



Examining Possible Causes of Gulf War Illness

RAND Policy Investigations and Reviews of the Scientific Literature

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Veterans of the 1991 Persian Gulf War have reported a variety of physical and psychological symptoms, some of which remain unexplained. In an effort to do everything possible to understand and explain the illnesses, inform veterans and the public, and recommend changes in Department of Defense (DoD) policies and procedures to minimize such problems in the future, the Secretary of Defense in 1996 designated that a Special Assistant for Gulf War Illnesses and his office (OSAGWI) oversee all DoD efforts related to illnesses of Gulf War veterans.

To complement its investigations, the OSAGWI commissioned the RAND National Defense Research Institute and RAND Health Center for Military Health Policy Research to examine the scientific literature and conduct other policy investigations on the health effects of eight areas of possible causes of illness. It was hoped that combining what scientific investigations had to say about what happened in the Gulf War would produce a more complete understanding of illnesses among veterans of that war.

This research brief outlines RAND's investigations into the health effects of infectious diseases, pyridostigmine bromide (PB), immunizations, wartime stress, chemical warfare and biological warfare (CW/BW) agents, oil well fires, depleted uranium (DU), and pesticides. Many of these studies were scientific literature reviews that generally focused on information published or accepted for publication in peer-reviewed journals, books, government publications, and conference proceedings. RAND occasionally used unpublished information, but only to develop hypotheses. In a few instances, RAND commissioned independent investigations into the nature or extent of potential causes of Gulf War illness.

Abstract

Shortly after the 1991 Persian Gulf War ended, veterans of that conflict began reporting a variety of physical and psychological symptoms, some of which remain unexplained. To track this issue, the Secretary of Defense in 1996 designated that a Special Assistant for Gulf War Illnesses (OSAGWI) oversee all Department of Defense efforts related to these conditions. This research brief outlines assistance that RAND provided to the OSAGWI in investigating the health effects of eight areas of possible causes of illness: infectious diseases, pyridostigmine bromide, immunizations, wartime stress, chemical and biological warfare agents, oil well fires, depleted uranium, and pesticides.

Infectious Diseases

A RAND review of the scientific literature examined known or plausible infectious diseases (with the exception of the flu or common cold) that were actually diagnosed in people who served in the Gulf War or that are known to exist in the Persian Gulf area. The study found that the incidence of infectious disease was very low among U.S. troops in the Gulf War, and that known infectious diseases were properly diagnosed and treated. The study could not, however, rule out the possibility that some as-yet-unknown infectious diseases could have been a contributing cause to undiagnosed illnesses among Gulf War veterans. While most commonly recognized infectious diseases have been ruled out, one theory that continues to merit attention concerns the role of mycoplasma,

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a difficult-to-detect bacteria, which the published work of one researcher theorizes is a cause of illness in Gulf War veterans.

Pyridostigmine Bromide

Pyridostigmine bromide was distributed to U.S. and allied troops as a pretreatment to enhance the effectiveness of post-exposure treatments in the event that Iraq employed the nerve agent soman during the Gulf War. RAND examined the role that PB played in the ongoing chronic health problems documented in Gulf War veterans. After examining the known effects of PB on the central and peripheral nervous systems, the RAND research team could not reject PB as a possible contributing factor to the undiagnosed health problems of some veterans. The RAND team evaluated three possible mechanisms by which some individuals could experience increased susceptibility to PB in the Gulf War. The researchers found evidence consistent with each mechanism and pointed to the need for additional studies to evaluate what, if any, role they played in Gulf War-related health problems. The researchers also evaluated four hypotheses regarding possible ways PB could lead to chronic illness. They found adequate evidence to discount one hypothesis but not enough evidence to truly assess the second. They also found that the final two closely related mechanisms were biologically plausible but that additional studies were needed to confirm or refute whether those mechanisms contributed to health effects from Gulf War service. The report on this study calls for additional research to clarify the role of PB.

Use of Drugs Not Yet Approved by the FDA for CW/BW Defense

In another study, RAND investigated the regulatory issues surrounding DoD's use of "investigational" drugs and vaccines to protect U.S. service members against chemical and biological weapons. The U.S. Food and Drug Administration (FDA) has allowed the DoD to administer such drugs and vaccines in certain situations, even though these substances have not been specifically tested for use in those circumstances. RAND examined (1) the rule that authorized the FDA commissioner to waive informed consent with respect to these substances, (2) how this authority was used with regard to PB and botulinum toxoid vaccine during the Gulf War, and (3) the controversy surrounding the rule, its application, and its implications.

