

### **Chemical Exposures in Gulf War Caused Veterans' Illness**

By Crystal Phend, Staff Writer, MedPage Today Published: March 11, 2008 Reviewed by [Zalman S. Agus, MD](#); Emeritus Professor University of Pennsylvania School of Medicine.

SAN DIEGO, March 11 -- Chronic illness among Gulf War veterans may be caused, in part, by exposure to acetylcholinesterase inhibitors, including pesticides and nerve agents, according to a systematic review. These chemicals have consistently been linked to illness in epidemiologic and animal studies and in dose-response to exposure among service members, reported Beatrice A. Golomb, M.D., Ph.D., of the University of California, San Diego, online in the Proceedings of the National Academy of Sciences. The evidence satisfied criteria for causality, suggesting exposure to this class of chemicals "may account for some or perhaps much of the excess illness seen in Gulf War veterans," Dr. Golomb said.

#### **Action Points**

Explain to interested patients that acetylcholinesterase inhibitors are a class of chemicals that are used in agriculture as pesticides and for other industrial and military purposes.

Note that Gulf War veterans' symptoms are frequently in domains controlled by cholinergic systems.

This has implications for current and future deployments as well as in some civilians with unexplained chronic multisymptom complaints, she said.

Persian Gulf War veterans have had a higher prevalence of chronic multisymptom health problems (26% to 32%) than those sent elsewhere or not deployed. The symptoms typically include fatigue, muscle or joint pain, memory problems, trouble sleeping, rash, and breathing problems.

Since these problems are in systems governed by central and peripheral cholinergic systems, the wide exposure of troops to organophosphate and carbamate acetylcholinesterase inhibitors has been suspected as a cause. Some military personnel were exposed to the nerve gas sarin while destroying Iraqi weapons. As many as 250,000 among the about 700,000 deployed also took pills containing the carbamate pyridostigmine bromide to protect against potential nerve agent exposure.

Pesticides, particularly carbamates and organophosphates, were also used aggressively to control sand flies and other insects, which the Department of Defense has estimated led to overexposure of at least 41,000 service members.

Studies have reported a significant, typically strong, association between acetylcholinesterase inhibitor exposure and chronic illness with high consistency, Dr. Golomb found in her analysis of 115 papers on Gulf War illness and acetylcholinesterase effects.

In some of these studies, exposures related to acetylcholinesterase inhibitors accounted for all of the strongest odds ratios for Gulf War illness as defined by the CDC. In others, these exposures were the only ones significantly linked to multisymptom illness after multivariable adjustment.

#### **These risks among Gulf War veterans include:**

Pyridostigmine bromide pills were associated with 1.6-fold increased risk of mild to moderate symptoms (P=0.010) and 2.9-fold increased risk of severe illness (P=0.006).

Insect repellent was associated with 1.7-fold (P=0.001) and 2.4-fold (P=0.006) increased risk of mild to moderate and severe symptoms, respectively.

Chemical warfare agent exposure, such as sarin, was associated with 2.3-fold increased risk of mild to moderate illness and 3.5-fold increased risk of severe symptoms (both P0.001).

Although exposure to nerve agents and pesticides was hard to quantify, one study linked neuropsychological function and loss of white matter and total brain volume with higher estimated organophosphate nerve agent exposure.

Studies showed that the health of U.S. service members in the Gulf War worsened the higher their cumulative dose of pyridostigmine bromide pills. A similar study of Australian veterans showed worse physical, but not mental, health with increased use of the pills.

The associations were also supported by studies that found greater illness among veterans with genetic variants that reduce enzymes involved in clearance of organophosphates and pyridostigmine bromide from the body. Notably, civilians exposed to acetylcholinesterase inhibitors in occupational settings, particularly agriculture, had symptoms mirroring those of Gulf War veterans with higher rates of fatigue, muscle complaints, and cognitive dysfunction and more overall symptoms compared with controls.

Likewise, people exposed to sarin gas during terrorist attacks in Japan have been reported to have long-term problems with cognition, fatigue, and muscles, "hallmark symptoms of ill Gulf War veterans," Dr. Golomb said. Animal studies showed acetylcholinesterase inhibitor exposure altered regulation of cholinergic function and low-level sarin exposure, in particular, persistently altered DNA, protein content, and gene expression. Together, this evidence draws a "plausible and substantially supported connection" between acetylcholinesterase inhibitor exposure and illness, Dr. Golomb concluded. "We should be cautious about exposing people, whether military personnel or civilians, to these chemicals," she said.

The findings also suggest that Gulf War veterans may be at increased risk of amyotrophic lateral sclerosis (ALS) as well as Parkinson's disease, which have both been linked to pesticides in other studies although in agricultural rather than military settings, she said. "One of the implications of this research is that we should perform surveillance for Parkinson's disease in Gulf War veterans," Dr. Golomb added. Dr. Golomb reported no conflicts of interest.

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