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The nation's leading supporter of biomedical research on disorders of the brain and nervous system.

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Funding Announcements

- **Funds Available for Administrative Supplements for Research on Medical Countermeasures to Chemical Terrorism** [[Summary](#)]

Release Date: 2005-01-26

Announcement Number: [NOT-NS-05-004](#)

Funding Contact: [Jett, David](#) Program Area: [Technology Development](#)

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- [NINDS Counterterrorism and Neuroscience Workshop](#)

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Background

[Chemicals, toxins](#), and [infectious agents](#) that target the nervous system

[Countermeasures development](#) ("animal efficacy rule")

[Regulations for conducting research with toxins and infectious agents](#) ("select agent rule for pathogens and toxins")

Chemical Agents

The Chemical Weapons Convention (CWC) and the U.S. Armed Forces define a chemical warfare agent as any chemical intended for use in military operations to kill, seriously injury, or incapacitate humans or animals. Traditional chemical warfare agents include [nerve agents](#), [incapacitating agents](#), and [blood agents \(cyanide\)](#). [Other chemicals](#), such as industrial compounds and pesticides, could also be used in a terrorist attack. The list of chemical agents described on this web site is intended to be representative rather than comprehensive.

Nerve agents

Nerve agents are anti-acetylcholinesterase, organophosphate compounds that bind to acetylcholinesterase (AChE) and inhibit its ability to degrade the neurotransmitter acetylcholine. Excess acetylcholine overstimulates synapses throughout the brain, nervous system, glands, skeletal and smooth muscles, resulting in seizures, flaccid muscle paralysis, cardiorespiratory depression, excess secretions, and death. The chronic effects of low-dose exposure to these compounds are not known, although studies of animal models and other organophosphate chemicals suggest that neurodegeneration and other neurological effects could occur. The relationship between possible exposure of military personnel to nerve agent during the 1991 Gulf War and Gulf War illnesses remains unclear.

Nerve agents fall into two classes, the G-series and the V-series, based on their physical properties and toxicities (Table 1). The G-series nerve agents are volatile liquids at room temperature that can be deadly when inhaled as a vapor or absorbed, in liquid form, through the skin. V-series agents have a consistency similar to oil and do not evaporate rapidly. As a result, V-series agents pose more of a risk of exposure via skin contact than by inhalation and can remain on clothing and other surfaces for a long time. Agents in the V-series are approximately 10-fold more toxic than those in the G-series.

Table 1. Nerve agents

<u>G-series</u>	<u>V-series</u>
Tabun (GA)	VE
Sarin (GB)	VG
Soman (GD)	VM
Cyclosarin (GE and GF)	VX (most common)
GV	VR
	VS

The standard treatment regimen for individuals who have been exposed to nerve agents includes a combination of atropine sulfate, an oxime, and an anticonvulsant drug.

- Atropine sulfate blocks muscarinic acetylcholine receptors (in the parasympathetic nervous system), with the effect of drying secretions and reducing smooth muscle constriction. Atropine has no effects on skeletal muscles and causes side effects in individuals who have not been exposed to nerve agents.
- Oximes remove nerve agents from AChE and have the most marked effect at nicotinic receptors, resulting in increased skeletal muscle strength. Oximes are ineffective once the AChE-nerve agent complex has “aged”; aging is a chemical change (deacylation) in AChE that results in its permanent inactivation. Aging times vary according to the nerve agent (2 minutes for soman, 3-4 hours for sarin, longer for others). Pralidoxime chloride (2-PAM Cl) is the oxime of choice in the US. Other countries use different oximes, including P2S (England), obidoxime (several European countries), TMB4 (Israel), and 2-PAMI (Japan).
- Diazepam is commonly used as an anticonvulsant following nerve agent exposure.

Prophylactic use of pyridostigmine bromide (PB), taken prior to nerve agent exposure, may also improve outcome. PB, a carbamate, prevents AChE from binding nerve agents by reversibly inhibiting the active site of AChE. To be effective, pretreatment with PB must be combined with post-exposure therapy. PB offers some benefit for exposure to soman or tabun but none for sarin or VX. Reported side effects of PB include increased salivation, increased tearing, urinary urgency and frequency, nausea, vomiting, muscle weakness, abdominal cramps and diarrhea; these effects disappear when individuals stop taking PB.

