensive as possible.

15.2 Identify any emerging medical countermeasures, intended for use at the point of exposure that can reduce or eliminate longer term health effects arising from acute, prolonged and repeated organophosphorus exposure

- (a) The crucial approach - how to reduce or eliminate longer term health effects arising from acute, prolonged and repeated nerve agent exposure - is to treat correctly the acute phase of nerve agent poisoning (acute cholinergic crisis). Only rapidly administered adequate antidotal treatment consisting of a reactivator of NA-inhibited AChE (preferably the oxime HI-6 or obidoxime), an anticholinergic drug (preferably atropine), and an anticonvulsive drug (preferably a benzodiazepine), can stop the overstimulation of peripheral and central cholinergic receptors and subsequent clinical signs and symptoms.
- (b) Delayed and prolonged effects of nerve agents are mostly caused by damage to the CNS (frontal cortex, piriform cortex, hippocampus, and amygdala) through centrally-mediated seizures (due to prolonged overstimulation of central cholinergic muscarinic receptors and subsequent activation of glutamatergic receptors). To prevent these seizures, it is necessary to prevent prolonged stimulation of muscarinic receptors by a centrally-acting anticholinergic drug (preferably scopolamine or benactyzine) and an anticonvulsive drug (preferably selected from diazepam, alprazolam, or

midazolam during the initial seizures; with addition of other drugs such as ketamine during refractory status epilepticus that can only be properly treated in hospital). The antidotes must be administered as soon as possible to prevent delayed and prolonged health effects of NAs. If adequate medical countermeasures are insufficiently effective or are not realised sufficiently rapidly after the onset of nerve agent poisoning, longer term health effects (especially neurological and including symptoms such as increased excitability and a deficit of cognitive function) emerge. In that case, the treatment is insufficient to eliminate such damage. However symptomatic and supportive treatment should be recommended in this situation.

- 15.3 The role of prophylactic antidotes against nerve agents in the prevention of longer term health effects arising from acute, prolonged and repeated exposure to organophosphorus compounds
- (a) Prophylactic antidotes against NAs have been developed and introduced into military service for two reasons, to increase the:
 - (i) Resistance of the organism against acute toxicity of nerve agents
 - (ii) Efficacy of post-exposure antidotal treatment of NA poisoning
 - (b) Prophylactic antidotes to NAs should be administered in response to the threat of exposure to NAs. Generally, the combination of the administration of prophylactic antidotes (pre-treatment) and post-exposure adequate antidote treatment increases the probability of avoiding the delayed and prolonged effects of NAs resulting from CNS damage caused by centrally-mediated seizures (via protracted overstimulation of central cholinergic muscarinic receptors and the subsequent activation of glutamatergic receptors in the CNS).
 - (c) Pyridostigmine bromide is a common prophylactic antidote against NA poisoning. Unfortunately, it has several drawbacks. Its dosage is limited due to the risk of adverse effects and it cannot penetrate the blood-brain barrier. Thus, pyridostigmine can only protect peripheral AChE against irreversible inhibition by NAs. Therefore, a combined oral prophylaxis called PANPAL was developed in the Czech Republic. Clinical approval from the FDA and EMA would be necessary prior a general recommendation. PANPAL consists of a reversible AChE inhibitor (pyridostigmine) to protect peripheral AChE from irreversible inhibition by NAs and two centrally-acting anticholinergic drugs (benactyzine and trihexyphenidyl) to increase slightly the dose of pyridostigmine bromide and to antagonise the overstimulation of central cholinergic muscarinic receptors. This combination introduced into the Czech Army shows higher efficacy than pyridostigmine alone to avoid or at least diminish the acute toxicity and to prevent delayed and long-lasting health effects from acute, prolonged and repeated exposure to NAs.

