



## **Organophosphates**

### **September 2003**

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Chemical warfare, in a mass casualty sense, came into being during World War I as the developing chemical industries of Europe and the United States became capable of mass-producing such toxic agents as chlorine and the mustards. These early chemicals were irritants designed to harass and incapacitate enemy soldiers. Over 110,000 tons of these chemicals were dumped onto the battlefields of Western Europe during WWI. Two decades later, highly lethal chemicals took the place of these early agents, but the idea of actually using them was so abhorrent that they did not see use in World War II. Among these most deadly agents are the organophosphates, a diverse and widely stocked group of chemical agents available in liquid, gas, or aerosol form. The military forms are known as nerve agents or gases, but the more widely available organophosphates include common pesticides for home and farm use and some of these chemicals are just as deadly as their military cousins.

### **Overview: Nerve Agents**

The current collections of military nerve agents are classified as one of two types: G-agents, which are non-persistent and cause death primarily by inhalation, and V-agents, which are persistent and cause death by inhalation or dermal, conjunctival, and mucosal absorption. The military grade nerve agents are Tabun, with the military designation of GA, Sarin or GB, Soman or GD, and VX. These agents are absorbed within minutes, and can kill in 15 to 30 minutes. Of these agents, it is believed that Sarin and VX are the agents most likely to be used in a terrorist strike, with VX being ten times more toxic. Evidence of the use of Sarin by Iraq against its Kurdish population and in its war against Iran was revealed by U.N. inspectors after that war in 1988. Over 90,000 Iranians died from these chemical attacks. Iraq is also suspected of manufacturing VX, as are Cuba and a host of other nations, which supply the world's terrorist

networks and revolutionary armies. Sarin made its debut as a terrorist weapon in 1995, when the Aum Shinrikyo, a Japanese Buddhist cult, used Sarin in an attack on subway passengers in Tokyo, killing 11 people and injuring 5,500.

### **Overview: Pesticides**

Common household and agricultural pesticides pose a significant risk, as they are commercially and easily available. In addition, there are thousands of such toxic compounds, including non-organophosphate chemicals like nicotine sulfate. To obtain the most lethal of these chemicals, one needs only an exterminator's license. Of this vast group of chemicals, the literature has reported numerous deaths from exposure to TEPP – tetraethyl pyrophosphate – and parathion. In fact, in the right concentrations these two agents are as lethal as their military counterparts, yet they are essentially unregulated.

### **Overview: Toxicity**

As you can see from this slide, the toxicity of military nerve agents increased as each new agent was created. The  $LC_{t50}$  is the lethal concentration per unit of time in which 50% of those exposed will die. For Tabun, this concentration is 400 mg-min/m<sup>3</sup> of exposure, while for Sarin, Soman, and VX this concentration is 100, 50 and 10 mg-min/m<sup>3</sup> respectively. For dermal or percutaneous exposure, you can see the difference between G and V agents, with much greater skin exposure required of the older G agents. The dermal  $LD_{50}$ s for Tabun, Sarin, and Soman are 1000 mg, 1700mg, and 350 mg respectively; while it is only 6-10 mg for VX.

With these agents, a single mild exposure, requiring no treatment, is unlikely to be lethal and full recovery is expected. Moderate to severe exposures do require treatment for survival. Repeated exposures produce a cumulative response. To put the idea of mild, moderate and severe exposures into proper perspective, however, 10 mg of VX, its  $LD_{50}$  dose, can be contained in a droplet the size of a pinhead and can be lethal to an adult within 20 minutes.

### **Protective Equipment**

Semi-permeable, active carbon containing protective clothing and a full-face gas mask with an appropriate filter are the only gear that can fully protect against nerve agents. However, even these military-grade suits can slowly allow these agents to penetrate, and must be decontaminated periodically and discarded after a period of continued or repeated exposure. If unavailable, protective gowns, masks, and gloves can minimize skin exposure.

The major drawback to the use of protective equipment is that you must be forewarned of the danger in order to don the gear and assure that it is functioning properly before being exposed. In a terrorist strike, such an

advanced warning is unlikely and few, if any, civilian emergency rooms or EMS systems possess this equipment. It is therefore critical to have the appropriate antidotes, as will be discussed later, readily available.

## **Detection**

Although ideal protection requires advanced warning and the use of protective gear, the ability to detect these agents is also critical in order to confirm their presence in an area and possibly to provide advanced warning to those in need of protection. Single and three-color detector papers are available for individual use to detect liquid nerve agent. These strips are useful in determining whether or not a suspicious liquid on the ground or other objects contains a nerve agent. Area detectors and monitoring devices are also available for areas of high risk, such as government buildings, military posts, and large civilian venues such as sports arenas and their immediate surroundings. These detectors can be obtained through military or emergency management contacts.

