

# **Gulf War Illness and the Health of Gulf War Veterans**

**Scientific Findings and Recommendations**

**Research Advisory Committee on  
Gulf War Veterans' Illnesses**



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***Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations***  
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# | Gulf War Illness and the Health of Gulf War Veterans

## Findings in Brief

Gulf War illness, the multisymptom condition resulting from service in the 1990-1991 Gulf War, is the most prominent health issue affecting Gulf War veterans, but not the only one. The Congressionally-mandated Research Advisory Committee on Gulf War Veterans' Illnesses has reviewed the extensive evidence now available, including important findings from scientific research and government investigations not considered by earlier panels, to determine what is known about the health consequences of military service in the Gulf War. This evidence identifies the foremost causes of Gulf War illness, describes biological characteristics of this condition, and provides direction for future research urgently needed to improve the health of Gulf War veterans.

**Gulf War illness is a serious condition that affects at least one fourth of the 697,000 U.S. veterans who served in the 1990-1991 Gulf War.** This complex of multiple concurrent symptoms typically includes persistent memory and concentration problems, chronic headaches, widespread pain, gastrointestinal problems, and other chronic abnormalities not explained by well-established diagnoses. No effective treatments have been identified for Gulf War illness and studies indicate that few veterans have recovered over time.

**Gulf War illness fundamentally differs from trauma and stress-related syndromes described after other wars.** Studies consistently indicate that Gulf War illness is not the result of combat or other stressors and that Gulf War veterans have lower rates of posttraumatic stress disorder than veterans of other wars. No similar widespread, unexplained symptomatic illness has been identified in veterans who have served in war zones since the Gulf War, including current Middle East deployments.

**Evidence strongly and consistently indicates that two Gulf War neurotoxic exposures are causally associated with Gulf War illness: 1) use of pyridostigmine bromide (PB) pills, given to protect troops from effects of nerve agents, and 2) pesticide use during deployment.** Evidence includes the consistent association of Gulf War illness with PB and pesticides across studies of Gulf War veterans, identified dose-response effects, and research findings in other populations and in animal models.

**For several Gulf War exposures, an association with Gulf War illness cannot be ruled out. These include low-level exposure to nerve agents, close proximity to oil well fires, receipt of multiple vaccines, and effects of combinations of Gulf War exposures.** There is some evidence supporting a possible association between these exposures and Gulf War illness, but that evidence is inconsistent or limited in important ways.

**Other wartime exposures are not likely to have caused Gulf War illness for the majority of ill veterans.** For remaining exposures, there is little evidence supporting an association with Gulf War illness or a major role is unlikely based on what is known about exposure patterns during the Gulf War and more recent deployments. These include depleted uranium, anthrax vaccine, fuels, solvents, sand and particulates, infectious diseases, and chemical agent resistant coating (CARC).

**Gulf War illness is associated with diverse biological alterations that most prominently affect the brain and nervous system.** Research findings in veterans with Gulf War illness include significant differences in brain structure and function, autonomic nervous system function, neuroendocrine and immune measures, and measures associated with vulnerability to neurotoxic chemicals. There is little evidence of peripheral neuropathies in Gulf War veterans.

**Gulf War illness has both similarities and differences with multisymptom conditions in the general population.** Symptom-defined conditions like chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity occur at elevated rates in Gulf War veterans, but account for only a small proportion of veterans with Gulf War illness.

**Studies indicate that Gulf War veterans have significantly higher rates of amyotrophic lateral sclerosis (ALS) than other veterans, and that Gulf War veterans potentially exposed to nerve agents have died from brain cancer at elevated rates.** Although these conditions have affected relatively few veterans, they are cause for concern and require continued monitoring.

**Important questions remain about other Gulf War health issues.** These include questions about rates of other neurological diseases, cancers, and diagnosed conditions in Gulf War veterans, current information on overall and disease-specific mortality rates in Gulf War veterans, and unanswered questions concerning the health of veterans' children.

**Federal Gulf War research programs have not been effective, historically, in addressing priority issues related to Gulf War illness and the health of Gulf War veterans.** Substantial federal Gulf War research funding has been used for studies that have little or no relevance to the health of Gulf War veterans, and for research on stress and psychiatric illness. Recent Congressional actions have brought about promising new program developments at the Departments of Defense and Veterans Affairs, but overall federal funding for Gulf War research has declined dramatically since 2001.

**A renewed federal research commitment is needed to identify effective treatments for Gulf War illness and address other priority Gulf War health issues.** Adequate funding is required to achieve the critical objectives of improving the health of Gulf War veterans and preventing similar problems in future deployments. This is a national obligation, made especially urgent by the many years that Gulf War veterans have waited for answers and assistance.

## | Executive Summary

More than seventeen years have passed since the United States and its international allies liberated Kuwait from the grip of Saddam Hussein's Iraqi military forces in the 1990-1991 Gulf War. Despite the swift and decisive victory achieved in Operation Desert Storm, at least one fourth of the nearly 700,000 U.S. military personnel who served in the war have experienced a complex of difficult and persistent health problems since their return home. Illness profiles typically include some combination of chronic headaches, cognitive difficulties, widespread pain, unexplained fatigue, chronic diarrhea, skin rashes, respiratory problems, and other abnormalities. This symptom complex, now commonly referred to as Gulf War illness, is not explained by routine medical evaluations or by psychiatric diagnoses, and has persisted, for many veterans, for 17 years. While specific symptoms can vary between individuals, a remarkably consistent illness profile has emerged from hundreds of reports and studies of different Gulf War veteran populations from different regions of the U.S., and from allied countries.

For many years, diverse views about the cause or causes of Gulf war illness have been put forward and vigorously debated. Hundreds of burning oil well fires that turned the Kuwaiti sky black with smoke, dramatic reports of uranium-tipped munitions, sandstorms, secret vaccines, and frequent chemical alarms, along with the government's acknowledgment of nerve agent releases in theater, led many to believe that veterans were suffering from effects of hazardous exposures that occurred during their deployment. Government officials and special committee reports maintained that there was little evidence that this was the case, and noted that veterans returning from other wars have often experienced chronic health problems related to the stressful circumstances of serving in a war zone. All sides called for research to better understand the problem. Multiple official investigations were launched and hundreds of research studies funded.

In 1998, the U.S. Congress mandated the appointment of a public advisory panel of independent scientists and veterans to advise on federal research studies and programs to address the health consequences of the Gulf War. The Research Advisory Committee on Gulf War Veterans' Illnesses was appointed by the Secretary of Veterans Affairs in 2002 and directed to evaluate the effectiveness of government research in addressing central questions on the nature, causes, and treatments of Gulf War-related illnesses. According to its charter, the guiding principle for the Committee's work is the premise that the fundamental goal of all Gulf War-related government research is to improve the health of Gulf War veterans, and the choice and success of federal Gulf War research should be judged accordingly.

The Committee has convened public meetings on a regular basis to consider the broad spectrum of scientific research, investigative reports, and government research activities related to the health of Gulf War veterans. In addition to annual reports on Committee meetings and activities, it has periodically issued formal scientific recommendations and reports. The Committee's last extended report, *Scientific Progress in Understanding Gulf War Veterans' Illnesses*, issued in 2004, provided findings and recommendations on topics the Committee had considered up to that time. The present report provides a comprehensive review of information and evidence on topics reviewed by the Committee since that time, as well as additional information on topics considered in the 2004 report.

The central focus of this report is Gulf War illness, the multisymptom condition that affects veterans of the 1990-1991 Gulf War at significantly elevated rates. Despite considerable government, scientific, and media attention, little was clearly understood about Gulf War illness for many years. Now, 17 years after the war, the extensive body of scientific research and government investigations that is currently available provides the basis for an evidence-based assessment of the nature and causes of Gulf War illness. As

described throughout the report, scientific evidence leaves no question that Gulf War illness is a real condition with real causes and serious consequences for affected veterans. Research has also shown that this pattern of illness does not occur after every war and cannot be attributed to psychological stressors during the Gulf War.

Although Gulf War illness is the most prominent and widespread issue related to the health of Gulf War veterans, it is not the only one. Additional issues of importance include diagnosed medical and psychiatric conditions affecting Gulf War veterans, and questions related to the health of veterans' family members. Section 1 of this report provides an overview of information related to the prevalence and characteristics of Gulf War illness, and other health issues, from the large body of Gulf War epidemiologic research. Section 2 addresses evidence related to the causes of Gulf War illness, including what has been learned about effects of psychological stressors, oil well fires, depleted uranium, and other exposures of possible concern, and compares the weight of evidence related to each exposure as a cause or contributor to Gulf War illness. Section 3 addresses the nature of Gulf War illness, reviewing research on biological findings associated with Gulf War illness and its relationship with multisymptom conditions found in the general population. Section 4 reviews research programs sponsored by federal agencies to address Gulf War-related health issues. Research recommendations provided in relation to topics considered in each section are summarized and prioritized in Section 5 of the report.

Gulf War research has posed a complex scientific challenge for researchers. Most obviously, Gulf War illness does not fit neatly into well-established categories of disease. The underlying pathophysiology of Gulf War illness is not apparent from routine clinical tests, and the illness appears not to be the result of a single cause producing a well-known effect. There are relatively few sources of objectively measured data for studying Gulf War illness or its association with events and exposures in the Gulf War. Some observers have suggested that these complexities pose too difficult a challenge, and that it is unlikely that the nature and causes of Gulf War illness can ever be known. On the contrary, the Committee has found that the extensive scientific research and other diverse sources of information related to the health of Gulf War veterans paint a cohesive picture that yields important answers to basic questions about both the nature and causes of Gulf War illness. These, in turn, provide direction for future research that is urgently needed to improve the health of Gulf War veterans.

## **Epidemiologic Research: What is Gulf War Illness and How Many Veterans Are Affected?**

Gulf War illness refers to the complex of symptoms that affects veterans of the 1990-1991 Gulf War at significantly excess rates. It is characterized by multiple diverse symptoms not explained by established medical diagnoses or standard laboratory tests, symptoms that typically include a combination of memory and concentration problems, persistent headache, unexplained fatigue, and widespread pain, and can also include chronic digestive difficulties, respiratory symptoms, and skin rashes. A similar profile of excess symptoms has been described in every study of U.S. Gulf War veterans from different regions and units, and in Gulf War veterans from the United Kingdom and other allied countries.

Gulf War illness is not the only health condition related to Gulf War service, but it is by far the most common. Gulf War illness prevalence estimates vary with the specific case definition used. Studies consistently indicate, however, that an excess of 25 to 32 percent of veterans who served in the 1990-1991 Gulf War are affected by a complex of multiple symptoms, variously defined, over and above rates in contemporary military personnel who did not deploy to the Gulf War. That means that between 175,000 and 210,000 of the nearly 700,000 U.S. veterans who served in the 1990-1991 Gulf War suffer from this persistent pattern of symptoms as a result of their wartime service.

Research has not supported early speculation that Gulf War illness is a stress-related condition. Large population-based studies of Gulf War veterans consistently indicate that Gulf War illness is not the result

of combat or other deployment stressors, and that rates of posttraumatic stress disorder (PTSD) and other psychiatric conditions are relatively low in Gulf War veterans. Gulf War illness differs fundamentally from trauma and stress-related syndromes that have been described after other wars. No Gulf War illness-type problem, that is, no widespread symptomatic illness not explained by medical or psychiatric diagnoses, has been reported in veterans who served in Bosnia in the 1990s or in current conflicts in Iraq and Afghanistan.

Epidemiologic studies indicate that rates of Gulf War illness vary in different subgroups of Gulf War veterans. Gulf War illness affects veterans who served in the Army and Marines at higher rates than those in the Navy and Air Force, and enlisted personnel more than officers. Studies also indicate that Gulf War illness rates differ according to where veterans were located during deployment, with highest rates among troops who served in forward areas. More specifically, studies consistently show that the rate of Gulf War illness is associated with particular exposures that veterans encountered during deployment.

Identified links between veteran-reported exposures and Gulf War illness have raised a great deal of interest, but have also been the source of considerable confusion. The use of self-reported exposure information raises a number of concerns, most obviously in relation to recall bias. These concerns emphasize the importance of assessing findings across a broad spectrum of studies, rather than relying on results from individual studies, and of evaluating the impact of recall and other information bias on study results where possible.

The Committee identified an additional problem that has had a profound effect on epidemiologic study results and their interpretation. Exposures assessed in Gulf War studies are highly correlated, that is, veterans who had one type of exposure also usually had many others. In analyzing the effects of any single exposure during the war, it is essential that effects of other exposures be considered and adjusted for, to avoid the well-known problem of “confounding,” or confusing the effects of multiple exposures with one another. Many Gulf War epidemiologic studies failed to control for confounding effects, yielding illogical results that made it appear as if all, or nearly all, wartime exposures caused Gulf War illness. In contrast, adjusted results—that is, those that controlled for effects of other exposures in theater—consistently identified a very limited number of significant risk factors for Gulf War illness.

### **The Urgent Need for Effective Treatments for Gulf War Illness**

Gulf War illness has persisted for a very long time for most ill veterans—over seventeen years for many. Studies indicate that few veterans with Gulf War illness have recovered over time and only a small minority have substantially improved. The federal Gulf War research effort has yet to provide tangible results in achieving its ultimate objective, that is, to improve the health of Gulf War veterans. Few treatments have been studied and none have been shown to provide significant benefit for a substantial number of ill veterans.

Treatments that are effective in improving the health of veterans with Gulf War illness are urgently needed. In recent years, Congressional actions have led to promising initiatives in this effort at both the Department of Defense (DOD) and the Department of Veterans Affairs (VA). At DOD, the Office of Congressionally Directed Medical Research Programs has developed an innovative program aimed at identifying treatments and diagnostic tests for Gulf War illness. The program funded a limited number of new treatment studies in 2007 and has invited proposals for additional studies to be funded in 2009. In addition, VA has sponsored a center of excellence for Gulf War research at the University of Texas Southwestern, focused on identifying specific biological abnormalities that underlie Gulf War illness that can be targeted for treatment. Research to identify effective treatments for Gulf War illness has been given highest priority by the Committee and requires expanded federal support.

## **Other Health Issues Affecting Gulf War Veterans**

Although Gulf War illness has been the most prominent health issue associated with military service in the 1990-1991 Gulf War, a number of other health issues are extremely important. Studies have indicated that veterans of the 1990-1991 Gulf War have developed amyotrophic lateral sclerosis (ALS) at twice the rate of nondeployed veterans of the same era. Gulf War veterans who were downwind from nerve agent releases resulting from weapons demolitions at Khamisiyah, Iraq, in March of 1991, have also been found to have twice the rate of death due to brain cancer as other veterans in theater. Recent studies have suggested that excess cases of ALS have declined in recent years, but the seriousness of both ALS and brain cancer are clear causes for concern and require continued monitoring for the foreseeable future. These findings also highlight the need for information on rates of other diagnosed diseases, particularly neurological diseases and cancers, which have only minimally been assessed in Gulf War veterans. Multiple studies have reported that rates of PTSD and other psychiatric disorders are higher in Gulf War veterans than in nondeployed era veterans but are, overall, substantially lower than in veterans of other wars.

Hospitalization and mortality studies have identified only limited differences between Gulf War and nondeployed era veterans. Early U.S. mortality studies indicated that Gulf War veterans had higher death rates due to accidents, and somewhat lower disease-related mortality rates. Although identified differences appeared to diminish in the years after the war, the most recent year for which comprehensive mortality information has been reported for U.S. Gulf War veterans is 1997. Given concerns about diseases of longer latency, it is extremely important that current disease-specific mortality rates for U.S. Gulf War veterans be made publicly available, and reported on a regular basis.

For many years, concerns have been raised about rates of birth defects in Gulf War veterans' children and anomalous health problems in their family members. Large population-based studies in the U.S. and the U.K. have provided some evidence of excess rates of several types of birth defects among children born to Gulf War veterans, in comparison to nondeployed era veterans. The specific types of birth defects identified have differed in different studies, however, and rates, overall, have been in the normal range expected in the general population. Phase III of VA's large U.S. National Survey of Gulf War Era Veterans and their Families included clinical evaluations of veterans' spouses and children. On clinical evaluation, no notable differences were identified between spouses of Gulf War and nondeployed veterans. Findings from clinical evaluations of veterans' children have not been reported from this study, however. Further, no studies have provided comprehensive information on the health of Gulf War veterans' children, including rates of diagnosed conditions, symptomatic illness, and learning and behavioral disorders.

## **What Caused Gulf War Illness? Review of Evidence Relating Gulf War Illness to Experiences and Exposures During Deployment**

In addition to the many physical and psychological challenges common to other wartime deployments, military personnel who served in the 1990-1991 Gulf War were exposed to a long list of potentially hazardous substances. Many possible "causes" of Gulf War illness have been suggested and even promoted in different quarters since the war. Understanding the causes of Gulf War illness has been particularly challenging because of the lack of hard data on individual exposures in theater. Efforts by early government and scientific panels to address this issue were also limited by the sparsity of scientific research information on the health of Gulf War veterans for the first 10 years after the war.

This is no longer the case today, as a result of the extensive number of government investigations and scientific studies conducted to better understand events of the Gulf War and their association with Gulf War illness. Government reports have provided important insights into the types and patterns of

exposures encountered by Gulf War military personnel. The large number of epidemiologic and clinical studies of Gulf War veterans also allow assessment of associations between Gulf War experiences and chronic health problems across a broad spectrum of veteran groups and research designs. In addition, toxicological studies conducted in recent years have provided extensive information on biological effects of Gulf War-related exposures that were previously unknown. The Committee found that epidemiologic research on Gulf War veterans, assessed across diverse study designs and populations, provided clearer and more consistent findings than had previously been assumed. When combined with what has been learned about patterns of exposures in theater and findings from toxicological research, a coherent picture emerges about the most likely causes of Gulf War illness.

The Committee used a standardized approach for evaluating available evidence related to psychological stressors in theater and each of the other deployment-related hazards of possible concern. Three major categories of evidence were considered. First, the Committee reviewed what is known about the extent and patterns of veterans' exposure to each potential hazard. Second, the Committee reviewed the broad spectrum of available scientific research to determine what is known, in general, about health effects of each exposure. This included consideration of epidemiologic and clinical studies of human populations, and laboratory studies conducted in animal models. Third, the Committee reviewed, in detail, results from the many studies of Gulf War veterans that assessed associations between symptom complexes and the exposure in question.

Individually, single studies or types of information might suggest that a specific exposure *could* have caused Gulf War illness. But it is important to consider evidence of all types and studies from all sources to determine what the evidence most clearly indicates *did* cause Gulf War illness. Of the many experiences and exposures associated with Gulf War service, studies of Gulf War veterans consistently implicate only two wartime exposures as significant risk factors for Gulf War illness: use of pyridostigmine bromide (PB) pills as a nerve agent protective measure, and use of pesticides during deployment. This is consistent with what is known about the extent and patterns of these exposures in theater, and with general information from other human and animal studies. Studies of Gulf War veterans have also consistently indicated that psychological stressors during deployment are *not* significantly associated with Gulf War illness. For several other deployment exposures an association with Gulf War illness cannot be ruled out, due to inconsistencies or limitations of available information. Remaining exposures appear unlikely, from available evidence, to have caused Gulf War illness for the majority of affected veterans.

**Psychological stress.** Studies of Gulf War veterans consistently indicate that serving in combat and other psychological stressors during the war are not significantly associated with Gulf War illness, after adjusting for effects of other wartime exposures. Time-limited biological effects of psychological stressors have long been described in human studies, and more extreme psychological stressors and trauma can lead to chronic psychiatric disorders such as PTSD. Combat and extreme psychological stressors were less widespread and less sustained in the Gulf War than in other wars, including current Middle East deployments, and PTSD rates are lower in Gulf War veterans than in veterans of other wars. Population-based studies generally indicate that between three and six percent of Gulf War veterans are diagnosed with PTSD and that the large majority of veterans with Gulf War illness have no psychiatric disorders. Serving in combat and other wartime stressors are associated with higher rates of PTSD in Gulf War veterans, but not with higher rates of Gulf War illness.

**Kuwaiti oil well fires.** Widespread exposure to smoke from the Kuwaiti oil well fires was unique to military service in the 1991 Gulf War, and most prominently affected ground troops in forward locations. Epidemiologic findings relating oil well fire smoke exposure to Gulf War illness have been mixed, although a dose-response effect has been identified by several studies. There is little information from human or animal research to indicate whether intense exposure to petroleum smoke or vapors can lead to persistent multisymptom illness. Although studies of Gulf War veterans do not provide consistent

evidence that exposure to oil fire smoke is a risk factor for Gulf War illness for most veterans, questions remain about effects for personnel located in close proximity to the burning wells for an extended period. Limited findings from epidemiologic studies indicate that higher-level exposures to smoke from the Kuwaiti oil well fires may be associated with increased rates of asthma in Gulf War veterans, and that an association with Gulf War illness cannot be ruled out.

**Depleted uranium (DU).** Low-level exposure to spent DU munitions and dust is thought to have been widespread during the Gulf War and was most prominent among ground troops in forward locations. Recent animal studies have demonstrated acute effects of soluble forms of DU on the brain and behavior, but persistent effects of short term, low-dose exposures like those encountered by the majority of Gulf War veterans have only minimally been assessed. There is little information from Gulf War or other human studies concerning chronic symptomatic illness in relation to DU or uranium exposure. Exposure to DU in post-Gulf War deployments, including current conflicts in the Middle East, has not been associated with widespread multisymptom illness. This suggests that exposure to DU munitions is not likely a primary cause of Gulf War illness. Questions remain about long-term health effects of higher-dose exposures to DU, however, particularly in relation to other health outcomes.

**Vaccines.** Receipt of multiple vaccines over a brief time period is a common feature of overseas military deployments. About 150,000 Gulf War veterans are believed to have received one or two anthrax shots, most commonly troops who were in fixed support locations during the war. Although recent studies have demonstrated that the anthrax vaccine is highly reactogenic, there is no clear evidence from Gulf War studies that links the anthrax vaccine to Gulf War illness. Taken together, limited findings from Gulf War epidemiologic studies, the preferred administration to troops in support locations, and the lack of widespread multisymptom illness resulting from current deployments, combine to indicate that the anthrax vaccine is not a likely cause of Gulf War illness for most ill veterans. However, limited evidence from both animal research and Gulf War epidemiologic studies indicates that an association between Gulf War illness and receipt of a large number of vaccines cannot be ruled out.

**Pyridostigmine bromide (PB).** Widespread use of PB as a protective measure in the event of nerve gas exposure was unique to the 1990-1991 Gulf War. Pyridostigmine bromide is one of only two exposures consistently identified by Gulf War epidemiologic studies to be significantly associated with Gulf War illness. About half of Gulf War personnel are believed to have taken PB tablets during deployment, with greatest use among ground troops and those in forward locations. Several studies have identified dose-response effects, indicating that veterans who took PB for longer periods of time have higher illness rates than veterans who took less PB. In addition, clinical studies have identified significant associations between PB use during the Gulf War and neurocognitive and neuroendocrine alterations identified many years after the war. Taken together, these diverse types and sources of evidence provide a consistent and persuasive case that use of PB during the Gulf War is causally associated with Gulf War illness.

**Pesticides.** The widespread use of multiple types of pesticides and insect repellants in the Gulf War theater is credited with keeping rates of pest-borne diseases low. Pesticide use, assessed in different ways, is one of only two exposures consistently identified by Gulf War epidemiologic studies to be significantly associated with Gulf War illness. Multisymptom illness profiles similar to Gulf War illness have also been associated with low-level pesticide exposures in other human populations. In addition, Gulf War studies have identified dose-response effects, indicating that greater pesticide use is more strongly associated with Gulf War illness than more limited use. Pesticide use during the Gulf War has also been associated with neurocognitive deficits and neuroendocrine alterations in Gulf War veterans in clinical studies conducted many years after the war. Taken together, all available sources of evidence combine to support a consistent and compelling case that pesticide use during the Gulf War is causally associated with Gulf War illness.

**Nerve agents.** There have been no reports that U.S. forces encountered large-scale, high-dose exposures to chemical weapons during the Gulf War, but concerns have emerged related to possible long-term effects of low-dose nerve agent exposures. Recent animal studies have identified brain, autonomic, behavioral, neuroendocrine, and immune effects of low-level sarin exposure that were previously unknown. Studies of individuals exposed to symptomatic but sublethal doses of sarin in Japanese terrorist incidents in the 1990s have identified central nervous system effects that have persisted for many years. The extent of low-level exposure to nerve agents during the Gulf War, however, is unclear. Monitoring equipment used by U.S. forces had little capacity to detect nerve agents at levels that did not cause immediate symptoms. The Department of Defense estimates that about 100,000 U.S. troops may have been exposed to low levels of nerve agents following weapons demolitions in March of 1991 at Khamisiyah, Iraq, but questions have been raised about the models used to determine who was exposed, and at what levels. It is also unclear whether additional low-level exposures may have occurred in other locations. Veterans' self-reported experiences concerning low-level nerve agent exposure in the Gulf War are particularly uncertain, and findings from epidemiologic studies linking chemical agents with Gulf War illness are inconsistent. Studies of Gulf War veterans have identified increased rates of brain cancer and measurable differences in brain structure and function that relate, in a dose-response manner, to modeled nerve agent exposure levels resulting from the Khamisiyah demolitions. Findings from Gulf War clinical studies, and from other human and animal research, suggest that an association between Gulf War illness and low-level nerve agent exposure cannot be ruled out, for whatever subgroups of veterans were exposed.

**Infectious disease.** A substantial proportion of Gulf War military personnel contracted acute gastrointestinal and respiratory infections during deployment, but there is little information concerning patterns of infection in theater and no evidence of widespread chronic illness resulting from those infections. Atypical leishmania infections were identified in a limited number of veterans who served in the 1990-1991 Gulf War, and a much larger number of leishmaniasis cases have been reported in personnel serving in the current Iraq War. Several studies have identified DNA indicators of mycoplasma infection in about 40 percent of symptomatic Gulf War veterans, but questions about testing methods have not been adequately addressed. Taken together, there is little clear evidence implicating infectious diseases as prominent causes of Gulf War illness. Questions remain, however, concerning the possibility that some individuals with Gulf War illness have undetected chronic leishmania and mycoplasma infections.

