

## Toxicology Advice Centers • •

**Administrative Phone Numbers** - To obtain a consult in your area, call 1.800.222.1222.

**Western New York Poison Center (WNY)**

716.878.7871 • [www.chob.edu/poison](http://www.chob.edu/poison)

**Finger Lakes Regional Poison & Drug Info Center (FL)**

585.273.4155 • [stronghealth.com/services/poison/index.cfm](http://stronghealth.com/services/poison/index.cfm)

**Central New York Poison Center (CNY)**

315.464.7078 • [www.cnypoison.org](http://www.cnypoison.org)

**New York City Poison Control Center (NYC)**

212.447.8152

**Long Island Poison & Drug Info Center (LI)**

516.663.4574 • [www.LIRPDIC.org](http://www.LIRPDIC.org)

## Program Announcements • •

**FL:** Conference, Thursdays • 1:00-2:00pm

**CNY:** Case Conferences, Thursdays • 1:30-2:30pm

**Please mark your calendars** for the Eighth Annual Toxicology Teaching Day on November 3, 2004. More information to follow...

**NYC:** Consultants Case Conference • The first Thursday of the Month from 2-4pm

**LI:** *Polymorphism and Acute Toxicology* • Wednesday, April 28, 2004 • 12:15-2:00pm • Speaker: Dr. Michael McGuigan

• WUH New Life Center Conf Rms B & C  
*Heavy Metal Toxicity* • Wednesday, May 26, 2004 •

12:15-2:00PM • Speaker: Dr. Howard Mofenson • WUH  
New Life Center Conf Rms B & C

*Dangerous Drug Interactions* • Wednesday, June 23, 2004 •  
12:15-2:00PM • Speaker: Dr. David Juurlink • WUH New  
Life Center Conf Rms B & C

*Pre-Registration is required. Please contact T Caraccio at 516-663-2650 if interested in attending.*

*Televideo conferences can be arranged with institutions.*

**Please call administrative telephone numbers for more information.**

## Tox Trivia • •

1. On October 26, 2002, what type of gas was used by the Russian government to end the hostage crisis by Chechen rebels in Moscow?
2. On October 15, 2003 what toxic chemical was identified in an envelope found at a mail processing center in Greenville, South Carolina?
3. What toxin was mixed with fruit punch in the 1978 Jonestown mass suicide poisonings in Guyana, resulting in the deaths of more than 900 people?
4. In 1995 which toxic agent was released in the Tokyo subway system?

# FDA Safety Summaries 10/03 - 3/04

- **Duragesic (fentanyl transdermal system)**

A potential seal breach on one edge may allow drug to leak from the patch and could result in an increased absorption of the opioid component, fentanyl, leading to increased drug effect, including nausea, sedation, drowsiness, or potentially life threatening complications. Conversely, if the hydrogel contents leak out of the patch, there may not be adequate medication to treat the patients' pain. Feb 17, 2004

- **Counterfeit contraceptive patches**

FDA and Johnson and Johnson Co. of Raritan, NJ are warning the public about an overseas internet site selling counterfeit contraceptive patches that contain no active ingredients. February 4, 2004

- **Viramune (nevirapine)**

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with VIRAMUNE. February 2004

- **Antibody to HBsAg ELISA Test System 3**

- **Antibody to HBsAg ELISA Test System 3 Confirmatory Test**

Ortho-Clinical Diagnostics Inc. and FDA notified healthcare professionals of reports of increased initial reactive (IR) and repeat reac-

tive (RR) rates obtained with the Antibody to HBsAg ELISA Test System 3 donor screening assay, with false repeat reactive results being confirmed using the Antibody to HBsAg ELISA Test System 3 Confirmatory Test. December 23, 2003

- **Tamiflu (oseltamivir phosphate) Capsules and for Oral Suspension**

Preclinical findings in juvenile rats have raised concerns regarding the use of Tamiflu in infants less than 1 year of age. A single dose of 1000 mg/kg oseltamivir phosphate (about 250 times the recommended dose in children) in 7-day-old rats resulted in deaths associated with levels of oseltamivir phosphate in the brain approximately 1500 times those seen in adult animals. December 2003

- **Topamax (topiramate) Tablets/Sprinkle Capsules**

Topamax causes hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate). December 2003

- **Permax (pergolide mesylate)**

FDA and Lilly modified the WARNINGS and PRECAUTIONS sections to inform healthcare professionals of the possibility of patients falling asleep while performing daily activities,

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# Chemical Agents of Opportunity by Terrorists

## Case History:

**Contributed By:** *T Caraccio, Pharm.D.\*, Salamati A, Pharm.D. Candidate+, Varghese, Pharm.D. Candidate J+, Sakai J, Pharm.D. Candidate +*

*Long Island Regional Poison and Drug Information Center and St John's University College of Pharmacy and Allied Health Professions*

### Case Summary:

On March 30, 1995, Shoko Asahara, a cult leader of Aum Shinrikyo, released a nerve agent in 5 subway cars on 3 separate subway lines in Tokyo. Nearly 6,000 were injured with 12 fatalities(1). Ten percent of pre-hospital personnel including police and paramedics experienced symptoms of nerve agent poisoning and as many as 46% of the hospital staff became symptomatic through improper handling of victims. This episode along with the recent events of the terrorist attacks on 9/11 in the United States has heightened concerns about chemical agents that may be used in a similar manner on civilian populations.