- (d) Another approach to increase the resistance of humans to NAs and the efficacy of post-exposure antidotal treatment of poisoning is to administer reactivators of NA-inhibited AChE in advance. In the Czech Republic, a special prophylactic antidote called TRANSANT (involving the oxime HI-6) was developed and introduced into the Czech Army. Clinical approval of the FDA and EMA would be necessary prior a general recommendation. This makes it possible to administer percutaneously the oxime HI-6 before exposure to NAs. The presence of HI-6 in the bloodstream enables immediate reactivation of NA-inhibited AChE. The combination of both prophylactic antidotal means (PANPAL and TRANSANT) represents an effective prevention that is able to increase markedly the resistance of humans and prevent the centrally-mediated seizures as well as subsequent delayed and prolonged health effects from acute, prolonged and repeated exposure to NAs.
- (e) A recent alternative approach to the development of prophylaxis in the case of threat of exposure to NAs is administration of stoichiometric modified BChE or catalytic bioscavengers (modified paraoxonase or phosphotriesterase) able to bind or hydrolyse NAs before they reach the target of their acute toxicity (AChE in the peripheral and central nervous system). This type of prophylaxis is valuable but until now has not been prepared for clinical use. However, it represents a promising approach to preventing the longer term health effects arising from acute, prolonged and repeated NA exposure.

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17. REFERENCES

Aaron, C. and Howland, M. A.. Insecticides: organophosphates and carbamates, Goldfrank's Toxicologic Emergencies, eds. Goldfrank, L. R., Weisman, R. S., Flomenbaum, N. E et al., Appleton & Lange, Norwalk, CT, USA, 1994; pp. 1105-1116.

Abdollahi, M., Karami-Mohajeri, S.. A comprehensive review on experimental and clinical findings in intermediate syndrome caused by organophosphate poisoning. *Toxicol. Appl. Pharmacol.* 2012; 258(3): 309-314. doi: 10.1016/j.taap.2011.11.014.

Abdollahi, M., Mostafalou, S., Pournourmohammadi, S., Shadnia, S.. 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*, 2004; 137, pp. 29-34.

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

Abou-Donia, M. B.. Organophosphorus ester-induced chronic neurotoxicity. *Archives of Environmental Health* 2003; 58 (8): 484-497.

Abu-Qare, A. W. and Abou-Donia, M. B.. Sarin: health effects, metabolism, and methods of analysis. *Food & Chemical Toxicology* 2002; 40 (10): 1327-1333.

Akhgari, M., Abdollahi, M., Kebryaezadeh, A., Hosseini, R., Sabzevari, O.. Biochemical evidence for free radical induced lipid peroxidation as mechanism for subchronic toxicity of malathion in blood and liver of rats. *Human Expt. Toxicol.* 2003; 22(4): 205-211.

American Heart Association. Management of Cardiac Arrest. *Circulation* 2005; 112: 58-66.

Antonijević, B., Vučinić, S., Čupić, V.. Protective effect of HI-6 and trimesoxime combination in mice acutely poisoned with tabun, dichlorvos or heptenophos. *Acta Veterinaria (Beograd)*, 2012; 62(2-3): 123-135.

Aracava, Y., Pereira, E.F., Akkerman, M., Adler, M., Albuquerque, E.X.. Effectiveness of donepezil, rivastigmine, and (±) huperzine A in counteracting the acute toxicity of organophosphorus nerve agents: comparison with galantamine. *J. Pharmacol. Expt. Ther.* 2009; 331(3): 1014-1024.

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

Balali-Mood, M., Saber, H.. Recent advances in the treatment of organophosphorus poisoning. *IJMS* 2012; 37: 74-91.

Balali-Mood, M., Balali-Mood, K.. Neurotoxic disorders of organophosphorus compounds and their managements. *Arch. Iran Med.* 2008; 11: 65-89.

Balali-Mood, M., Shariat, M.. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *J. Physiol.* 1998; 92 (5-6): 375-378.

Basher, A., Rahman S.J.H., Ghose A., Arif S.M., Faiz M.A., Dawson, A.H.. Phase II study of magnesium sulfate in acute organophosphate pesticide poisoning. *J. Clin. Toxicol.* 2013; 51 (1): 35-40.

Bateman, D.. Are there long-term sequelae from repeated low dose organophosphorus insecticide exposures? *J. Clin. Toxicol.* 1999; 37 (3): 368-369.