**Other exposures in theater.** A number of other potentially hazardous exposures in theater have been suggested as causing or contributing to Gulf War illness. These include fine sand and airborne particulates, exhaust from tent heaters, other fuel exposures, solvents, and freshly-applied CARC (chemical agent resistant coating) paint. For most, there is limited evidence of the types considered for other exposures. Available information, however, suggests that these exposures are not likely to have caused Gulf War illness for most affected veterans. Epidemiologic studies have provided little clear information linking any of these exposures to Gulf War illness and most were not most prevalent among ground troops who were forward deployed. Some, like sand, solvents, and fuel exposures, have also been widely encountered by personnel in current Middle East deployments. Information from human and animal studies indicates that fuel and solvent exposures can have neurological effects compatible with symptoms of Gulf War illness, but neither has been associated with Gulf War illness in studies of Gulf War veterans.

**Combinations of exposures.** Compared to the diverse types of evidence available related to effects of individual exposures, research on effects of combinations of Gulf War-related exposures is limited. Gulf War studies consistently indicate that exposures in theater were highly correlated—that is, that personnel most often experienced individual exposures in connection with multiple other exposures. This includes correlations between use of PB and pesticides and among different types of pesticides. Animal studies have identified significant effects of exposure to combinations of PB, pesticides and insect

repellants, sarin, and stress, at dosage levels comparable to those experienced by veterans during the Gulf War. Diverse findings have been reported in relation to chemical absorption, metabolism, and biological effects of mixtures of neurotoxicants, which differ from those of individual exposures. There is little information from human studies, however, including the many epidemiologic studies of Gulf War veterans, concerning combined effects of Gulf War exposures.

A persuasive theoretical case can be made that exposure to mixtures of neurotoxic compounds in theater are likely contributors to Gulf War illness. Such a case would draw on the consistency of evidence from all sources indicating that both PB and pesticides are significantly associated with Gulf War illness, the high correlation between troops' use of PB and pesticides during deployment, and synergistic effects between these exposures demonstrated by animal studies. Many of the pesticides used in the Gulf War, as well as PB and nerve agents, exert toxic effects on the brain and nervous system by altering levels of acetylcholine, an important nerve signaling chemical. Although such a case is compelling, little evidence is available from studies of Gulf War veterans to indicate whether or not Gulf War illness is associated with combinations of these exposures. This important possibility can and should be fully evaluated in Gulf War studies. Pending such assessments, it is not possible to definitively determine the extent to which mixtures of cholinergic and other neurotoxicant exposures during deployment contributed to Gulf War illness. Based on evidence from toxicological research in animals and what is known about patterns of exposures during the Gulf War, an association between Gulf War illness and combined effects of neurotoxicant exposures cannot be ruled out.

There is almost no research to indicate if other wartime exposures interact synergistically with these neurotoxic compounds or with one another. That is, the biological effects of different combinations of PB, multiple pesticides, low-level nerve agents, oil and dense smoke from burning wells, DU dust, fuel vapors, exhaust from tent heaters, CARC paint, airborne particulates, infectious agents, and receipt of multiple vaccines, experienced concurrently or over a brief time period, are unknown. Many have suggested that unknown and difficult-to-characterize effects may have been precipitated by an "exposure cocktail" or "toxic soup" effect during Gulf War deployment. While such a theory is intriguing, there is currently little evidence to indicate whether or not such effects actually occurred, and the extent to which they may have contributed to Gulf War illness.

### **What the Weight of Evidence Tells Us About the Causes of Gulf War Illness**

Seventeen years after the Gulf War, answers to the question of what caused Gulf War illness remain vitally important. An extensive amount of available information now permits an evidence-based assessment of the relationship of Gulf War illness to the many experiences and exposures encountered by military personnel during the Gulf War. The strongest and most consistent evidence from Gulf War epidemiologic studies indicates that use of pyridostigmine bromide (PB) pills and pesticides are significant risk factors for Gulf War illness. The consistency of epidemiologic evidence linking these exposures to Gulf War illness, identified dose-response effects, findings from Gulf War clinical studies, additional research supporting biological plausibility, and the compatibility of these findings with known patterns of exposure during deployment, combine to provide a persuasive case that use of PB pills and pesticides during the 1990-1991 Gulf War are causally associated with Gulf War illness. Gulf War studies also consistently indicate that psychological stressors during deployment are *not* significantly associated with Gulf War illness.

Evidence related to other deployment-related exposures is not as abundant or consistent as evidence related to PB, pesticides, and psychological stressors. For several wartime exposures, there is some evidence supporting a possible association with Gulf War illness, but that evidence is inconsistent or limited in important ways. Clinical studies of Gulf War veterans, studies of other populations exposed to sarin, and findings from animal studies all suggest that low-level nerve agent exposure can produce

persistent neurological effects that may be compatible with symptoms of Gulf War illness. Therefore, an association between Gulf War illness and low-level nerve agents cannot be ruled out for those veterans who were exposed. However, inconsistencies in epidemiologic studies and unreliable exposure information preclude a clear evaluation of the extent to which such exposures occurred and may have contributed to Gulf War illness. Limited evidence from several sources also suggests that an association with Gulf War illness cannot be ruled out in relation to combined effects of neurotoxicant exposures, receipt of multiple vaccines, and exposure to the Kuwaiti oil fires, particularly for personnel in close proximity to the burning wells for an extended period.

There is little reliable information from Gulf War studies concerning an association of DU or anthrax vaccine to Gulf War illness. The prominence of both exposures in more recent deployments, in the absence of widespread unexplained illness, suggests these exposures are unlikely to have been major causes of Gulf War illness for the majority of affected veterans. Fine blowing sand, solvents, and fuel exposures were also widely encountered in both the 1990-1991 Gulf War and in the current Iraq War and results from studies of Gulf War veterans have not supported an association between these exposures and Gulf War illness. All of the exposures described can be hazardous in some circumstances, however, and some veterans may have experienced adverse effects on a more limited basis.

### **The Nature of Gulf War Illness: Biological and Clinical Findings in Gulf War Veterans**

Although veterans' symptoms are the most obvious and consistent indicators of Gulf War illness, dozens of research studies conducted by multiple investigators have identified objective measures that significantly distinguish veterans with Gulf War illness from healthy controls. Identified differences relate to structure and function of the brain, function of the autonomic nervous system, neuroendocrine and immune alterations, and variability in enzymes that protect the body from neurotoxic chemicals. These findings provide indicators of diverse biological differences associated with Gulf War illness, but have not, as yet, provided measures that can be used as diagnostic tests. While scientific progress has been made in understanding the biological nature of Gulf War illness, important work remains in characterizing the specific pathophysiological processes that underlie veterans' symptoms. The Committee reviewed the broad spectrum of studies that have evaluated biological and clinical parameters in Gulf War veterans, focusing most specifically on Gulf War illness.

**Identified effects on the brain and central nervous system.** Multiple lines of research have supported early indications that service in the Gulf War, for some veterans, resulted in long term effects on the central nervous system. Population-based studies of Gulf War veterans have consistently identified significantly excess rates of symptom complexes suggestive of central nervous system abnormalities. Studies have also indicated that Gulf War veterans developed amyotrophic lateral sclerosis (ALS) at twice the rate of nondeployed era veterans, and that veterans downwind from the Khamisiyah munitions demolitions have died from brain cancer at twice the rate of other Gulf War veterans. Earlier reports suggesting that Gulf War illness is not associated with neurological abnormalities generally referred to the lack of significant findings identified with standard clinical evaluations and peripheral nerve function testing. It is important to distinguish the lack of findings in these areas from the diverse central nervous system effects identified using specialized brain imaging scans, neuropsychological testing, and measures of balance and audiovestibular function.

**Neuroimaging studies.** Three research teams have identified significant differences between veterans with Gulf War illness and controls using proton magnetic resonance spectroscopy (MRS) scans of the brain. Findings indicate that symptomatic veterans have significantly reduced functioning brain cell mass in the brainstem, basal ganglia, and hippocampus. Reduced neuronal function in the left basal ganglia was correlated with increased central dopamine activity in one study. Symptomatic Gulf War veterans have also been reported to exhibit alterations in overall and regional cerebral blood flow, using

specialized SPECT scan analyses. In addition, a significant correlation has been reported between reduced white matter volume in Gulf War veterans and levels of nerve agent exposures resulting from the Khamisiyah weapons demolitions. Preliminary results from three unpublished federal Gulf War research projects are also of great interest, and will be reviewed in final form as they become available. These include early results from a larger MRS study that appear not to support earlier findings of reduced neuronal function in the brainstem and basal ganglia of symptomatic Gulf War veterans. Preliminary findings from an additional SPECT study suggest that symptomatic Gulf War veterans differ from healthy controls in cerebral blood flow responses to cholinergic challenge. Early results from a third study indicate that symptomatic Gulf War veterans have significantly reduced total white matter volume compared to healthy controls. In contrast to the diverse findings reported from studies using specialized brain imaging methods, few abnormalities have been identified in symptomatic veterans using electroencephalograms (EEG), computed tomography (CT) scans, or standard magnetic resonance imaging (MRI) of the brain.

Overall, of the seven identified Gulf War research projects that evaluated brain structure and function using proton MRS, specialized SPECT scans, and specialized MRI assessments, six have identified significant differences between veterans with Gulf War illness and healthy controls, and one identified no case/control differences. An additional study has identified significant brain volume differences in Gulf War veterans in relation to modeled nerve agent exposures during the Gulf War. These findings have been important in documenting brain alterations in Gulf War veterans, but have often come from relatively small studies that assessed different types of abnormalities in different areas. Additional research is needed to determine if these findings can be replicated and/or further extended in larger samples.

**Neuropsychological studies.** Neuropsychological studies provide objective measures of brain function and have been used for many years to quantify neurocognitive deficits resulting from chemical exposures. They constitute the largest body of research on central nervous system function in Gulf War veterans. A wide variety of specialized tests are used to assess cognitive domains that include attention, executive system functioning, motor skills, visuospatial functioning, memory, and mood. Changes in affect and emotional functioning can be symptoms of brain injury, and so are important to measure in neuropsychological tests. But PTSD and other psychiatric conditions can themselves affect neurocognitive function, and so must be appropriately controlled for when analyzing test outcomes.

Research studies have consistently identified significant differences in neurocognitive function between symptomatic Gulf War veterans and healthy controls. These include differences on tests of attention and executive system functioning, memory, visuospatial skills, psychomotor skills, and mood and emotional functioning. Some studies indicate that symptomatic veterans display a slowing of response speed that affects their mental flexibility across multiple cognitive domains. Identified differences have generally been modest, but have consistently been significant and remained significant after adjustments for emotional functioning and psychiatric disorders. Studies also indicate that many symptomatic veterans who report cognitive difficulties do not have objectively measurable neurocognitive deficits. Two studies have identified subgroups of symptomatic Gulf War veterans with more marked neurocognitive impairment on measures of memory, attention, and response time, suggesting this subgroup should be the focus of additional study.

Studies have also evaluated veterans' neurocognitive function in relation to exposures during the Gulf War. Significantly poorer performance on tests of memory, attention, and mood have been identified in relation to self-reported exposure to pesticides, PB, and chemical weapons. Neurocognitive effects have also been identified in relation to modeled nerve agent exposures resulting from the Khamisiyah weapons demolitions. Department of Defense-modeled nerve agent exposure levels were significantly correlated with slower performance on psychomotor and visuospatial tasks in a dose-response pattern—that is, greater exposure was associated with worse neurocognitive performance.

**Autonomic nervous system dysfunction.** The autonomic nervous system (ANS) is the part of the nervous system that regulates involuntary, or “automatic” physiological activities. Autonomic pathology can be associated with diverse symptoms such as dizziness, weakness, digestive abnormalities, and sexual dysfunction. Autonomic function is often assessed by determining effects of physiological challenges on ANS regulation of heart rate and blood pressure. The Committee reviewed results from seven published studies and two additional federal projects that assessed ANS function in symptomatic Gulf War veterans. Eight of nine projects identified significant ANS differences between veterans with Gulf War illness and healthy controls. Several studies demonstrated blunted autonomic responsiveness to physiological challenges, for example, reduced cardiovascular compensation in response to orthostatic challenge on tilt table testing. Studies have also identified a general reduction in heart rate variability in the high frequency range among veterans with Gulf War illness, observed over a 24-hour period in one study and during nighttime hours in another. Although ANS differences have consistently been reported in veterans with Gulf War illness, specific ANS alterations identified by different studies have varied, as a result of differences in study characteristics and testing methods. Additional comprehensive research is needed to provide a clear characterization of Gulf War illness-related autonomic dysfunction.

**Neuromuscular and sensory findings.** Symptoms reported by Gulf War veterans frequently include muscle pain and weakness, or numbness and tingling sensations in the extremities. Such symptoms potentially indicate abnormalities in peripheral nerve function related to sensation and motor function. Nine studies have assessed peripheral sensory and neuromuscular function in Gulf War veterans. Overall, based on standard clinical examination, electromyography, and nerve conduction tests, these studies have provided little indication that veterans with Gulf War illness are affected by generalized polyneuropathies or abnormal neuromuscular transmission. Three of four studies that evaluated sensory threshold measures identified significantly higher (that is, less sensitive) thresholds in symptomatic compared to healthy veterans, however. Two identified higher cold sensory thresholds, and one reported a higher threshold for detecting light touch, suggesting that some Gulf War veterans may have subtle small sensory fiber neuropathies. Consistent findings that Gulf War veterans are not affected by more generalized polyneuropathies or neuromuscular abnormalities indicate that veterans’ neuromuscular symptoms are not attributable to overt muscle damage or peripheral nerve pathology.

**Neuroendocrine alterations.** A series of recent studies have provided detailed evaluation of hypothalamic-pituitary-adrenal (HPA) axis functioning in Gulf War veterans. Studies indicated that Gulf War veterans are similar to nondeployed veterans on baseline measures of cortisol and ACTH (adrenocorticotropic hormone), but had significantly greater suppression of both hormones in response to dexamethasone challenge. These responses were significantly associated with veterans’ symptoms, most prominently their musculoskeletal symptoms, but were unrelated to combat exposure or whether veterans had PTSD. Cortisol suppression was most pronounced in veterans who reported using PB during deployment. In addition, 24-hour ACTH levels were significantly reduced among Gulf War veterans who did *not* have PTSD, and were associated with veterans’ use of pesticides and PB. No HPA alterations were associated with combat stress, with other self-reported exposures during deployment, or with PTSD in Gulf War veterans. Overall, these studies suggest that Gulf War service and symptoms of Gulf War illness are associated with a unique profile of HPA alterations many years after the war, effects that differ from HPA findings associated with other conditions, including PTSD. Identified effects were independent of combat stress, but significantly associated with veterans’ use of PB and/or pesticides.

**Vulnerability to neurotoxicants.** A question often asked about Gulf War illness is why some Gulf War military personnel developed chronic symptoms during and after deployment, while others who served along side them remained well. It is well established that some people are more vulnerable to adverse effects of certain chemicals than others, due to variability in biological processes that neutralize those chemicals, and clear them from the body. The enzyme paraoxonase (PON1) circulates in the blood and hydrolyzes organophosphate compounds such as pesticides and nerve agents, converting them to relatively harmless chemicals that are then excreted. Individuals who produce different types and

amounts of PON1 differ, sometimes dramatically, in their ability to neutralize different organophosphate compounds. The Committee reviewed results from four published studies and two additional federal projects that have assessed PON1 measures in Gulf War veterans. Five of the six projects identified significant PON1 differences that were associated with Gulf War illness or, more generally, with Gulf War service. Specific findings from these studies varied, however, reflecting different types of data that addressed different research questions. Additional research is needed to better characterize the precise nature of the PON1-Gulf War illness relationship. It is unknown if Gulf War illness is linked to biological variability in other enzymes that protect the body from neurotoxic exposures. Limited and preliminary information from three studies suggest a possible link between Gulf War illness and butyrylcholinesterase (BChE) that may involve the subset of veterans who have very low BChE activity and also experienced specific exposures during the war.

**Immune parameters.** There has been little indication that Gulf War service, overall, is associated with increased rates of diagnosable immune conditions, including autoimmune diseases and allergies, or with increased susceptibility to infectious disease. A well-known hypothesis, suggesting that Gulf War illness is related to a systemic shift favoring Th-2 type immunity, has not been supported by studies of Gulf War veterans. Veterans with Gulf War illness have been shown to differ from healthy controls on a number of immune parameters, however. A variety of specific differences have been identified by individual studies, and a number of consistent findings have emerged. Results from two studies, using different methods in different groups of symptomatic veterans, indicate that Gulf War illness is associated with a low-level, persistent immune activation, reflected in elevated levels of the cytokines IL-2, IFN- $\gamma$  and IL-10. Several studies have also reported that NK cell numbers and/or cytotoxic activity are significantly reduced in veterans with Gulf War illness. A fuller understanding of immune function in ill Gulf War veterans is needed, particularly in veteran subgroups with different clinical characteristics and exposure histories.

**Additional research and clinical findings in Gulf War veterans.** Additional information pertaining to biological and clinical characteristics of symptomatic Gulf War veterans is available from a variety of clinical reports and studies. Individual clinical studies have provided several findings of interest, such as increased sensitivity to pain and elevated rates of fibromyalgia in veterans with musculoskeletal symptoms, dyspepsia and persistent diarrhea similar to irritable bowel syndrome in veterans with gastrointestinal symptoms, abnormal pulmonary function in a subset of veterans with respiratory symptoms, and verification of rashes and other skin anomalies in veterans with dermatological symptoms. But overall, objective indicators of disease are often not identified in symptomatic Gulf War veterans who are referred for specialty evaluations. Clinical reports have also not provided explanations for identified problems, such as the causes of veterans' persistent diarrhea or rashes. One study evaluated Gulf War veteran males and their sexual partners who experienced a painful burning reaction to the veterans' seminal fluid, a problem reported by about seven percent of Gulf War veterans. Evaluations indicated that about 40 percent of the women had a hypersensitivity reaction to the veterans' seminal fluid, but provided no explanation for the phenomenon, overall. In general, very limited information is available on health problems specific to women veterans. Single studies have reported that Gulf War veteran women report elevated rates of yeast and bladder infections and breast lumps or cysts, but no results are available from medical evaluations.

Single studies have identified additional significant differences between symptomatic veterans and controls on a number of specific laboratory tests. These include elevated rates of coagulation abnormalities in symptomatic veterans, an elevated proportion of symptomatic veterans with insertion/deletion polymorphisms in the gene encoding for angiotensin-converting enzyme, and identification of atypical circulating polyribonucleotides potentially indicative of chromosome alterations.

### **Future directions in identifying physiological mechanisms that underlie Gulf War illness.**

To advance efforts to identify effective treatments and diagnostic tests for Gulf War illness, the Committee has recently expanded its work to review areas of research that may contribute to a better understanding of the specific pathophysiological mechanisms that underlie veterans' symptoms. This has included preliminary discussions in several areas, including biological processes associated with neuroplasticity, disordered sensory processing and neuroendocrine dysregulation, and mitochondrial insufficiency. The Committee has also reviewed, in greater detail, diverse scientific findings that suggest a potential role for central nervous system inflammatory processes in the pathophysiology of Gulf War illness, and has identified this as a promising area for future research. The research considered indicates that neurotoxic Gulf War exposures may activate inflammatory processes in the brain and that increased brain levels of proinflammatory cytokines can produce a complex of multiple symptoms similar to Gulf War illness. Additional research suggests that these processes can become dysregulated by mechanisms that include repeated cycles of brain cell injury and glial activation, as well as autonomic and neuroendocrine disruption. Research in this area is especially warranted because of its possible clinical implications. Imaging methods are available that can potentially identify these processes in the brain and a variety of therapeutic agents are being studied for their effectiveness in treating dysregulated central inflammatory processes.

### **Gulf War Illness in Relation to Other Multisymptom Conditions**

Parallels are commonly drawn between Gulf War illness and symptom-defined conditions such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS) found in the general population. The prevalence of CFS in Gulf War veterans is unique, and dramatically higher than CFS rates found in nondeployed veterans and in the general population. Rates of FM and MCS are also elevated in Gulf War veterans, but to a lesser degree. It is clear from multiple studies, however, that case definitions for CFS, FM, and MCS do not adequately describe the chronic symptom complex that affects Gulf War veterans at excess rates, and that only a fraction of veterans with Gulf War illness can be diagnosed with any of these conditions. Overall, research studies have identified both similarities and differences between Gulf War illness and other multisymptom conditions. General similarities are reflected in indicators of autonomic dysregulation and neurocognitive impairment in Gulf War illness, FM, and CFS, and by indications that Gulf War illness and MCS are linked to PON1 variability. In contrast, the epidemiologic profile of Gulf War illness significantly differs from multisymptom conditions in the general population. Studies have also identified immune parameters and a number of other measures that differ in veterans with Gulf War illness, compared to patients with CFS or FM. Many objective measures associated with these conditions have not been evaluated in veterans with Gulf War illness, however. Additional research in these areas can potentially provide useful insights into biological mechanisms that underlie Gulf War illness and contribute to identifying beneficial treatments.

### **Federal Gulf War Research Programs**

In addition to scientific studies and government reports, the Committee is charged with reviewing federal research programs established to address health consequences of the 1991 Gulf War. Since 1994, the U.S. government has reported expenditures of \$340 million, over \$440 million if indirect costs are considered, for hundreds of studies identified as Gulf War research in interagency reports to Congress. This research has been funded primarily by the Department of Defense (DOD) and the Department of Veterans Affairs (VA). Many federally-funded studies have provided valuable insights regarding the health of Gulf War veterans, as detailed throughout this report. But much of the federally funded research has not advanced understanding of Gulf War illness or other Gulf War-related health problems. Consequently, federal Gulf War research programs have not, as yet, succeeded in achieving the primary objective of Gulf War research, that is, to improve the health of Gulf War veterans.

The Committee identified major problems related to the historical use of research funds identified as “Gulf War research” expenditures by federal agencies. Historically, the large majority of Gulf War research funding was provided by DOD. In recent years, DOD has dramatically cut funding for projects identified as Gulf War research from nearly \$30 million annually in 2001 to under \$5 million in 2006. More troubling, many studies identified as “Gulf War research” at DOD over that period had little or no relevance to Gulf War illness or the health of Gulf War veterans. The DOD “Gulf War” portfolio consisted largely of costly projects that addressed broad questions related to current deployments and other health issues unrelated to the Gulf War. By 2006, less than 10 percent of the \$4.7 million identified as DOD funding for “Gulf War research” supported studies that related to Gulf War illness or other health problems associated with Gulf War service.

The Department of Veterans Affairs had historically funded a smaller proportion of federal Gulf War research, but increased funding in recent years from a low of \$4 million annually in 2002 to nearly \$13 million in 2006. VA also historically identified a large number of studies as “Gulf War research” that had little relevance to Gulf War health issues. Until 2004, this included substantial funding for research on stress and psychiatric illness. By 2006, a larger number of studies had been funded that were related to Gulf War illness and effects of Gulf War exposures. Still, the largest amount of funding in VA’s Gulf War research portfolio, nearly 40 percent of the \$13 million in 2006, supported projects focused on amyotrophic lateral sclerosis (ALS), few of which included Gulf War veterans or research issues related to the development of ALS in Gulf War veterans.

A number of important changes have taken place in federal Gulf War research programs in recent years. Beginning in 2006, Congressional actions brought about major changes in Gulf War research at both VA and DOD. Congress allocated an additional \$15 million annually for Gulf War research at VA, and directed that it be used to support a center of excellence for Gulf War research at the University of Texas Southwestern (UTSW) in Dallas. The VA/UTSW program is focused on identifying biological abnormalities associated with Gulf War illness that can be targeted to develop diagnostic tests and treatments. Congress also appropriated \$5 million in 2006 and \$10 million in 2008 to support an innovative Gulf War research program managed by DOD’s Office of Congressionally Directed Medical Research Programs. The new DOD Gulf War research program is focused on identifying treatments for Gulf War illness and objective measures that distinguish ill from healthy veterans. Early indications suggest that developments at both VA and DOD represent promising new directions in the federal Gulf War research effort. The overall federal funding commitment for Gulf War research, however, remains substantially below historical funding levels and far below that warranted by the scope of the problem.

## **Research Priorities and Recommendations**

The Committee is charged with determining what has been learned about the nature, causes, and treatments for Gulf War illness and advising on federal research, with the primary goal of improving the health of Gulf War veterans. In reviewing information on the broad variety of topics related to the health of Gulf War veterans, the Committee identified many scientific issues for which additional research was needed. Specific research recommendations have been provided in relation to each topic considered, and are compiled and prioritized in the final section of the report.

The Committee recommends that highest priority be given to research directed at identifying beneficial treatments for Gulf War illness. This includes clinical studies that systematically evaluate the effectiveness of currently available treatments, as well as research to identify specific pathophysiological mechanisms associated with Gulf War illness that can be targeted for treatment. The Committee also gives high priority to research aimed at identifying objective biological markers associated with Gulf War illness, especially those that advance efforts to improve diagnostic testing. Recommended research includes studies that expand on existing biological findings in Gulf War veterans—comprehensive

research on brain structure and function, autonomic function, neuroendocrine and immune alterations, and processes associated with biological vulnerability to neurotoxicants—as well as studies that investigate neuroinflammatory processes and utilize genomic and related technologies to identify biological characteristics of Gulf War illness. Additional research priority areas include studies that characterize effects of neurotoxic exposures associated with Gulf War illness, and epidemiologic studies to assess rates of neurological diseases in Gulf War veterans.

The Committee identified additional areas of research needed to address other important Gulf War health issues. These include epidemiologic studies to identify mortality and cancer rates in Gulf War veterans, evaluation of health problems in veterans' children, and improved characterization of Gulf War-related health problems in relation to exposures in theater. Recommendations are also provided for improving clinical and epidemiologic research on Gulf War veterans, and emphasize the importance of evaluating outcomes in subgroups of Gulf War veterans identified by illness characteristics and exposures in theater.

The Committee recognizes the vital importance of Congressional support, agency commitment and leadership, and adequate federal funding for achieving critical scientific objectives related to the health of Gulf War veterans and preventing similar problems in future deployments. It therefore recommends that the Administration request and that Congress allocate not less than \$60 million annually in the federal budget for Gulf War research, an amount commensurate with the scope of the problem, and compatible with funding levels between 1999 and 2001. The Committee also recommends that this funding be specifically directed to research most capable of improving the health of Gulf War veterans, as outlined in this report.