The purpose of this newsletter is to review the types of common agents, health effects and managements for chemical exposures that may be associated with acts of terrorism. We will emphasize recognition of four classical syndromes or toxidromes that are applicable to the deliberate release of chemicals as in acts of chemical terrorism. The classes of substances that correspond to these clinical syndromes are cholinesterase inhibitors (e.g., organophosphorus nerve agents), respiratory tract irritants (e.g., chlorine and phosgene), asphyxiants (e.g., cyanide), and vesicants (e.g., mustard).

How do accidental industrial releases of chemicals differ than deliberate release as in acts of chemical or biological terrorism?

In accidental industrial releases, information about the presence of specific chemicals may be available from the personnel of the facility, safety officials, and other sources. In contrast, an act of terrorism is more likely to involve substances that cannot be immediately identified. Owing to the rapidity of the onset of similar symptoms in a group of persons or the close proximity of a group of persons to a release of hazardous materials, chemical exposures are more quickly recognizable than are exposures to biologic agents (2). However, in contrast to the period of latency that is associated with the effects of biologic agents, when serious chemical intoxication occurs, the window for effective therapy is often narrow. Furthermore, real-time identification of specific chemicals by means of environmental or clinical laboratory testing is difficult (3).

Nerve Agents: What are they and how do they produce toxicity?

Like organophosphate insecticides, nerve agents phosphorylate and inactivate acetylcholinesterase, leading to accumulation of acetylcholine at nicotinic and muscarinic receptors, and at other receptors in the CNS. Nerve agents that have been used in chemical weapons include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF) and VX.

What are the Properties of Nerve Agents?

At room temperature, all except VX are volatile. VX has the consistency of motor oil and becomes volatile only at high ambient temperatures. Nerve agent vapors are denser than air and tend to accumulate in low-lying areas. All nerve agents are lipophilic and hydrophilic, rapidly penetrating clothing, skin and mucous membranes.

What Clinical effects can be produced?

Exposure to a liquid or vapor nerve agent produces dose-dependent peripheral and CNS effects (4). Respiratory effects include rhinorrhea, bronchorrhea and bronchospasm (muscarinic), respiratory muscle paralysis (nicotinic) and depression of CNS respiratory drive. Cardiovascular effects include bradycardia and heart block (muscarinic) or tachycardia (nicotinic). CNS effects range from headache, agitation and vertigo, to rapidly decreasing level of consciousness and seizures. Peripheral motor effects include initial fasciculations followed by flaccid paralysis (nicotinic). Gastrointestinal effects include nausea, vomiting and diarrhea (muscarinic). Ocular effects include miosis, eye pain, blurred vision, dim vision, conjunctival injection and tearing (muscarinic) (5).

When are symptoms expected with Liquid Nerve agents?

Dermal exposure to a large dose of liquid nerve agent may be transiently asymptomatic (10-30 minutes), followed by rapid onset of respiratory and neurologic effects. With dermal exposure to a minimal amount of nerve agent liquid, the onset of localized symptoms (sweating, fasciculations) may be delayed for up to 18 hours.

When are symptoms expected with Vapor exposures?

Inhalation of a large amount of nerve agent vapor causes fulminant respiratory failure within seconds to minutes. Exposure to a small amount of vapor typi-

Continued on page 4

cally produces more limited ocular (miosis, eye pain) and airway (hypersecretion, bronchospasm) effects.

How should decontamination be provided?

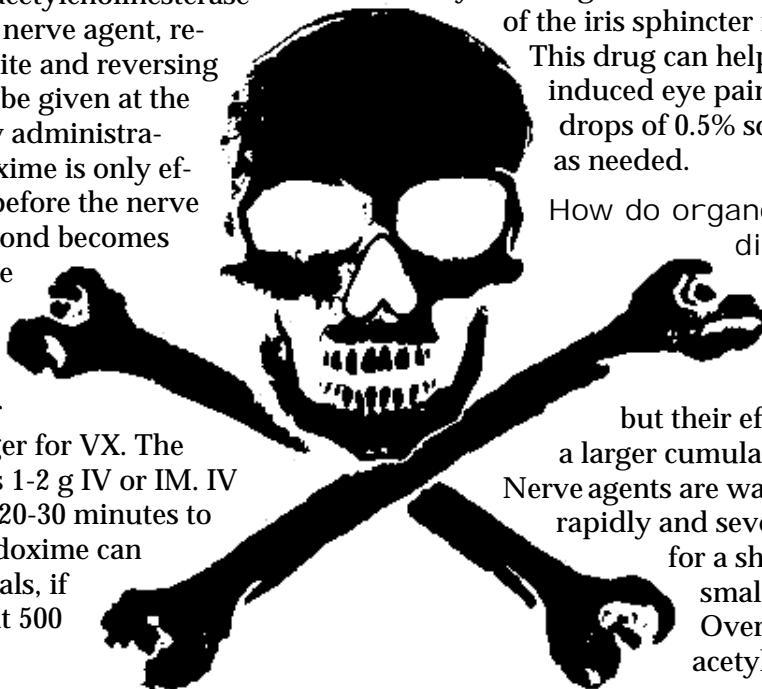
Patients exposed to liquid nerve agent require immediate decontamination to prevent further absorption. Decontamination consists of rapid removal of clothing and jewelry, followed immediately by irrigation with tepid water and washing with soap and water. If water is limited or unavailable, 0.5% hypochlorite solution, which inactivates nerve agents, can be helpful (6).

What Antidotes are recommended?

Even in severe cases of nerve gas exposure, treatment with antidotes can be life-saving (7).

