



Low Level Chemical Agent Exposure

Existing research suggests that exposure to low levels of organophosphorous nerve agent for limited time periods and particularly when there are no overt acute symptoms, is unlikely to result in long term, adverse health effects. However, knowledge gaps in the existing literature and improved research technologies suggest the need for the current studies.

As part of the DoD Gulf War Illnesses (GWI) research program, 16 peer-reviewed studies totaling \$15 million address health consequences of low-level exposure to chemical weapons. Studies cover exposure to sarin (GB), soman (GD), VX, and sulfur mustard. The first three of these are organophosphorous nerve agents while the last is a blistering agent. The study findings impact Persian Gulf veteran's health assessment, future military deployments, and the welfare of civilian terrorist victims.

Background

Acetylcholine (ACh) is responsible for transmitting nerve impulses to other nerves, organs, and muscles. Acetylcholinesterase (AChE) is an enzyme that breaks down the ACh at nerve junctions. AChE is targeted by organophosphorous nerve agents. The agents form a stable bond with AChE and prevent AChE from breaking down ACh. ACh then accumulates and results in harmful, and eventually fatal, continuous stimulation of nerves, organs, and muscles. The immediate cause of death is exhaustion of respiratory muscles and suffocation.

Recent terrorist attacks in Japanese subways provided information on the sub-lethal effects of sarin exposure in humans. Approximately 20,000 people were exposed; more than 5,500 patients were treated and 12 died. Most of those who survived had marked miosis (constriction of the eye's pupil) and decreased serum AChE activity. Other signs included headache, difficulty breathing, nausea, ocular pain, blurred vision, vomiting, coughing, muscle weakness, and agitation; 6-8 months after the attack victims had delayed behavioral and central nervous system's effects; some changes were more severe in females. Genetic after-effects showed alterations in chromosomes (DNA adduct formation) in peripheral white blood cells.

Some GW veterans may have been exposed to very low levels of sarin and cyclosarin in March of 1991 during the disposal of Iraqi munitions at Khamisiyah in southern Iraq. After the demolition, it was discovered that some of the munitions contained sarin and cyclosarin. Investigations from the Tokyo attack indicate that miosis is a very sensitive indicator of exposure to sarin (more sensitive than the usual laboratory method of monitoring red blood cell AChE). It is estimated that any U.S. troop exposure level would have been 100 times less than the level needed to cause miosis; thus any exposures suffered by GW veterans were very low.

Current Studies

Organophosphate Nerve Agents: Sarin

Three epidemiological studies investigate the possibility of delayed health consequences of nerve agent exposure. One study integrates information on troop locations and movements, analyses of dispersion modeling patterns of the vapor clouds at Khamisiyah, and databases of medical outcomes. A second study will compare health outcomes of potentially exposed individuals within the modeled exposure area (plume) at Khamisiyah with unexposed military personnel. A third study of 1,581 volunteers who were exposed to low-levels of organophosphate agents between 1955 and 1975 will compare central nervous system and behavioral indices of the volunteers with a matched group of unexposed individuals.

A completed study using a non-nerve-agent organophosphate compound (diisopropylfluorophosphate: DFP), found that, in rats and monkeys, sub-chronic exposures at doses above those considered "low-level" cause abnormalities in central nervous system ACh function (receptor expression) and impaired cogni-

Current Studies of Potential Interactions with Low Level Sarin Exposure							
Test Conditions							
Sarin	PB	DEET	Pest.	Bot	Heat	Stress	Institution
X	X						Univ of CA, Davis TNO
X	X						
X	X	X	X				Battelle
X	X	X	X	X			Battelle
X*					X		Lovelace
X						X	So Illinois Univ
X	X	X	X		X	X	Duke Univ
X	X					X	NYU Med Cntr

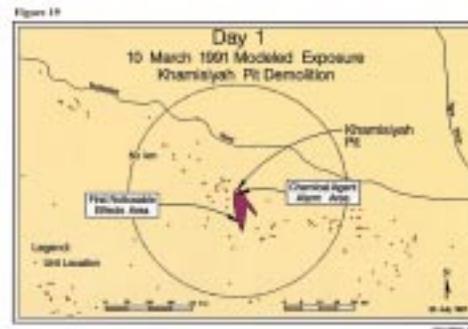
* = inhalation route; Pesticides = permethrins or chlorpyrifos; Bot = botulinum toxoid; Stress = psychological and physical changes

tive function for several weeks after the exposure. Pre-trained tasks were not affected and the induced spatial memory impairment in rats was completely inhibited by pretreatment with pyridostigmine bromide (PB: a pretreatment for nerve agents) or by post-exposure injection of nicotine.