## **Conclusions**

Veterans of the 1990-1991 Gulf War had the distinction of serving their country in a military operation that was a tremendous success, achieved in short order. But many had the misfortune of developing lasting health consequences that were poorly understood and, for too long, denied or trivialized. The extensive body of scientific research now available consistently indicates that Gulf War illness is real, that it is the result of neurotoxic exposures during Gulf War deployment, and that few veterans have recovered or substantially improved with time. Addressing the serious and persistent health problems affecting 175,000 Gulf War veterans remains the obligation of the federal government and all who are indebted to the military men and women who risked their lives in Iraq, Kuwait, and Saudi Arabia 17 years ago. This obligation is made more urgent by the length of time Gulf War veterans have waited for answers and assistance.



## | Introduction

More than 17 years have passed since the Gulf War. The events and successes of Operation Desert Storm are becoming a distant memory for some, with international attention now focused on current military operations in Iraq and Afghanistan. But for too many who served in the Persian Gulf theater in 1990 and 1991, the Gulf War has had lasting consequences—health consequences beyond the well-recognized effects of bullets and bombs and the psychological impact of war. This report describes what has been learned in the last 17 years about the health effects of military service in the Gulf War and identifies priority research issues that remain to be addressed. Although the report covers the broad spectrum of health concerns related to Gulf War service, its primary focus is the multisymptom condition that has come to be known as Gulf War illness. Over the years, this condition has been the foremost Gulf War-related health issue and the focus of intense political and scientific interest. It is also the condition for which the largest numbers of Gulf War veterans are still seeking clear answers and effective treatments.

The Gulf War was unlike any war fought before or since. In the days following Iraq's invasion of Kuwait in August 1990, an international effort was swiftly mounted to stand up to the aggression of Saddam Hussein's forces. During Operation Desert Shield, hundreds of thousands of American troops, along with military forces from the United Kingdom and dozens of other allied countries, established a strong foothold in the region over the course of a few months. By mid-January, 1991, Operation Desert Storm began with a massive air campaign. Six weeks later, on February 24, 1991, the ground offensive was launched as U.S. and allied troops moved into Southern Iraq and Kuwait. In just three days the allies achieved their primary objective, retaking Kuwait City as the Iraqis fled. The next day, just 100 hours after the ground war had begun, a cease fire was established. Kuwait was free and the U.S. and its allies had achieved a great victory in the desert.

The 1990-1991 Gulf War was an overwhelmingly successful campaign. Following the six-week air war and four-day ground war, victorious troops were welcomed home and hailed as heroes in parades and ceremonies across the nation. Just under 150 combat-related deaths occurred among the 700,000 Americans who deployed to the region, far fewer than had been anticipated before the war.<sup>1633,1813</sup> The military medical system established for the war had also performed impressively. Even with the quick mobilization and harsh, unfamiliar desert environment, a record low number of troops required medical attention during deployment.<sup>664,1595,1607</sup> The Gulf War was unquestionably a unique war—for its brevity, for the success with which it was executed, and for the decisive nature of the victory.

Yet, despite the successful staging and outcome of the Gulf War, military personnel who served in theater reported persistent, baffling symptoms during deployment and in the months and years that followed their return home. Reports indicated that Gulf War veterans who had served in different units, from all parts of the U.S. and from allied countries were affected by similar types of symptoms. Illness profiles typically included a complex of multiple symptoms not explained by conventional medical or psychiatric diagnoses—cognitive difficulties, persistent and widespread pain, fatigue, headaches, chronic diarrhea and other digestive abnormalities, and skin rashes. Just what these problems were and what had caused them was unknown.

Over the years, Gulf War illness has posed diverse and difficult challenges for veterans who are ill and for healthcare providers and research scientists working to address this condition. From the earliest time veterans' symptoms became known, they have been surrounded by controversy and conjecture.<sup>31,210,283,409,536,1350</sup> And for most of the decade that followed the Gulf War, relatively little was understood about the nature and causes of Gulf War illness. Since the middle 1990s, Gulf War-related

health problems have been the subject of numerous expert panel reports, U.S. and international government investigations, and hundreds of scientific studies. As a result, an enormous amount of information is now available on events and circumstances of the Gulf War and the health of Gulf War veterans. These resources, when considered in aggregate, provide long-needed answers to questions concerning Gulf War illness and provide a focus for the scientific research needed to effectively address it.

**The Research Advisory Committee on Gulf War Veterans' Illnesses.** In 1998, with many questions remaining about veterans' unexplained health problems, Congress mandated the appointment of an independent panel of scientists and veterans to review all federal research programs and available evidence relating to the health of Gulf War veterans. In response to Section 104 of Public Law 105-368,<sup>1243</sup> the Research Advisory Committee on Gulf War Veterans' Illnesses was appointed in 2002 by then Secretary of Veterans Affairs Anthony J. Principi. The Committee was charged with assessing the effectiveness of the federal research effort in answering "central questions on the nature, causes, and treatments for Gulf War-associated illnesses" (Appendix B) and with providing scientific recommendations on federal research programs and studies.

Over the past six years, the Committee has had the privilege and responsibility of reviewing diverse types of information on the many topics pertinent to the health of Gulf War veterans. A challenge common to earlier government and expert panels was the sparsity of scientific information on which to base findings and recommendations. In contrast, the Committee found that the quantity of currently available information created a different kind of challenge, requiring a comprehensive review and cohesive synthesis of a voluminous number of reports and studies. A complete picture of what is currently known about the Gulf War and the health of Gulf War veterans was needed in order to make meaningful research recommendations on the best way forward.

Since its inception, the Committee has conducted its work in public meetings, convened three times per year. Due to the breadth of information to be considered, a systematic approach has been used in reviewing each area of interest. For each topic considered, relevant materials have been reviewed by the Committee, and scientists and government representatives with diverse expertise and perspectives have been invited to present results of their investigations. The information presented typically addressed what has been learned about particular exposures and events in theater and/or results of scientific studies concerning health effects of those exposures. Committee meetings have functioned in large part as symposia, providing opportunities for Committee members, visiting scientists, and government officials to review and discuss available information on each topic, as well as opportunities for comments and questions from members of the public.

In addition to annual reports on its activities and ongoing discourse with federal research officials, the Committee has periodically issued recommendations and formal reports concerning topics it has considered. An early "Interim Report" was issued in June, 2002, that provided the Committee's preliminary impressions and recommendations based on an initial overview of available research information.<sup>1267</sup> The Committee's first extensive report was issued in the fall of 2004, providing detailed information on topics considered to that time.<sup>1268</sup> These included the scope of Gulf War illness and the need for treatment research, evidence concerning effects of Gulf War-related neurotoxic exposures, studies of birth defects in veterans' children, and programmatic and funding issues related to federal research on the health of Gulf War veterans. In January, 2006, the Committee provided updated recommendations that outlined priority research objectives and topics to VA's Office of Research and Development.<sup>1270</sup> Additional recommendations were provided to the Secretary in February, 2007, concerning the need for updating Gulf War illness-related research and educational materials for VA clinicians.<sup>1271</sup> In 2008, the Committee reported its findings and recommendations concerning initial plans and research activities at the VA-funded Gulf War Illness and Chemical Exposure Research Program at

the University of Texas Southwestern.<sup>1272</sup> Committee members have also testified before Congress on issues related to Gulf War illness research, including the need to identify effective treatments.

The present report summarizes information reviewed by the Committee since its last major report in 2004 and synthesizes all information considered by the Committee thus far. This synthesis forms the basis for the scientific recommendations made in each area, and for identification of research priorities. In the current report, as in all its activities, the Committee has been mindful of the guiding principle designated for its work, as described in the Committee's charter. It states that "the fundamental goal of Gulf War-related government research, either basic or applied, is to ultimately improve the health of ill Gulf War veterans, and that the choice and success of research efforts shall be judged accordingly"(Appendix B).

The current report differs from earlier Gulf War panel and committee reports in several important respects. First, the central focus of this report is Gulf War illness. The Committee reviewed available information on all health issues associated with Gulf War service, but prioritized information relating to the nature and causes of the undiagnosed, multisymptom illness affecting Gulf War veterans. Despite the prominence of this condition in the lives of ill veterans and the amount of government and media attention given to this problem, Gulf War illness has received surprisingly little in-depth consideration by previous scientific panels. The present report is also distinct from earlier Gulf War reports because it comes at a time when an unprecedented amount of information is available to inform the work and conclusions of the Committee, information that was not available to earlier review panels and scientific committees.

Lastly, this report is unique because of the specific charge and scope of activities assigned to the Committee. This has enabled a single panel to consider the extensive range of topics related to the health of Gulf War veterans. It has also required full consideration of the many types of scientific studies and government reports relevant to veterans' health and effects of veterans' experiences and exposures during the war. As a result, the Committee has had the opportunity to engage these complex issues in a more comprehensive manner than previously has been possible. Most importantly, it has permitted the Committee to synthesize diverse information from diverse sources in order to identify patterns and inconsistencies across a broad spectrum. In effect, the Committee was given the opportunity to assemble and evaluate all available pieces from a complex puzzle, and to determine what, collectively, they tell us about the nature and causes of Gulf War illness.

It is regrettable that, 17 years after the war, so little clear information has emerged from scientific committees that specifically addresses the nature and causes of Gulf War illness. It is perhaps understandable, in light of the many complexities related to research in this area, as will be described throughout this report. Most obviously, Gulf War illness does not fit neatly into our current concepts of disease. The underlying pathobiology of Gulf War illness is not apparent from routine clinical tests, and the illness appears not to be the result of a single cause producing a well-known effect. Researchers and clinicians are generally not familiar with methods required to evaluate and address health problems identified entirely by veterans' symptoms. This might explain why Gulf War researchers and committees have often focused their attention on problems that are more routinely assessed and measured. It has become clear over the years, however, that the important questions surrounding Gulf War illness do not have simple answers. Addressing these questions requires that complex issues be engaged in a complex and comprehensive manner. Overly simplistic and compartmentalized approaches have provided little progress.

The present report is divided into several sections that reflect different aspects of available information on Gulf War-related health issues. The first section provides an overview of what has been learned from population studies, the large body of epidemiologic research on Gulf War veterans. The second section addresses the cause of Gulf War illness, reviewing what has been learned about the many Gulf War-related experiences and exposures that potentially contributed to veterans' ill health—from the

psychological stress of war to the effects of oil well fires, nerve agents, vaccines, and depleted uranium. The third section addresses the nature of Gulf War illness, reviewing research on biological abnormalities associated with veterans' symptoms, the relationship of Gulf War illness with multisymptom conditions in civilian populations, and topics the Committee has considered in exploring physiological mechanisms that may underlie veterans' symptoms. The fourth section summarizes the current status of federal research programs related to the health of Gulf War veterans. Each of the first four sections includes research recommendations related to the specific topics considered. The fifth section summarizes and prioritizes these recommendations.

As is described throughout the report, there is no question that Gulf War illness is a real condition with real causes and serious consequences for affected veterans. Study after study has consistently documented this multisymptom condition in large numbers of Gulf War veterans. Research has also shown that this pattern of illness does not occur after every war and cannot be attributed to psychological stressors during the Gulf War. Because research studies have so compellingly demonstrated that Gulf War illness cannot be explained simply as the expected result of wartime stress, it remains the responsibility of the federal government to fully elaborate the source and nature of this condition, to care for affected veterans, and to prevent similar problems from happening in the future.

Some have suggested that the many scientific and political challenges that have impeded understanding of Gulf War illness are too complex, that the events of the war are too remote, and that answers to the many questions surrounding Gulf War illness might never be known.<sup>870,1765</sup> On the contrary, the Committee has found that the diverse sources of information and research data associated with Gulf War service paint a cohesive picture that yields important answers to basic questions about both the nature and causes of Gulf War illness. These, in turn, provide direction for future research that is most capable of improving the health of Gulf War veterans. Completing this mission, that is, finding answers and treatments for ill Gulf War veterans, requires continued dedicated effort and cooperation between government officials, scientists, clinicians, and veterans. As will be evident from the information and recommendations that follow, the Committee believes that this is a challenge that can be met. It is also, unquestionably, an obligation that must be met.

## 1 | Gulf War Illness and the Health of Gulf War Veterans

I arrived in Theater on January 6, 1991 ... During official visits to strategic military cities there were frequent SCUD attacks during which I heard chemical alarms sound. When I asked if these alarms meant chemicals had been detected, I was told that the chemical alarms had malfunctioned. I became ill and was treated for nausea, headaches, vomiting, diarrhea, and high temperature. Rashes I had over my body I thought were normal and expected since I spent most days in the sand, wind, and sun with all the attendant fleas, flies, and desert parasites. Headaches I attributed to fatigue and lack of sleep. The symptoms...continued after I returned home and got progressively worse.

--COL GR, Gulf War veteran<sup>1684</sup>

**Unexplained illness in the wake of Desert Storm.** In the years immediately following Desert Storm, widespread reports indicated that Gulf War veterans were suffering from a complex of symptoms that included memory problems, profound fatigue, chronic pain, persistent diarrhea, and unusual skin lesions. Similar symptom complexes were widely reported by veterans from different units in different parts of the U.S., and also by veterans from allied countries. Medical evaluations provided limited insights, since veterans' symptoms were typically not associated with abnormalities on laboratory tests or other diagnostic measures. No clear explanation was apparent for this unexplained symptom complex, labeled "Gulf War Syndrome" by the media.

Veterans and other observers soon raised questions about whether hazardous exposures encountered during the Gulf War had made troops sick. Suggested causes included the billowing clouds of thick black smoke produced by the Kuwaiti oil wells that were set afire by retreating Iraqi soldiers in the closing days of the war. There were also widespread reports that alarms designed to detect chemical agents repeatedly sounded in some areas of theater after Coalition air bombing began in January of 1991. Additional concerns were raised about the use of measures that had never before been fielded by the military on a widespread basis. These included use of munitions and armoring containing depleted uranium, use of an anti-nerve agent prophylaxis regimen that included regular doses of the drug pyridostigmine bromide, and administration of the anthrax and botulinum toxoid vaccines.

Since the mid-1990s, the federal government has funded hundreds of research studies to investigate the health problems affecting Gulf War veterans.<sup>340</sup> Multiple large epidemiologic studies and impressive data collections have been conducted in diverse populations of Gulf War veterans. These studies have provided extensive documentation of the symptoms and symptom complexes associated with Gulf War service, rates of psychiatric conditions in Gulf War veterans, and limited data on the extent to which Gulf War veterans have been affected by diagnosed medical diseases. Without exception, studies of Gulf War veterans have found that the most prevalent health problem associated with Gulf War service is the complex of multiple symptoms not explained by familiar medical or psychiatric diagnoses.

The condition once labeled "Gulf War Syndrome" by the media is now commonly referred to as Gulf War veterans' illnesses or Gulf War illness. The Committee has adopted the term Gulf War illness for simplicity's sake. It is used as an umbrella term to represent varying definitions and descriptions of the complex of multiple symptoms found at significantly excess rates in Gulf War veterans. As with other conditions, the specific symptoms affecting veterans with Gulf War illness can vary somewhat from person to person. The overall consistency of the types of health problems described in Gulf War veterans, however, indicates that it is most useful to consider this excess symptomatology as a cohesive "entity" to

be studied as a “multisymptom illness” as opposed to considering symptoms individually. This is the approach adopted by most epidemiologic studies of Gulf War veterans. Use of the specific term, Gulf War illness, also allows this multisymptom condition to be clearly distinguished from other, more familiar, diagnosed conditions that affect individual veterans.

Although Gulf War illness is the most prominent condition affecting Gulf War veterans, it is just one health issue to be addressed in the larger context of the health of Gulf War veterans. Other Gulf War-related health issues of importance include rates of diagnosable medical conditions and post-war mortality among Gulf War veterans, and questions related to the risk of birth defects and other health problems in veterans’ family members.

## Characteristics and Impact of Gulf War Illness: Epidemiologic Research

My symptoms began in the Gulf with severe abdominal cramping and severe diarrhea. I also had terrible headaches and bouts of dizziness and tingling. Once I returned to the base in Germany, the headaches persisted, and I experienced the cramps and diarrhea on a cyclic basis. I also went through periods of night sweats. And there were periods when I would sleep a lot because I was so fatigued. My joints were stiff, and my knees would swell after I ran. It was harder for me to do things without feeling short of breath. These symptoms became worse as time passed...

Ever since my return from the Gulf, I've been plagued by multiple rashes and lesions on my face, neck, arms, and back. They come and go.

--SSgt BJ, Army Gulf War veteran<sup>716</sup>

Significant scientific progress has been made in characterizing the health of Gulf War veterans, as described in the Committee's 2004 report.<sup>1268</sup> This progress has relied, in large part, on the many Gulf War epidemiologic studies conducted in the past decade. Epidemiologic research uses established methods to study patterns of disease and related factors in populations. Among the strengths of this research approach is its capacity for providing "big picture" information about the health of populations and statistical assessment of the relationship of health problems with demographic characteristics, biological and chemical exposures, and other factors that can affect health. It is, in fact, the only scientific approach capable of evaluating health problems in relation to the actual complex conditions of the Gulf War. Consequently, epidemiologic research has been a particularly important resource for understanding Gulf War illness and the health of Gulf War veterans.

The extensive body of Gulf War epidemiologic research has provided a consistent picture of the general characteristics of Gulf War illness and the patterns in which it affects diverse groups of Gulf War veterans. This research is not without limitations, however. It is important that findings from individual population studies of Gulf War veterans be evaluated in the context of identified limitations, and also considered in the context of the larger body of studies addressing similar questions and issues.

### How many Gulf War veterans have Gulf War illness?

The prevalence of Gulf War illness reported by different studies has varied with how Gulf War illness or "chronic multisymptom illness" (CMI) cases are defined. Because no specific Gulf War illness case definition has been widely accepted, the Committee reviewed prevalence estimates from all studies reporting rates of multisymptom illness, by any case definition, in both Gulf War veterans and nondeployed Gulf War-era veterans. The burden of multisymptom illness attributable to service in the Gulf War was determined by comparing rates found in Gulf War veterans to those in nondeployed era veterans. The excess rate in Gulf War veterans, that is, the rate over and above that in veterans who did not serve in the Gulf War, reflects the proportion of veterans whose multisymptom condition can be attributed to participation in the Gulf War.

As shown in Table 1, nearly all epidemiologic studies have reported that, regardless of the case definition used, an excess of 25 - 32 percent of Gulf War veterans have multisymptom illness related to service in the Gulf War. The only exception comes from results reported from Phase III of the U.S. National Survey of Gulf War Era Veterans and Their Families, which found only a 13 percent excess rate of multisymptom illness in Gulf War veterans.<sup>142</sup> It is not clear why the rate of excess illness from this study was lower, by about half, than all other studies, including a later follow-up of veterans from the same U.S.

**Table 1. Prevalence of Multisymptom Illness in Gulf War Veterans and Nondeployed Era Veterans**

<i>Veterans Studied</i>	<i>Number of Gulf War Veterans Assessed</i>	<i>Year(s) of Assessment</i>	<i>Case Definition Used</i>	<i>Prevalence In Nondeployed Veterans</i>	<i>Prevalence in Gulf War veterans</i>	<i>Excess Illness in Gulf War Veterans</i>
Air Force veterans <sup>464</sup>	1,155	1995	CMI	15%	45%	30%
New England Army veterans <sup>1238</sup>	180	1994-1996	CMI (modified)	33%	65%	32%
U.K. male veterans <sup>1698</sup>	4,428	1998	CMI (modified)	36%	62%	26%
U.K. female veterans <sup>1699</sup>	226	1998	CMI (modified)	35%	64%	29%
Kansas veterans <sup>1476</sup>	1,548	1998	GWV (KS) CMI	8% 20%	34% 47%	26% 27%
U.S. national study, Phase III <sup>142</sup>	1,035	1999-2001	CMI (modified)	16%	29%	13%
U.S. national study, longitudinal sample <sup>745,748</sup>	5,767	2005	Multisymptom illness*	10%	35%	25%

Abbreviations: CMI = chronic multisymptom illness as defined by Fukuda,<sup>464</sup> Gulf War illness = Gulf War illness, KS = Kansas case definition<sup>1476</sup>  
 Notes: \*Multisymptom illness defined as multiple types of symptoms occurring together, not explained by medical or psychiatric diagnoses

national study. Like other studies, the Phase III study relied on veterans' self-reported symptoms to assess rates of multisymptom illness.<sup>142</sup> The difference potentially relates to modifications made in the CMI definition, as adapted for the Phase III study. Those modifications, for example, limited the number of Gulf War veterans identified as being fatigued, a central criterion of the CMI case definition, to about half the expected total.<sup>142,751</sup> The excess rate of 13 percent identified in the Phase III study is particularly unexpected in light of a later study of a larger sample taken from the same population. The later study found an excess of 25 percent of Gulf War veterans affected by multisymptom illness, similar to rates reported by all other studies.<sup>745,748</sup>

A similar degree of excess ill health related to Gulf War service is suggested by studies that have assessed veterans' health using more general indicators. For example, half of Iowa Gulf War veterans, but only 14 percent of nondeployed era veterans, indicated they had health problems that they attributed to their military service in 1990-1991, an excess of 36 percent in Gulf War veterans.<sup>350</sup> Similarly, an excess of 35 percent of Kansas Gulf War veterans reported having health problems attributable to military service in 1990-1991.<sup>1476</sup> A 2002 British study determined that 53 percent of Gulf War veterans fell into one of four clusters defined by patterns of elevated symptom scores, compared to 28 percent of nondeployed era veterans, an excess of 25 percent in Gulf War veterans.<sup>421</sup> A more recent British study reported that 61 percent of Gulf War veterans, and 37 percent of nondeployed era veterans reported new health problems since the Gulf War, an excess of 24 percent in Gulf War veterans.<sup>1411</sup> Overall, these studies provide a consistent indication that excess subjective ill health attributable to service in the Gulf War affects between 24 and 36 percent of those who served.

Due to the consistency of estimates of the excess prevalence of multisymptom illness from diverse studies, the Committee concludes that approximately 25 to 30 percent of veterans who served in the Gulf War have been affected by Gulf War illness. That is, studies indicate that between 175,000 and 210,000 of the 700,000 American veterans of the 1990-1991 Gulf War are affected by a complex of multiple symptoms attributable to their service in the war.

## Characteristics of Gulf War Illness

Gulf War illness has been widely described in government testimony, media reports, and scientific studies. The condition is typically characterized as a combination of diverse symptoms such as memory problems, chronic headaches, widespread pain, unexplained fatigue, mood changes, persistent diarrhea, respiratory problems and skin rashes. One of the major challenges of identifying, treating, and understanding Gulf War illness is that ill veterans often have no abnormal findings on clinical diagnostic tests. As a result, Gulf War illness is characterized on the basis of veterans' symptoms that are, by definition, self-reported. While this presents a number of difficulties in clinical practice, it is not an impediment to assessing Gulf War illness in epidemiologic studies of large groups of veterans, where general patterns of symptoms can be assessed and compared.

In research studies, Gulf War illness is routinely defined by the presence of multiple symptoms affecting different systems. The majority of these symptoms fall into general categories, or domains, that have often been characterized statistically in large studies. Symptom domains identified in broadly representative populations of Gulf War veterans are summarized in Table 2. Despite the diverse methods used to characterize symptoms, the categories of symptoms that affect Gulf War veterans at excess rates are remarkably consistent across studies. The two symptom groups most commonly identified include those indicative of neurological/cognitive problems (e.g., chronic headache, cognitive difficulties, mood disturbances, vision and balance abnormalities) and symptoms of persistent, widespread pain in joints and muscles. Symptoms related to persistent fatigue (e.g. extreme tiredness, sleep abnormalities) are reported just as frequently, classified in different studies either as a specific symptom domain, or as part of the neurological domain.

Two additional symptom groups are also consistently found at excess rates in Gulf War veterans, but are typically reported by fewer veterans than neurological, pain, and fatigue symptoms. These include respiratory symptoms (e.g. wheezing, coughing) and gastrointestinal problems (e.g. chronic diarrhea, abdominal cramping). Skin symptoms (unexplained rashes and lesions) are also routinely reported, but have usually not been assessed by multiple variables, as required for identifying symptom "groups."

**Factor analysis of symptoms.** A number of Gulf War studies have defined symptom domains that affect Gulf War veterans using factor analysis. This statistical technique is generally used as a data reduction method in developing psychometric instruments or defining patient subgroups in studies of identified medical or psychiatric conditions. Factor analysis identifies "latent" constructs, or factors, that may underlie sets of highly correlated variables. When applied to general health symptoms in diverse populations, the factor constructs typically reflect the correlation between symptoms resulting from problems affecting particular organs or biological processes. These correlations tend to be independent of the specific diseases causing those symptoms. For example, symptoms of coughing, wheezing, and shortness of breath are highly correlated in any population, regardless of whether different individuals in that population have pneumonia, emphysema, or colds.