**Atropine:** Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors that reverses the hypersecretory, bronchoconstrictive and gastrointestinal effects of nerve agents. The usual adult dose of atropine is 2 mg IM for mild dyspnea and 6 mg for severe dyspnea. Appropriate therapeutic end points are drying of secretions and ease of ventilation. Heart rate and pupil size are poor clinical indicators of adequate atropinization, since tachycardia may reflect hypoxemia, stress or severe nicotinic effects, and miosis may persist for weeks. Repeat 2-mg doses can be given every 5-10 minutes; patients with nerve agent exposure rarely require more than 20 mg of atropine in the first 24 hours.

**Pralidoxime Chloride:** Pralidoxime chloride (*Protopam Chloride*) is an oxime acetylcholinesterase reactivator that binds to the nerve agent, removing it from its binding site and reversing muscle weakness. It should be given at the same time as atropine. Early administration is critical, since pralidoxime is only effective when administered before the nerve agent acetylcholinesterase bond becomes permanent ("ages"); the time it takes for half of the nerve agent to "age" is about 2 minutes for Soman, 5 hours for Sarin, 13 hours for Tabun, and 48 hours or longer for VX. The usual dose of pralidoxime is 1-2 g IV or IM. IV doses should be given over 20-30 minutes to prevent hypertension. Pralidoxime can be repeated at hourly intervals, if necessary, or continuously at 500 mg/hour by IV infusion.



**Auto-Injectors:** Spring-loaded auto-injectors for IM use containing (separately) atropine 2 mg, pralidoxime 600 mg, diazepam 10 mg and morphine 10 mg are available from Meridian Medical Technologies, Columbia, MD ([www.meridianmeds.com/civdef.html](http://www.meridianmeds.com/civdef.html)).

**Diazepam:** Early administration of the anticonvulsant diazepam (*Valium*), 10 mg IM may prevent permanent CNS damage in patients with severe nerve agent toxicity.

What is the rationale for using Pyridostigmine for a Nerve agent exposure?

Pyridostigmine bromide (*Mestinon*) is an acetylcholinesterase inhibitor with a short half-life used in the treatment of myasthenia gravis. Since it can bind to peripheral acetylcholinesterase for several hours, it is useful because it can temporarily block inactivation by a nerve agent. Pyridostigmine itself does not counteract the effects of the nerve agents; it only **enhances** the effects of antidotes. The usual adult dose is 30 mg PO q8h. (8). If there is a risk of imminent exposure, one dose of pyridostigmine at least 2 hours before may be helpful; 2 doses 8 hours apart are preferable. In animal studies, pretreatment with pyridostigmine has been effective against Tabun or Soman, ineffective against Sarin or VX, and variably effective against Cyclosarin, depending on the species.

What ocular medication may be useful for these exposures?

Tropicamide (*Mydracyl*), is a topical cycloplegic-mydriatic agent, that blocks cholinergic stimulation of the iris sphincter muscle and ciliary body.

This drug can help in relieving nerve-agent induced eye pain (9). The adult dose is 1-2 drops of 0.5% solution in each eye, repeated as needed.

How do organophosphate insecticides differ from Nerve agents?

Organic phosphorus insecticides are oily, less volatile liquids. They have a slower onset of toxicity,

but their effects last longer and require a larger cumulative dose of atropine (10).

Nerve agents are watery and volatile, acting rapidly and severely, but their effects last for a shorter time and require a smaller total dose of atropine (11). Over time, organophosphorus-acetylcholinesterase binding

becomes irreversibly covalent and resistant to reactivation by pralidoxime, in a process known as "aging." Aging has clinical implications for Soman, which ages in minutes, and Sarin, which ages over a period of three to five hours (12). Pralidoxime should never be withheld, however, out of concern that it might be administered too late after exposure. For organophosphorus insecticides, aging is not clinically relevant because these agents age at a slow rate (13). Among nerve agents, VX has several unique characteristics. It is oily, is persistent in the environment, and ages minimally, but even one drop of the substance on the skin can be lethal (14).

How do Carbamate insecticides differ from Nerve agents?

Carbamate insecticides have a more limited penetration of the central nervous system, inhibit acetylcholinesterase reversibly, and result in a shorter, milder course than nerve agents. Nevertheless, in the treatment of severe cholinergic syndromes, it is prudent to use both atropine and pralidoxime (13).

Which Chemical agents might a terrorist utilize to produce Respiratory Irritation?

The pulmonary toxicants most likely to be used can include chlorine, phosgene and diphosgene. Other respiratory irritants are tear gas and lacrimators but these are generally considered weaker because because their duration of action is usually of a shorter and reversible nature especially in an open area.

What are the properties of these Respiratory Irritants?

Chlorine, phosgene and diphosgene exist as gases under ambient conditions. Diphosgene readily degrades to phosgene and nontoxic levels of chloroform. Pulmonary toxicants are denser than air and accumulate in low-lying areas. Chlorine, phosgene, and diphosgene all react with water to produce hydrochloric acid, which damages tissue, but phosgene also acylates amino, hydroxyl and sulfhydryl groups in tissue, causing a chain of oxidative injury. The most common sites of injury are mucous membranes such as the conjunctiva and respiratory tract, including the alveolar-capillary membrane.

What clinical effects can be produced?

Chlorine dissolves readily in the moist mucosa of the upper respiratory tract, producing rhinorrhea, hypersalivation and laryngeal edema, as well as lower respiratory tract reactions such as coughing, wheezing and rales (15).