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

Benson, B., Tolo, D. et al.. Is the intermediate syndrome in organophosphate poisoning the result of insufficient oxime therapy? *J. Clin. Toxicol.* 1992; 30 (3): 347-349.

Brandeis, R., Raveh, L., Grunwald, J., Cohen, E., Ashani, Y.. Prevention of soman-induced cognitive deficits by pretreatment with human butyrylcholinesterase in rats. *Pharmacol. Biochem. Behav.* 1993; 46: 889-896.

Braue, E.H., Boecker, J.D., Doxzon, B.F., Hall, R.L., Simons, R.T., Nohe, T.L. et al.. Nanomaterials as active components in chemical warfare agent barrier creams, in: *Defense Application of Nanomaterials*; eds. Miziolek A. et al., ACS Symposium Series; American Chemical Society: Washington, DC, 2005; downloaded by 193.52.234.176 on October 21, 2009./http://pubs.acs.org.

Brown, M.A., Brix, K.A.. Review of health consequences from high-, intermediate- and low-level exposure to organophosphorus nerve agents. *J. Appl. Toxicol.* 1998; 18(6): 393-408.

Buckley, N.A., Karalliedde, L. 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.* 2004; 42 (1): 113-116.

Buckley, N.A., Eddleston, M., Li, Y., Bevan, M., Robertson J.. Oximes for acute organophosphate poisoning. *Cochrane Database Syst. Rev.* 16(2): 2011; CD005085.doi:10.1002/14651858.CD005085.pub2.

Cerasoli, D.M., Griffiths, E.M., Doctor B.P. et al.. In vitro and in vivo characterization of recombinant human butyrylcholinesterase (Protexia) as a potential nerve agent bioscavenger. *Biotechnol. Bioeng.* 2011; 75: 259-266.

Chilukuri, N., Parikh, K., Sun, W. et al.. Polyethylene glycosylation prolongs the circulation ability of recombinant human butyrylcholinesterase. *Chem. Biol. Interact.* 2005; 157-158: 115-121.

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

Colosio, C., Tiramani, M., *et al.*. Neurobehavioral effects of pesticides: state of the art, *Neurotoxicology* 2003; 24 (4-5): 577-591.

Daniels, J.L., Olshan, A.F., *et al.*. Residential pesticide exposure and neuroblastoma, *Epidemiology* 2001; 12(1): 20-27.

Dart, R. C., Stark, Y., *et al.*. Insufficient stocking of poisoning antidotes in hospital pharmacies, *Journal of the American Medical Association* 1996; 276 (18): 1508-1510.

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

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

De Silva, H. J., Wijewickrema, R., *et al.* Does pralidoxime affect outcome of management in acute organophosphorus poisoning? *Lancet* 1992; 339 (8802): 1136-1138.

Dorandeu F., Barbier L., Dhote F., Testylier G., Carpentier P.. Ketamine combination for the field treatment of soman – induced self – sustaining status epilepticus. Review of current data and perspectives. *Chem Biol Interact* 2013; 20 (1): 154 - 9.

Dote, F., Carpentier, P., Barbier, L., Peinnequin, A., Baille, V., Perrot, F., Testylier, G. *et al.*. Combination of ketamine and atropine are neuroprotective and reduce neuroinflammation after a toxic status epilepticus in mice. *Toxicol. Appl. Pharmacol.* 2012; 259: 195-209.

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

Eddleston, M., Szinicz, L. *et al.*. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. *QJM* 2002; 95 (5): 275-283.

Erdman, A.R. Pesticides, in *Medical Toxicology*, Dart R. C., Lippincott Williams & Wilkins, Philadelphia USA, 2004, pp. 1475-1496.

Eyer, P. Optimal oxime dosage regimen, a pharmacokinetic approach, in: eds. Szinicz, L., Eyer, P., Klimmek, R., Role of oximes in the treatment of anticholinesterase agent poisoning, Spektrum Akademischer Verlag, Oxford UK, 1996, pp. 33-51.

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

Fernández, M. Atropine, *Medical Toxicology*, ed. Dart R.C., Lippincott Williams & Wilkins, Philadelphia USA, 2004, pp. 163-165.

