

# ***GULF WAR RISK FACTOR REPORT REPRINT***

## **Pyridostigmine Bromide**

*The first three articles originally appeared in the December 1999 issue of the Gulf War Review newsletter and the fourth articles in the March 2000 issue. For information about the newsletter, contact Mr. Donald J. Rosenblum, Deputy Director, Environmental Agents Service (131), VA Central Office, 810 Vermont Avenue, N.W., Washington, DC 20420, telephone: 202-273-8580.*

## **Rand Report Raises Concerns About Anti-Nerve Gas Pill (PB)**

On October 19, 1999, the Department of Defense released a report by its contractor, the Rand Corporation, that focuses on pyridostigmine bromide (PB), used during the Gulf War as a pretreatment to protect military personnel from death in the event of an attack with the nerve agent soman.

For background information about PB, see the next article, which is an excerpt of an article that appeared in the January 1995 issue of this newsletter. Also see the article that follows entitled PAC and IOM on PB.

The Rand report considers a wide array of issues regarding the safety and effectiveness of PB. The discussion of safety explores seven hypotheses of how PB might lead to adverse health effects. Each of these hypotheses is investigated to determine if it can be rejected as a possible cause of the unexplained illnesses reported by some Gulf War veterans. The report authors explained that if sufficient evidence cannot be found to rule out a hypothesis, this does not imply that it is necessarily a causal factor, only that the possibility cannot be dismissed.

The 385-page scientific literature review contained two major conclusions. First, PB cannot be “ruled out” as a possible contributor to the development of unexplained or undiagnosed illness in some Gulf War veterans. Second, uncertainties remain regarding the effectiveness of PB in the protection of humans against nerve agents.

The report notes that most data on the effectiveness of PB in primates comes from studies using higher doses. It is unclear what these results mean for humans taking smaller doses. The authors added that some literature indicates that the use of PB may reduce somewhat the effectiveness of post-exposure treatment for some non-soman nerve agents. The extent and importance this reduction would have in humans is unknown.

The report concludes that these findings “raise many questions and have important implications relating to the use of PB in military deployments. The authors call for more and prompt research into the effectiveness of PB for humans. Meanwhile, the issue is a complex one, involving trading off uncertain health risks—but risks that

cannot with certainty be ruled out—against possibly uncertain gains from the use of PB in the warfare setting.”

According to Dr. Sue Bailey, former Assistant Secretary of Defense for Health Affairs, there are 26 scientific studies, peer-reviewed or research projects underway that specifically address the health consequences of PB as a nerve pretreatment. The funding for this research is about \$20 million. These studies include evaluations of the interaction of PB with other chemicals and low-level exposure to nerve agents. Bailey declared that while most of the ongoing studies to date reveal no definitive results to link PB to illnesses, those seen in Gulf War veterans, we must continue this “very important” research to really determine any causal relationship.

She concluded that “our leadership would be very judicious in deciding to use PB in the future. The decision would involve weighing the concerns about possible long-term effects with a threat-risk assessment of how likely it is that soman would be used against our troops.”

The PB report is one of five that the Rand Corporation has prepared for DoD’s Office of the Special Assistant for Gulf War Illnesses, then headed by Bernard Rostker. According to Rostker, the most important of those reports focused on stress, oil well fires, depleted uranium, and now PB.

Dr. Rostker indicated that this report was “unique because, for the first time, Rand did not reach a conclusion that the issue under study was not likely a cause of Gulf War illness. In this report they have reached the conclusion that they just don’t know...”

The text of the report is available on the internet at <http://www.gulflink.osd.mil>.

---

## **Background Information About PB**

Some Persian Gulf veterans have expressed concern about the possible long-term health consequences of pyridostigmine bromide (PB), which was issued to nearly all U.S. troops in the Persian Gulf as a nerve agent pretreatment drug.

PB has been approved by the Food and Drug Administration as a treatment for patients who have myasthenia gravis, a neuromuscular disease. It has been effectively used for this purpose for over forty years. Myasthenia gravis patients are known to take PB for many years in doses that are many times higher than those administered to troops without long term adverse health effects.

During Operation Desert Shield/Storm (ODS), sufficient safety data in humans and effectiveness data in animals was presented to the FDA for them to concur in the use of pyridostigmine as a pretreatment for nerve agent poisoning; a waiver of informed consent was granted.

ODS military personnel were provided with packets containing twenty-one, thirty milligrams PB tablets to be self-administered orally. The recommended dose of PB is one tablet every three hours to be initiated and stopped by the direction of the commanding officer. Other coalition troops also used PB as a pretreatment for nerve agents. Although it is not known how much PB was taken by individual servicemembers, it is likely that most members took at least one but not more than twenty-one tablets.