Phosgene and diphosgene, which are relatively insoluble, pass further into the respiratory tract where they are more slowly absorbed, producing bronchoalveolar injury, dyspnea, bronchospasm and permeability pulmonary edema. Clinical effects of pulmonary toxicants vary with the concentration and duration of exposure. Low-dose inhalation causes minor pulmonary irritation and bronchospasm. High-dose inhalation may produce laryngospasm, pneumonitis and acute lung injury with acute respiratory distress syndrome (ARDS). The delayed onset of ARDS (up to 48 hours in initially asymptomatic patients) is characteristic of pulmonary toxicant inhalation.

The chemical agents used for riot control - tear gas or other "lacrimators" - are aerosolized solids that cause intense, immediate, and usually self-limited burning on exposed body surfaces, especially the eyes (16).

What Managements should be provided?

**Oxygen:** Supplemental oxygen may improve tissue oxygenation in patients with pulmonary signs and symptoms. Airway or ventilatory compromise requires intubation. Ventilatory support management of ARDS requires positive end-expiratory pressure.

**Bronchodilators:** Beta2-adrenergic agonists relax airway smooth muscle, increasing airway diameter and reducing hyperactivity in pulmonary toxicant inhalation (17). The usual adult dose of albuterol (*Proventil*, and others) is 2.5 mg in 3 ml of sterile water, nebulized and repeated as needed. Theophylline may also be helpful (18).

**Corticosteroids:** Corticosteroids such as prednisolone have been used in an attempt to prevent pulmonary edema in the asymptomatic latency phase following phosgene inhalation. The dose of prednisolone has been 250 mg IV. A dose of 1 g IV has been recommended for treatment of phosgene-induced pulmonary edema (19). Whether it would also be helpful for chlorine inhalation is unknown.

**Others:** In animals, one or two large doses of ibuprofen decreased the toxicity of exposure to phosgene (20). An acetylcysteine aerosol, 20 ml of a 20% solution given by nebulizer, has also been effective in animals.

What are chemical Asphyxiants?

Asphyxiants are substances that cause tissue hypoxia with prominent neurologic and cardiovascular signs. Mild symptoms of asphyxia include headache, fatigue, dizziness, and nausea. More severe symptoms range from dyspnea, altered mental status, cardiac ischemia, and syncope to coma and seizure. Respira-

tory failure, if it occurs, generally results from depression of the central nervous system. Asphyxiants are classified as either simple or chemical on the basis of the mechanism of toxicity. Simple asphyxiants (e.g., methane and nitrogen) physically displace oxygen in inspired air, and their inhalation results in oxygen deficiency and hypoxemia. Chemical asphyxiants (e.g., carbon monoxide, cyanide, and hydrogen sulfide) interfere with oxygen transport and cellular respiration and thereby cause tissue hypoxia.

Which asphyxiant is considered to be the most useful by a terrorist and why?

Cyanide (CN) is one of the oldest toxins known, and has killed millions throughout the ages. Few poisons are more rapidly lethal. It has been experimented with by the Islamic jihad in Israel and Al Qaeda in their training camps. It was used most recently as a tool of murder in January 2003 when a teenager was murdered by an acquaintance who laced his soft drink with potassium cyanide that was purchased over the internet. In 1982, Tylenol® capsules laced with cyanide killed 7 in Chicago area and led to the tamper proof packaging for medications that we have today. In November 1978, Potassium cyanide laced Kool Aid was used by Jim Jones to kill himself and 913 of his Jonestown Guyana Cult members. It was used in executions by the ancient Greeks, Egyptians and Romans and by Nazi Germany in gas chambers with Zyklon B to exterminate millions of Jews. The potential for industrial accidents involving cyanide, accidents during the shipment of these chemicals, or through deliberate terrorist acts upon industrial complexes or shipments of these chemicals is a major concern. There are a variety of the industrial processes and occupations that utilize cyanide including semiconductors, electroplating, photography, fumigation, and mining of ores. It is also produced by fires involving polyurethane, wool, cotton and silk. Cyanogenic glycosides in the seeds of fruit stones (as amygdalin in apricots, peaches, apples, peach) in the presence of intestinal  $\beta$ -glucosidase forms cyanide (the seeds are harmful only if the capsule is broken); Sodium nitroprusside, the antihypertensive vasodilator contains 5 cyanide groups.

What is the toxic mechanism?

Cyanide blocks cellular electron transport mechanism and cellular respiration by inhibiting the mitochondrial cytochrome oxidase system and other enzymes. This results in cellular hypoxia and lactic acidosis (21).

What is the toxic dose?

The ingestion of 1 mg/kg or 50 mg of hydrogen cyanide (HCN) can produce death within 15 minutes.

The lethal dose of potassium cyanide is 200 mg. Five to 10 mL of 84% acetonitrile is lethal. The volatile HCN permissible exposure limit (PEL) is 10 ppm, 300 ppm is fatal in minutes.

What are the kinetics?

Cyanide is rapidly absorbed by all routes. In stomach it forms hydrocyanic acid. Protein binding is 60% and the volume of distribution is 1.5 L/kg. Cyanide is detoxified by metabolism in the liver via the mitochondrial endogenous thiosulfate-rhodanese pathway which catalyzes the transfer of sulfur donor to cyanide forming the less toxic irreversible thiocyanate that is excreted in the urine. Cyanide elimination half life from the blood is 1.2 hrs. Cyanide is also detoxified by reacting with hydroxocobalamin (vitamin B-12a) to form cyanocobalamin (vitamin B-12). The elimination route is through the lungs (22).