Food and Drug Administration (20 June 2003). FDA talk paper: FDA approves pediatric doses of atropen, retrieved on 4 November 2005 from <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01232.html>.

Galloway, T., Handy, R.. Immunotoxicity of organophosphorus pesticides. *Ecotoxicology* 2003; 12 (1-4): 345-363.

Garcia, G.E., Vernon, A., Moorad-Doctor, D., Ratcliffe, R.H.. (-)-Huperzine A replacement for pyridostigmine bromide as nerve agent pretreatment, measured in guinea pig plasma by new ultrahigh-pressure liquid chromatography (UHPLC)-MS method. *FASEB J.* 2009; 23 Suppl.

Geller, R.. 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.

Geller, R.J., Lopez, G.P., *et al.* Atropine availability as an antidote for nerve agent casualties: validated rapid reformulation of high-concentration atropine from bulk powder. *Annals of Emergency Medicine* 2003; 41 (4): 453-456.

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

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

Grunwald, J., Raveh, L., Doctor, B.P., Gordon, R.K., Nambiar, M.P.. [+]Huperzine A treatment against *N*-methyl-D-aspartate-induced seizures/status epilepticus in rats. *Chem. Biol. Interact.* 2008; 175: 387-395.

Gullapalli, R.P., Aracava, Y., Zhuo, J., Helai-Neto, E., Wang, J., Makris, G., Merchenthaler, I., Pereira, E.F., Albuquerque, E.X.. Magnetic resonance imaging reveals that galanthamine prevents structural brain damage induced by an acute exposure of guinea pigs to soman. *Neurotoxicology* 2010; 31(1): 67-76.

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

Harris, L.W., Talbot, B.G., *et al.* The relationship between oxime-induced reactivation of carbamoylated acetylcholinesterase and antidotal efficacy against carbamate intoxication. *Toxicology & Applied Pharmacology* 1989, 98 (1): 128-133.

Hayes, A.L., Wise, R.A. *et al.* Assessment of occupational exposure to organophosphates in pest control operators. *Am. Ind. Hyg. Assoc.* 1980; J41 (8): 568-575.

Hayes, W.J. and Laws, E.R.. Diagnosis and treatment of poisoning, *Handbook of Pesticide Toxicology*, eds Hayes W.J., Laws, E.R.; San Diego, Academic Press Inc., 1991; pp. 388-403.

Hilmas, C.J., Poole, M.J., Finneran, K., Matthew, G.C., Williams, P.T.. Galantamine is a novel post-exposure therapeutic against lethal VX challenge. *Toxicol. Appl. Pharmacol.* 2009; 240: 166-173.

Horton, D.K., Berkowitz, Z. *et al.*. Secondary contamination of ED personnel from hazardous materials events, 1995-2001. *American Journal of Emergency Medicine* 2003; 21 (3): 199-204.

Hosseini, A., Abdollahi, M.. Diabetic neuropathy and oxidative stress: therapeutic perspectives. *Oxid. Med. Cell Longev.* 2013; 168039. doi: 10.1155/2013/168039.

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

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

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

Jaga, K., Dharmani C.. Sources of exposure to and public health implications of organophosphate pesticides. *Pan American Journal of Public Health* 2003; 14 (3): 171-185.

Jamal, G.A.. Neurological syndromes of organophosphorus compounds. *Adverse Drug React. Toxicol. Rev.* 1997; 16 (3): 133-170.

Johnson, M.K., Vale, J.A., *et al.*. Pralidoxime for organophosphorus poisoning. *Lancet* 1992; 340 (8810): 64.

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

Jokanovic, M., Stukalov, P.V. *et al.*. Organophosphate induced delayed polyneuropathy. *Current Drug Targets - CNS & Neurological Disorders* 2002; 1 (6): 593-602.

Kaji, A.H., Lewis, R.J.. Hospital disaster preparedness in Los Angeles County, California. *Annals of Emergency Medicine* 2004; 44 (4): S33.

Karalliedde, L.. Organophosphorus poisoning and anaesthesia. *Anaesthesia* 1999; 54 (11): 1073-1088.

Karalliedde, L.. Cholinesterase estimations revisited: the clinical relevance. *European Journal of Anaesthesiology* 2002, 19 (5): 313-316.