With limited exception,<sup>752</sup> the types of symptom domains identified in Gulf War studies by factor analysis also occur in nondeployed veterans, and in diverse, nonveteran populations.<sup>1127,1341,1786,1830</sup> This would generally be expected, since factor-identified symptom "groupings," in studies that assess general health symptoms in heterogeneous populations, simply reflect the high correlation between symptoms resulting from distress in a particular organ or biological process, regardless of the underlying disease.<sup>1082</sup>

What is unique to Gulf War veterans is that persistent symptoms occur concurrently in multiple domains at excess rates, and with greater severity, than in nondeployed veterans.<sup>240,464,698,752,1395,1476</sup> As described in the Committee's 2004 report, individual Gulf War veterans experience chronic symptoms in multiple domains at the same time. If a unique pattern of Gulf War symptoms were to be identified using factor analysis, it would likely require consideration of higher-order factors, that is, second or third-level factors that reflect "groupings" of the symptom factors identified in both Gulf War and nondeployed veterans.<sup>1082</sup>

**Table 2. Symptom Domains Affecting Gulf War Veterans at Excess Rates**

Gulf War Veterans Studied	Method Used to Identify Domains	Symptom Domains Described				
		Neuro/ Cognition/ Mood	Muscle/ Joint Pain	Respir- atory	Gastro- intestinal	Fatigue
<u>U.S. Veterans, All Branches</u>						
10,423 veterans in national survey <sup>752</sup>	Factor analysis	+	+	+	+	+
1,548 Kansas veterans <sup>1476</sup>	Correlation analyses	+	+	+	+	+
1,161 veterans from 7 states <sup>*570</sup>	Factor analysis	+	+	+	+	±
867 veterans in Washington, Oregon <sup>*160</sup>	Factor analysis	+	+	+	±	±
1,896 Iowa veterans <sup>350</sup>	Factor analysis	±	+		±	
<u>Other Countries</u>						
9,588 U.K. veterans <sup>240</sup>	Factor analysis	+	+	+	+	±
3,454 U.K. veterans <sup>698,1125</sup>	Factor analysis	+	na	+	+	±
1,322 Australian veterans <sup>448</sup>	Factor analysis	+	+	±	+	±

Notes: + multiple symptoms of this type were significantly correlated in a defined domain  
 ± multiple symptoms of this type were significantly elevated, but correlated with another defined domain  
 na the study did not assess multiple symptoms in this category  
 \* symptom domains assessed in Gulf War veterans only (no nondeployed comparison group)

Higher order analyses might indicate if symptoms in different domains are correlated with one another in ways not typical of the general population.<sup>566,1082</sup> Gulf War studies have thus far not compared higher-order factors of this type in Gulf War and nondeployed veterans. A unique pattern of symptom expression in Gulf War veterans has been described in one study using a parallel approach, however. A study of over 2,000 Kansas Gulf War era veterans characterized six different symptom domains that affected Gulf War veterans at higher rates than nondeployed era veterans. A similar number of Gulf War (30%) and nondeployed era veterans (29%) had symptoms in just one or two of the defined domains. In contrast, a significantly higher proportion of Gulf War veterans (34%) than nondeployed era veterans (8%) was affected by more severe symptomatology concurrently in three or more symptom domains.<sup>1476</sup>

Similarities between the types of symptoms that fall into factor-defined domains in Gulf War and nondeployed veterans are sometimes cited as an indication that there is no “unique Gulf War syndrome”.<sup>350,686,698,821</sup> But a certain level of symptoms, ill health, and disease occur in any population.<sup>840,1712</sup> Symptom factors identified in diverse populations, including Gulf War veterans, generally describe the symptoms expressed when problems affect particular biological systems, regardless of their causes. Many investigators have pointed out that factor analysis has limited, if any, value in determining whether there is or is not a unique Gulf War syndrome.<sup>429,668,821,1082,1395,1477</sup> The Committee found no examples in the scientific literature where factor analysis of health symptoms in a general population sample, as typically used in Gulf War studies, has ever identified either a well-known chronic disease, like diabetes, or a completely new syndrome.

**Defining Gulf War illness.** Several research teams have developed case definitions for use in their investigations of the prevalence of and risk factors for Gulf War-related multisymptom illness. Generally, case definitions that are nonspecific, that is, those based on a small number of common symptoms, identify a relatively large number of “cases” among both Gulf War and nondeployed era veterans. More restrictive case definitions, in terms of the types and severity of symptoms required, identify fewer cases. Case definitions used to describe Gulf War illness and the methods for arriving at them have varied between studies, as summarized below.

**Haley syndromes.** In 1997, Dr. Robert Haley and colleagues at the University of Texas Southwestern Medical School defined three syndromes based on factor analysis of an extensive, detailed battery of dichotomous and scaled symptoms in 249 members of the 24<sup>th</sup> Reserve Naval Mobile Construction Battalion.<sup>565</sup> Syndrome 1, labeled “impaired cognition,” included problems with attention, memory, depression, and sleep abnormalities. Syndrome 2, labeled “confusion-ataxia,” was characterized by problems with thinking and balance and was the most severe of the three syndromes. Syndrome 3, labeled “arthro-myo-neuropathy” was associated with joint and muscle pain. Twenty percent of the veterans in the study had one of more of the three defined syndromes.

**Chronic multisymptom illness (CMI).** In 1998, Dr. Keiji Fukuda and investigators from the U.S. Centers for Disease Control and Prevention (CDC) defined a complex of symptoms, termed “chronic multisymptom illness” in a population of 3,723 deployed and nondeployed Air Force Gulf War era veterans.<sup>464</sup> The symptom complex was defined using two parallel methods: one assessed symptoms that affected more than 25 percent of Gulf War veterans, and the other used factor analyses of dichotomous symptoms reported by both Gulf War and nondeployed veterans assessed together. The resulting CMI definition required cases to report one or more symptoms lasting six months or longer in at least two of three categories: fatigue, mood-cognition (feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words, difficulty sleeping) and musculoskeletal pain (joint pain, joint stiffness, muscle pain). Severe CMI cases rated each defining symptom as severe, other cases were labeled “mild-to-moderate” CMI. As defined, the CMI symptom complex affected 45 percent of Gulf War veterans in the Air Force sample, and 15 percent of nondeployed era veterans.

**Oregon-defined Gulf War unexplained illness.** In 1998, Dr. Peter Spencer and colleagues from the Oregon Health Sciences University defined cases of Gulf War-related unexplained illness (GWUI) for inclusion in a case control study.<sup>1465</sup> GWUI cases were veterans who had at least one defining symptom from any of three categories, but no diagnostic explanation for that symptom. The three categories included unexplained symptoms associated with fatigue, cognitive/psychological problems, and musculoskeletal complaints.

**Kansas-defined Gulf War illness.** In 2000, Dr. Lea Steele reported a case definition for Gulf War illness, identified empirically as the pattern of symptoms that significantly distinguished 1,548 Gulf War veterans from 482 nondeployed era veterans in the Kansas Gulf Veterans Health Study.<sup>1476</sup> Kansas-defined Gulf War illness criteria excluded veterans diagnosed with specified medical or psychiatric conditions that might explain their symptoms. Symptom criteria required that veterans report multiple or moderately severe symptoms in at least three of six defined categories: fatigue/sleep problems, pain symptoms, neurological/cognitive/mood symptoms, gastrointestinal symptoms, respiratory symptoms, and skin symptoms. Gulf War illness, as defined in the Kansas study, affected 34 percent of Gulf War veterans, and eight percent of nondeployed veterans.

**U.S. National Survey-defined Gulf War syndrome.** VA investigators identified a complex of four neurological symptoms that constituted a unique factor in Gulf War veterans but not in nondeployed era veterans in a large U.S. national sample.<sup>752</sup> These symptoms included blurred vision, loss of balance, tremors/shaking, and speech difficulty. Investigators reported that 277 (2%) of the over 10,000 Gulf War veterans in the study were “cases” who endorsed all four symptoms. Cases were also significantly more

likely to report a number of other symptoms and diagnosed conditions including migraines, seizures, and diarrhea.

Other studies have distinguished ill from healthy veterans in ways that did not require veterans to report specific symptoms. The 2002 Navy Seabee Health Study defined Gulf War illness “cases” as veterans who reported being diagnosed with at least one of four conditions (chronic fatigue syndrome, posttraumatic stress disorder, multiple chemical sensitivity, irritable bowel syndrome) and/or veterans who reported having at least 12 health problems.<sup>527</sup> Researchers evaluating a cohort of Army veterans who returned from theater through Fort Devens, Massachusetts, have used several methods to classify symptomatic veterans. In some studies of this cohort, veterans who reported having five or more frequent symptoms from the Health System Checklist were identified as “high symptom” cases, and compared to veterans with fewer symptoms.<sup>1802</sup> An alternate approach relied on comparison of scores in nine defined “body system” groups.<sup>1239</sup> A separate study of veterans enrolled in VA’s Gulf War Registry also distinguished “high symptom” and “low symptom” veteran subgroups, with categories defined statistically using results of factor and cluster analyses.<sup>570</sup> Studies have also used the chronic fatigue syndrome case definition<sup>465</sup> to distinguish symptomatic Gulf War veterans from controls.<sup>321,435,1090</sup>

Seventeen years after the Gulf War, no case definition has been widely accepted as the preferred standard for defining the complex of multiple symptoms affecting Gulf War veterans, nor have there been published efforts to optimize or validate a Gulf War illness case definition. The Fukuda CMI case definition has been modified for use in several surveys and for two Gulf War illness clinical trials. That definition is generally considered overly broad, that is, nonspecific for the health problems affecting Gulf War veterans. The only case definition developed by characterizing a pattern of multiple symptom types that differed between Gulf War and nondeployed era veterans is the Kansas case definition. In a random sample of over 2,000 Kansas Gulf War era veterans, the Kansas definition more specifically distinguished symptomatic Gulf War from nondeployed era veterans than the CMI case definition.<sup>1476</sup>

**The severity and functional impact of Gulf War illness.** Although not well characterized by any research studies, anecdotal reports indicate that the severity of Gulf War illness is highly variable. Some veterans are mildly or moderately affected by their symptoms, but still able to maintain many of their usual activities. Others veterans have more severe, even disabling, illness. Different studies have shown that between 13 and 50 percent who meet CMI criteria for Gulf War illness can be classified as “severe” cases.<sup>142,464,1804</sup> Illness severity is also said to vary for individuals, with symptoms waxing and waning over time.

Several studies have evaluated the degree to which Gulf War illness has affected veterans’ functional status, including their ability to work. The Medical Outcomes Study Short Form Survey (SF36),<sup>1753</sup> and a special SF36 developed for veteran populations,<sup>779</sup> have been widely used in Gulf War studies. The SF36 evaluates functional status in eight defined areas (e.g., physical functioning, social functioning, general health), providing a quantitative measure of health-related quality of life. Studies consistently report that veterans meeting any case definition of Gulf War illness have significantly lower scores on all SF36 indicators than population norms and than healthy veterans.<sup>87,142,160,449,464,567,1542,1726</sup> Veterans seen at VA’s specialty referral clinics for multisymptom illness, the War Related Injury and Illness Study Centers, exhibit considerable functional impairment. Those veterans’ mean score of 30 on the SF36 physical component scale (PCS) is substantially below the national average score of 50.<sup>907</sup> In Gulf War studies, SF36 scores vary with the case definition used and the domains assessed. The highly symptomatic Gulf War veterans who meet defining criteria for the Haley syndromes had lower SF36 domain scores, indicating worse functional status, than scores for conditions such as congestive heart failure and chronic obstructive pulmonary disease.<sup>567</sup> In contrast, veterans meeting the CMI case definition in the U.S. national survey were considerably less functionally impaired, with a mean SF36 PCS score of 43.<sup>142</sup>

In general, studies indicate that most veterans with Gulf War illness continue to work, although this varies with illness severity. A relatively high rate of unemployment (29%) was reported in Gulf War veterans seeking treatment at a VA Gulf War illness clinic in Seattle.<sup>1281</sup> More representative figures come from a population-based study in the Pacific Northwest, where 21 percent of Gulf War veterans with two or more unexplained health problems were unemployed, compared to 13 percent of veterans without symptoms. Employed-but-symptomatic veterans were also more likely to miss at least seven days of work due to illness over a one-year period (29%) than healthy veterans (4%).<sup>160</sup>

## Which Veterans are Most Affected by Gulf War Illness?

Epidemiologic studies traditionally describe patterns of disease in populations. Insights about the causes of a condition can often be drawn from identifying subgroups that are affected at higher and lower rates. Studies of Gulf War illness have reported patterns of this type, identifying different rates of illness in relation to the characteristics of veterans' military service and deployment to the Gulf War theater.

**Differences related to branch of service and military rank.** Epidemiologic studies have consistently indicated that Gulf War veterans who served in the Army and Marines have higher rates of multisymptom illness than those in the Navy and Air Force.<sup>753,1466,1476</sup> Similarly, Army veterans are disproportionately represented in VA and DOD Gulf War Registry programs. That is, Army personnel constituted just 50 percent of the deployed force, but account for 77 percent of Gulf War veterans enrolled in registries. Conversely, Air Force and Navy veterans are significantly underrepresented in U.S. Gulf War registries.<sup>1651</sup>

Studies also consistently report that enlisted personnel have higher rates of Gulf War illness than officers.<sup>241,511,697,753,1124,1466,1476</sup> Comparisons between reservists and active duty personnel have produced mixed results, with some studies finding similar Gulf War illness rates in the two groups, and others reporting somewhat higher rates in either active duty or reserve veterans.<sup>692,697,753,1466,1476,1804</sup>

**Demographic characteristics.** Rates of Gulf War illness have generally not differed markedly with veterans' demographic characteristics such as gender, age, and race. Gulf War illness affects women at about the same, or slightly higher rates than men,<sup>142,160,240,464,753,1476,1699,1804</sup> and younger veterans at about the same rates as older veterans.<sup>511,753,1124,1476,1804</sup> Whites and nonwhites are also affected at similar rates.<sup>142,160,240,464,753,1466,1476,1699,1804</sup>

**Location in theater.** Several studies have reported that Gulf War illness rates differ with the locations where veterans served during the war. That is, veterans who served in some areas of theater have higher rates of Gulf War illness than veterans who were in other locations. The study of Kansas veterans indicated that veterans who entered Iraq or Kuwait, countries where all battles took place, had significantly higher rates of Gulf War illness (42%) than veterans who served exclusively in support areas on land (32%) or on board ship during deployment (21%).<sup>1476</sup> Similarly, U.S. and Canadian ground troops had higher rates of multisymptom illness than those who served on board ship<sup>511,753</sup> and Iowa veterans who had been in Iraq, Kuwait, or Saudi Arabia had more health conditions than those located elsewhere in theater.<sup>692</sup>

Two studies have reported increased illness risk in more narrowly defined locations. Navy Seabees located in a specific sector of northeastern Saudi Arabia on the third day of the air war had over four times the rate of Gulf War illness as veterans in other areas, suggesting a link with a particular event or exposure in that location.<sup>564</sup> A more recent report, using troop location data and geographical information system (GIS) methods, identified several localized spatial clusters where veterans with severe Gulf War illness were more likely to have been located at certain time periods.<sup>1236</sup> Taken together, these studies

indicate that Gulf War illness did not randomly affect all Gulf War veterans who deployed to the region, but occurred as a result of events, experiences, or exposures that differed by location.

In fact, epidemiologic studies have consistently found that Gulf War illness rates do vary significantly according to veteran-reported experiences and exposures during the war. Observed associations between Gulf War illness and veterans' exposures have raised a great deal of interest, but have also been the source of considerable confusion. Research related to illness-exposure associations will be considered throughout this report, and analyzed in detail in Section 2. It is important that it be considered in the larger context of limitations inherent in the use of self-reported data, as well as other methodological issues affecting studies of Gulf War veterans.

## **Evaluating Causal Factors in Gulf War Illness**

**Limitations and shortcomings of Gulf War epidemiologic research.** A great deal has been learned from the many epidemiologic studies conducted in different populations of Gulf War veterans. But like all areas of scientific investigation, epidemiologic research has limitations, some of which are especially problematic in Gulf War studies. In addition to issues that are specific to Gulf War research, broader issues such as shortcomings in how research questions have been posed or how studies have been designed and executed have also greatly affected the degree to which Gulf War epidemiologic studies have been useful and informative. Therefore, it is essential that research limitations be identified and carefully considered when interpreting results of Gulf War epidemiologic studies.

Research on the health of Gulf War veterans is unusually complex and challenging for a number of reasons. Relatively little objectively measured information is available on either the primary health outcome of interest—Gulf War illness—or on potential causal factors assessed in epidemiologic studies. Gulf War illness is generally identified on the basis of veterans' symptoms which are, by definition, self-reported. In addition, wartime events and exposures have most often been assessed using veterans' own reports of what they experienced during deployment. Although not generally an optimal data resource, it is the only option available for many Gulf War exposures of interest.

To add to these complexities, both the primary health outcome of interest—Gulf War illness—and the etiologic factors being investigated are multifactorial. That is, Gulf War illness encompasses multiple symptoms that co-occur in different ways. Likewise, the Gulf War experience included a wide array of potentially hazardous and stressful exposures. Even under the best circumstances, understanding relationships between multifaceted exposures and multifaceted health outcomes can be a complex challenge.

Such issues, particular to studies of Gulf War illness, must also be considered in the context of limitations and problems more generally associated with epidemiologic research. Typical issues relate to biases that can result from the size and characteristics of the study sample, the response rate, identification of suitable comparison groups, the content and wording of questions, methods used to assess outcomes, and statistical problems stemming from multiple comparisons. These issues are well recognized and have been discussed at length in reviews and committee reports on the health of Gulf War veterans.<sup>104,646,686</sup>

An additional concern that has received less attention, but one that can have serious consequences, relates to methods used in analyzing and reporting the data collected in Gulf War studies. The present discussion focuses on sources of error in epidemiologic studies that have had the greatest impact on research findings, and interpretation of findings, in studies of Gulf War veterans.

Some reports have suggested that, given the limitations associated with studies of Gulf War veterans and the lack of data on measured exposures in theater, little useful information can be obtained from epidemiologic studies for understanding Gulf War illness and its relationship to exposures.<sup>79,667,686</sup>

But after reviewing results from the many Gulf War epidemiologic studies and carefully considering the impact of identifiable limitations, the Committee has concluded that data from these studies are interpretable and informative. In its analysis of Gulf War epidemiologic research, the Committee has emphasized patterns of illness and associations that are consistent across multiple studies. It has also given more credence to findings from studies that have used preferred methods in sampling, data collection, and data analysis.

A key methodological issue raised in the Committee's 2004 report is the importance of evaluating health outcomes in identifiable subgroups of Gulf War veterans, as opposed to assessing all deployed veterans as a single group. This requires assessing the health status of veterans who served in particular locations, those in particular units, or those known to have had specific exposures.<sup>79,210,593,1477</sup> Combining all Gulf War veterans into a single group may obscure or completely mask health effects due to events or exposures that did not affect all deployed personnel. For example, studies have reported selected health outcomes in veteran subgroups identified by modeled exposure to oil well fire smoke as well as nerve agents in relation to the Khamisiyah demolitions. Several have provided stark examples of links between exposures and disease or biological abnormalities that were not apparent when all deployed veterans were evaluated as a single group.<sup>190,192,599,1237</sup>

**Confounding and risk factors for Gulf War illness.** A major challenge in understanding results from Gulf War epidemiologic studies relates to the complex exposure scenario present in the Gulf War theater. Studies have typically evaluated effects of 20 or more experiences and exposures in theater—everything from combat experiences and other sources of stress, to oil well fires, vaccines, pesticides, and chemical alarms. Studies have consistently found that Gulf War exposures are highly correlated.<sup>161,241,458,1466</sup> That is, veterans who reported some specific exposures during deployment were significantly more likely to also report other specific types of exposures. Those familiar with epidemiologic methods will quickly recognize the serious potential this raises for confounding, that is, confusing the effects of one deployment-related exposure with effects of multiple other exposures.<sup>811</sup>

In less complex settings, confounding can be a major source of error that gives rise to incorrect—even nonsensical—findings, misleading both investigators and those who read their studies.<sup>734</sup> In a uniquely complex exposure scenario such as the Gulf War, the impact of confounding can be profound. Fortunately, familiar analytic methods are available that can both identify which exposures are related to which other ones, and “tease out” effects of individual exposures. This allows epidemiologic studies to identify “independent” associations between illness and each exposure in a complex setting. In scenarios like the Gulf War, where many veterans encountered multiple varied exposures, use of such methods is essential to determine which Gulf War experiences are truly linked to ill health and which only appear to be, as a result of confounding.

Many Gulf War epidemiologic studies were careful to control for possible confounding by demographic factors such as age and gender, or military characteristics such as rank and branch of service. As detailed in Appendix A, adjustment for demographic factors typically had little effect on study results. In contrast, consistent, sometimes dramatic, confounding effects were demonstrated by studies that adjusted preliminary results for effects of multiple deployment-related exposures, as shown in Table 3. Invariably, unadjusted, or “crude” analyses suggested that most exposures and experiences in theater—from bagging sand to hearing chemical alarms—were significant risk factors for Gulf War illness. But relatively few significant risk factors were identified after adjustments were made for the effects of multiple exposures, as demonstrated in Table 3 and detailed in Appendix A.

The Committee was concerned and somewhat surprised to find that many Gulf War epidemiologic studies had not accounted for the high degree of confounding introduced by the complex Gulf War exposure scenario. As a result, some studies involving impressive population samples and data collections actually reported that nearly all of the exposures in the Gulf War appeared to be significant risk factors for chronic

**Table 3. Effects of Confounding by Multiple Exposures in Theater: Examples from Studies of Gulf War Veterans**

<i>Gulf War Veterans Studied</i>	<i>Number of Veterans</i>	<i>Health Outcome</i>	<i>Experience or Exposure Assessed</i>	<b>Association of Gulf War Illness with Experiences and Exposures in Theater</b>	
				<i>No Adjustment for Confounding by Multiple Exposures</i>	<i>Adjusted for Effects of Confounding by Multiple Exposures</i>
U.S. Air Force veterans <sup>1124</sup>	1,155	Severe CMI	Bagging/digging sand	sign* (OR = 3.1)	no association
			Came under attack	sign* (OR = 2.4)	no association
			Took pyridostigmine	sign* (OR = 3.0)	sign* (OR = 2.9)
U.S. Navy Seabees <sup>527</sup>	3,831	Gulf War Illness	Anthrax vaccine	sign* (OR = 3.7)	no association
			Saw dead bodies	sign* (OR = 2.6)	no association
			Pesticides	sign* (OR = 3.5)	sign* (OR = 1.9)
Army veterans in Northeastern U.S. <sup>1804</sup>	1,290	CMI	10+ chemical alerts	sign* (OR = 2.7)	no association
			Diesel fuel	sign* (OR = 2.7)	no association
			Oil fire smoke	sign* (OR = 2.9)	sign* (OR = 2.4)

Abbreviations: CMI = chronic multisymptom illness,<sup>464</sup> sign\* = statistically significant association, OR = odds ratio

ill health in Gulf War veterans.<sup>104,692,1698</sup> Such a conclusion is, of course, illogical. Nonsensical findings of this type were sometimes dismissed by investigators as the result of veterans' over-reporting of exposures. But such results are actually an expected result of confounding introduced by multiple highly correlated exposures during deployment.

Seven Gulf War population-based studies systematically evaluated exposure/illness relationships using analyses that adjusted for effects of multiple exposures in theater. These included the CDC study of Air Force veterans,<sup>1124</sup> two studies of Army veterans from the northeastern U.S. who returned from the war through Fort Devens, Massachusetts,<sup>1239,1804</sup> large studies of British Gulf War veterans<sup>241</sup> and U.S. Navy Seabees,<sup>527</sup> and studies that assessed neurological and gastrointestinal symptoms in Danish veterans.<sup>695,1507</sup> In addition, two studies evaluated a limited number of individual exposures while adjusting for effects of one or two other selected exposures, as opposed to controlling for confounding in a more comprehensive way. These included a large study of Gulf War veterans from the states of Washington and Oregon<sup>1466</sup> and the study of Navy Seabees from the 24<sup>th</sup> Naval Mobile Construction Battalion.<sup>564</sup> Studies that assessed illness-exposure relationships using statistical methods that accounted for effects of multiple exposures were generally considered the most informative by the Committee. Moreover, the limited number of risk factors for Gulf War illness identified by these studies were surprisingly consistent.

**Information bias: Misclassification.** An additional source of error that can occur in epidemiologic studies stems from inaccurate classification of the exposures and/or health outcomes being assessed. This is a particular concern in Gulf War studies, which have usually relied on self-reported information for both exposures and health status. As a result, recall bias—the tendency for individuals to recall or report information inaccurately—has the potential to be particularly problematic in Gulf War research.

No external, objective validation is possible for most veteran-reported exposures. However, several studies have assessed the reliability with which veterans report exposures using test-retest methods.<sup>988,1165,1767,1804</sup> Overall, veterans have reported some exposures more reliably than others. Generally, the most reliably reported exposures were those that veterans experienced first hand and were unique to the war, including encountering smoke from oil well fires, taking pyridostigmine bromide, and having a SCUD missile explode nearby. Lower, but fair reliability was associated with exposure to substances such as pesticides and fuels, and hearing chemical alarms. Exposures about which veterans

might have had little first-hand knowledge at the time of exposure, such as exposures to depleted uranium and CARC paint, were reported least reliably.<sup>988,1165,1767</sup>

Questions about the accuracy of veterans' self-reported exposures require that identified risk factors for Gulf War illness be assessed and interpreted with caution. Errors resulting from misclassification can produce both overestimates and underestimates of the degree to which a particular exposure is actually associated with illness. It is useful to note that studies of both U.S. and U.K. Gulf War veterans have found that the reliability of self-reported exposures was unrelated to veterans' health status, that is, symptomatic veterans report exposures with the same degree of reliability as healthy veterans.<sup>988,1767,1804</sup> This indicates a potential for "nondifferential" misclassification of exposures, that could lead to *underestimates* of the degree of risk resulting from some Gulf War exposures, particularly those reported less reliably.

Unlike exposures, Gulf War studies have generally found that veterans report medical conditions with a high degree of reliability.<sup>692,751,789,989</sup> For example, medical record reviews for a subset of veterans participating in the U.S. national survey of Gulf War era veterans indicated that self-reported conditions related to clinic visits and hospitalizations were reported accurately 93 percent of the time.<sup>751</sup>

Studies have assessed the impact of reporting biases on epidemiologic findings in Gulf War studies using different approaches.<sup>692,988,1088,1165</sup> One recent study, for example, reported that veterans in VA's national survey who had been notified that they were potentially exposed to nerve agents following weapons demolitions at Khamisiyah, Iraq, were no more likely to report symptoms, medical conditions, or healthcare visits than other veterans. Investigators concluded that, contrary to expectation, veterans who believed they may have been exposed to nerve gas showed no tendency to "over report" health problems.<sup>1165</sup> A study of Gulf War veterans in the Pacific Northwest found that media coverage of both the Khamisiyah weapons demolitions and studies showing adverse effects of Gulf War exposures had very little impact on veterans' reports of chemical agents and other exposures in theater.<sup>988</sup> Iowa investigators reported that Gulf War veterans were no more likely to respond to health questions in a socially desirable way than nondeployed era veterans.<sup>692</sup> And in a study of the Fort Devens cohort, inclusion of a measure of recall bias in multivariable analyses had no impact on identified associations between exposures and Gulf War illness.<sup>1804</sup>

Taken together, such studies suggest that despite obvious concerns related to the potential effect of recall bias on Gulf War studies, its actual impact does not appear to have been extensive enough to render study results uninformative. Still, the potential for error introduced by recall bias and other sources of information bias is an important reason for considering patterns of results provided by multiple studies, rather than relying on individual studies, especially when assessing relationships between experiences in theater and Gulf War illness.