What are the manifestations of HCN?

Hydrogen cyanide has the distinctive odor of bitter almonds or silver polish, (only 30-40% of the population can detect the odor). The clinical findings develop rapidly and include: flushing, hypertension, headache, hyperpnea, seizures, stupor, cardiac dysrhythmias, pulmonary edema (22). Cyanosis is absent or appears late. Various ECG abnormalities may be present.

What Management should be provided?

Protect rescuers and attendants. Immediately administer 100% oxygen and continue during and after the administration of the antidote. If inhaled, remove patient from contaminated atmosphere. Attendants should not administer mouth-to-mouth resuscitation.

**Cyanide antidote kit:** The clinician must decide whether to use any or all components of the kit.

- a) **The mechanism of action of the antidote kit** is to form methemoglobinemia (Methb) which has a greater affinity for cyanide than cytochrome oxidase system and forms cyanomethemoglobinemia. The cyanide is transferred from methemoglobinemia by sodium thiosulfate which provides a sulfur atom that is converted by the rhodanese-catalyzed enzyme reaction (thiosulfate sulfur transferase) to convert cyanide into the relatively non-toxic sodium thiocyanate which is excreted by the kidney (21-22).
- b) **The Procedure for using the Antidote kit: Step 1 Amyl nitrite inhalant perles** are only a temporizing measure (forms only 2-5% Methb) and can be omitted if venous access is established. Administer 100% oxygen and the inhalant for

30 seconds of every minute. Use a new perle every 3 minutes. **Step 2 Sodium nitrite ampul** is administered IV to produce Methb of 20-30% at 35-70 minutes after administration. In **adults**, administer 10 mL of 3% solution of sodium nitrite, **child** 0.33 mL/kg of 3% is diluted to 100 mL 0.9% saline **slowly** IV at 5 mL/min. If hypotension develops, slow the infusion. **Step 3 In adults** administer 12.5 grams of **sodium thiosulfate** or 50 mL of 25% solution, **child** 1.65 mL/kg of 25% solution IV over 10-20 minutes. Note: **Sodium thiosulfate is useful alone** in smoke inhalation, nitroprusside toxicity and acetonitrile toxicity.

- c) **If cyanide symptoms** recur, repeat the IV antidotes in 30 minutes. Give 1/2 of the initial doses. The children dosage regime on the package insert must be carefully followed.
- d) **One hour after antidotes** are administered, the Methb level should be obtained and should not exceed 20%. Methylene blue should **not** be used to reverse excessive Methb.

**GI decontamination** by activated charcoal is recommended for an oral ingestion but is not very effective (1 gram binds only 35 mg of cyanide).

Treat **seizures** with IV diazepam. Correct acidosis with sodium bicarbonate if it does not rapidly resolve with therapy.

**Other antidotes.** In France **hydroxocobalamin (vitamin B-12a)** which exchanges its hydroxyl with free cyanide to form cyanocobalamin is used (23). It has proven effective when given immediately after exposure in large doses of 4 grams (50 mg/kg) or 50 times the amount of cyanide exposure with sodium thiosulfate. Unfortunately the more concentrated form of hydroxocobalamin is not readily available in the US.

What laboratory investigations should be monitored?

Obtain and monitor ABGs, oxygen saturation, blood lactate, blood cyanide, hemoglobin, blood glucose, and electrolytes. Lactic acidemia, a decreased arterial-venous oxygen difference and bright red venous blood can occur.

What are Vesicants?

Vesicants are agents that were developed to produce "blisters" and burns on skin. Mustard gas was first used offensively by the Germans at Ypres, Belgium in July 1917. Typical agents include Sulfur mustard and Lewisite.

**Properties:** Mustards were named for their pungent mustard-garlic odor. Sulfur mustard, an oily liquid that vaporizes at high ambient temperatures, is the most common vesicant used in chemical weapons. Mustard is lipophilic and readily penetrates skin, most textiles and rubber. It irreversibly alkylates DNA, RNA and protein, causing cell death. Moist, warm tissues (mucosa, perineum, axillae) are most vulnerable, because the chemical reaction is water- and temperature-dependent.

Lewisite is a colorless oily liquid with the odor of geraniums. It is an arsenical derivative which is added to Mustard to keep it a liquid at temperatures below 57°F. As an arsenical, it can interfere with cellular enzymes.

What are the clinical effects of mustard?

Dermal exposure to liquid mustards causes burns that progress from superficial (erythema, pain) to partial thickness (bullae) and, uncommonly, to full thickness (deep bullae, ulcers). Skin contact with sulfur mustards may produce pain after a delay of minutes to hours. Inhalation exposure to mustard vapor can cause mucosal sloughing and airway obstruction. Ocular effects from exposure to liquid or vapor mustard range from ocular irritation and conjunctivitis to corneal burns and blindness. After exposure to high doses, bone marrow suppression can begin in 3-5 days, resulting in leukopenia that reaches its nadir around day 10, followed by thrombocytopenia and sometimes anemia. Nausea and vomiting are common 4-5 days post-exposure; diarrhea and bleeding can occur (24).

Lewisite can cause severe burns to the eyes and skin. Its effects occur faster (within minutes) compared to mustard (takes hours) and can result in larger and deeper burns. These burns can result in considerable necrosis of tissue, gangrene and slough. Respiratory lesions and ocular effects are similar to mustard.

What is the management?