Karalliede, L., Baker, D., Marrs, T.C.. Organophosphate-induced intermediate syndrome: aetiology and relationships with myopathy. *Toxicol. Rev.* 2006; 25 (1): 1-14.

Karalliedde, L., Wheeler, H. *et al.*. Possible immediate and long-term health effects following exposure to chemical warfare agents. *Public Health* 2000; 114 (4): 238-248.

Karami-Mohajeri, S., Abdollahi, M.. Mitochondrial dysfunction and organophosphorus compounds. *Toxicol. Appl. Pharmacol.* 2013; 270(1): 39-44; doi: 10.1016/j.taap.2013.04.001.

Karami-Mohajeri, S., Nikfar, S., Abdollahi, M.. A systematic review on the nerve muscle electrophysiology in human organophosphorus pesticide exposure. *Hum. Exp. Toxicol.* 2014; 33: 92, doi: 10.1177/0960327113489047.

Kassa, J.. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J. Toxicol.-Clin. Toxicol.* 2002; 40 (6): 803-816.

Kassa, J.. Therapeutic and neuroprotective efficacy of pharmacological pretreatment and antidotal treatment of acute tabun or soman poisoning with the emphasis on pretreatment drug PANPAL. *Arh. Hig. Rada Toksikol.* 2006; 57: 427-434.

Kassa, J., Jun, D., Kuca, K.. A comparison of reactivating efficacy of newly developed oximes (K074, K075) and currently available oximes (obidoxime, HI-6) in cyclosarin and tabun poisoned rats. *J. Enzyme Inhib. Med. Chem.* 2007; 22: 297-300.

Khan, S., Hemalatha, R., *et al.*. Neuroparalysis and oxime efficacy in organophosphate poisoning: a study of butyrylcholinesterase. *Human & Experimental Toxicology* 2001; 20 (4): 169-174.

Koplovitz, I., Schulz, S.. Perspectives on the use of scopolamine as an adjunct treatment to enhance survival following organophosphorus nerve agent poisoning. *Mil. Med.* 2010; 175: 878-882.

Kuca, K., Cabal, J., Jung, Y.S., Musilek, K., Soukup, O., Jun, D., Pohanka, M., Musilofva, L., Karasova, J., Novotny, L., Hrabanova, M.. Reactivation of human brain homogenate cholinesterases inhibited by tabun using newly developed oximes K117 and K127. *Basic Clin. Pharmacol.* 2009; 105: 207-210.

Kwong, T.C.. Organophosphate pesticides: biochemistry and clinical toxicology. *Therapeutic Drug Monitoring* 2002; 24 (1): 144-149.

Lallement, G., Clarençon, D., Galonnier, M., Baubichon, D., Burchart, M.F. Peoc'h M.. Acute soman poisoning in primates neither pretreated nor receiving immediate therapy: value of gacyclidine (GK-11) in delayed medical support. *Arch. Toxicol.* 1999; 7(2): 115-122.

LeBlanc, F., Benson, B.E., *et al.*. A severe organophosphate poisoning requiring the use of an atropine drip. *J. Clin. Toxicol.* 1996; 24: 69-76.

Leikin, J.B., Thomas, R.G., *et al.*. A review of nerve agent exposure for the critical care physician. *Crit. Care Med.* 2002; 30 (10): 2346-2354.

Leon, S.F., Pradilla, A.G. *et al.*. Multiple system organ failure, intermediate syndrome, congenital myasthenic syndrome, and anticholinesterase treatment: the linkage is puzzling. *J. Toxicol. Clin. Toxicol.* 1996; 34 (2): 245-247.

Levitin, H.W., Siegelson, H.J., Dickinson, S., *et al.*. Decontamination of mass casualties - re-evaluating existing dogma. *Prehospital and Disaster Medicine* 2003; 18(3): 200-207.

Lotti, M.. Central neurotoxicity and behavioral effects of anticholinesterases, in: Clinical and experimental toxicology of organophosphates and carbamates, Ballantyne B., Marrs, T.C.; Butterworths, London UK, 1992, pp. 75-83.