Two studies are based on the premise that GW veterans with unexplained physical symptoms suffer from central nervous system damage due to chemical exposures. One study developed neurobehavioral screening tests for nerve damage. The second study, having previously determined associations of specific GW exposures and three distinct symptoms groupings, will enlarge the original sample population to verify previous observations and provide a strong basis to support identification of anatomic damage and biologic mechanisms producing the nerve damage.

Eight studies examine health consequences of low-level sarin either alone or in combination with other health risk factors. One study investigates the dosimetry of inhaled sarin (the most likely route of veteran exposure) and the effects of sarin and heat stress on biologic indicators in a rat model. Another study assesses the long-term effects of low-level sarin, PB and the effect of exercise on peripheral nerve and muscle damage in hen and mouse models. Another study examines the effect on neurons, in monkeys, of exposure to low-level sarin alone or with co-administered PB, pesticides, and vaccination against botulism. A study of interactive effects of PB and low-level sarin in mice under physical stress indicates that, in mice exposed only to low levels of sarin and

blood-brain-barrier. A study will determine the lowest observable effect level of sarin exposure in guinea pigs and marmosets and correlate induced biologic alterations and degraded performance. A new study examines the effect of low-level inhalation exposure to sarin or soman in monkeys and rats and the effect on cholinesterase activity, respiratory function, and behavior. Correlation of the concentration of air exposures and biomarkers with toxic effects will allow extrapolation to humans and permit a determination of whether toxic effects of the compounds are reversible.



Modeled Plume of Nerve Agent

Organophosphate Nerve Agents: VX

A study on the effects of the persistent organophosphate agent VX in rats, guinea pigs, and monkeys, may provide information on distribution and metabolism and indicate whether metabolites of VX are themselves toxic. There is no indication that GW veterans were exposed to this agent during the GW; but, as VX is the most specific AChE inhibitory agent, it represents a significant hazard to military personnel. The information may permit extrapolation of animal toxicity data to man, aid in determining pretreatment options for VX exposure, and help protect troops in future deployments. Results to date indicate that VX persists longer *in vivo* than the G-agents (sarin, soman, tabun). Metabolites in the liver have been detected and are being identified.

Sulfur Mustard [bis-(2-chloroethyl) sulfide]

As it is known that Iraq used sulfur mustard in its war with Iran, it is suspected that some of the munitions disposed of at Khamisiyah contained sulfur mustard. This agent is used more frequently to incapacitate than to kill though it can be lethal at high doses.

One study investigates the adducts formed with red blood cell proteins and other cellular proteins such as albumin and keratin. As the mustard agent is very reactive but does not itself persist *in vivo*, assessment of exposure is determined by identification of adducts to DNA and proteins in tissue samples. The study will permit diagnosis of sulfur mustard exposure long after exposure. Ultimately it is hoped that the study makes possible the construction of a fieldable diagnostic unit.

Detailed information on the status of individual projects may be obtained from the **Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses** at the web site below.

<http://www.va.gov/resdev/report3.htm>



given 10 weeks of exercise, neurotoxinesterase (NTE) activity significantly decreased in the cerebral cortex: inhibition of NTE is associated with chronic nerve damage. However, no electron microscopic changes were seen in spinal cord or sciatic nerve in any group. Another study is investigating the hypothesis that exposure to low levels of sarin, by itself or with other chemicals or biologic changes (heat or stress), causes nerve damage by: accumulated ACh alteration of nerve transmission, binding of sarin to physiologically active protein, or increased permeability of the