# **Gulf War Illness Prognosis and the Need for Treatments**

## **Are Veterans with Gulf War Illness Getting Better or Worse With Time?**

The question of whether veterans with Gulf War illness have generally recovered or become worse is an important one. Four studies have assessed the health of Gulf War veterans over time, all leading to the same conclusion. In 1998, investigators from the Boston VA Environmental Hazards Center reported that veterans in the Fort Devens cohort, evaluated at two time periods between 1992 and 1996, exhibited no significant differences in either the types or average number of symptoms reported.<sup>1239</sup> When veterans from the same group were evaluated a third time two years later, 90 percent of those who had previously been identified as CMI cases continued to meet defining criteria for CMI.<sup>1804</sup>

Similarly, a study of over 1,000 British Gulf War veterans found that their symptomatic ill health remained relatively stable over time. In two evaluations, four years apart, British Gulf War veterans exhibited a slight worsening of functional status, but improved slightly on measures of fatigue and psychological distress.<sup>644</sup> Declining health was most associated with veterans' having more severe symptoms at baseline, believing they had "Gulf War Syndrome," and having more psychological distress.<sup>643</sup> Recently, New Jersey investigators also reported little change in the health of symptomatic Gulf War veterans over time. Among nearly 400 U.S. Gulf War veterans surveyed in both 1995 and 2000, no significant changes in the average number or severity of symptoms were found. Veterans who had been highly symptomatic in 1995 remained so in 2000, although as a group they experienced a slight reduction in symptoms.<sup>1163</sup>

Additional insights into the development and prognosis of Gulf War illness were provided by preliminary results from VA's longitudinal study of nearly 6,000 Gulf War veterans, presented to the Committee by Dr. Han Kang.<sup>745,748</sup> In this national sample, 35 percent of Gulf War veterans indicated they had developed multisymptom illness since the war, with most (67%) reporting that onset occurred between 1991 and 1993. Only two percent of those who had developed multisymptom illness said they had since recovered. Seven percent felt they were "much improved" but 15 percent indicated their condition had become "much worse" over time.

Results from all longitudinal Gulf War studies clearly indicate that few veterans with Gulf War illness have recovered over time and only a small minority have substantially improved. Studies also indicate that the majority of symptomatic Gulf War veterans have not become progressively worse with time. However, a subgroup of veterans do appear to have become worse in the years since they first became ill.

## **The Urgent Need for Effective Treatments for Gulf War Illness**

Gulf War illness has persisted for a very long time for most ill veterans—seventeen years for many. Special panels and government committees assembled to address questions related to the health of Gulf War veterans have consistently emphasized the importance of providing adequate treatments for affected veterans. But effective treatments for Gulf War illness have not yet been identified. The federal government has sponsored just three completed clinical trials to study treatments for Gulf War illness, only two of which have published study results. In addition, many thousands of ill veterans have been seen for this condition in government and private healthcare settings in the 17 years since the war. But few systematic evaluations have reported on the degree to which the treatments veterans receive have been useful in improving their health. The Committee's 2004 report indicated that the federal government had spent over 21 million dollars for treatment research up to that time, the majority (\$15 million) for two large multi-center clinical trials. Additional funding was provided for an unpublished

**Table 4. Studies Reporting Effects of Treatments for Gulf War Veterans with Multisymptom Illness**

<i>Study</i>	<i>Sponsor</i>	<i>Number of ill veterans</i>	<i>Design</i>	<i>Major Findings</i>
Multiple courses of antibiotic treatment for mycoplasma infection <sup>1118,1119</sup>	none	2 series of 73, 14 veterans	case series	In 1 <sup>st</sup> report, 55 of 73 symptomatic veterans interviewed indicated good response with doxycycline therapy; in 2 <sup>nd</sup> report, 11 of 14 veterans who tested positive for mycoplasma infection recovered after multiple cycles of antibiotic therapy.
Multidisciplinary Treatment for Medically Unexplained Symptoms <sup>406</sup>	DOD	109 veterans	case series	3 months after completion of 3 week multidisciplinary treatment, mean increase of 1 point on SF36 PCS, women improved more than men; little change in symptoms.
Louisiana Medical Foundation Antibiotic Treatment Trial <sup>332,670</sup>	DOD	36 veterans	RCT	Antibiotic treatment group had significant reduction in headaches and measures of fatigue and pain compared to placebo. Treatment group had median improvement of 22 points on SF36 PCS.
Antibiotic Treatment of Gulf War Veterans' Illnesses <sup>355</sup>	DOD/VA	491 veterans at 26 sites	multi-center RCT	No significant difference between doxycycline treatment and placebo on 1 <sup>o</sup> outcome (7 point improvement on SF36 PCS over 12 months): 18% of treatment group improved and 17% of placebo group improved. Treatment group had mean increase of 2 points on SF36 PCS.
Exercise/Cognitive Behavioral Therapy in Veterans with Gulf War Illnesses <sup>354</sup>	DOD/VA	1,092 veterans at 20 sites	multi-center RCT	CBT provided statistically significant benefit on 1 <sup>o</sup> outcome (7 point improvement on SF36 PCS over 12 months): 12% of "usual care" and exercise only groups improved; 18% of both CBT and CBT+exercise groups improved. CBT arm had mean increase of 1 point on SF36 PCS.

Abbreviations: DOD = U.S. Department of Defense, VA = U.S. Department of Veterans Affairs, RCT= randomized, controlled trial, SF36 PCS = Physical Component Score of the Medical Outcomes Short Form, CBT = cognitive behavioral therapy

antibiotic trial (\$3 million) and for five VA case management demonstration projects (\$3 million). Findings from two published case series and the three federally-sponsored clinical trials are summarized in Table 4.

**Available information on Gulf War illness treatments.** The two federal multi-center clinical trials are the largest and best known of the Gulf War treatment studies. Briefly, the antibiotic treatment trial evaluated whether a 12 month course of doxycycline treatment improved the health of Gulf War veterans, as reflected in at least a seven point increase in the physical component score (PCS) of the SF36.<sup>353</sup> Veterans participating in the study were required to test positive for mycoplasma infection using polymerase chain reaction methods. Although the study showed some benefit for the doxycycline treatment group after three months, there were no differences between treatment and placebo groups after 12 and 18 months.<sup>355</sup>

The exercise/behavioral therapy trial studied the effects of 12 months of a directed exercise regimen and cognitive behavioral therapy (CBT), individually and combined, on Gulf War illness. Again, improvement was measured by a seven point increase in the SF36 PCS. Only CBT provided a statistically significant benefit over usual treatment, with 18 percent of participants improving with CBT compared to 12 percent with usual treatment.<sup>354</sup> Despite the modest benefit provided by CBT, results of the two large trials, conducted at a cost of over 15 million dollars, were generally disappointing in that neither intervention provided improvement for a substantial number of veterans.<sup>639</sup> Overall, mean

improvement on veterans' SF36 PCS scores was only one point for CBT and two points for doxycycline treatment.

The only other completed Gulf War illness clinical trial was a study of a complex, high dose antibiotic regimen conducted by the Louisiana Medical Foundation, headed by the late Dr. Edward Hyman.<sup>670</sup> The intervention was unconventional, and the theory on which it was based was controversial.<sup>331,671,672,1454,1455</sup> Study results were never published, but were presented to the Committee by two of Dr. Hyman's co-investigators, Dr. Quentin Deming and Mr. William Weiss. Briefly, the study was a randomized, double blind, placebo controlled trial of intravenous, then oral antibiotics over a four month period. Specific regimens and dosages varied, according to the presence of excreted gram-positive cocci detected by microscopic evaluation of patients' urine, and by patients' symptoms.<sup>332,670</sup>

Although both the theory and intervention were unconventional, investigators used standard methods to evaluate the health status of veterans before and after treatment. Results shared with the Committee indicated that the treatment group improved significantly compared to the placebo group, with reductions in the mean number of headaches per month (from 12.5 to 2.5,  $p < 0.001$ ), significantly improved scores on two fatigue scales, and improvement on the McGill Pain Inventory. The median SF36 PCS score was reported to improve 22 points for the treatment group, compared to seven points for the placebo group, and investigators indicated that no excess of side effects had been observed in the treatment group. No significant differences were seen on measures of sleep quality, neuropsychological impairment, or frequency of diarrhea.<sup>332</sup> The Committee was intrigued by the apparent benefit provided by the treatment, but concerned that study results had not been scientifically peer reviewed and published. The biological rationale for the treatment approach was also puzzling. So although the empirical results appeared extremely promising they were overshadowed by questions surrounding the study, most prominently the role of excreted bacteria and the lack of scientific review and successful publication. Therefore, the Committee was unable to come to firm conclusions regarding the meaning and importance of the study findings and appropriate follow up.

There are few other sources of systematically-collected data on the effects of treatments used for Gulf War illness. Two investigators have published observational findings on treatment outcomes in case series of ill Gulf War veterans, as shown in Table 5. Dr. Garth Nicolson reported substantial benefit for a subset of Gulf War veterans treated with multiple courses of antibiotics,<sup>1118,1119</sup> and Dr. Charles Engel reported slight functional improvement in veterans treated with a multidisciplinary intervention that included CBT.<sup>406</sup>

Gulf War veterans with multisymptom illness who participated in VA's national longitudinal study were asked about their experience with treatments and lifestyle practices in relation to their symptoms. Preliminary findings were presented to the Committee by Dr. Han Kang.<sup>745</sup> Symptomatic veterans reported using prescription and over-the-counter medications most frequently, followed by physical therapy and nutritional supplements. The most highly rated category was over-the-counter medication, which eight percent of ill veterans said had provided benefit for their symptoms, most prominently headache and joint pain. About the same proportion indicated that diet and nutritional supplements had helped, mostly for fatigue, joint pain, and gastrointestinal symptoms. Six percent reported physical therapy had helped with somatic pain and five percent indicated that antidepressants had been helpful for improving depression symptoms and sleep difficulties. Among unconventional therapies, about two percent of symptomatic veterans reported that relaxation therapy had been helpful for joint pain, fatigue, and headache. A similar number indicated that herbal medicines had provided benefit for memory loss, fatigue, and joint pain.

Veterans also reported whether different activities and lifestyle behaviors had affected their symptoms. Factors most often associated with improved symptoms were avoiding stressful situations (25%), maintaining a well-balanced diet (20%), and cutting back on work or social activities (18%). The factors

most often said to make symptoms worse were vigorous exercise (35%) and maintaining a busy schedule (23%). About the same number of veterans indicated that light exercise improved (16%) as worsened (18%) their symptoms. These findings provide an interesting first look at the general types of approaches veterans have used in addressing their illness. The Committee looks forward to reviewing additional results from this study to learn, in more detail, about veterans' appraisals of specific treatments.

No other systematically-collected data are available on effects of treatments for Gulf War illness. Two physicians have provided public testimony on their clinical experience in treating a limited number of veterans. In 1993, Dr. Myra Shayevitz provided testimony to Congress describing improvements in 25 symptomatic Gulf War veterans treated in an environmental clinic piloted at the Northampton, Massachusetts VA Medical Center (VAMC).<sup>1399</sup> The clinic intervention included reduced exposures to chemicals, improved nutrition, and patient education and support. Several of Dr. Shayevitz's patients also provided written comments attesting to their improved health. Dr. David Root provided testimony to the Presidential Special Oversight Board in 1998 and to the CDC Gulf War Research Planning Conference in 1999 about dramatic improvements observed in several highly symptomatic Gulf War veterans he had treated with an intensive sauna/detoxification regimen used routinely for treatment of chemical injury and substance abuse.<sup>1307,1308</sup>

VA's Gulf War research portfolio currently includes three clinical studies that provide treatments for symptomatic Gulf War veterans. A study conducted at the East Orange, New Jersey, VAMC is evaluating the effectiveness of CBT administered by telephone to veterans with Gulf War illness.<sup>226</sup> A second study, conducted at the Northport, New York, VAMC, is evaluating continuous positive airway pressure (CPAP) treatment for Gulf War veterans with disordered sleep. The third study, conducted by investigators at the Salt Lake City VAMC, will treat small bowel bacterial overgrowth in veterans with persistent diarrhea.

In addition, VA and DOD collaborated in convening expert panels that developed clinical guidelines for evaluating veterans with post-deployment health concerns,<sup>1656</sup> and for evaluation and management of veterans with medically unexplained fatigue and pain.<sup>1655</sup> Treatment guidelines for medically unexplained symptoms were based on what was known about treatment of fibromyalgia and chronic fatigue syndrome at the time the guidelines were developed in 2001. No information is available that indicates whether government clinicians have used these guidelines in treating ill Gulf War veterans, or if recommended treatments have been effective. The treatment guidelines have also become outdated. Since 2001 a large amount of additional information has become available on medical treatments for these conditions, particularly fibromyalgia, as will be described in a later chapter.

**Future prospects for federally-sponsored Gulf War illness treatment research.** As described in the Committee's 2004 report, there are two general approaches for identifying effective therapeutic interventions. The first, an empirical approach, is based on clinical observations that certain treatments provide improvements for certain conditions. Potentially beneficial treatments identified in this way can be systematically assessed using outcomes research and randomized clinical trials to scientifically determine their effectiveness. The second approach requires that specific biological mechanisms underlying a disease be identified, so that treatments to counteract those processes can be identified and tested for their effectiveness. For Gulf War illness, a complex condition for which specific pathophysiological mechanisms are not well understood, both approaches will likely be needed in order to identify the most effective treatments in the most timely way.

In response to recommendations in the Committee's 2004 report, the Secretary of Veterans Affairs announced that VA would fund a Gulf War illness treatment research initiative, largely focused on identifying and evaluating treatments already available and being used to treat Gulf War illness and conditions with similar features. Although a draft funding announcement for a treatment research center

was provided for Committee review in late 2005, no final announcement was released and a treatment research center has not been funded.

In 2006, two major changes occurred in federal funding for Gulf War illness research, as will be described in detail in a later section. These changes included a total of 15 million dollars allocated in FY2006 and FY2008 for a Gulf War illness research program managed by the Office of Congressionally Directed Medical Research Programs (CDMRP) at DOD,<sup>1596</sup> and a 15 million dollar annual allocation for a comprehensive Gulf War illness research center at the University of Texas Southwestern (UTSW), funded by VA. The two recently-funded programs have been directed to coordinate their efforts and will, fundamentally, utilize the two approaches previously described for identifying effective treatments.

The initial funding solicitation issued by the CDMRP Gulf War illness research program indicated that highest priority would be given to studies that identify and evaluate treatments for Gulf War illness. This included funding for smaller scale studies to provide data on treatments currently being used for Gulf War illness and similar conditions as well as treatments that address biological processes thought to underlie Gulf War illness. The UTSW program, on the other hand, is focused on determining specific biological mechanisms that underlie veterans' symptoms, in order to identify treatments to address those processes. Both programs have only recently begun implementing studies, and the Committee looks forward to monitoring their progress. The CDMRP program announced, in 2007, that nine Gulf War illness studies were funded with the initial program allocation. These included pilot trials of treatments for veterans with Gulf War illness, and animal studies that will evaluate effects of treatments on biological processes identified in animal models for Gulf War illness.<sup>737</sup> The Committee regards both programmatic initiatives to be positive steps forward in focusing Gulf War research on the highest priority objective, that is, to improve the health of ill veterans.

## Is There a Unique Gulf War Syndrome?

The question of whether the multisymptom illness affecting Gulf War veterans should be considered a “unique Gulf War Syndrome” has been widely discussed and interpreted.<sup>134,252,324,556,667,668,686,918,1089,1757</sup>

What is meant by the question has often been unclear, as have attempts to answer it. For some observers, a “unique syndrome” has meant that there should be just one constellation of symptoms affecting Gulf War veterans—a single symptom complex constituting a single syndrome. For others, a “unique syndrome” has meant that a single, unique *cause* for the symptoms should be demonstrated. For still others, a “unique syndrome” has meant that similar symptoms would not be found in people who did not serve in the Gulf War. And for several researchers, the question has hinged on whether a particular statistical technique, factor analysis, identifies symptom correlations in Gulf War veterans that are not found in other groups.

However the question of a unique syndrome is interpreted, extensive descriptive and analytic research has clearly demonstrated that an illness, characterized by a complex of multiple symptoms, resulted from service in the Gulf War. The specific symptoms affecting individual veterans can differ from person to person, but the general types of symptoms are remarkably consistent across diverse Gulf War veteran populations. Whether this Gulf War-related symptom complex represents several syndromes, or one syndrome with several subtypes, is an issue of taxonomy that can only be definitively resolved as objective markers become more firmly established.

Gulf War illness, as a consistent complex of symptoms affecting a defined population, fits most definitions of what constitutes a syndrome. But this syndrome might not be considered unique, from different perspectives. That is, there could be more than one type of pathophysiological process affecting Gulf War veterans that leads to similar, overlapping symptom profiles. There could also be more than one cause for these symptoms. And, lastly, Gulf War illness has some similarities to multisymptom conditions found in other populations, as will be discussed in detail in a later section of this report.

The central issue of importance is that at least one fourth of veterans who deployed to the Gulf War as healthy men and women developed an identifiable pattern of persistent, difficult symptoms as a consequence of their military service. Whether this illness should be referred to as one or more syndromes—unique or otherwise—is of less consequence. There is overwhelming evidence demonstrating that Gulf War illness, however labeled, is a widespread problem in Gulf War veterans and no evidence to the contrary.

**Is Gulf War illness the same thing that happens after every war?** Several commentaries and reviews have described Gulf War illness as a condition that parallels syndromes historically described in soldiers after they return from war.<sup>669,720,721,1500</sup> These have included “irritable heart” or “Da Costa’s syndrome” in Civil War veterans,<sup>302</sup> shell shock and “effort syndrome” in World War I veterans, battle fatigue in World War II veterans, and posttraumatic stress disorder in Vietnam veterans. In all eras, soldiers serving in war have suffered from acute and chronic health problems that often affect more troops than the number injured and killed in battle. This has historically included the effects of infectious disease and extreme environmental conditions, but in more recent times has also included effects of radioactive fallout, chemical defoliants, and chemical weapons.<sup>191</sup>

Experiences common to all wars include combat and the hardships of deployment, both of which can have long-term physical and psychological consequences. Commentators who have characterized Gulf War illness in the context of other post war syndromes have suggested—explicitly or implicitly—that because the psychological impact of war can have long-term consequences, Gulf War illness is probably another post-war stress syndrome, the result of psychological factors. This idea was accepted by some at face value before data that specifically addressed these issues became available.

Research studies have not supported the view that Gulf War illness is the same type of problem that occurs after every war, nor that it can accurately be considered a post-war stress syndrome. As early as 1994, a National Institutes of Health Technology Assessment panel observed that symptom profiles affecting Gulf War veterans differed from those of Vietnam veterans. Data from VA registries indicated that symptoms of fatigue, muscle pain, headache, joint pain, and shortness of breath were more common in Gulf War than Vietnam veterans.<sup>1121</sup> British investigators have since systematically evaluated the health and symptoms of military personnel who served in the 1990-1991 Gulf War, in Bosnia during the 1990s, and in Iraq in the current conflict. No “Gulf War syndrome”-like effect, that is, no pattern of excess symptoms affecting a sizable number of veterans, was found in Bosnia or Iraq War veterans.<sup>631,642,1698</sup> The effect was only observed in veterans who served in the 1991 Gulf War.<sup>1088</sup> Clinical reports on U.S. veterans who served in Operations Iraqi Freedom and Enduring Freedom also have indicated that returning personnel have not been affected by high rates of symptomatic illness that is not explained by diagnosable medical or psychiatric conditions.<sup>615,653</sup>

In contrast to Vietnam veterans and personnel returning from current conflicts in the Middle East, population-based studies have consistently found that 1990-1991 Gulf War veterans have low rates of posttraumatic stress disorder and other psychiatric conditions, as detailed in the next section of the report. Further, studies that have comprehensively assessed risk factors associated with the Gulf War consistently indicate that Gulf War illness is *not* associated with serving in combat or other stressors during deployment.

Available evidence therefore indicates that Gulf War illness is not the same thing that happens after every war and is not a post-war stress syndrome. Each war is unique, each has its own profile of risks and health consequences.<sup>291,1216,1723</sup> All wars present some degree of trauma for troops in battle, but many wars also present other hazards. The effects of blister agents in World War I or the Iran-Iraq War, for example, should not be equated to the psychological consequences of soldiers fearing for their lives or seeing a buddy die on the battlefield. Neither should the effects of Agent Orange be confused with the effects of the traumatic experiences many soldiers encountered in the jungles of Vietnam. Service in the 1991 Gulf War resulted in a complex health problem not typical of other wars that cannot be understood simply as the expected result of deployment-related stress.

## Other Gulf War Health Issues

Gulf War illness is the most prevalent health problem affecting Gulf War veterans, but not the only health issue related to Gulf War service. Additional important issues include rates of diagnosed medical and psychiatric conditions in Gulf War veterans, particularly neurological conditions, cancers, and respiratory diseases, as well as causes and rates of mortality. Although Gulf War epidemiologic studies have commonly reported hospitalization and mortality rates, relatively little information is available concerning diagnosed diseases not normally associated with hospitalization or premature death. In addition, important questions about health problems affecting veterans' children and other family members have persisted since the Gulf War.

### Diagnosed Diseases Affecting Gulf War Veterans

**Amyotrophic lateral sclerosis.** The most serious condition reported to affect Gulf War veterans at a higher-than-expected rate is amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease. This serious and progressive neurodegenerative disease most often strikes individuals between age 55 and 75, affects men more often than women, and is almost universally fatal. A 2003 VA study reported that Gulf War veterans were about twice as likely to have ALS as nondeployed era veterans based on 40 confirmed Gulf War-deployed ALS cases.<sup>636</sup> The excess risk was particularly pronounced in Air Force Gulf War veterans, who had ALS at nearly three times the rate of their nondeployed peers.

The VA research team made a concerted effort to determine whether the excess ALS rate observed in Gulf War veterans could be an artifact of ascertainment error, that is, failure to detect some ALS cases among the nondeployed. After adjusting for this potential bias using three different methods, results still indicated a significant excess of ALS in Gulf War veterans.<sup>260,633</sup> Research from the University of Texas Southwestern raised additional concern that Gulf War veterans may have developed ALS at a younger-than-normal age, finding that a large number of cases occurred in veterans under age 45.<sup>557</sup> In addition, military hospitalization data indicated that active duty personnel who had served in the Gulf War had a 1.7 times higher rate in ALS hospitalizations between 1991 and 1997, compared to nondeployed era veterans, an excess that was not statistically significant.<sup>1432</sup>

A later report from a 2005 study of over 400,000 men in an American Cancer Society cohort indicated that men who had served in the military, overall, were more likely to have died of ALS than men who were not in the military.<sup>1759</sup> This raised questions about whether an excess risk of ALS is related to military service in general, rather than Gulf War service specifically.<sup>1206,1310</sup> As a result, VA commissioned a special report from the Institute of Medicine, which concluded that there was limited, but suggestive evidence that ALS is associated with military service in general.<sup>685</sup>

Results of the Cancer Society study are important in providing a preliminary indication that military service could be a risk factor for ALS. But it is unclear why researchers and government officials have suggested, based on findings from this study, that ALS may be linked to military service, but not specifically with Gulf War service. The VA Gulf War ALS study found that ALS affected Gulf War veterans at twice the rate of nondeployed Gulf War era military personnel. If military personnel are, overall, at increased risk for ALS, the observed excess of ALS in Gulf War veterans compared to other military personnel would be of particular concern.

The Cancer Society study provided information on ALS among military veterans serving from World War II through the Vietnam eras, but no insights on rates of ALS in deployed vs. nondeployed veterans or in Gulf War veterans compared to veterans of other eras.<sup>1759</sup> Therefore, results of this study do not diminish concerns raised by studies that have identified an excess of ALS specific to Gulf War

deployment. This excess could be of greater concern if military service in general is also a risk factor for ALS.

Recently, additional findings reported from the large VA ALS study indicated that most new ALS cases among Gulf War veterans identified in the 10 years after the war had their initial onset by 1996. The excess of ALS cases declined after that time—both in Gulf War veterans overall, and in those under age 45.<sup>634,635</sup> Additional analyses also identified differences in ALS risk related to geographical areas where troops were located during deployment.<sup>1052,1053</sup> These recent reports indicate that ALS in Gulf War veterans occurred in the pattern of a time-limited disease “outbreak,” resulting from events or exposures during Gulf War deployment. If the post-1996 pattern of new onset ALS cases continues, the number of excess ALS cases among Gulf War veterans will be less than had initially been suggested by early studies. But it is not known if the risk of ALS, which normally increases after age 55, will differ in Gulf War veterans as they age. The seriousness of this disorder requires that ALS rates in Gulf War veterans continue to be monitored for the foreseeable future.

In response to early reports that ALS was associated with Gulf War service, VA developed an ALS registry for Gulf War era veterans. That registry has since been expanded to include all veterans with ALS who served in the military during any period.<sup>756</sup> In addition, VA has developed a brain tissue bank that will enroll and collect tissues from veterans with ALS identified in the registry.<sup>441,1225</sup>

**Other neurological diseases.** Very little information is available concerning rates of other diagnosed neurological diseases in Gulf War veterans. In light of the excess of ALS in Gulf War veterans, as well as consistent findings related to persistent neurological symptoms, it is important to determine if other neurological diseases have disproportionately affected Gulf War veterans. In its 2004 report, the Committee recommended that rates of multiple sclerosis (MS), Parkinson’s disease, brain cancers, and difficult-to-characterize neurological disorders be identified in Gulf War veterans and suitable comparison groups. Since the Committee’s report was issued, veterans’ organizations and members of Congress have called on the federal government to conduct research to determine the rate of MS in Gulf War veterans.<sup>1694,1721</sup> In 2008, VA initiated a case/control study of veterans who were service-connected for MS disability by the Veterans Benefits Administration (VBA).<sup>1747</sup> This study will not identify incidence or prevalence rates of MS in Gulf War veterans but may provide insights concerning characteristics of MS and risk factors for MS potentially related to Gulf War service.