## **Decontamination**

Once exposure has been confirmed either clinically or by use of a detection strip, it is imperative to decontaminate the victims immediately. The decontamination process not only reduces the individual's exposure but also decreases the risk of secondary exposures. Fortunately, **Tabun, Sarin, Soman,** and **VX** hydrolyze rapidly in strongly alkaline or chlorinated solutions, so decontamination procedures for skin, equipment and material can be accomplished with commonly available and inexpensive active neutralizing chemicals such as the chloramine solutions found in 5% household bleach. Liquid agents can also be adsorbed by neutral adsorbing powders such as Fullers earth or talcum powder, which prevent the agent from being absorbed into the skin. In addition to neutralizing chemicals and adsorbing powders, copious amounts of water can also dilute and remove these agents. For eye exposure, copious irrigation with water is needed to dilute and remove these agents from the conjunctival sac.

With respect to secondary exposure risks, it is essential to safely remove and contain the victim's clothing, which can be a source of secondary contamination to healthcare workers. Likewise, precautions must be taken when performing CPR on victims, as mouth-to-mouth ventilation can be a source of secondary contamination. It should be noted, however, that the victim's body fluids, urine and feces, do not present a hazard.

Decontamination is critical in preventing healthcare workers, as well as other bystanders and emergency response personnel, from becoming casualties.

## **Signs and Symptoms**

The diagnosis of organophosphate poisoning is a clinical one that can be confirmed by the detection of the agent at the scene of exposure. Nerve agents and organophosphate insecticides inhibit tissue cholinesterases at synaptic sites, and cause the accumulation of excess acetylcholine at nicotinic and muscarinic receptors. The earliest signs of poisoning depend upon the route of exposure: respiratory signs are first if inhaled, GI disturbances if ingested, and local skin signs with dermal contact. Symptoms following inhalation are immediate, while symptoms following mild skin exposure can be delayed as much as 18 hours.

### **Signs and Symptoms**

In most exposures, if death is delayed, the muscarinic effects are dominant first, followed by the nicotinic effects. However, respiratory symptoms quickly predominate in moderate to severe exposures no matter what the route of exposure. If there is no direct eye contact, the ocular signs may come later. There are no specific clinical tests to confirm the exposure physiologically, however, decreased serum cholinesterase activity has been used to try to confirm exposure to nerve agents. This testing is limited in that it is non-specific and useful only when greater than 20% cholinesterase inhibition is present. By that time, severe miosis, headache, eye pain, conjunctival hyperemia, rhinorrhea, and chest tightness are already evident.

### **Signs and Symptoms**

After a localized skin exposure the following signs and symptoms are expected: miosis, usually pinpoint and sometimes unequal; frontal headache; nausea and vomiting; weakness; and fasciculations or sweating at the exposure site. With severe exposures, a rapid progression of signs and symptoms occurs to include: eye pain on focusing; dimmed vision; rhinorrhea; chest tightness; wheezing suggestive of increased secretions and bronchoconstriction; cough; and generalized muscular twitching, weakness, or paralysis. Untreated, the victim will quickly develop convulsions, a loss of consciousness, and the loss of bladder and bowel control before circulatory and pulmonary depression and severe hypotension lead to death.

### **Signs and Symptoms**

Following a mild inhalation exposure, the first signs and symptoms of toxicity will involve the mucous membranes and respiratory tract. Miosis, dimmed vision, headache, rhinorrhea, salivation, and dyspnea with chest tightness can be expected. As in dermal exposures, severe inhalation exposure will produce a quick progression of symptoms that include: slight chest pain, and worsening pulmonary symptoms including increased bronchial secretions, pulmonary edema and cyanosis. Gastrointestinal disturbances, including: anorexia, abdominal cramps, "heartburn" and eructation, diarrhea, tenesmus, and involuntary defecation will also become evident. As stated earlier, muscarinic effects

dominate initially, followed by nicotinic signs. So, in addition to the pulmonary and gastrointestinal effects, the patient will also experience increased sweating, salivation, and lacrimation, slight bradycardia, urinary frequency, and involuntary micturition (incontinence) followed by easy fatigue, muscular twitching or fasciculations, incoordination, generalized weakness that includes the respiratory muscles, pallor, and occasionally hypertension. As the poisoning progresses, CNS signs become evident with giddiness, anxiety or jitteriness, emotional lability, excessive dreaming, insomnia, nightmares, apathy, withdrawal and depression, drowsiness, difficulty in concentrating, slowness of recall, confusion, slurred speech, ataxia, and, ultimately, coma with the absence of reflexes. In its terminal stage, organophosphate poisoning produces Cheyne-Stokes respiration, convulsions, depression of respiratory and circulatory centers, and hypotension – all leading to death.

## **Treatment**

As previously stated, full recovery may occur after a single, mild exposure; but repeated daily exposures are cumulative and may result in severe poisoning. Moderate to severe poisonings necessitate treatment for survival, as inhibition of acetylcholinesterase rapidly becomes more or less irreversible.