Patients exposed to sulfur mustard require rapid removal of clothing, followed immediately by flushing with soap and water (25). Sloughing of the airway epithelium requires endotracheal intubation. Overhydration should be avoided; chemical burns produce less fluid loss than thermal burns. Mustard burns are especially painful and require liberal opioid analgesia. Severe burns usually require irrigation, debridement and topical antibiotics such as silver sulfadiazine 1% (26). Eye care includes irrigation, topical antibiotics and cycloplegic-mydratics; application of petroleum jelly can prevent burned lids from sticking (27). Gran-

ulocyte colony-stimulating factor or filgrastim (*Neupogen*) can be used for treatment of mustard-induced neutropenia (28,29).

British Antilewisite or BAL in oil(10%), (Dimercaprol) can be given IM for the systemic effects produced by Lewisite. It acts to displace arsenic from its combination with sulhydryl groups of enzyme proteins.

Should civilians use Gas Masks?

Use of military gas masks by untrained civilians is not recommended; the usual full-face mask imposes a large respiratory load and excessive dead space. The ability of military gas masks (e.g., a US military M40 mask) to provide ocular and respiratory protection depends on the fit and the integrity of the filter canister, which can be damaged by handling, water and excessive breathing pressures and must be replaced every 30 days. In Israel during the Gulf War, improper use of gas masks by civilians resulted in 13 deaths due to suffocation (failure to remove the filter cap creates a negative-pressure suction effect that can make the masks difficult to take off), and a total of 114 people died from cardiorespiratory causes while using masks in sealed rooms (30).

*References will be provided on request*



## Tox Trivia ••

Continued from page 1

5. What chemical was launched by the Germans on the battlefield of Ypres, Belgium in April 1915?
6. What chemical was released by a Union Carbide plant in Bhopal India in December 1984 that caused injuries in tens of thousands of people and 3000 deaths?
7. What was the most toxic chemical used by the Germans in WWI that caused blisters on the skin, respiratory irritation and ocular injuries?
8. What was the name of the chemical used in the Nazi gas chambers in WWII?
9. What was the name of the chemical that was placed in a can of vanilla soda to kill a 17 year male in Maryland on January 6, 2003?
10. What was the toxin that the Russians used to kill Georgi Markov, a Bulgarian defector in 1978?

*answers below*

1. Carfentanil, a fentanyl derivative 2. Ricin 3. Potassium Cyanide 4. Sarin nerve gas 5. Chlorine 6. Methylisocyanate 7. Mustard gas 8. Zyklon B or hydrogen cyanide pellets. 9. Potassium cyanide 10. Ricin

## Tox Trivia Answers ••

# SPI CORNER TOPIC: RICIN

**Contributed By:** Long Island Regional Poison and Drug Information Center Staff

On October 15, 2003, an envelope containing ricin was found at a mail facility in Greenville, South Carolina. Many Poison Centers received questions about what this toxin is, what manifestations it could produce and what managements could be effective. The following is a brief review to answer these questions.

Ricin is a biologic toxin derived from the castor bean plant *Ricinus communis*. Ricin is one of several toxalbumins that exert toxicity by inhibiting protein synthesis in eukaryotic cells. Routes of exposure to ricin include ingestion, inhalation, parenteral, dermal, or ocular; however, systemic toxicity has been described in humans only after ingestion or injection. Ricin is considered to be a much more potent toxin when inhaled or injected compared with other routes of exposure. Ricin poisoning is not contagious, and person-to-person transmission does not occur.

Processed and purified ricin can be disseminated by aerosol, contamination of food or water, or injection. Data about the effects of ricin poisoning on humans are limited. Because ricin poisoning might resemble typical gastroenteritis or respiratory illness, it might at first be difficult to discern from other illnesses. For this reason, suspicion of cases should occur in conjunction with epidemiologic clues suggestive of chemical release (e.g., an unusual increase in the number of patients seeking care or unexpected progression of symptoms in a group of patients) or a credible threat of chemical release in the community.

## Clinical Manifestations:

**Ingestion:** Signs and symptoms from oral exposure to purified ricin are presumed to be similar to reports of illness after castor bean mastication and ingestion. Toxicity can range from mild to severe and can progress to death. Mild illness can include nausea, vomiting, diarrhea, and/or abdominal cramping. Onset of gastrointestinal symptoms typically occurs in 1-4 hours. In moderate to severe illness, gastrointestinal symptoms (i.e., persistent vomiting and voluminous diarrhea [bloody or non-bloody]) typically lead to substantial fluid loss, resulting in dehydration and possibly hypovolemic shock. In severe poisoning, liver and renal failure and death are possible.

**Inhalational Exposure:** Workers exposed to castor bean dust have described allergic reactions (e.g., nasal and throat congestion, eye irritation, hives, chest tightness, and wheezing). Aerosol exposures to ricin can be followed within 4-8 hours by fever, chest tightness, cough, dyspnea, nausea, and arthralgias followed by diaphoresis.

**Parenteral Exposure:** In a single human trial evaluating low doses of intravenous ricin as a chemotherapeutic agent, influenza-like symptoms with fatigue and myalgias for several days were reported. Ricin injection in one case caused weakness within 5 hours, fever and vomiting within 24 hours, followed by shock and multi-organ failure, and death in 3 days.