Other than limited information from hospitalization studies, the only other studies that have assessed neurological disease in Gulf War veterans evaluated rates of mortality due to neurological disease. A 2005 study, conducted by investigators from the Washington, D.C., VAMC, identified an excess rate of brain cancer deaths among Gulf War veterans who, according to DOD models, were potentially exposed to low levels of nerve agents in relation to chemical weapons demolitions at Khamisiyah, Iraq, in 1991.<sup>192</sup> Veterans in affected areas were twice as likely, overall, to have died from brain cancer between 1991 and 2000 as veterans in other locations. Excess rates were most apparent during the last few years of follow up (1997-2000). A dose-response effect was also noted, wherein higher brain cancer mortality occurred in veterans who were in affected areas for longer periods of time.<sup>190,192</sup>

Researchers are currently conducting an updated mortality study to evaluate causes of death in U.S. Gulf War veterans through 2004.<sup>105</sup> Preliminary results, shared with the Committee in 2008, are similar to findings reported in 2005. Investigators continue to identify a significant excess of brain cancer deaths among Gulf War veterans potentially exposed to nerve agents related to the Khamisiyah demolitions. These mortality studies provide useful information on deaths due to brain cancer, and demonstrate the importance of evaluating diseases in subgroups of Gulf War veterans with specific exposure and/or location histories. However, other types of research are still needed to determine whether Gulf War service is associated with excess rates of diagnosed neurological diseases that have not been fatal.

**Cancer in Gulf War veterans.** Government committees and special panels have long called for studies to determine if Gulf War veterans have developed cancer at higher-than-expected rates since Desert Storm.<sup>1227,1673,1682</sup> Identifying cancer rates in Gulf War veterans is especially important now, 17 years after the war, since many cancers first become apparent 10 to 20 years after an initiating event. The most comprehensive study of cancer in Gulf War veterans comes from Great Britain. A 2003 study identified the incidence of multiple types of cancer between the years 1991 and 2002 in the entire cohort of U.K. Gulf War veterans and a matched comparison group, using data from the British National Health Service.<sup>943</sup> No differences were found between Gulf War and era veterans for rates of all cancers combined, nor for any site-specific cancers.

In the absence of a similar cancer data resource in the United States, comprehensive information on cancer rates in U.S. Gulf War veterans has not been reported. As previously described, results from a national study found an excess of brain cancer deaths in relation to the Khamisiyah weapons demolitions. The 2005 study identified 25 brain cancer deaths in veterans potentially exposed to nerve agents, an excess of 14 brain cancer deaths per 100,000 exposed veterans.<sup>190</sup> In contrast, in a population-based survey of about 1,800 Gulf War veterans in five U.S. states, no excess of physician-diagnosed cancer was reported by veterans who had been within 50 kilometers of Khamisiyah. Overall, however, three times as many Gulf War veterans as nondeployed era veterans in this sample reported being diagnosed with some type of cancer. The excess of reported cancer diagnoses—21 cases among Gulf War veterans, and three cases among nondeployed veterans—did not reach statistical significance.<sup>989</sup>

Only limited information is available concerning verified cancer diagnoses in U.S. Gulf War era veterans. An early hospitalization study reported that, in the months immediately following Desert Storm, active duty Gulf War veterans were twice as likely to be hospitalized for testicular cancer as nondeployed era veterans.<sup>523</sup> This difference was no longer apparent after five months, leading investigators to conclude that the temporary rate spike had been due to Gulf veterans deferring care for this condition until they returned home from deployment.<sup>820</sup>

A later study, using 1991-1999 data from cancer registries in New Jersey and the District of Columbia (D.C.), reported a two-fold proportional excess of testicular cancer in Gulf War veterans, compared to nondeployed era veterans.<sup>894</sup> Proportional excesses were also reported for non-Hodgkin's lymphoma and brain cancer from D.C. registry data, but not the New Jersey registry. This team has continued to collect and analyze cancer data on Gulf War and era veterans from additional state cancer registries. Preliminary results from a total of eight registries were shared with the Committee by Dr. Paul Levine. Data from some states suggested slight excesses in the crude incidence of testicular and brain cancers in Gulf War veterans compared to nondeployed era veterans between 1991 and 1999. Proportional differences were not significant, however, after adjustments for age and race.<sup>892</sup> This ongoing investigation currently includes data from 28 state cancer registries, which cover about 83 percent of U.S. Gulf War and era veterans.<sup>959</sup> The Committee looks forward to reviewing additional results from this important research.

Although studies to date have raised only limited concerns about cancer in Gulf War veterans, a number of important questions have not yet been adequately addressed. Very limited cancer data have been reported for U.S. Gulf War veterans in general, and no published research on cases occurring after 1999. Because of the extended latency periods associated with most cancers, it is important that cancer information be brought up to date and that cancer rates be assessed in Gulf War veterans on an ongoing basis. In addition, cancer rates should be evaluated in relation to identifiable exposure and location subgroups, as was done in the 2003 British study and the U.S. mortality study related to Khamisiyah. Data from VA's longitudinal study can also be used to provide an indication of whether veteran-reported cancers are associated with exposures in theater.

**Other diagnosed conditions affecting Gulf War veterans.** Limited information is available on rates of other diagnosed diseases in Gulf War veterans. In addition to symptoms, epidemiologic studies

have asked veterans to report if they had been diagnosed with a variety of medical conditions. Several types of diagnoses are consistently reported at higher rates by Gulf War veterans than nondeployed era veterans. These include migraines,<sup>527,751,1476,1698</sup> seizures,<sup>748,751,989,1476</sup> digestive conditions,<sup>527,748,751,1411,1476</sup> respiratory conditions,<sup>527,751,1411,1476,1698</sup> and skin disorders.<sup>527,751,1411,1476,1698</sup> Generally, fewer excess medical conditions have been reported by Australian and Danish Gulf War veterans than U.S. and U.K. Gulf War veterans.<sup>696,789</sup>

Rates of respiratory conditions have been evaluated in several Gulf War studies.<sup>285,866,1434</sup> As will be described in more detail, one study reported that a higher proportion of Gulf War than nondeployed veterans had been hospitalized for respiratory conditions, including asthma.<sup>528</sup> In addition, one well-conducted study found that the subset of Gulf War veterans with greatest exposure to pollutants from oil well fires had significantly elevated asthma rates.<sup>285</sup>

Multiple studies have evaluated rates of diagnosed psychiatric conditions in Gulf War veterans. Gulf War veterans generally have higher rates of posttraumatic stress disorder and other psychiatric diagnoses than nondeployed Gulf War era veterans,<sup>1488</sup> but lower rates of psychiatric illness than combat veterans of other wars. Findings on psychological stressors and psychiatric conditions are described in detail in the next section of the report.

Most of the studies that have provided clinical examinations of Gulf War veterans have either included a relatively small number of veterans<sup>464,565</sup> or were case/control studies<sup>160</sup> and so could not provide reliable prevalence estimates for diagnosed conditions. Prevalence rates of selected diagnosed medical conditions were provided in 2005 from Phase III of the U.S. National Survey of Gulf War era veterans.<sup>393</sup> This portion of the large U.S. national study provided clinical evaluations of 1,061 Gulf War veterans and 1,128 nondeployed era veterans 10 years after the war. Reported outcomes included SF36 PCS scores and 12 medical conditions: fibromyalgia, chronic fatigue syndrome, skin conditions, dyspepsia, hypertension, hepatitis, symptomatic arthralgias, obstructive lung disease, diabetes, peripheral neuropathy, and both hypo- and hyperthyroidism.

Results from the U.S. national study indicated that Gulf War veterans had a dramatically higher rate of chronic fatigue syndrome than nondeployed veterans (1.6% vs. 0.1%, OR = 40.6), and significantly higher rates of fibromyalgia (2.0% vs. 1.2%, OR = 2.3), skin conditions (34.6% vs. 26.8%, OR = 1.4), and dyspepsia (9.1% vs. 6.0 %, OR = 1.9). None of the other 12 conditions were significantly more common in Gulf War veterans. On average, the general health status of Gulf War veterans, measured by the SF36 PCS, was only slightly worse in Gulf War than nondeployed veterans (49 vs. 51). This difference was statistically significant, but of minor clinical significance. Abnormalities identified on clinical examination and mean values for all laboratory tests were also similar for Gulf War and nondeployed veterans.<sup>393</sup>

These long-awaited findings from the large VA clinical study provided useful information about the 12 conditions assessed but few additional insights concerning the health of Gulf War veterans. It is not clear why the 12 outcomes assessed were selected for evaluation, since many had not been shown in earlier phases of the study to be problematic for Gulf War veterans. For conditions like diabetes and hepatitis, clinical evaluations largely provided validation of what veterans had already reported. Regrettably, this large clinical study has not provided information on many of the conditions found to affect Gulf War veterans at excess rates in earlier phases of the study, conditions like recurrent headaches and migraines, diarrhea and colitis, seizures, and sinusitis. Neither was information provided on other medical conditions of interest such as cancers, autoimmune disorders, and heart disease. Mean values for deployed and nondeployed veterans were reported for all measures, but no information was provided on subgroups of potential interest, for example, subgroups of veterans with abnormal findings on laboratory tests, and subgroups of veterans who reported specific exposures.

So, while additional insights have been provided from VA's Phase III clinical study, important questions remain about the extent to which Gulf War veterans may be disproportionately affected by diagnosed medical conditions. It is important to determine if Gulf War veterans and, in particular, subgroups of Gulf War veterans with specific exposures during the war, have excess rates of diagnosable neurological conditions, cancer, respiratory diseases, or other chronic diseases.

## **Mortality Rates Among Gulf War Veterans**

The question of whether there is an abnormally high rate of death among Gulf War veterans, or if veterans have died at younger-than-expected ages, is of great interest and importance. In the seventeen years since Desert Storm, government reports and research studies from both the U.S. and the U.K. have consistently indicated that Gulf War veterans have not, overall, had higher rates of death due to diseases but have had higher rates of accident-related deaths than nondeployed era veterans. Overall mortality rates in both deployed and nondeployed era veterans are lower than in the general population, however. Post-war mortality statistics are available from three published studies of U.S. Gulf War veterans and two studies of British veterans, along with regular mortality reports provided by the U.K. Ministry of Defence.

The most recent published information on mortality in U.S. Gulf War and nondeployed veterans reports on deaths through 1997, identified by VA's Beneficiary Identification and Records Locator Subsystem (BIRLS) and the Social Security Administration, with causes of death identified by the U.S. National Death Index.<sup>749</sup> That study reported that early post-war figures indicating lower disease-related mortality in Gulf War veterans, and higher accident-related mortality, had become more similar over time. By 1996-1997, rates of mortality resulting from both disease and accidents were nearly identical in deployed and nondeployed veterans. Later information has been published on mortality rates through the year 2000 for Gulf War veterans only, in relation to the Khamisiyah plume models, as previously described.<sup>192</sup>

Preliminary findings from an ongoing mortality study conducted by investigators at the Washington, D.C., VAMC were shared with the Committee in 2008.<sup>105</sup> That study is evaluating overall and cause-specific deaths that occurred among U.S. Gulf War and nondeployed era veterans through 2004. Early results indicate that, overall, Gulf War veterans continue to have a lower mortality rate due to diseases, and a higher mortality rate due to accidents, than nondeployed era veterans. However, investigators reported that female Gulf War veterans have significantly greater mortality, overall, than nondeployed female era veterans, and excess deaths due to digestive system diseases and external causes, including motor vehicle accidents. Preliminary findings also continue to indicate that brain cancer mortality is elevated among Gulf War veterans in relation to modeled levels of exposure to nerve agents. These preliminary findings are provocative, and the Committee looks forward to further reviewing results of this important study as they are finalized.

Mortality rates among British Gulf War veterans through 2006 have shown trends similar to those observed in U.S. veterans. Over time, excess rates of accident-related deaths identified in the years just after the war have become more comparable to those of nondeployed veterans. In a recent report, however, the U.K. Ministry of Defence reported that between 1991 and 2007, veterans of the 1991 Gulf War had a higher rate of suicide, or possible suicide, than nondeployed veterans of the same era.<sup>1569</sup> Overall rates of death due to diseases remained somewhat lower in Gulf War veterans, compared to nondeployed era veterans.<sup>1569</sup> Additional details of interest are provided by a report on mortality in British veterans in relation to experiences/exposures during the war.<sup>944</sup> Just two associations were identified, neither of which reached statistical significance. Veterans who reported handling pesticides during the war were twice as likely as unexposed veterans to die from accident-related causes, and veterans who reported depleted uranium exposure were twice as likely to die from disease-related causes.

A number of theories have been put forward to explain why Gulf War veterans have experienced higher rates of fatal accidents, most prominently motor vehicle accidents.<sup>124</sup> These have included indications that veterans have a greater propensity for risk taking behavior after hostile deployments,<sup>750</sup> findings of poorer attention and response speed in cognitively impaired veterans,<sup>554</sup> reports of greater use of alcohol by combat veterans,<sup>908</sup> and the general similarities between characteristics of deployed military personnel and people with the highest rates of motor vehicle accidents in the general population.<sup>629,908</sup>

Mortality studies have provided little indication that Gulf War veterans, overall, have suffered excess rates of deaths due to diseases. However, the most recent comprehensive comparisons between U.S. Gulf War and nondeployed veterans that have been published only include deaths that occurred before 1998. Deaths due to diseases with longer latency periods would likely only have become apparent in more recent years. Therefore, it is important that current figures for overall mortality, as well as disease-specific mortality, for U.S. Gulf War era veterans be comprehensively evaluated and made publicly available. Information on disease-specific mortality rates during the past 10 years are of particular importance, and the Committee urges VA to make this information available at the earliest possible time. Additional information on mortality rates among subgroups of Gulf War veterans—defined, for example, by exposures and locations in theater and by branch of service—is also needed to determine if Gulf veteran subgroups have been affected by any causes of death not apparent when all veterans are assessed as a single group.

### **Hospitalization Rates Among Gulf War Veterans**

Between 1996 and 2006, 14 studies reported rates of hospitalization in Gulf War veterans and comparison groups.<sup>526,1428</sup> Nearly all of these studies were limited to information on active duty military personnel who were admitted to military hospitals. They therefore do not include the vast majority of Gulf War veterans or hospital admissions. Recent VA figures indicate that over 90 percent of Gulf War veterans had left the military by 2007.<sup>1650</sup>

Few differences between Gulf War and nondeployed era veterans have been reported from Gulf War hospitalization studies. Both all-cause hospitalization rates and disease-specific hospitalizations have been similar, overall, in comparisons between active duty Gulf War and nondeployed military personnel from the same era. The few exceptions come from just three studies. The first reported that Gulf War veterans were hospitalized for fibromyalgia at significantly excess rates between 1991 and 1997, but not for lupus. Findings on ALS hospitalizations during this period were inconclusive due to small numbers, as previously described.<sup>1432</sup> No more recent information concerning hospitalizations for these conditions has been reported. A second study found that a higher proportion of Gulf War Marine Corps veterans than Vietnam Marine veterans were hospitalized for musculoskeletal conditions.<sup>148</sup> The third study included hospitalization information from nonmilitary hospitals. That study included 1991-1994 national data from DOD and VA hospitals, as well as civilian hospitals in the state of California. Results indicated a higher proportion of Gulf War than nondeployed era veterans had been hospitalized for injuries and for respiratory and digestive diseases.<sup>528</sup> Excess hospitalizations due to cardiac dysrhythmia were also reported among active-duty personnel who were, according to DOD models, potentially exposed to low-level nerve agents in relation to the Khamisiyah weapons demolitions.<sup>1433</sup> Modeled exposure to pollutants from oil well fire smoke was not associated with increased hospitalization risk.<sup>1434</sup>

As discussed in the Committee's 2004 report, the large majority of cases of Gulf War illness would not be identified using hospitalization data, since it is extremely uncommon for patients with undiagnosed, symptom-defined illness to be hospitalized. There is also little reason to expect that a number of other types of conditions reported to affect Gulf War veterans at excess rates would be identified by the hospitalization studies conducted to date. Nearly all studies report only on hospitalizations among active duty personnel in military hospitals. Veterans with serious conditions that might lead to hospitalization,

but who were no longer in the military, would not have been included in the studies. In addition, medical conditions shown by some studies to have affected subgroups of Gulf War veterans affected by a particular exposure, such as asthma and brain cancer, would potentially go undetected in hospitalization studies that simply compare all deployed veterans to nondeployed veterans. Further, diseases with long latency periods, potentially detectable at their later stages using hospital admission data, would not likely be found in studies evaluating hospital admissions before 2000, the most recent year for which Gulf veteran hospitalization data have been reported.

An enormous amount of effort and care have been used to analyze and report military hospitalization rates in Gulf War veterans. Results of these studies have been reassuring, to some degree, by indicating that Gulf War veterans have not been admitted to military hospitals at exceedingly high rates in conjunction with the types of injuries and acute and chronic diseases that normally lead to hospitalization.

Gulf War hospitalization studies have largely been used to report on disease rates that are easiest to quantify using data routinely collected for administrative purposes. Unfortunately, this “low hanging fruit” is not particularly informative with respect to the types of health problems known or expected to be of greatest concern for Gulf War veterans. Consequently, hospitalization studies have added little to our understanding of health issues related to Gulf War service. It is possible that hospitalization data may be more informative in future years, if diseases of long latency that require hospitalization emerge in sufficient numbers. It will be important, however, that any future studies of hospitalization rates in Gulf War veterans include nonmilitary hospitalizations, and determine disease-specific rates in relation to Gulf War veteran subgroups of interest.

## **Birth Defects and the Health of Gulf War Veterans’ Family Members**

In addition to issues related specifically to the health of veterans, concerns have persisted since the mid 1990s that veterans’ family members, particularly their children born after the war, have had health problems related to some aspect of veterans’ Gulf War service. These issues were reviewed and discussed in detail in the Committee’s 2004 report, including results of studies conducted to assess rates of birth defects in veterans’ children. Since that time, findings from a large VA study that evaluated spouses of Gulf War veterans have been published, providing a first look at whether veterans’ spouses have been affected by excess health problems in the wake of Desert Storm.

**Birth defects in children of Gulf War veterans.** In 1995, a cover story in Life magazine reported on several children, born to Gulf War veterans, who had serious birth defects including Goldenhar Syndrome, a congenital disorder characterized by abnormal development of facial structures.<sup>171</sup> This, along with reports of birth anomalies in a National Guard unit that had served in Desert Storm,<sup>1194</sup> raised public concern and stimulated research to determine whether children born to Gulf War veterans had abnormally high rates of birth defects. As discussed in the Committee’s 2004 report, early studies found little evidence of a problem<sup>284,285,1194</sup> but had important limitations relating both to the samples and sources of data used. Later studies used larger and/or more representative samples of Gulf War veterans, and more comprehensive methods to identify health problems in children under one year. These studies did find that a limited number of adverse birth outcomes, though rare, occurred more commonly in Gulf War veterans than nondeployed veterans.

A study of over 75,000 children born in military hospitals between 1991 and 1993 indicated that infants born to Gulf War veterans were about three times more likely to have Goldenhar syndrome-related diagnoses than infants born to nondeployed veterans.<sup>56</sup> This excess was not statistically significant, however, because the total number of cases in both Gulf War and nondeployed veterans was extremely small. The first indication of a significant excess of birth defects related to Gulf War service came from a 2001 report from VA’s large national survey of Gulf War era veterans. Study results indicated that

children born to male Gulf War veterans after the war had twice the rate of “likely” birth defects as children born to nondeployed era veterans. Children born to female Gulf War veterans had three times the rate of “likely” birth defects.<sup>747</sup> Because these data relied on veterans’ self-reports, investigators conducted medical record reviews to evaluate diagnoses for veteran-reported birth defects where possible. These reviews, conducted for two-thirds of reported birth defects, confirmed veterans’ reports in 88 percent of cases. Resulting adjusted estimates continued to indicate that children of Gulf War veterans had significantly more birth defects than children of era veterans.<sup>744</sup>

A large British survey of Gulf War veterans also reported a significant excess of veteran-reported birth defects among children conceived between 1991 and 1997 by male Gulf War veterans, compared to nondeployed veterans. Birth defects affecting the musculoskeletal and genitourinary systems were most prominent.<sup>361</sup> For the subset of birth defects confirmed by medical records, excess rates were similar but less pronounced. Both the U.S. and U.K. national studies have therefore suggested that birth defect rates were higher in children of Gulf War veterans than children of nondeployed veterans, but fell within the normal range expected in the general population.

Results of an impressive data collection effort by the U.S. Naval Health Research Center also indicated an excess of birth defects in children of Gulf War veterans. This study linked Gulf War military service information to 1989-1993 data from six states with active birth defects surveillance programs.<sup>57</sup> Results indicated that three types of birth defects were significantly more common in children born to Gulf War veterans, conceived after the war. Children of male veterans had higher rates of two types of heart valve defects—tricuspid valve insufficiency and aortic valve stenosis. Male children of female Gulf War veterans were more likely to be born with hypospadias, a defect in the urethral opening. In contrast, there were similar rates of birth defects in children of Gulf War and nondeployed veterans who had been conceived before the war.

Studies have also reported other adverse pregnancy outcomes in relation to Gulf War service. Military hospital data revealed a significant excess of ectopic pregnancies and spontaneous abortions among women Gulf War veterans whose pregnancies were conceived soon after their return from theater.<sup>55</sup> In addition, male Gulf War veterans in both the large U.S. and U.K. Gulf War surveys reported higher rates of miscarriages, but not still births, in pregnancies they had fathered.<sup>361,747</sup> British Gulf War veterans were also reported to have higher rates of infertility than nondeployed veterans.<sup>949</sup>

Few additional studies related to pregnancy outcomes have been reported in the years since the Committee’s 2004 report. A postal survey collected data on pregnancy outcomes between 1991 and 1995 reported by over 4,000 U.S. Gulf War and nondeployed era veterans. No significant excess of low birth weight, ectopic pregnancies, stillbirths, or miscarriages were reported for male or female Gulf War veterans, when analyzed separately.<sup>1761</sup> Similar results were reported from a postal survey of Australian Gulf War veterans.<sup>791</sup> Neither study provided information on birth defects, however.

It is difficult to draw firm conclusions related to birth defects and pregnancy outcomes in Gulf War veterans, due to the diversity and limitations of study results reported to date. The three studies most representative of Gulf War era veterans in the U.S. and U.K. have all indicated significant, but modest, excess rates of birth defects in children of Gulf War veterans. Information on specific types of birth defects has been inconsistent, however,<sup>362</sup> and overall rates are still within the normal range found in the general population.

Some of the remaining important questions concerning birth defects in children of Gulf War veterans might be answerable using existing data. For example, differences in specific types of birth defects reported in different studies might relate to effects of combining all deployed Gulf War veterans into a single group, rather than analyzing birth defects in relation to characteristics of the veteran parents’ deployment or health. Birth defect rates, if related to veterans’ service in the Gulf War, could be most

pronounced in identifiable subgroups of veterans, for example, veterans with multisymptom illness, veterans who were in certain areas of theater, or those exposed to certain hazardous substances. Birth defects might also have been more problematic during certain periods after veterans returned, for example, in pregnancies conceived soon after Desert Storm, as opposed to more recent conceptions.

Identifying patterns and risk factors for birth defects in defined populations can be extremely challenging, particularly for birth defects that are uncommon.<sup>57</sup> In addition to strategies aimed at obtaining additional information from existing data, other research approaches will be needed to determine if birth defects might be associated with Gulf War service generally, or with specific aspects of Gulf War service. This could include case-control studies to evaluate Gulf War service and specific parental exposures as risk factors for extremely rare types of birth defects.<sup>54</sup> A study of this type recently reported that Gulf War service was not a significant risk factor for new cases of Goldenhar Syndrome between 1996 and 2002, although military service in the Army was a modest risk factor.<sup>1764</sup>

Another innovative approach for assembling and evaluating data on birth defects was presented to the Committee by Ms. Betty Mekdeci. Ms. Mekdeci directs Birth Defect Research for Children (BDRC), a private nonprofit organization that maintains special registries of children with birth defects, including children of Gulf War veterans. The analytic approach of the organization involves comparing proportional patterns of birth defects in different populations, in order to raise hypotheses about potential problems in a given group. BDRC has identified a number of problems that appear to disproportionately affect the over 3,000 children of Gulf War veterans in their birth defect registry. This includes 33 children with Goldenhar syndrome—substantially more cases than had been identified in the large military hospital study. BDRC data also indicates that the majority of identified children with Goldenhar Syndrome born to Gulf War veterans were born in 1992 and 1993, with fewer cases born after 1993.<sup>1020</sup>

**Health problems in other family members.** Media reports have also suggested that family members and close contacts of Gulf War veterans have experienced anomalous health problems since veterans returned from Desert Storm.<sup>130,1055,1250</sup> Suggested causes have included transmissible infections or contamination by chemical substances brought home on veterans' uniforms and gear. A 1994 report from the U.S. Senate Banking Committee indicated that many of the 1,200 ill veterans interviewed reported that family members had developed health problems similar to their own.<sup>1688</sup> In response to these reports, VA provided free medical examinations to family members of Gulf War veterans who were enrolled in the Gulf War Registry. No information from VA's Gulf War family registry program has ever been issued, however. Research studies have provided some information on the health of veterans' family members, but have been limited to studies of birth defects among infants and the recent study on veterans' spouses. Research on rates of diagnosed diseases, symptomatic illness, and learning and behavioral disorders among older children of Gulf War veterans is needed in order to determine whether they have been affected by excess health problems, as has been suggested by media and veterans' reports and by the 1994 Senate investigation.

The large national U.S. study of Gulf War veterans included, in Phase III, clinical evaluations of a sample of 539 spouses of Gulf War veterans and 600 spouses of nondeployed Gulf War era veterans. Standardized medical, psychiatric, and neuropsychological examinations were performed ten years after the war at 16 VA medical centers throughout the U.S. Nearly ninety percent of spouses evaluated in the study were women. Health problems self-reported by Gulf veterans' spouses were very similar to those of nondeployed veterans' spouses, except that Gulf veterans' spouses were significantly more likely to report having skin rashes (28%) and hepatitis (1%) than nondeployed spouses. There were no significant differences between the two groups on medical examination, however, except that Gulf veterans' spouses had significantly fewer "group 1" or mild skin anomalies, such as moles, skin tags, and scars. There were no significant differences in rates of fibromyalgia or chronic fatigue syndrome in veterans' spouses. Nor were there differences in diagnosed conditions such as diabetes, lung diseases, or hepatitis. Functional status, as measured by the SF36 PCS, was also nearly identical in the two groups.<sup>394</sup>

The long-anticipated results of this important study thus indicated that, overall, the health of spouses of Gulf War veterans was similar to that of spouses of veterans who did not serve in the Gulf War. These results are reassuring, in some measure. But additional information is needed before the question of Gulf War illness, or other health problems in family members, can be laid to rest. As with Gulf War veterans, the most prominent remaining questions about the health of veterans' family members relate to undiagnosed symptoms and symptom complexes. Specifically, are symptoms or groups of symptoms more common in spouses of Gulf War veterans than nondeployed veterans? Are higher rates of symptoms or diagnosed conditions experienced by spouses of veterans with Gulf War illness? And are any health problems in veterans' spouses associated with characteristics of veterans' service in the Gulf War, such as veterans' locations, experiences, or exposures in theater? The majority of these questions should be answerable using data already collected for the Phase III study.