First aid for nerve agent victims is the first step. Remove them from additional exposure. Flush the eyes with copious amounts of water for 10 to 15 minutes and decontaminate the skin with liquid household bleach followed by flushing with water. For ingestions, administer activated charcoal and a cathartic, but do not induce vomiting. If needed, begin CPR, avoiding direct mouth-mouth contact, which can produce secondary exposure to the agent.

The mainstays of treatment are anticholinergic and anticonvulsant agents. Atropine sulfate, an antimuscarinic agent, blocks the parasympathetic effects in the periphery and partially counteracts the convulsive effects and respiratory depression in the CNS. Loading doses range between 1 and 5 mg IV every 30 minutes until full atropinization is achieved, as noted by dry mouth, skin, and bronchi; and a heart rate greater than 90 beats per minute. Maintenance therapy should continue for at least 24 hours at doses between 0.5 and 2 mg/hr. Victims should be monitored for arrhythmias secondary to the atropine. Titration of atropine in the individual patient is based on producing a decrease in bronchial constriction and secretions. Heart rate changes are easier to follow but less important. Besides atropine, a centrally acting anticonvulsant should be given, such as diazepam at an initial dose of 10mg IM. Assisted ventilation and general supportive measures will also be required, sometimes for several days.

## **Treatment**

In addition to the anticholinergic and anticonvulsant agents used initially, oximes, which are acetylcholinesterase reactivators, are used to relieve the

important nicotinic symptoms of skeletal neuromuscular blockade. Most clinical experience is with pralidoxime chloride, pralidoxime methanesulfonate or methylsulfate, and obidoxime chloride. Some of the common or brand names of these antidotes are also listed on the slide. These agents have poor CNS penetration and must be repeatedly injected or given as a loading dose followed by a maintenance dose.

In discussing treatment, prophylaxis should also be mentioned. Pretreatment is useful for individuals who work with these chemicals or who are otherwise exposed to them on a regular basis. In the scenario of a terrorist strike, this treatment could be started to protect emergency response personnel. For prophylaxis, the reversible anticholinesterase agent, pyridostigmine, is recommended at a dose of 30 mg three times daily, to produce a blood cholinesterase inhibition of about 30%. In severe poisonings, this 30% level of inhibition will allow the spontaneous reactivation of these inhibited cholinesterases and the recuperation of the victim.

### **Long-term Medical Sequelae**

The organophosphate agents do have some long-term medical sequelae of which the physician must be aware. First, full recovery of the victim can take up to 3 months and, following recovery, an increased susceptibility may persist for up to 3 months. In addition, persistent paralysis, organophosphate induced delayed neuropathy (OPIDN), and axonal death followed by demyelination, have been reported in animal exposures to **Sarin**. Fortunately, they have not yet been reported in humans.

### **Environmental Sequelae**

The organophosphates will also affect the environment of the exposure area, leading to the potential for additional exposure if individuals do not take protective measures upon the entering the area.

**Tabun** lasts 1 to 2 days in the environment, depending upon weather conditions. It takes 20 times longer than water to evaporate and persists in water for up to one day at 20°C and up to six days at 5°C.

**Sarin** has little persistence and will evaporate as rapidly as water or kerosene.

Like Tabun, **Soman** also lasts 1 to 2 days in the environment, depending upon weather conditions, but it evaporates more quickly, at a rate 4 times longer than water. Thickeners, which are typically added to increase its efficacy as a weapon, can extend its persistence.

From an environmental and prolonged exposure risk perspective, **VX** is the agent of greatest concern. It can persist in an area for weeks to months,

particularly in temperatures near or below the freezing mark, and evaporates 1,500 times more slowly than water. An area or building exposed to VX must be thoroughly decontaminated before reentry.

## **Summary**

In summary, the organophosphates include military grade G agents – Tabun, Sarin, and Soman – and V agents – VX, plus commercial pesticides such as tetraethyl pyrophosphate (TEPP) and parathion. These agents have high potential for terrorist use because they are easily manufactured and readily commercially available. The organophosphates inhibit tissue cholinesterases at their synaptic sites, and cause the accumulation of excess acetylcholine at muscarinic and nicotinic receptors. The resulting muscarinic followed by nicotinic, effects lead to severe respiratory, cardiovascular, gastrointestinal, and CNS symptoms that can be fatal within minutes. The mainstays of treatment include atropine, an anticholinergic, and diazepam, an anticonvulsant. Atropine loading doses range between 1 and 5 mg IV every 30 minutes until full atropinization is achieved, and maintenance therapy should continue for at least 24 hours the initial dose diazepam, is 10 mg IM. In addition, an acetylcholinesterase reactivator such as pralidoxime chloride should be used to abate the nicotinic symptoms of skeletal neuromuscular blockade. For those at high risk of exposure, prophylactic treatment can be provided with pyridostigmine at 30 mg three times a day.