Lotti, M., Moretto, A.. Organophosphate-induced delayed polyneuropathy. *Toxicol. Rev.* 2005; 24(1): 37-49.

Marrs, T.C., Dewhurst, I. Toxicology of pesticides: general and Applied Toxicology, Ballantyne, B., Marrs, T.C., Syversen, T.; Macmillan Reference Ltd., London UK, 2000, pp. 1993-2012.

Maxwell, D.M., Castro, C.A., De La Hoz, D.M., *et al.*. Protection of rhesus monkeys against soman and prevention of performance decrement by pretreatment with acetylcholinesterase. *Toxicol. Appl. Pharmacol.* 1992; 115: 44-49.

Moshiri, M., Darchini-Maragheh, E., Balali-Mood, M.. Advances in toxicology and medical treatment of chemical warfare nerve agents. *Daru* 2012; 20(1): 81.

Namba, T.. Cholinesterase inhibition by organophosphorus compounds and its clinical effects. *Bulletin of the World Health Organization* 1971; 44(1): 289-307.

Namba, T., Nolte, C.T. *et al.*. Poisoning due to organophosphate insecticides: acute and chronic manifestations. *American Journal of Medicine* 1971; 50: 475-492.

Newmark, J.. Therapy for nerve agent poisoning. *Archives of Neurology* 2004; 61(5): 649-652.

Okudera, H.. Clinical features on nerve gas terrorism in Matsumoto. *Journal of Clinical Neuroscience* 2002; 9 (1), pp. 17-21.

Okudera, H., Morita, H. *et al.*. Unexpected nerve gas exposure in the city of Matsumoto: report of rescue activity in the first sarin gas terrorism. *American Journal of Emergency Medicine* 1997; 15 (5): 527-528.

Okumura, T., Suzuki, K. *et al.*. Lessons learned from the Tokyo Subway sarin attack. *Prehospital & Disaster Medicine* 2000; 5 (Supplement 2): S32.

Okumura, T., Takasu, N. *et al.*. Report on 640 victims of the Tokyo Subway sarin attack. *Annals of Emergency Medicine* 1996; 28(2): 129-135.

Pajoumand, A., Shadnia, S., Rezaie, A., Abdi, M., Abdollahi, M.. Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides. *Hum. Exp. Toxicol.* 2004; 23(12): 565-569.

Perera, P.M.S, Shahmy, S., Gawarammana, I., Dawson, A.H.. Comparison of two commonly practiced atropinisation regimens in acute organophosphorus and carbamate poisoning, doubling doses vs 'ad hoc' - a prospective observational study. *Hum. Exp. Toxicol.* 2008; 27(6): 513-518.

Raveh, O.L., Eisenkraft, A., Wessman, B.A.. Caramiphen edisylate: an optimal antidote against organophosphate poisoning. *Toxicology* 2014; 325: 115-124.

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

Schier, J.G., Ravikumar, P.R., *et al.*. Preparing for chemical terrorism: stability of injectable atropine sulfate. *Academic Emergency Medicine* 2004; 11 (4): 329-334.

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

Sidell, F.R. *Nerve Agents. Medical Aspects of Chemical and Biological Warfare*, in: Sidell, F.R., Takafuji, E.T., Franz D.R.. Falls Church, Virginia, Office of The Surgeon General, United States Army, USA, 1997, pp. 129-179.

Singh, S., Batra, Y., *et al.*. Is atropine alone sufficient in acute severe organophosphorus poisoning? Experience of a North West Indian Hospital. *International J. Clin. Pharmacol. Therap.* 1995; 33: 628-630.

Singh B, Prasad, G.K., Pandey, K.S., Danikhel, R.K., Vijayaraghavan, R.. Decontamination of chemical warfare agents. *Defence Science Journal* 2010; 60(4): 428-441.

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

Suzuki, J., Kohno, T. *et al.*. Eighteen cases exposed to sarin in Matsumoto, Japan. *Internal Medicine* 1997; 36 (7): 466-470.

Tareg, A.B., *et al.*. Organophosphate and carbamate insecticides, in: *Clinical Environmental Health and Toxic Exposures*, Lippincott Williams & Wilkins, Philadelphia USA, 2001, pp. 1046-1057.