**Management:** Treatment for ricin toxicity is primarily supportive, including intravenous fluids, vasopressors, respiratory support, and cardiac monitoring. No specific antidotal therapy exists, and ricin cannot be removed by dialysis. Prophylactic vaccine and immunotherapy are not available. A single dose of activated charcoal should be administered as soon as possible if the patient is suspected of ricin ingestion and is not vomiting. The efficacy of gastric lavage is controversial but may be considered for known or suspected substantial ingestions if presentation to the hospital occurs within 1 hour of ingestion. Ipecac, whole bowel irrigation, and cathartics should not be used. Clinical presentations and their management can vary considerably. Clinicians are strongly advised to contact their regional poison control center immediately upon suspicion of a case of ricin exposure for guidance and further individualized management. Skin decontamination for ricin exposure should be performed if a powder or similar substance is found on the patient, preferably in a designated area outside the main emergency department. Potentially exposed persons should be advised to wash their hands thoroughly with soap and water and refrain from any hand-to-mouth activities.

**Laboratory:** Methods for the detection of ricin in biologic fluids are not commonly available. Ricinine is a separate compound from ricin present in the castor bean and might be more feasible to monitor in persons exposed to ricin-containing plant material. Preparations of ricin-containing substances and environmentally collected specimens can be tested for the presence of ricin by a time-resolved fluorescence immunoassay, available at CDC and member Laboratory Response Network state public health laboratories. In addition, CDC performs a polymerase chain reaction assay on similar type specimens that will detect the gene in the plant material that codes for the ricin protein. Several commercial handheld or test-strip detection devices are available, but the performance of these assays is unknown.

**Reporting:** Suspected or known cases of ricin poisoning should be reported immediately to the regional poison control center (telephone, 1-800-222-1222) and to local or state public health agencies, which will report cases to other health departments, CDC, and other federal agencies.

including operation of motor vehicles, while receiving treatment with Permax. December 15, 2003

- **Acetaminophen, Dixon's 325 mg Analgesic Tablets**

The tablets contained in the mislabeled bottles are 500 mg Acetaminophen, instead of 325 mg Acetaminophen. December 4, 2003

- **Arava (leflunomide)**

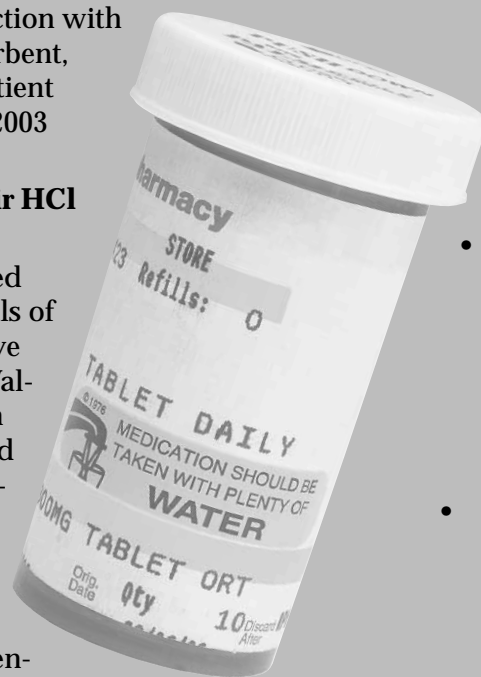
In postmarketing experience worldwide, rare, serious hepatic injury, including cases with fatal outcome, have been reported during treatment with Arava. October, 2003

- **Ultane (sevoflurane)**

Reports of fire or extreme heat in the respiratory circuit of anesthesia machines when Ultane is used in conjunction with a desiccated CO<sub>2</sub> absorbent, which can result in patient injury. November 17, 2003

- **Valcyte (valganciclovir HCl tablets)**

FDA and Roche notified healthcare professionals of the findings of an active comparator study of Valcyte and ganciclovir in heart, liver, kidney, and kidney-pancreas transplant patients at high risk for CMV disease. Based on those findings: (1) Valcyte is indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk, (2) Valcyte is not indicated for use in liver transplant patients. September 30, 2003



- **Viread (tenofovir disoproxil fumarate)**

High rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor (NRTI) resistance associated mutations observed in a clinical study of HIV-infected

treatment-naïve patients receiving a once-daily triple NRTI regimen containing didanosine enteric coated beads (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead). October 14, 2003

- **Keppra (levetiracetam) Tablets and Oral Solution**

FDA and UCB Pharma advised healthcare professionals of the risk of dispensing errors between KEPPRA (levetiracetam), an antiepileptic, and KALETRA (lopinavir/ritonavir), an antiretroviral. September, 2003

- **Roxanol (morphine sulfate) Concentrated Oral Solution**

Serious adverse events and deaths resulting from accidental overdose of high concentration morphine sulfate oral solutions. In most of these cases, morphine oral solutions ordered in milligrams (mg) were mistakenly interchanged for milliliters (mL) of the product, resulting in 20-fold overdoses. October 22, 2003

- **FD&C Blue No. 1 (Blue 1) in enteral feeding solutions**

FDA alerted healthcare professionals of several reports of toxicity, including death, associated with the use of FD&C Blue No. 1 (Blue 1) in enteral feeding solutions. Sept 29, 2003

- **Prandin (repaglinide)**

Drug-drug interaction between repaglinide (PRANDIN), a short-acting insulin secretagogue, and gemfibrozil (Lopid) a lipid-lowering agent used to treat dyslipidemia. Sept, 2003