Immunizations

Immunizations are among the factors that have been widely considered as possible contributors to illness in Gulf War veterans. Service men and women receive a variety of vaccines as part of their military service, and several additional vaccines were administered to those serving in the Gulf War, including the anthrax and botulinum toxoid vaccines. RAND reviewed evidence in the scientific literature and elsewhere (such as newspapers and the Internet) pertaining to a possible connection between these two vaccines and chronic health problems reported in ill Gulf War veterans. RAND also looked at whether multiple vaccinations (i.e., administering

one or both of these vaccinations in combination with other vaccines) had any connection to symptoms experienced by Gulf War veterans. RAND additionally investigated the efficacy of the anthrax and botulinum toxoid vaccines and reviewed the history of anthrax vaccine production. The results of that review will appear in a forthcoming RAND report, which is expected to be published in 2005.

Stress

The Gulf War presented U.S. military personnel who served in the Gulf theater with an array of stressful experiences before, during, and after deployment, and those experiences may have contributed to their reported health difficulties. A RAND report notes that research recorded in the general scientific literature has shown that stress can produce myriad health effects, and these effects can manifest themselves as symptoms and conditions similar to those that Gulf War veterans have reported. The RAND report also notes that while empirical studies of Gulf War veterans indicate that stress plays some role in the etiology or exacerbation of illness, available research does not demonstrate the causal role of stress in the unexplained illnesses of Gulf War veterans.

Another RAND study took an historical view of the psychological and psychosocial consequences of combat and deployment, paying special attention to the Gulf War. The study argues that the stress of combat or simple deployment can have immediate and long-term physical and psychological consequences. The study also notes that while it would be an oversimplification to assert that stress caused Gulf War illnesses, it nevertheless contributes to many psychological and somatic symptoms, e.g., by rendering soldiers more vulnerable to environmental pathogens. Because stress is likely to affect and be affected by many factors synergistically, this report argues that the existence of a single independent cause of illness seen among Gulf War veterans is unlikely.

Chemical and Biological Warfare Agents

RAND reviewed the scientific literature on the effects of exposure to certain chemical or biological weapons. With respect to Gulf War veterans, RAND found that militarily effective doses of any of the agents reviewed would have produced severe health effects that would have required clinical treatment or resulted in death. But such health effects were not seen among Gulf War veterans; as such, no evidence was found of exposures to militarily effective doses. However, because low-level exposures could have produced mild clinical symptoms that may have been overlooked or misinterpreted, the study could not rule out low-dose exposures as possible contributors to some conditions that Gulf War veterans experienced. However, the study found it implausible that exposures affecting large numbers of people would have escaped clinical recognition. Furthermore, no references in the literature review substantiated what veterans reported was the case for about half of Gulf War health problems: that their clinical symptoms only began years after they initially were exposed to CW/BW doses.