Incapacitating agents

Incapacitating agents (class II chemical agents) are designed not to injure or kill but rather to induce disorientation and impair performance. Incapacitating agents cover a broad range of chemicals with different physical properties but can be ordered into four general categories (Table 2).

Table 2. Examples of incapacitating agents

<u>CNS stimulants</u>	<u>CNS depressants</u>	<u>Psychedelics</u>	<u>Deliriants</u>
Amphetamines	Barbiturates (methohexital)	LSD-25	BZ
Cocaine	Opioids	Psilocybin	Agent 15
Caffeine	Antipsychotics (haloperidol)	Ibogaine	Atropine
Nicotine	Benzodiazepines	Harmine	Scopolamine
Strychnine	Fentanyl congeners	Ecstasy	Oxybutynin/Ditropan
Metrazole		PCP	Anticholinergic antihistamines
		PCP	Benactyzine

The compound 3-quinuclidinyl benzilate (BZ) is the only incapacitating agent known to have been weaponized. BZ is a muscarinic acetylcholine receptor antagonist that blocks the stimulatory action of acetylcholine, and thereby has the opposite effect of nerve agent poisoning. Consequences of BZ exposure include confusion, illusions, visual hallucination, disturbances in judgment and insight, attention and memory deficits, deficits of expression and comprehension, disorientation to time and place, paranoia, and “phantom” behaviors such as plucking and disrobing. BZ can have psychosocial effects, causing those exposed to have similar illusions and hallucinations.

A stable crystalline solid, BZ can be dispersed by heat-producing munitions. BZ is usually delivered as an aerosol, which is absorbed primarily by inhalation. Ingestion is effective secondary route; percutaneous adsorption is possible if BZ is dissolved in an organic solvent like DMSO.

Physostigmine can be used as an antidote for BZ. Physostigmine is a carbamate anticholinesterase; like nerve agents, it elevates acetylcholine levels by inhibiting AChE. Treatment is minimally effective within the first four hours after BZ exposure but is very effective after four hours. The effects of treatment last only 45-60 minutes and can cause side effects similar to nerve agent exposure.

Blood agents

Blood agents bind the iron ions in cytochrome cyt a_3 , thereby interrupting oxidative phosphorylation in the mitochondria and preventing the extraction of oxygen from the blood (histotoxic anoxia). The failure of the brain to receive sufficient oxygen results in headache, vertigo, and seizures.

Blood agents include cyanide and arsine. Cyanide ions (CN⁻) can be created from hydrogen cyanide (HCN) or cyanogen chloride (CNCl), both very volatile liquids. Cyanide salts (NaCN, KCN, CaCN) can be mixed with acid to produce HCN vapor. Arsine gas is formed when arsenic-containing materials react with freshly formed hydrogen in water or acids.

Several countermeasures have been developed for cyanide poisoning. The goals of antidotal therapy are to displace CN⁻ from cytochrome a_3 , convert CN⁻ to thiocyanate enzymatically, or sequester CN⁻.

- Methemoglobin formers displace CN⁻ from cytochrome a_3 ; CN⁻ has a higher affinity for methemoglobin (metHb) than for cytochrome a_3 . Amyl nitrite converts hemoglobin (Hb) to metHb and is administered by inhalation. Sodium nitrite converts HgO₂ to metHb and is administered intravenously. Methemoglobin formers have the adverse effect of raising metHb levels too high, which can be toxic.
- Sodium thiosulfate reacts irreversibly with CN⁻ to form thiocyanate and sulfite. It is administered intravenously. Adverse effects are usually not serious, and include nausea.
- Cobalt compounds, including hydroxycobalamin (Vitamin B12a) act by chelating (sequestering) CN⁻. Cobalt compounds are used in the UK, France, and the Netherlands as a treatment for cyanide poisoning but have not been approved by the FDA for this purpose.

There are no pretreatment options currently available for CN poisoning.