Phase III of the U.S. national study also included clinical examinations of children of Gulf War and nondeployed era veterans. Results have not yet been reported, but are of great interest and importance. Reported information should include rates of symptoms and symptom complexes in veterans' children, as well as comprehensive information on diagnosed medical and behavioral conditions. Comparisons should also be made between health outcomes in children of veteran subgroups of interest, as described previously. The Committee urges investigators to complete and publish results of the children's evaluations, as well as additional results from the spouses' evaluations, as soon as possible.

## Special Committee and Government Reports on the Health of Gulf War Veterans

In the seventeen years since Desert Storm, numerous government committees and specially-appointed expert panels have been assembled to investigate the health problems affecting Gulf War veterans and/or the government's response to these problems. Relatively few scientific studies were available to inform the conclusions of early panels. Their reports routinely called for more research, specifically epidemiologic studies, to better characterize the health of Gulf War veterans. As described throughout the present report, many studies of the types recommended by previous panels have now been completed, allowing a more comprehensive evaluation of Gulf War-related health issues.

In 1994, the Defense Science Board Task Force on Persian Gulf War Health Effects reported that “veterans in the hundreds have complained of a range of symptoms not yet explained by any clear-cut diagnosis” and indicated that research was needed to determine if these complaints were precipitated by service in Desert Storm.<sup>1595</sup> In the same year, a panel convened at the National Institutes of Health recommended that comprehensive epidemiologic studies be undertaken to better characterize health problems affecting Gulf War veterans and their causes.<sup>1121</sup> The Senate Banking Committee also issued reports in 1994 that detailed their investigations of chemical exposures in the Gulf War and unexplained health problems affecting veterans and their families. This report also called for in-depth epidemiologic investigations to determine the nature and causes of veterans' conditions.<sup>1688</sup>

The Presidential Advisory Committee on Gulf War Veterans' Illnesses, a panel of scientists and veterans appointed by President Clinton, issued reports in 1996 and 1997 that recommended additional research to characterize veterans' health problems. The panel indicated that research was needed on effects of individual and combined chemical exposures, and physical responses to stress.<sup>1227</sup> Similarly, reports issued by the Institute of Medicine (IOM) during this period called for additional research focused on priority questions about the health of Gulf War veterans and emphasized the importance of coordinating data collection efforts between the federal agencies involved in this effort.<sup>675,676</sup>

Perception of Gulf War veterans' unexplained health problems and federal efforts to address them changed markedly when DOD announced, in 1996, that demolition of Iraqi munitions caches at Khamisiyah, Iraq, in March of 1991 had potentially exposed thousands of U.S. troops to low levels of the nerve agents sarin and cyclosarin. The Department of Defense established the Office of the Special Assistant for Gulf War Illnesses (OSAGWI), which initiated an extensive series of investigations, and commissioned the RAND Corporation to provide scientific reports on specific topics of concern. Special House and Senate committees undertook investigations and issued comprehensive reports detailing their findings.<sup>1684,1690</sup> Federal research conferences were held to highlight emerging results from scientific studies on the health of Gulf War veterans. At the direction of Congress, the U.S. General Accounting Office (GAO) investigated diverse Gulf War health and programmatic issues, issuing multiple reports that evaluated the status of the federal response and gaps that had not been adequately addressed. A second committee, the Presidential Special Oversight Board (PSOB) for Department of Defense Investigations of Chemical and Biological Incidents, was appointed by President Clinton in 1998. The PSOB issued its final report in 2000, providing general support for DOD's investigations of exposures during the Gulf War, but again calling for additional scientific research to better characterize the relationship of toxic exposures to Gulf War illness.<sup>1232</sup>

**The Institute of Medicine's *Gulf War and Health* reports.** In 1998, with few conclusive answers to continuing questions about Gulf War illness and the federal response to this problem, Congress directed VA to contract with the National Academy of Sciences (NAS) to review available research in order to assist the Secretary of Veterans Affairs in making decisions about Gulf War-related disability compensation. Public Laws 105-277 and 105-368<sup>1242,1243</sup> directed that this review identify conditions that

affect Gulf War veterans at excess rates and assess the scientific evidence concerning associations between those conditions and a detailed list of Gulf War exposures. In response, VA commissioned the Institute of Medicine (IOM), of the National Academies, to conduct a series of reviews using a methodology previously established to evaluate diseases affecting Vietnam veterans in relation to Agent Orange.<sup>663</sup> To date, the resulting *Gulf War and Health* series has included nine reports, including two updated reports, and provided hundreds of conclusions.<sup>177,679,682-689,1740</sup> The Committee was concerned to find that the IOM reviews were not conducted in accordance with the laws that mandated them. As a result, the *Gulf War and Health* reports have provided little information that is directly relevant to health conditions that affect Gulf War veterans at excess rates, or their association with Gulf War exposures.

The 1998 legislation specifically directed that VA commission reviews that identify both diagnosed and undiagnosed illnesses that affect Gulf War veterans at excess rates and, based on a comprehensive consideration of available research, determine whether there is evidence that those illnesses are associated with Gulf War exposures or Gulf War service. However, the health conditions considered in the IOM *Gulf War and Health* reports have primarily included multiple types of cancer and a number of other diagnosed diseases—conditions for which there are no indications that Gulf War veterans have been affected at excess rates. In contrast, the IOM reports have provided almost no information on conditions that *do* occur at excess rates in Gulf War veterans. That is, the *Gulf War and Health* reports have not provided findings on possible associations between Gulf War illness or ALS and most Gulf War exposures. Nor do they provide findings on conditions like migraines and seizures, which preliminary information suggests may affect Gulf War veterans at excess rates, in relation to Gulf War exposures.

The legislation also directed that determinations be based on scientific evidence provided by both human and animal studies. Most studies that evaluate biological effects of hazardous exposures are done in animals, for ethical reasons. In recent years, a large number of animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown. Although animal research was sometimes described in the IOM reports, findings from animal studies were not considered in drawing conclusions about the evidence that Gulf War exposures were associated with health outcomes. Unlike IOM's earlier Agent Orange reports, the standards used to determine levels of evidence for the *Gulf War and Health* reports were expressly limited to consideration of results from human studies.<sup>137,678,679</sup> The omission of animal studies was especially striking in IOM's updated report on sarin, which had been requested by the Secretary of Veterans Affairs in 2003 specifically because of new research in animals that demonstrated adverse effects of low-level sarin exposure.<sup>683,1641</sup>

A very limited number of exposure-disease associations have been identified in the IOM reviews. For example, in Volume 3 of the series, the IOM panel concluded that there is sufficient evidence to indicate that lung cancer is associated with petroleum combustion products.<sup>684</sup> Findings of this type might potentially be relevant to the health of Gulf War veterans in future years. But there has been no indication that lung cancer, or the vast majority of conditions considered in the IOM *Gulf War and Health* reports, have affected Gulf War veterans at excess rates. The hundreds of findings provided in the IOM reports are largely inconclusive, indicating that there is insufficient evidence to determine if the diseases considered are associated with the exposures considered, based on the types of studies considered.

The specific information included in the *Gulf War and Health* reports is also problematic, in that it appears to reflect a process of reporting selected results from subgroups of studies, rather than integrating and analyzing results from all available research. This is a pervasive problem, but several examples are illustrative. A very prominent example relates to the limited or complete lack of consideration, in all *Gulf War and Health* reports, of results from the many epidemiologic studies that have assessed associations between Gulf War exposures and Gulf War multisymptom illness. Another straightforward example comes from Volume 4, which reported the rate of multisymptom illness in Gulf War veterans from just one study, as opposed to the seven studies identified by the present report. The one Gulf War illness prevalence estimate provided was atypical, and substantially lower than all other studies.<sup>686</sup> An additional

example relates to a highly publicized finding that, although Gulf War veterans have multiple excess symptoms, there is no unique Gulf War syndrome.<sup>232,686</sup> This conclusion was based solely on several studies that had unsuccessfully attempted to identify a unique syndrome using factor analysis and a related statistical technique, as previously described. The finding did not consider basic questions about whether the statistical techniques were capable of identifying syndromes—unique or otherwise. Unfortunately, this conclusion was widely misinterpreted in media reports to indicate that there was no widespread problem associated with multisymptom illness in Gulf War veterans.

In short, IOM's *Gulf War and Health* series of reports have been skewed and limited by a restrictive approach to the scientific tasks mandated by Congress, an approach directed by VA in commissioning the reports. These limitations are most notably reflected in the selective types of information reviewed and the lack of in-depth analysis of the research literature and scientific questions associated with the health of Gulf War veterans. There is a fundamental disconnect between the Congressional directive to VA and VA's charge to IOM for reviewing evidence on Gulf War exposures and their association with illnesses affecting Gulf War veterans. The reports have particularly fallen short in advancing understanding of associations between Gulf War exposures and Gulf War illness, the most prominent health issue affecting Gulf War veterans.

## Recommendations

Despite the brief duration and successful execution of the 1990-1991 Gulf War, 25-32 percent of Gulf War veterans developed the chronic multisymptom condition known as Gulf War illness as a consequence of their Gulf War service. Longitudinal studies indicate that few veterans with Gulf War illness have recovered or significantly improved with time. The Committee gives highest priority to research focused on identifying effective treatments for Gulf War illness. This research should include:

- Studies that identify and systematically evaluate the effectiveness of currently available treatments used for Gulf War illness or conditions with similarities to Gulf War illness. Preliminary research should include pilot trials and/or observational studies capable of identifying promising treatments suitable for evaluation in larger clinical trials.
- Research to identify specific pathophysiological mechanisms underlying Gulf War illness that are potentially amenable to treatment interventions.
- Research to evaluate novel therapies based on scientific findings as they emerge.

The Committee considers the information provided by VA's national longitudinal study of Gulf War veterans and continued monitoring of the health of Gulf War veterans over time to be extremely important and recommends that VA:

- Make results from the national longitudinal study of Gulf War veterans publicly available at the earliest possible time, including comprehensive findings related to multisymptom illness, treatments and practices used by veterans to address their symptoms, and rates of medical diagnoses. Results should include outcomes assessed according to the guidelines for epidemiologic research provided below.
- Continue to monitor health and disease outcomes among veterans assessed in the National Survey of Gulf War Era Veterans and Their Families, conducting longitudinal surveys and appropriate clinical follow-up studies at five year intervals.

Although it is the most prevalent health problem affecting Gulf War veterans, Gulf War illness is just one of a number of important Gulf War health issues. To provide needed information on other health issues of concern for Gulf War veterans, the Committee recommends the following research:

- Epidemiologic research to identify rates of diagnosed neurological diseases (including multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, and brain cancers), as well as central nervous system abnormalities that are difficult to precisely diagnose, in Gulf War veterans and appropriate comparison groups.
- Completion of current research comparing cancer rates in Gulf War and nondeployed era veterans, and repeated assessment of cancer rates in Gulf War era veterans at regular intervals.
- Provide current information on overall and cause-specific mortality rates in Gulf War veterans, and update this information, at minimum, at five year intervals. This should include information on mortality in subgroups of Gulf War veterans identified by deployment locations, branch of service, and exposures reported in the National Survey of Gulf War-era Veterans and Their Families.

- Further evaluate indications of possible increased risk of specific types of birth defects, and other health problems in children of Gulf War veterans, using innovative study designs.
- That VA make available comprehensive information on family members of Gulf War veterans from the national study of Gulf War era veterans and family members. This should include information on diagnosed conditions, multisymptom illness, behavioral problems, and birth defects. Health parameters should also be assessed in subgroups of interest, such as family members of veterans with/without Gulf War illness, and subgroups defined by Gulf War exposures and other characteristics of veterans' wartime service.

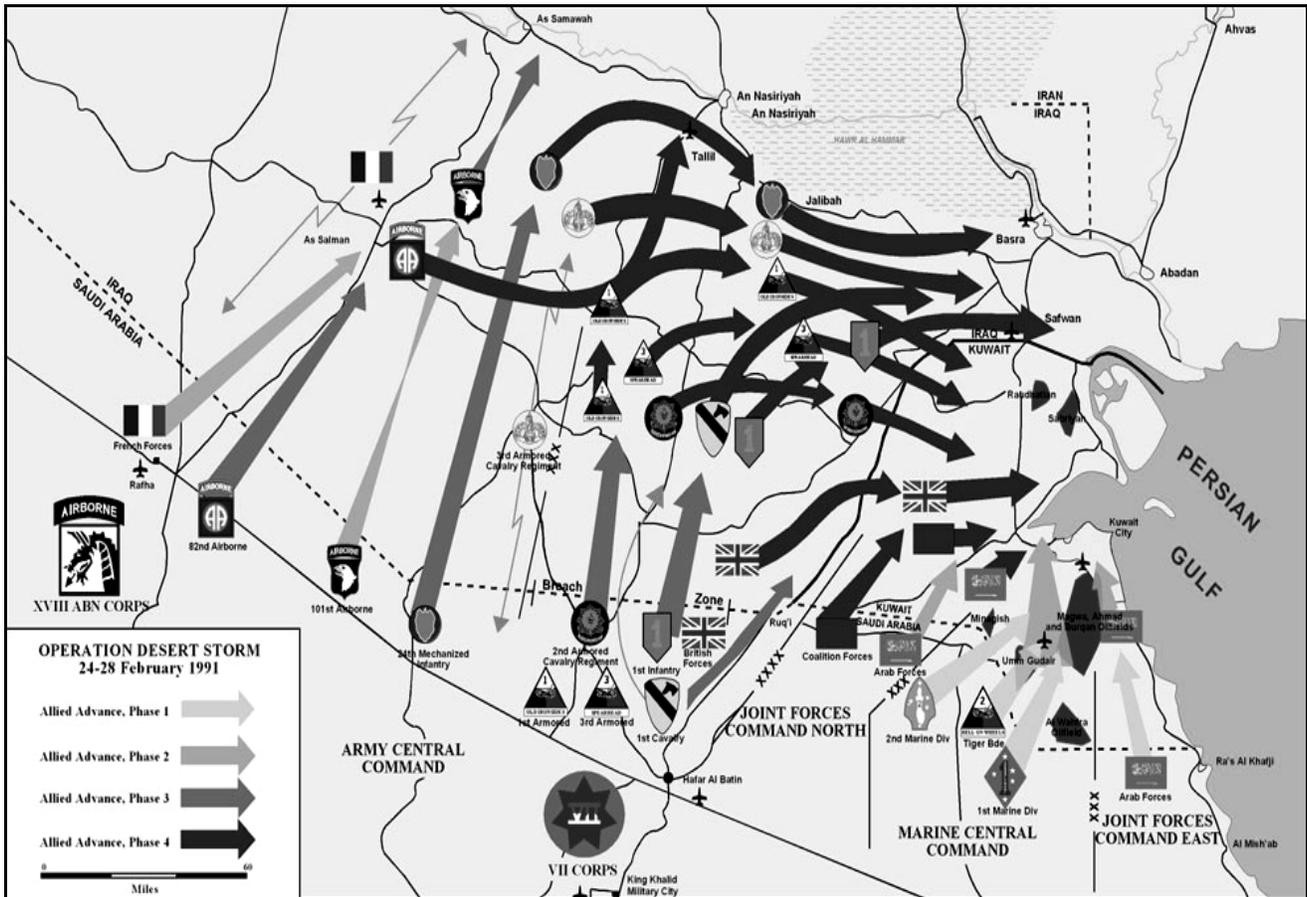
Because of shortcomings and limitations in many epidemiologic studies of Gulf War veterans, the Committee recommends the following principles for collecting and analyzing data on Gulf War illness and the health of Gulf War veterans in ongoing and future studies and, where indicated, for reanalyzing data in studies already completed.

- Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups. Pending more widespread acceptance of an established case definition, preferred case definitions are those that most clearly distinguish the pattern of symptoms in Gulf War veterans from those in nondeployed era veterans, such as the Kansas Gulf War illness case definition.
- In addition to general comparisons between Gulf War and nondeployed veterans, Gulf War research studies should analyze results in relation to Gulf War veteran subgroups of interest, including ill vs. well veterans and subgroups defined according to veterans' locations in theater, exposures, and other military and deployment characteristics potentially relevant to the outcomes evaluated.
- Associations between deployment-related exposures and health outcomes in Gulf War veterans should be evaluated using analytic methods that appropriately control for the effects of confounding introduced by multiple exposures during deployment.

The Department of Veterans Affairs has not adhered to requirements set forth by Congress in commissioning the *Gulf War and Health* series of reports produced by the Institute of Medicine. As a result, these reports have not addressed fundamental questions regarding Gulf War-related health conditions and their relation to Gulf War exposures. The Committee therefore recommends:

- That VA, in commissioning reports mandated by Congress in PL 105-277 and 105-368, substantially change the approach designated for reviewing scientific information and preparing the reports. As directed by Congress, these reports should address both diagnosed and undiagnosed illnesses affecting Gulf War veterans. Conclusions should be based on findings from the full range of Gulf War epidemiologic studies, animal studies, and other research that provides information on effects of Gulf War-related exposures.
- That VA contract with the Institute of Medicine to redo previously completed Gulf War and Health reports to adhere to requirements set forth by Congress.
- That responsibility for contracting reports mandated by PL 105-277 and PL 105-368 be reassigned from VA's Office of Public Health and Environmental Hazards to another office within VA, to be designated by the Secretary.

## Operation Desert Storm: Summary of the Offensive in the Four Day Ground War



U.S. Department of Defense

## 2 | What Caused Gulf War Illness? Effects of Gulf War Experiences and Exposures

In addition to the many physical and psychological challenges that come with serving in a war zone, military personnel in the 1990-1991 Gulf War encountered a unique mix of exposures during deployment. These included a number of substances used for the first time by the military on a widespread basis—pyridostigmine bromide pills given to protect troops from the effects of nerve agents, depleted uranium munitions, and anthrax and botulinum toxoid vaccines. The oil and smoke that spewed for months from hundreds of burning oil wells presented another exposure hazard not previously encountered in a war zone. Military personnel also had to cope with teeming and biting insects, especially in the warmer months, that required persistent environmental pest control measures and ample use of personal pesticides. In some areas, troops frequently donned their chemical protective gear as chemical alarms sounded again and again. Personnel were usually told the alarms were false and given the all clear, and some units eventually turned off the alarms because they were thought to be malfunctioning. Years later, the Department of Defense verified that chemical agents had been released in southeastern Iraq when U.S. troops destroyed Iraqi weapons stored in a large compound, and launched multiple investigations into other reported chemical incidents.

As an increasing number of reports of a mysterious Gulf War syndrome emerged in the months and years after the war, many believed that veterans were suffering from effects of hazardous exposures they had encountered during their deployment. Government officials and special committee reports maintained that there was little evidence that this was the case, and suggested that veterans' symptoms could be due to the stress of deployment. In the first years after the war, scientific committees and government panels attempted to investigate veterans' unexplained health problems, but there were few facts to go on. Little documentation was available about specific types and levels of exposures in theater, and relatively little research had been done to evaluate veterans' health problems.

Now, 17 years after the war, the situation is markedly different. Although there are relatively few data from real time exposure measurements taken during the war, federal agencies have worked to provide information on likely exposure patterns and levels using a variety of wide-ranging and innovative efforts. For example, weather and satellite information has been used to determine daily patterns of wind dispersion of smoke from oil well fires and chemical plumes resulting from weapons demolitions. Sophisticated simulations have measured levels of depleted uranium that soldiers might have inhaled or gotten on their skin if their vehicles had mistakenly been hit by friendly fire rounds containing depleted uranium. Attempts have been made to gather immunization logs from units that administered anthrax vaccine to their troops, but did not record the vaccine in soldiers' individual shot records. As a result of these efforts, a substantial amount of information is now available that provides important insights into the types, levels, and patterns of exposures likely encountered by Gulf War military personnel during deployment.

There is also an extensive body of epidemiologic research that makes it possible to identify patterns of health problems in Gulf War veterans and to evaluate associations between veterans' health and their deployment experiences across a broad spectrum of studies. In addition, a large number of toxicological studies have been conducted in recent years that provide insights concerning biological effects of exposures associated with the Gulf War. These have yielded extensive information on effects of exposures that had previously not been known, and effects of combinations of exposures that had never before been looked at.

The Committee used a standardized approach for evaluating available evidence related to psychological stressors in theater and each of the other hazards of possible concern. Three major categories of evidence were considered. First, the Committee reviewed what was known about the extent and patterns of veterans' exposure to each potential hazard. Second, the Committee reviewed the broad spectrum of available scientific research to determine what was known, in general, about health effects of each exposure. This included consideration of effects of exposures identified in epidemiologic and clinical studies of human populations, and laboratory studies conducted in animal models. Third, the Committee reviewed, in detail, results from the many studies of Gulf War veterans that assessed associations between symptom complexes and the exposure in question.

The Committee found that epidemiologic research on Gulf War veterans, assessed across diverse study designs and populations, provided clearer and more consistent findings than had previously been assumed. When combined with what has been learned about exposure patterns in theater and findings from toxicological research, a coherent picture emerged about the most likely causes of Gulf War illness.

## Psychological Stressors and the Health of Gulf War Veterans

Major BK, a career Army pilot who had passed 15 flight physicals in the 11 years prior to deployment to the Gulf War began to feel increasingly ill in April 1991 but dismissed the symptoms as related to the harsh desert environment. On May 8 he reported 'violent nausea, vomiting, diarrhea attack.' On May 28, now back in Germany, he was admitted to a military hospital with 'cardiac arrhythmias, severely bleeding gums, cough with sputum production, shortness of breath, severe fatigue, diarrhea, hair loss, skin rashes/lesions, and abdominal discomfort.' Military doctors diagnosed Major BK with 'post traumatic stress.' With severe brain, nerve, heart and gastrointestinal problems but still being diagnosed with 'somatoform disorder' he was given a discharge from the Army.

--1997 Congressional report on Gulf War Army pilot<sup>1684</sup>

Since soon after the Gulf War, when reports of poorly understood symptoms and conditions in veterans first became widely known, the most prominent controversy to emerge was whether these illnesses were the result of psychological factors or hazardous exposures during deployment. In those early years, opinion camps formed on both sides of the issue. Both sides relied to a large extent on assumptions and conjecture to support their views, with little scientific data to settle the debate. This is no longer the case, 17 years after Desert Storm. Hundreds of studies have explored population patterns of veterans' health problems, and provided important insights concerning their biological and psychological correlates. Commentators have pointed out that it is somewhat artificial, perhaps even harmful, to label Gulf War illness as being one or the other—psychiatric or medical.<sup>404,405,654</sup> This is an important consideration in relation to any health problem, including Gulf War illness, with all that has been learned in recent decades about biological aspects of psychiatric illness and psychological aspects of medical conditions.<sup>23</sup> But the question of the essential nature of Gulf War illness remains an important one for veterans, who want to know why they are ill, for clinicians and researchers working to identify useful treatments, and for policy makers tasked with preventing similar problems in the future.

The “mental or physical” quandary has played out both on a national level and in the lives of individual veterans seeking care for Gulf War illness whose healthcare providers, lacking objective information from diagnostic tests, find their condition difficult to diagnose and treat. A survey of clinicians at two VA medical centers in the Pacific Northwest found that mental healthcare providers were more likely to consider Gulf War illness to have resulted from a chemical or infectious exposure, whereas general internal medicine clinicians more often considered Gulf War illness a “mental disorder” attributable to psychological factors.<sup>1282</sup> Consequently, mental health clinicians were more likely to support biological treatments for veterans' conditions, and medical providers more often favored psychological interventions. This supports the general impression conveyed by veterans that clinicians, unable to adequately diagnose or treat Gulf War illness using tools from their own armamentaria, are sometimes inclined to attribute symptoms and conditions to realms outside their own areas of expertise. This scenario leaves both veterans and their providers with more questions than answers, and provides no clear basis for providing rational treatment options.

Similarly, on the national level in the 1990s, little scientific information was available to shed light on the nature and causes of Gulf War illness. When no single cause or biological explanation was readily apparent, those who developed research programs and healthcare policy for ill Gulf War veterans largely focused on psychiatric issues, likely assuming that Gulf War illness was the result of deployment stress. In the intervening years, however, numerous scientific studies have been conducted that, in aggregate, provide insights regarding the nature and causes of Gulf War illness. Most prominently, this research consistently indicates that Gulf War illness is not the result of psychological trauma or stressors during the Gulf War. This information can be used to focus Gulf War illness-related policy and research questions more precisely on the causes and biological mechanisms underlying Gulf War illness.

The word “stress” is used in a variety of contexts and carries diverse meanings in both scientific and lay usage. In its review of scientific studies and other available information concerning the health of Gulf War veterans, the Committee thought it important to underscore the distinction between (1) psychological *stressors*, that is, stressful experiences that occurred during deployment, versus (2) stress-related disorders, that is, psychiatric diagnoses or other persistent health problems that may result from trauma or other psychological stressors during deployment. This distinction between the concept of “stress” as a challenging experience and “stress” as a health outcome is often not apparent to casual observers. It can be illustrated by the observation that “stressful” experiences (more precisely, psychological stressors) might lead to the development of psychiatric conditions such as posttraumatic stress disorder (PTSD), so would be considered the “cause” for those conditions, whereas PTSD or other psychiatric conditions would be considered the “result” of stressors. More simply put, “stress” may cause PTSD but it is not the same thing as PTSD.

The Committee reviewed research findings related to both psychological stressors and psychiatric disorders in Gulf War veterans. Evidence concerning the degree to which psychological stressors in theater are associated with Gulf War illness was reviewed in the same way as evidence related to other deployment-related exposures. In addition, research on psychiatric disorders in Gulf War veterans was reviewed in the same way as other health outcomes such as Gulf War illness, asthma, or cancer.

The central question in the mental-versus-physical Gulf War illness debate is “Why are veterans ill?” In reviewing the extensive amount of research conducted to address this question, the Committee has found that, of the many complex issues associated with understanding Gulf War illness, the evidence that informs the “mental or physical” debate is the most voluminous, the most consistent, and the most straightforward to interpret.