Tattersall, J.. Seizure activity post organophosphate exposure. *Front. Biosci.* 2009; 14: 3688-3711.

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

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

Thiermann, H., Seidl, S., Eyer, P.. HI-6 dimethanesulfonate has better dissolution properties than HI-6 dichloride for application in dry/wet autoinjectors. *Int. J. Pharm.* 1996; 137: 167-176.

Thiermann, H., Szinicz, L., Eyer, P., Felgenhauer, N., Zilker, T., Worek, F.. Lessons to be learnt from organophosphorus pesticide poisoning for the treatment of nerve agent poisoning. *Toxicology* 1997; 233:145-154.

Timperley, C.M., Tattersall, J.E.H.. Toxicology and medical treatment of organophosphorus compounds, in: *Best Synthetic Methods – Organophosphorus (V) Chemistry* (co-authored and edited by Timperley C.M.), Academic Press, Elsevier, Oxford UK, 2014, Chapter 1, pp. 1-90.

Treat, K.N., Williams, J.M. *et al.*. Hospital preparedness for weapons of mass destruction incidents: an initial assessment. *Annals of Emergency Medicine* 2001; 38 (5): 562-565.

U.S. 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 on 18 August 2005, from: www.osha.gov/dts/osta/bestpractices/html/hospital_firstreceivers.html

Vale, J.. Are there long-term sequelae from a single acute organophosphorus insecticide exposure? *Clinical Toxicology* 1999; 37 (9): 367-368.

Van Helden, H.P., Joosen, M.J., Philippens, I.H.. Non-enzymatic pretreatment of nerve agent (soman) poisoning: a brief state-of-the-art review. *Toxicol. Lett.* 2011; 206(1): 35-40.

Vučinić, S., Antonijević, B., Ilić, N., Ilić, T.. Oxime and atropine failure to prevent intermediate syndrome in acute organophosphate poisoning. *Vojnosanit. Pregl.* 2013; 70(4): 420-424.

Vučinić, S., Antonijević, B., Brkić, D.. Occupational and Environmental Aspects of Organophosphorus Compounds. In: *Basic and Clinical Toxicology of Organophosphorus Compounds*. Eds: Balali-Mood, Mahdi, Abdollahi, Mohammad, Springer-Verlag, London, 2014, Chapter 8, pp. 213-245. ISBN: 978-1-4471-5625-3.

Wagner G.W., Procell, L.R., Koper, O.B., Klabunde, K.J.. Decontamination of chemical warfare agents with nanosize metal oxides, in: *Defense Application of Nanomaterials*; ed. Miziolek, A. *et al.*, ACS Symposium Series; American Chemical Society: Washington DC, USA, 2009; downloaded by 193.52.234.176 on October 21, 2009./<http://pubs.acs.org>.

Weissman, B.A., Raveh, L.. Therapy against organophosphate poisoning:the importance of anticholinergic drugs with antiglutamergic properties. *Toxicol. Appl. Pharmacol.* 2008; 232: 351-358.

Wessels, D., Barr, D.B., *et al.*. Use of biomarkers to indicate exposure of children to organophosphate pesticides: implications for a longitudinal study of children's environmental health. *Environmental Health Perspectives* 2003; 111 (16): 1939-1946.

Wiener, S.W., Hoffman, R.S.. Nerve agents: a comprehensive review. *Journal of Intensive Care Medicine* 2004; 19(1): 22-37.

Wolfe, A.D., Rush, R.S., Doctor, B.P., Koplovitz, I., Jones, D.. Acetylcholinesterase prophylaxis against organophosphate toxicity. *Fundam. Appl. Toxicol.* 1987; 9: 266-270.

Worek, F., Backer, M., *et al.*. Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. *Human & Experimental Toxicology* 1997; 16 (8): 466-472.

Worek, F., Thiermann, H., Szinicz, L., Eyer, P.. Kinetic analysis of interactions between human acetylcholinesterase, structurally different organophosphorus compounds and oximes. *Biochem. Pharmacol.* 2004; 68: 2237-2248.

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