RAND Gulf War Illness Studies		
Literature Review	Analysis and Findings	Possible Cause of Gulf War Illness?
Infectious diseases	<ul style="list-style-type: none"> Incidence of infectious disease was very low among U.S. troops in the Gulf War as compared with other wars. Known infectious diseases were properly diagnosed and treated. 	<ul style="list-style-type: none"> Commonly recognized infectious diseases have been ruled out, but the possibility exists that some unknown infectious disease could have been a contributing cause of undiagnosed illnesses. A theory under continuing investigation concerns the role of mycoplasma, a difficult-to-detect bacteria that was posited in one researcher's published work as a cause of illness.
Pyridostigmine bromide	<ul style="list-style-type: none"> PB was distributed to U.S. and allied troops as a pretreatment for possible Iraqi use of the nerve agent soman. PB is an acetyl cholinesterase inhibitor. RAND examined the known effects of PB on the central and peripheral nervous systems and the validity of hypotheses of how PB might contribute to illness. 	<ul style="list-style-type: none"> Based on the scientific evidence to date, RAND could not rule out PB as a possible contributor to some symptoms in Gulf War veterans. The report calls for additional research on the safety and effectiveness of administering PB to humans.
Stress	<ul style="list-style-type: none"> The general scientific literature has shown that stress can produce myriad health effects. These effects can manifest themselves as symptoms and conditions similar to those reported by Gulf War veterans. 	<ul style="list-style-type: none"> Although the scientific literature shows that stress can produce the sort of symptoms seen in Gulf War veterans, there are presently no empirical studies proving that this is the case. It is inappropriate either to rely on stress as a default explanation for the myriad health problems reported by Gulf War veterans without evidence to support that position or to assume that stress played no role.
Chemical and biological warfare agents	<ul style="list-style-type: none"> No evidence was found of exposures to militarily effective doses. Such exposures would have resulted in death or severe symptoms. Low-level exposure could have produced mild symptoms that could have been overlooked. Little research exists on the effects of low-dose exposures below the dosage level that causes symptoms. 	<ul style="list-style-type: none"> Nerve agents, which are acetylcholinesterase inhibitors, could have produced symptoms similar to those seen in Gulf War veterans. Exposure to militarily effective doses was ruled out. Although, based solely on the scientific literature, there is no evidence that exposure occurred, the possibility that low-dose exposure to some CW agents contributed to symptoms seen in Gulf War veterans cannot be ruled out. More research is needed in this area.
Oil well fires	<ul style="list-style-type: none"> Concentrations of pollutants in Kuwait and Saudi Arabia were magnitudes lower than recommended U.S. occupational standards and comparable to ambient levels. Particulate concentrations were high, but were largely sand granules of a size that would affect the respiratory systems of smokers, asthmatics, or other sensitive populations. 	<ul style="list-style-type: none"> Nothing in the scientific literature review suggests that there are health effects associated with the pollutant levels measured during the oil well fires.
Depleted uranium	<ul style="list-style-type: none"> Armor and anti-armor rounds made from DU saw widespread use during the Gulf War. While very little literature directly addresses the health effects of DU exposure, a wide body of literature deals with the health effects of natural uranium and enriched uranium. DU is toxicologically identical to but less radioactive than natural uranium. 	<ul style="list-style-type: none"> RAND found no negative health effects noted in the literature as a result of exposure to natural uranium at levels exceeding those that were likely in the Gulf War. Gulf War veterans with the most exposure to DU—those with embedded fragments—have shown neither adverse toxicological effects attributable to DU nor any adverse health effects related to DU radiation.
Pesticides	<ul style="list-style-type: none"> RAND examined the scientific literature on 12 of 35 pesticides used during the Gulf War. RAND focused on known exposures and doses and related health outcomes, paying particular attention to long-term, chronic effects of exposure to organophosphate and carbamate pesticides, which are acetylcholinesterase inhibitors. 	<ul style="list-style-type: none"> Little evidence of long-term effects was found for four pesticides studied. Organophosphates and carbamates have been shown to produce symptoms similar to those reported by some Gulf War veterans. Evidence suggests that these pesticides potentially could contribute to some of the Gulf War veterans' undiagnosed illnesses. However, no prospective studies have positively identified pesticides as causative agents.

Oil Well Fires

Measurements taken in combat areas in Kuwait and Saudi Arabia, where most troops were assigned during the Gulf War, showed that concentrations of pollutants in those areas were orders of magnitude lower than the recommended occupational standards in the United

States and were comparable to ambient levels, RAND's literature review noted. Nothing in this RAND review of the scientific literature suggests that there were health effects associated with pollutants at the levels measured during the oil well fires. Particulate-matter concentrations were high but were largely attributable to sand gran-

ules of a size that would likely affect the respiratory systems of sensitive population subgroups, such as smokers or asthmatics.

Depleted Uranium

Because of depleted uranium's density and metallurgical properties, DU saw widespread use during the Persian Gulf War in improved armor and anti-armor munitions. A RAND report examines the scientific literature regarding the possible health effects on U.S. troops from exposure to DU. While very little literature directly addresses DU, a wide body of literature deals with the health effects of natural uranium and enriched uranium. DU is toxicologically identical to natural uranium, but because it is less radioactive, it is radiologically more benign. RAND's literature review found no negative health effects as a result of exposure to natural uranium at levels exceeding those levels that military personnel likely experienced during the Gulf War. This literature review pays close attention to an ongoing study of a group of Gulf War veterans who, due to embedded fragments, received the highest DU exposure. Those with embedded fragments have exhibited elevated levels of uranium in their urine, but the literature review revealed neither adverse renal effects attributable to DU nor any adverse health effects related to DU radiation.

Pesticides

A RAND report summarizes the scientific literature on 12 of the 35 pesticides that were likely to have been used during the Gulf War. The report focuses on known pesticide exposures and doses and related health outcomes, paying particular attention to long-term, chronic effects of reported exposures to organophosphate and carbamate pesticides. Epidemiological studies, along with studies of genetic and biological differences between ill and healthy subjects and studies of the physiological mechanisms of organophosphate

and carbamate pesticides, are suggestive but not conclusive. The studies suggest that these pesticides could be among the agents potentially contributing to some of the undiagnosed illnesses seen in Gulf War veterans. However, no prospective studies have been conducted that positively identify pesticides as causative agents.

Another report presents the results of a RAND survey of 2,005 Gulf War veterans, which attempted to quantify service members' in-theater use of pesticides before and during the conflict. While the majority of personnel were exposed to some pesticides, RAND found that pesticide use differed by service, season, rank, and living arrangements. RAND found no evidence of widespread misuse of pesticides, but it did identify some cases of possible misuse.