- **Orlaam (levomethadyl acetate hydrochloride)**

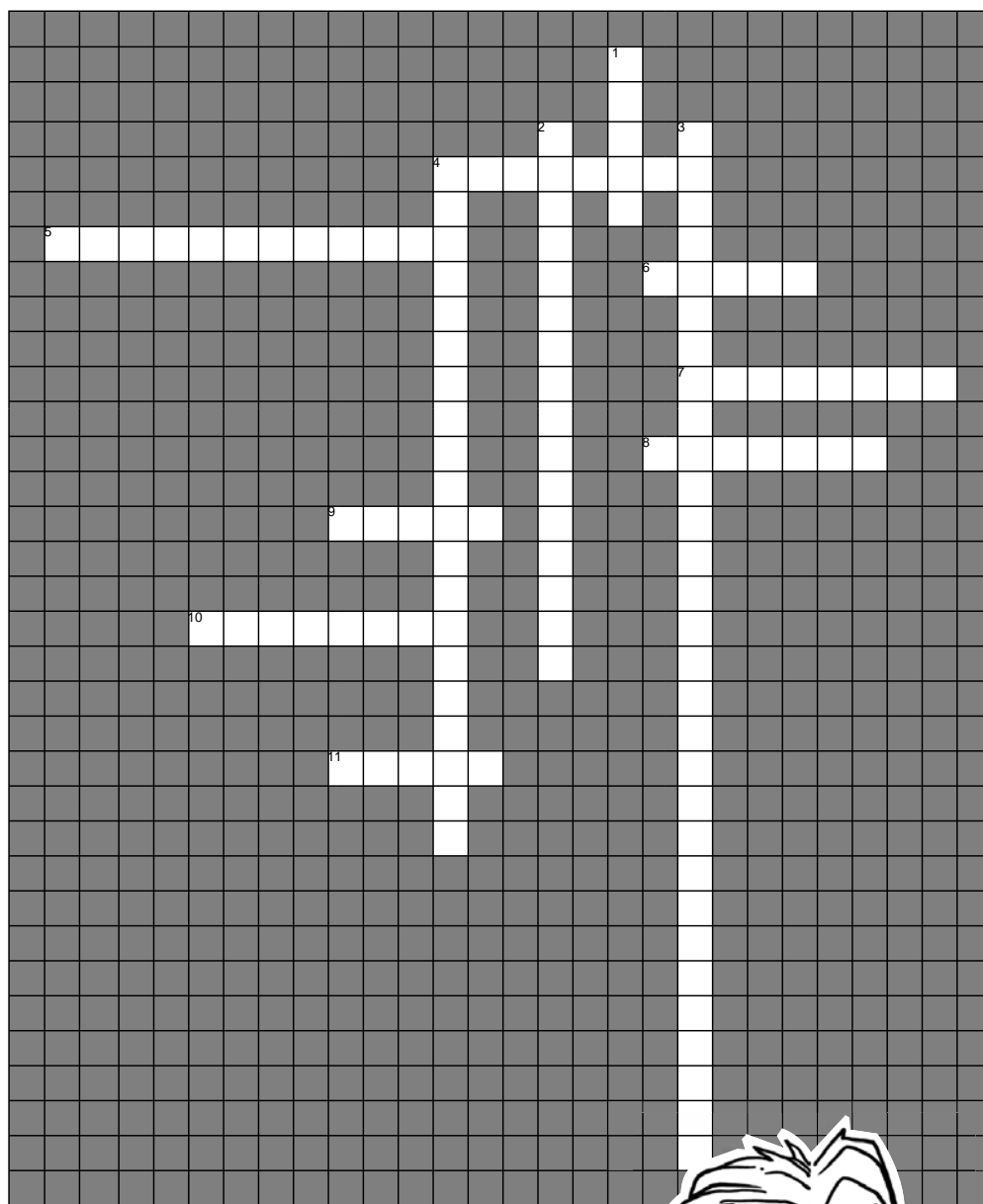
Roxane Laboratories, Inc. is discontinuing the sale and distribution of ORLAAM. ORLAAM was removed from the European market in March 2001 following reports of severe cardiac-related adverse events, including QT interval prolongation, Torsades de Pointes and cardiac arrest. Sept 2, 2003

# TOXICOLOGY CROSSWORD CHEMICAL WEAPONS

Contributed by the Long Island Regional Poison and Drug Information Center

Down

1. A nerve agent developed by the Germans after WWI.
2. What was the name of the chemical that was placed in a can of vanilla soda to kill a 17 year male in Maryland on January 6, 2003?
3. What chemical caused refractory seizures to develop in a 15 month old Chinese girl after she ingested some of the powder that her parents had purchased to kill rodents in their kitchen?
4. What is the name of the enzyme that is blocked by the nerve agents?



Across

4. A drugs that can be used in the management of a severe Nerve agent poisoning
5. What chemical was added to heroin that caused over 300 addicts to show up in various emergency departments on the east coast with anticholinergic manifestations in 1995?
6. Another nerve agents that was developed by the Germans after WWI.
7. What substance was injected into Marzipan candy on Valentine's day a few years ago that caused the victims to lose their hair and have painful paresthesiaes in their hands and feet?
8. What was the name of the chemical used in the Nazi gas chambers in WWII?
9. On October 15,2003 what toxic chemical was identified in an envelope found at a mail processing center in Greenville, South Carolina?
10. In 1995 which toxic agent was released in the Tokyo subway system?
11. Another nerve agent developed by the Germans after WWI.



Answers: Down: 1. Sarin 2. Potassiumcyanide 3. Tetramethylethylenedisulfotetramine 4. Acetylcholinesterase Across: 4. Atropine 5. Scopolamine 6. Tabun 7. Thallium 8. Zyklon B 9. Ricin 10. Sarin 11. Soman



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