Common side effects of PB include nausea, vomiting, abdominal cramps, diarrhea, increased salivation, sweating, and muscle cramps. These effects appear within a short time after ingesting the PB tablet and reverse with discontinuation of the medication.

Two expert panels (the National Institutes of Health Technology Assessment Workshop and the Defense Science Board) made up of non-government scientists reviewed the use, safety, metabolism and toxicity of PB by troops in the Gulf War. Both groups concluded that the current scientific studies suggest that PB is an unlikely cause of the unexplained illnesses of Persian Gulf veterans.

---

## **PAC and IOM on PB**

What did the Presidential Advisory Committee (PAC) on Gulf War Veterans' Illnesses conclude about the risks of PB to Gulf War veterans?

The PAC's *Final Report*, dated December 1996, includes the following language:

Given the extensive cumulative experience with the use of PB in patients with myasthenia gravis and data collected from military personnel, the Committee concludes it is unlikely that health effects reported today by Gulf War veterans are the result of exposure simply to PB. Ongoing federally funded studies should help the scientific community draw conclusions about the synergistic effects of PB and other risk factors.

**What did the National Academy of Sciences' Institute of Medicine (IOM) conclude about the risks of PB to Gulf War veterans?**

The IOM report, entitled *Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems*, dated 1996, includes the following sentence:

There have been no documented long-term side effects of PB.

---

## **VA Testifies on Gulf War Benefits, Anti-Nerve Gas Pill**

Department of Veterans Affairs (VA) officials are frequently called before Congress to testify about what the Department is doing on behalf of Gulf War veterans. The following are excerpts from prepared statements for hearings held in Fall 1999.

The first excerpt is from the statement of Mr. Joseph Thompson, Under Secretary for Benefits, before the House Committee on Veterans' Affairs Subcommittee on Benefits. The hearing took place on October 26, 1999, in Washington, DC. The second excerpt is from the statement of Frances M. Murphy, M.D., M.P.H., Acting Deputy Under Secretary for Health, before the House Committee on Veterans' Affairs Subcommittees on Health and Oversight and Investigations on November 16, 1999, in Washington, DC. The October hearing focused on the adjudication of Gulf War veterans' claims. The November hearing was on the possible adverse health effects of the drug pyridostigmine bromide (PB) on Gulf War veterans...

### **Pyridostigmine Bromide Hearing**

*Dr. Murphy:* PB is an FDA-approved treatment for the chronic muscle disorder myasthenia gravis and has been used for that purpose for over 40 years. PB was used as an unapproved, investigational drug during the Gulf War as a pre-treatment to reduce the toxicity of the chemical warfare nerve agent soman.

Several external independent scientific committees have reviewed the medical and scientific literature on Gulf War health exposures and have not ruled out the possibility of long-term health effects from taking this drug. These reviews, conducted by teams of scientists, physicians, public health specialists, veterans and others, include the 1994 "NIH Technology Assessment Workshop"; the 1996 Institute of Medicine, "Report of the Committee to Review the Health Consequences of Service During the Persian Gulf War"; the 1996 "Presidential Advisory Committee on Gulf War Veterans' Illnesses"; and independent scientific reviews contracted by the Committee on Veterans' Affairs, U.S. Senate, reported in its 1998 "Report of the Special Investigation Unit on Gulf War Illnesses".

Based on these reviews and other information, there is insufficient evidence to conclude that health effects experienced by Gulf War veterans today are related to PB during the Gulf War. However, additional research is needed to answer specific outstanding questions about the long-term effects of PB, either PB exposure alone or in combination with exposure to other risk factors, such as pesticides.

Based upon these recommendations, which predate the RAND report, the interagency Research Working Group solicited and funded a number of research studies on potential health effects of PB. Twenty-six such studies have been funded with a total estimated cost of approximately \$20 million. Five of the studies have been completed and 21 are ongoing.

The RAND report declared that its conclusions that PB cannot be excluded as a contributor to illnesses in Gulf War veterans differs from conclusions of some prior investigating bodies, such as the Presidential Advisory Committee and the Institute of Medicine. We think that this statement overstates the differences. The other investigating bodies have not ruled out PB as a possible cause of or contributor to the illnesses that some Gulf War veterans are reporting. The RAND report differs in some important ways from the previously described, independent scientific and medical literature reviews. But, in the most critical aspects, the reports are similar. All of them concluded that further research on possible health effects from PB is warranted. The earlier reviews were focused on whether scientific evidence existed that suggested PB was *likely* to be associated with health problems, while the recent RAND review focused on whether PB *could be excluded* as a possible cause of health problems....