What RAND's Policy Investigations and Scientific Literature Reviews Mean

Although no definitive cause has been found to explain the health symptoms reported by Gulf War veterans, RAND's research—along with the investigations of other researchers—identified a number of areas that could not be ruled out as possible causes of symptoms and, as such, require further research. Based on the published RAND work to date, these areas for further research include health effects from pyridostigmine bromide and pesticides. RAND's published research on the potential role of immunizations is forthcoming. Moreover, because the battlefield is "dirty" in the sense that troops are exposed to many occupational hazards and to high levels of stress, RAND calls for additional investigations into the effect of factors in combination and of individuals' susceptibility to such exposures. These RAND studies also point to the critical need for better data collection and record keeping related to possible causes of Gulf War illness, an effort that DoD already has begun to significantly enhance. ■

This research brief describes work documented in *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 1: Infectious Diseases*, Lee H. Hilborne and Beatrice Alexandra Golomb, MR-1018/1-OSD, 2001, 140 pages, \$15, ISBN: 0-8330-2676-3 (available at <http://www.rand.org/publications/MR/MR1018.1/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 2: Pyridostigmine Bromide*, Beatrice Alexandra Golomb, MR-1018/2-OSD, 1999, 423 pages, \$30, ISBN: 0-8330-2677-1 (available at <http://www.rand.org/publications/MR/MR1018.2/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 4: Stress*, Grant N. Marshall, Lois M. Davis, and Cathy D. Sherbourne, MR-1018/4-1-OSD, 2000, 141 pages, \$15, ISBN: 0-8330-2679-8 (available at <http://www.rand.org/publications/MR/MR1018.4.1/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 5: Chemical and Biological Warfare Agents*, William S. Augerson, MR-1018/5-OSD, 2000, 284 pages, \$30, ISBN: 0-8330-2680-1 (available at <http://www.rand.org/publications/MR/MR1018.5/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 6: Oil Well Fires*, Dalia M. Spektor, MR-1018/6-OSD, 1998, 96 pages, \$15, ISBN: 0-8330-2668-2 (available at <http://www.rand.org/publications/MR/MR1018.6/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 7: Depleted Uranium*, Naomi H. Harley, Ernest C. Foulkes, Lee H. Hilborne, Arlene Hudson, and C. Ross Anthony, MR-1018/7-OSD, 1999, 146 pages, \$15, ISBN: 0-8330-2681-X (available at <http://www.rand.org/publications/MR/MR1018.7/>); *A Review of the Scientific Literature As It Pertains to Gulf War Illnesses—Volume 8: Pesticides*, Gary Cecchine, Beatrice A. Golomb, Lee H. Hilborne, Dalia M. Spektor, and C. Ross Anthony, MR-1018/8-OSD, 2000, 216 pages, \$15, ISBN: 0-8330-2682-8 (available at <http://www.rand.org/publications/MR/MR1018.8/>); *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense: Lessons from the Gulf War*, Richard Rettig, MR-1018/9-OSD, 1999, 122 pages, \$15, ISBN: 0-8330-2683-6 (available at <http://www.rand.org/publications/MR/MR1018.9/>); *Psychological and Psychosocial Consequences of Combat and Deployment with Special Emphasis on the Gulf War*, David H. Marlowe, MR-1018/11-OSD, 2001, 210 pages, \$15, ISBN: 0-8330-2685-2 (available at <http://www.rand.org/publications/MR/MR1018.11/>); *Pesticide Use During the Gulf War: A Survey of Gulf War Veterans*, Ronald D. Fricker, Jr., Elaine Reardon, Dalia M. Spektor, Sarah H. Cotton, Jennifer Hawes-Dawson, Jennifer E. Pace, and Susan D. Hosek, MR-1018/12-OSD, 2000, 150 pages, \$15, ISBN: 0-8330-2895-2 (available at <http://www.rand.org/publications/MR/MR1018.12/>); and *Documentation for the Survey of Pesticide Use During the Gulf War: The Survey Instrument*, Dalia M. Spektor, Elaine Reardon, and Sarah K. Cotton, MR-1226-OSD, 2000, 207 pages, \$25, ISBN: 0-8330-2900-2 (available at <http://www.rand.org/publications/MR/MR1226/>). These reports are also available from RAND Distribution Services (phone: 310-451-7002; toll free: 877-584-8642; or email: order@rand.org). The RAND Corporation is a nonprofit research organization providing objective analysis and effective solutions that address the challenges facing the public and private sectors around the world. RAND's publications do not necessarily reflect the opinions of its research clients and sponsors. RAND® is a registered trademark.



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