Other chemicals that target the nervous system

A number of toxic chemicals that are not traditional warfare agents are known to target the nervous system. For example, organophosphate pesticides, like malathion and diazinon are chemically similar to nerve agents and can cause nerve agent-like effects in high doses. Sevin, a carbamate insecticide, has similar properties to pyridostigmine. Additional examples of toxic chemicals that target the nervous system may be found at the following web sites:

[Agency for Toxic Substances and Disease Registry \(ATSDR\)](#)

[National Institute of Environmental Health Sciences \(NIEHS\)](#)

[Centers for Disease Control and Prevention \(CDC\)](#)

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Neurotoxins

Toxins are poisons produced by living organisms. In general, toxins are extremely potent, with a toxicity several orders of magnitude greater than that of the nerve agents. Neurotoxins tend to be highly specific, targeting a particular ion channel, neurotransmitter receptor, or vesicle trafficking protein.

Botulinum neurotoxins (BoNTs)

BoNTs are a class of 7 distinct proteins (A-G) produced by the bacterium *Clostridium botulinum*. The toxins prevent acetylcholine release at neuromuscular junctions by cleaving components of the vesicle fusion machinery. Symptoms include muscle paralysis and respiratory failure. No approved vaccine currently exists, although investigational toxoid is available in limited quantities to induce immunity in lab workers. Post-poisoning treatment by passive immunization with equine antitoxin minimizes nerve damage and disease severity but does not reverse any paralysis that has already occurred.

Dinoflagellate toxins

Saxitoxin (Mytilotoxin) is a sodium channel blocker produced by algae consumed by the butter clam *S. giganteus* and the California sea mussel *M. californicus*. The toxin can be isolated from these marine organisms or synthesized *de novo*. Saxitoxin causes numbness, muscle weakness, and respiratory paralysis. Ciguatoxins, which accumulate in tropical fish, and brevetoxins, which accumulate in oysters, are sodium channel activators.

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Infectious Agents

Anthrax meningitis

Anthrax meningitis is characterized by bleeding in CNS and brain, leading to headache, delirium, coma, and, often, death. Meningeal anthrax is exceedingly rare in endemic anthrax outbreaks, but 50 percent of the 42 patients who had died from inhalational anthrax following the accidental release of spores from the Sverdlovsk bioweapons plant in 1979 had evidence of meningitis. Americans who inhaled anthrax spores in the 2001 terrorist attacks and survived have since reported short-term memory loss and other cognitive deficits.

Viral encephalitides

Viral encephalitides include West Nile Virus, LaCrosse, California encephalitis, Japanese Encephalitis Virus, Kysanur Forest Virus, equine encephalitis viruses, and tickborne encephalitis viruses. Clinical signs of infection include fever, ataxia, circling, head pressing, convulsions, and death. Mortality ranges from 20-90 percent. Vaccines for some of these viruses are commercially available.

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Animal Efficacy Rule

Countermeasures for chemical and biological warfare agents often cannot be tested in human subjects for ethical or logistical reasons. The FDA-issued “animal efficacy rule,” effective June 30, 2002, allows the use of animal data for evidence of a drug’s effectiveness under certain circumstances. For complete text of the animal efficacy rule, see the [FDA web site](#)

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Select Agent Rule for Pathogens and Toxins

As part of new regulations enacted by the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188), researchers are now required to register with the federal government and get approval to possess or use any pathogen or toxin defined as a “select agent.” These regulations are designed to ensure these infectious agents and toxins are shipped only to institutions or individuals equipped to handle them appropriately and only to those who have legitimate reasons to use them. The Centers for Disease Control and Prevention (CDC) is responsible for the implementation of this regulation; for more information, see their [web site](#).

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Additional Resources

- [Department of Homeland Security](#)
- [Homeland Security at HHS](#)
- [Biodefense Research at NIAID](#)
- [Homeland Security at CDC](#)
- [Animal Efficacy Rule](#) (for development of countermeasures)
- [Select Agent Rule](#) (for research with infectious agents and toxins)
- [US Army Medical Research and Materiel Command](#)
- [US Army Medical Research Institute of Chemical Defense](#)

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