SSG CK reported: ‘While still in the Gulf I began experiencing symptoms that continue to this day. I had difficulty remembering significant events that happened days earlier... my knees and shoulders were especially painful and fatigue stayed with me constantly.’ After the war, his symptoms worsened and included intestinal problems and headaches. He sought treatment in 1992 from VA doctors who—without any physical exam—referred him to the mental health clinic where he was diagnosed ‘PTSD’. ‘I reported blinding headaches with only offers of aspirin, I reported memory loss...dismissed as stress.’

--1997 Congressional report on Gulf War Army Reservist<sup>1684</sup>

## **Traumatic Experiences and Psychological Stressors in the Gulf War**

There is considerable information concerning the types of psychological stressors experienced by Gulf War veterans during the war. It is one of the few areas for which “exposure” data were collected during deployment. In 1990 and 1991, a team from Walter Reed Army Institute of Research (WRAIR) conducted interviews and surveys of personnel in combat units at different periods during deployment to assess sources of psychological stress and the proportion of troops affected.<sup>966</sup> Both qualitative and quantitative data were collected from thousands of individuals in multiple precombat and post combat interviews and surveys. Overall, investigators found that the morale of troops was good, and commitment to the mission was high. In the early months of deployment, the most common stressors related to disruption of individuals’ normal lives at home and adaptation to their living circumstances in theater. The most frequently-cited stressors during this period were “not having the opposite sex around” (69%), flies (54%), lack of family contact (46%), and lack of privacy (43%).<sup>966</sup>

Stressors reported by members of these combat units during the combat period were more typical of those expected in war. The most frequently reported stressors during that time were seeing an enemy soldier killed or wounded (60%), being attacked by enemy fire (43%), and having a buddy wounded in action (30%). Having a buddy killed in action was considered the most extreme stressor for those who

experienced it (9%). Data also indicated that personnel experienced much lower levels of combat-related stress than they had anticipated prior to combat, owing largely to the short duration of the ground war and the one-sided nature of the fighting. In fact, during interviews many personnel were said to have expressed sympathy for their Iraqi prisoners, whose war fighting efforts had been so “utterly outclassed” by the Americans.<sup>966</sup> Unfortunately, these data did not allow assessment of whether stressors in theater were associated with subsequent development of chronic multisymptom illness. But they did provide real time data indicating that traumatic combat exposure put military personnel at increased risk for developing PTSD.

Many epidemiologic studies have provided retrospective assessments of veteran-reported stressors during deployment, ranging from severe trauma (e.g., witnessing deaths, sexual assault) to experiences that, while stressful, would not ordinarily be considered traumatic (e.g., having a family problem during deployment, uncertainty about the use of chemical weapons). Representative rates of veteran-reported stressful experiences during deployment are provided in Table 1. Overall, about 30 percent of U.S. and U.K. veterans report they had participated in combat. A higher proportion report hearing chemical alarms sound or being in the vicinity of a SCUD missile, but only about 10 percent thought they had been attacked by chemical weapons. Additional studies indicate that, overall, psychological stressors were reported at lower rates in Navy and Air Force veterans than in samples that included all branches of service.<sup>241,1124</sup>

**Table 1. Psychological Stressors Reported by U.S. and U.K. Gulf War Veterans**

	<i>U.S. National Survey</i> <sup>751</sup>	<i>U.K. National Survey</i> <sup>698</sup>
Heard chemical alarms	66 %	71 %
SCUD missile explosion within 1 mile	43 %	32 %
Participated in combat	27 %	32 %
Witnessed death	26 %	19 %
Experienced a chemical/nerve gas attack	10 %	9 %
Sexually assaulted	1 %	

### Health Effects of Psychological Stressors

It has long been observed that psychologically stressful experiences, most prominently those associated with acute trauma or significant sustained distress, can lead to different types of health problems—psychiatric illness, psychological symptoms, and biological changes that affect different bodily systems.<sup>23,247,801</sup> A 2000 report prepared by the RAND National Defense Research Institute for the Department of Defense provided an excellent summary of the extensive research literature in this area, with special attention to information available on Gulf War veterans at that time.<sup>969</sup> Among other findings, the report summarizes information indicating that stress-related symptoms and psychiatric difficulties typically appear soon after the traumatic experience but can take longer, sometimes decades, to emerge. Psychological problems related to time-limited stressful events are generally short-lived, typically disappearing within six to 18 months, but can last longer in some individuals. The RAND report concluded that a limited amount of evidence suggested a link between stressful exposures in theater and PTSD in Gulf War veterans, with less evidence regarding other psychiatric disorders. The report also indicated that few studies had directly assessed associations between stressful experiences in the Gulf

War and the subsequent development of chronic somatic health problems. As a result, the report concluded that “it is inappropriate to rely upon stress exposure as a default explanation for the myriad health problems reported by Gulf War veterans” and that it is “equally inappropriate to assume that stress played no role.”<sup>969</sup>

**Animal studies evaluating the interaction of stress with Gulf War exposures.** In the past decade, concerns have been raised about the potential for psychological and/or physiological stressors to have interacted with, and perhaps exacerbated, effects of chemical exposures encountered by Gulf War veterans. Attention was drawn to this issue over a decade ago by research indicating that stress and adrenergic stimulation increased the biological effects of pyridostigmine bromide (PB) in mice.<sup>227,460</sup> Ethical considerations prohibit studies of the effects of most toxic exposures in humans, so nearly all research on interactions between stress and Gulf War-related exposures has been done in animal models. Results of these studies should be applied to the human situation with caution, however, due to limitations in the comparability of war-related human stressors to stressors used in animal research. In humans, for example, stressful experiences can be predominantly of a psychological (e.g., trauma, emotional challenge, mental stress) or physical nature (e.g. physical exertion, extreme temperatures) but in animals this distinction is often not possible.

Stress and the effects of pyridostigmine bromide. In 1996, a study conducted by Israeli investigators reported that mice subjected to an intense stressor, forced swimming, had a strikingly enhanced brain response to PB compared to unstressed mice.<sup>460</sup> Under normal conditions it was generally believed that PB does not cross the blood brain barrier and very high doses are required to affect a marked decrease in brain acetylcholinesterase (AChE) activity. But this study reported that in stressed mice, just one one hundredth the dose of PB was required to cause a 50 percent reduction in brain AChE activity, compared to unstressed mice. Researchers suggested that stressful conditions may have allowed PB to cross the blood brain barrier.

This unexpected finding raised a great deal of attention and concern, prompting additional research related to the potential for stress to alter effects of PB and other Gulf War-related exposures. The largest number of studies were done to evaluate the hypothesis raised by the Israeli study, that is, that stress enhances central nervous system effects of PB. Multiple studies failed to support the Israeli study, finding that stressors of various types and intensities did not cause PB to cross the blood brain barrier or reduce AChE activity in the brain.<sup>519,857,1394,1414,1444,1539</sup>

Other studies that addressed different questions related to specific chemical or regional responses, have found that stress may interact with PB in causing central nervous system effects. Studies from the East Orange, New Jersey, VAMC found that stressed rats treated with PB had significantly reduced levels of AChE activity in the basal forebrain and striatum but not in other brain regions.<sup>115,116</sup> A 2005 study from France reported that a combination of stressors led to elevated levels of circulating glucocorticoids and associated increases in serotonin (5-HT) in several regions of the brain. Concurrent administration of PB at dosages similar to those used in the Gulf War resulted in increased levels of the serotonin metabolite 5-HIAA in additional brain regions, as well as increased dopamine levels in the striatum/hippocampus.<sup>1528</sup>

In addition, researchers from Wright State University School of Medicine demonstrated a significant interactive effect between PB and stress on autonomic function, as reflected in enhanced heart rate variability and baroreflex sensitivity.<sup>714</sup> The combination of low-dose PB and exercise stress has also been shown to decrease plasma levels of butyrylcholinesterase (BChE) and muscle AChE levels, and to increase indicators of oxidative stress in peripheral muscle.<sup>658,703,1442</sup>

Interaction of stress with multiple combined exposures. Studies evaluating the effects of stress in combination with two or more Gulf War-related exposures of potential concern, including PB, have consistently found this combination to have greater effects than either stress or chemicals alone.

Neurotoxicologists at Duke University have conducted extensive research evaluating interactive effects of Gulf War-related exposures using protocols designed to parallel levels actually encountered by Gulf War veterans in theater, in the presence and absence of stress. This has included studies of the combined effects of low-level exposures to PB, permethrin, and DEET together—both with and without concurrent exposure to a moderate level of restraint stress. Results indicated that combined exposure to PB, DEET, and permethrin, in combination with stress, produced disruption of the blood brain barrier and neuronal cell death in four specific brain regions—the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus.<sup>6</sup> The combination of chemicals plus stress also produced reduced AChE activity in the forebrain. These effects were not observed with either stress or low-dose chemicals alone. A second report indicated that, in areas of the brain where there was no apparent disruption of the blood brain barrier, AChE activity was decreased in the midbrain, brainstem, and cerebellum. Significant neuronal cell death and evidence of glial cell activation were also observed in the cerebral cortex and hippocampus. Again, these changes were observed only following combined exposure to stress and low-level exposure to the three chemicals, and not as a result of stress or chemicals alone.<sup>3</sup>

Studies from Southern Illinois University have reported that exercise stress, when combined with both PB and low-dose sarin, reduced levels of neurotoxic esterase (NTE), an enzyme that metabolizes neurotoxic chemicals) in the cerebral cortex, spinal cord, and sciatic nerve. This combination was also found to increase lipid peroxidation and reduce AChE activity in skeletal muscle.<sup>658</sup>

A limited number of studies have evaluated the potential for other types of Gulf War exposures to interact with stress-related changes in animal models. A recent study from Great Britain demonstrated that differing combinations of vaccines and PB did not produce peripheral indicators of an enhanced stress response or impaired immune function.<sup>632</sup> A study from the Boston University School of Medicine, however, suggested that if PB and vaccines do interact with stress, the effects may more likely be observed in the brain than in peripheral immune parameters. The Boston study found that production of stress-activated kinases in the mouse brain was significantly enhanced and prolonged by immunization with KLH, a vaccine analog, and that these effects were further enhanced by PB.<sup>1752</sup> Researchers concluded that the combined effects of stress, vaccines, and PB may produce neuroinflammatory damage in the brain.

There is little indication that stress potentiates effects of depleted uranium or exposure to organophosphate pesticides.<sup>727</sup> Multiple studies have reported that stress does not enhance effects of depleted uranium (DU) on the brain or on reproduction.<sup>35,97,98,125,906,1343</sup> On the contrary, research conducted at the University of Florida suggested that stress may increase clearance of DU from the brain, thereby ameliorating its effects.<sup>97-99</sup> Studies have also demonstrated no, or only limited interactive effects between various stressors and organophosphate insecticides in animal models.<sup>576,728,1244,1393</sup>

**Human studies: Stress and Gulf War-related chemical exposures.** Several studies have evaluated effects of stress, in combination with relatively low doses of Gulf War-related exposures, in humans. Reports on American and Israeli soldiers who used PB during the Gulf War indicated that side effects were greater than had been predicted by clinical studies, and hypothesized that taking PB during wartime, under stressful conditions, may enhance PB's potential to cause biological side effects.<sup>781,1396</sup> Clinical studies involving healthy subjects had not found heat stress or physical exercise to exacerbate symptoms or significantly alter physiological or cognitive performance in relation to PB.<sup>53,411,1386</sup> More recently, a clinical trial demonstrated that one hour stress sessions that included both exercise and mental stressors had minimal or no effects on physical and cognitive performance following exposure to permethrin, DEET, and PB. Chemical exposures occurred over a 24 hour period, at dosages similar to those currently directed by military policy.<sup>1323</sup> Plasma PB levels were found to be significantly elevated during and immediately after stress sessions, but were comparable to unstressed subjects within three hours.

Taken together, human and animal studies indicate that extreme and/or sustained stressful experiences can precipitate short term somatic health problems as well as sustained psychiatric illness. There is no evidence indicating whether more moderate stressors, of limited duration, is associated with the development of the types of symptom complexes associated with Gulf War illness, particularly symptoms that persist for an extended period—17 years—after cessation of the stressful experience. Questions also remain concerning the potential for stressors in theater to have altered or amplified the biological effects of some chemical exposures encountered in the Gulf War. Early suggestions that stress allows PB to enter the brain through a general disruption of the blood brain barrier have not been supported, but more recent studies have suggested that stress may exacerbate effects of PB in more delineated ways, for example, enhancing its effects on autonomic regulation. Animal studies have also demonstrated biological effects resulting from stress in conjunction with combined chemical exposures—effects that exceed those of chemicals or stress alone. Human studies that have evaluated effects of stress in relation to low-level exposure to PB, permethrin, and DEET for short periods have found no significant effects on cognitive or physical performance.

The Gulf War involved a complex mix of extreme and less extreme stressors of relatively short duration, in combination with diverse chemical exposures in a unique environment. Neither general studies from human populations nor animal studies provide evidence that can specifically determine whether psychological stressors experienced during the Gulf War are responsible for the types of chronic symptom complexes that constitute Gulf War illness. As with other wartime exposures, it is important not to assume that because psychological stressors *might* have adverse health effects that they actually did so in a large proportion of Gulf War veterans and are responsible for Gulf War illness. A more complete understanding of the connection between Gulf War-related stressors and the health of Gulf War veterans requires consideration of the many studies of Gulf War veterans that have specifically evaluated this relationship.

## **Research on the Health of Gulf War Veterans in Relation to Psychological Stressors**

**Symptoms, symptom complexes, and Gulf War multisymptom illness.** As detailed in Appendix A-8, a large number of epidemiologic studies have provided information on many different types of psychological stressors that Gulf War veterans experienced in theater, and the degree to which those stressors are associated with chronic symptoms and multisymptom illness. Similar to other exposure-illness assessments, many of these studies provided results only from preliminary analyses, that is, analyses that did not consider confounding effects of other exposures during deployment. The most valid and informative results were provided by studies that determined independent associations between stressful experiences and health outcomes, while controlling for effects of other deployment-related exposures.

As shown in Appendix A-8, results of preliminary analyses frequently indicated that psychologically stressful experiences in theater were associated with increased rates of chronic symptomatic illness. In these analyses, symptomatic illness was associated with a variety of extreme and less extreme psychological stressors, for example, being sexually assaulted during deployment,<sup>752</sup> seeing someone killed or dismembered,<sup>527,1264</sup> coming under fire<sup>1124,1264,1507,1698</sup> and reports of family problems back home.<sup>1124</sup>

In contrast, when analyses controlled for effects of other exposures during deployment, studies consistently found that psychological stressors were *not* significantly associated with Gulf War illness. Diverse stress-related variables assessed in six different Gulf War veteran populations, were consistently not identified as significant risk factors for Gulf War illness, when effects of other exposures were considered. This included extreme stressors, such as being in combat or seeing dead bodies,<sup>241,527,1124</sup>

**Table 2. Participation in Combat as a Risk Factor for Chronic Symptoms and Multisymptom illness in Gulf War Veterans**

<i>Study</i>	<i>Sample</i>	<i>Combat Association Evaluated</i>	<i>Unadjusted Association</i>	<i>Association Adjusted For Other Exposures</i>
Cherry <sup>241</sup> 2001	7,971 U.K. Gulf War vets	Correlation of combat with seven symptom domains, overall symptom severity, peripheral neuropathy, widespread pain	Not reported	None significant
Gray <sup>527</sup> 2002	3,831 Navy Seabees	Combat as a risk factor for study-defined Gulf War illness	OR = 2.6*	Not significant
Nisenbaum <sup>1124</sup> 2000	1,002 Air Force vets	Combat duty in relation to severe or mild-moderate CMI	Not significant	Not significant
		Coming under attack in relation to severe or mild-moderate CMI	OR (severe) = 2.4* OR (mild-moderate) = 1.1	OR (severe) = 1.2 OR (mild-moderate) = 0.7

Abbreviations: OR = odds ratio, CMI = chronic multisymptom illness<sup>464</sup>  
\* = statistically significant

and less acute stressors, such as having family problems during deployment.<sup>1124</sup> Only one stress related variable in one study was significantly associated with Gulf War illness after controlling for effects of other wartime exposures. The large study of Navy Seabees used two different modeling approaches to assess associations between stressors and Gulf War illness. “Seeing someone killed” was reported to be modestly associated with Gulf War illness (OR = 1.6) in one model but not the other.<sup>527</sup>

Although not listed as a “psychological stressor” in Appendix A-8, several studies indicated that variables related to chemical weapons exposures were significantly associated with multisymptom illness, after controlling for effects of other exposures.<sup>564,1124,1239</sup> As will be described in detail in a later section, chemical alarms and other indicators of possible chemical weapons exposures were fairly common during the Gulf War. There are many uncertainties, however, related to who was actually exposed to low levels of chemical agents and where. Veterans’ ability to know whether or not they had been exposed to chemical weapons is especially problematic. Reported associations between Gulf War illness and veteran-reported chemical weapons exposures might reflect effects of psychological stress, chemical exposure, both, or neither. It is not possible to disentangle psychological effects related to concern about chemical exposures from physical effects that might relate to actual exposure. Associations between Gulf War illness and variables associated with chemical weapons exposures are therefore summarized separately, in Appendix A-2, and considered in a later section of the report.

A consistent, but somewhat unexpected, finding is that serving in combat is not identified as a significant risk factor for Gulf War illness, when effects of deployment exposures are considered. As shown in Table 2, Gulf War veterans who report being in combat or coming under enemy attack during deployment did not have elevated rates of chronic symptoms or multisymptom illness in any of the studies that adjusted for effects of multiple exposures in theater.<sup>241,527,1124</sup> Further, many studies that reported unadjusted results, which typically over-identified exposure risk, also found no link between serving in combat and multisymptom illness.<sup>161,564,697,752,1124,1802</sup> The consistency of this finding across multiple studies of different veteran populations, particularly studies that controlled for confounding by multiple exposures, provides strong evidence that serving in combat during the Gulf War was not a cause of Gulf War illness. This is an important observation, since interviews with Gulf War veterans during deployment and after their return from theater indicate that combat-related events were their most stressful experiences.<sup>966,969</sup>

The lack of association between combat and multisymptom illness parallels general findings from the broader range of studies of psychological stressors in theater. Taken together, these studies consistently indicate that psychological stressors during deployment were not risk factors for Gulf War illness. Possible exceptions may include veterans who were sexually assaulted during deployment. This severe stressor was associated with a high risk (OR = 8.3) for a unique symptom complex in one study<sup>750</sup> but was not evaluated in adjusted analyses. In addition, one study reported that seeing someone killed in theater was mildly associated with Gulf War illness using one modeling method, but not another.<sup>527</sup>

Results from these studies also provide an excellent example of how epidemiologic studies that do not adequately account for effects of multiple exposures during deployment routinely misidentify risk factors for Gulf War illness. This is well illustrated by the apparent association of Gulf War illness with several psychological stressors in studies that did not consider effects of other exposures, as opposed to consistent findings that psychological stressors are *not* risk factors for Gulf War illness in studies that did adjust for effects of other exposures. As previously described, studies have consistently found that Gulf War-related exposures are highly correlated with one another and cluster in groups.<sup>161,241,458,1466</sup> These data suggest that some personnel who experienced the most extreme levels of psychological stressors during the war (e.g., being in combat, seeing casualties, witnessing deaths) would also have more frequently had other exposures that were most prominent in combat areas such as the use of pyridostigmine bromide, smoke from oil well fires, and spent depleted uranium munitions.

**Psychiatric conditions in relation to psychological stressors in theater.** In addition to Gulf War illness, a limited number of diagnosed conditions have been associated with service in the 1990-1991 Gulf War. Psychiatric conditions have been evaluated in more studies of Gulf War veterans than any other type of diagnosis.<sup>969,1488</sup> These studies have consistently found that veterans who served in the Gulf War have higher rates of psychiatric conditions, prominently posttraumatic stress disorder (PTSD), than era veterans who did not serve in the war. The Gulf War, although brief, was like other hostile deployments in a number of important respects. Hard fought battles resulted in casualties, death, and trauma for some American soldiers in the war zone. Some troops returned from Desert Storm with psychological wounds that are slow to heal. The actual and expected consequence of the Gulf War, as with other wars, is that returning veterans have higher rates of psychiatric conditions than veterans who did not serve in war. But it might also be expected that, given the short duration and decisive victory of the 1991 Gulf War, rates of psychiatric conditions in Gulf War veterans would be lower than rates found after other wars.

In contrast to the lack of association between Gulf War illness and psychological stressors in theater, studies have consistently found that Gulf War veterans who experienced more extreme stressors during deployment have higher rates of PTSD.<sup>80,501,746,753,855,1195,1456,1480,1729</sup> For example, a report on a small cohort of Gulf War veterans referred for psychiatric evaluation as part of the CCEP indicated that veterans who reported combat-related stressors (direct combat, wounded in action, witnessed casualties, witnessed SCUD attacks, chemical alarms) were significantly more likely to be diagnosed with PTSD than those who did not.<sup>855</sup> Similarly, personnel tasked with grave registration duty during the war were found to have an extremely high rate of PTSD (48%) six months after their return.<sup>1519,1520</sup> The rate of PTSD was also extremely high (49%) among Gulf War veterans who reported being sexually assaulted during deployment.<sup>746</sup>

In more representative samples, findings from both the U.S. National Survey of Gulf War era veterans and the Iowa Gulf War study indicate that veterans who participated in combat were significantly more likely to have PTSD than those who were not in combat.<sup>103,746,753</sup> There is also evidence of a dose-response effect between wartime stressors and the development of PTSD. This includes findings from a large study of Australian Gulf War veterans indicating that military personnel who experienced intermediate levels of deployment stressors had four times the rate of PTSD of veterans with minimal deployment stress, and those with the highest level of stressors had 14 times the rate of PTSD.<sup>674</sup>

**Table 3. Prevalence of Clinically Diagnosed Post Traumatic Stress Disorder in Gulf War and Nondeployed Gulf War Era Veterans**

<i>Study</i>	<i>Sample</i>	<i>PTSD Measure</i>	<i>PTSD Prevalence</i>	
			<i>Gulf War Veterans</i>	<i>Nondeployed Veterans</i>
<u>Population-based samples</u>				
Blanchard <sup>142</sup>	2,189 U.S. vets	CIDI	3.3 %	2.0 %
Toomey <sup>1548</sup>		CAPS	6.2 %	1.1 %
Ikin <sup>674</sup>	2,758 Australian vets	CIDI	5.1 %	1.7 %
Wolfe <sup>1803</sup>	252 U.S. Army vets	CAPS, SCID	5.4, 7.2 %	0 %
<u>Gulf War Registries</u>				
Engel <sup>408</sup>	21,232 U.S. vets in CCEP	Clinical diagnosis	5.6 %	
VA <sup>1651</sup>	70,385 U.S. vets in VA Registry	Clinical diagnosis	3.8 %	
Lee <sup>879</sup>	3,233 in U.K. MAP	Clinical diagnosis	12.0 %	

Abbreviations: CCEP = DOD Comprehensive Clinical Evaluation Program, MAP = British Medical Assessment Program, CIDI = Composite International Diagnostic Interview, CAPS = Clinical Assessment of PTSD, SCID = Structured Clinical Interview for DSM-III-R

Findings from the U.S. national survey indicate that PTSD rates in Gulf War era veterans increased across six levels of stressor intensity, ranging from three percent among veterans with little or no deployment-related stress, to 22 percent among veterans who reported the greatest number of combat-related stressors.<sup>753</sup>

**How many Gulf War veterans have PTSD?** Rates of PTSD have been assessed in multiple studies of Gulf War veterans. Overall, identified PTSD rates are generally below 10 percent in population-based samples of Gulf War veterans but are somewhat variable, with differences related to the type of PTSD assessment done and the measures used.<sup>969</sup> Table 3 summarizes results of studies that have assessed PTSD using clinical evaluations, the preferred and most reliable method of diagnosing PTSD.<sup>688</sup> As shown, estimates of PTSD prevalence among Gulf War veterans who were clinically evaluated are surprisingly consistent. In U.S. Registry and two population-based samples that included all service branches, PTSD rates in clinically-evaluated veterans range from 3.3 to 6.2 percent, with modestly higher rates (5.4%, 7.2 %) in two small cohorts of Army Gulf War veterans.<sup>1803</sup> The prevalence of PTSD in veterans participating in Gulf War registries would normally be expected to exceed rates from population studies of Gulf War veterans, since most veterans who request evaluation in Gulf War registries have health concerns. This was not the case in the U.S. CCEP but may explain, in part, why the rate of diagnosed PTSD in the U.K. Ministry of Defence’s registry, the Medical Assessment Program (MAP), was higher than in any other clinically evaluated sample of Gulf War veterans.<sup>879</sup>

Because clinical evaluation was not practical in most of the large Gulf War epidemiologic studies, PTSD prevalence was typically estimated using screening instruments that rely on symptom checklists. As shown in Table 4, PTSD estimates from these studies were more variable, yielding both higher and lower rates than clinically evaluated samples. The variability in PTSD rates reflected in the table appears to result, in part, from the methods and instruments used. For example, when the PTSD Checklist was used in the U.S. National Survey of Gulf War era veterans the estimated PTSD rate of 10.1 percent<sup>753</sup> was three times higher than the 3.3 percent rate obtained when a subset of those veterans was clinically

**Table 4. Prevalence of Post Traumatic Stress Disorder Assessed by Questionnaire in Population Studies of Gulf War and Nondeployed Gulf War Era Veterans**

<i>Study</i>	<i>Sample</i>	<i>PTSD Measure/cutoff</i>	<i>PTSD Prevalence</i>	
			<i>Gulf War Veterans</i>	<i>Nondeployed Veterans</i>
Barrett <sup>103</sup>	3,695 Iowa vets	PTSD Checklist $\geq$ 50	1.9 %	0.8 %
Goss Gilroy <sup>511</sup>	6,552 Canadian vets	PTSD symptoms	2.1 %	0.6 %
Fiedler <sup>436</sup>	1,767 U.S. vets	CIDI (telephone interview)	3.4 %	0.9 %
Holmes <sup>620</sup>	1,090 vets in Air Guard unit	Mississippi Scale $\geq$ 89	6.8 %	1.7 %
McKenzie <sup>1003</sup>	2,791 Australian vets	PTSD Checklist $\geq$ 50	7.9 %	4.6 %
Stretch <sup>1503</sup>	4,334 PA, HI vets	WRAIR algorithm	8.6 %	1.6 %
Kang <sup>753</sup>	20,917 U.S. vets	PTSD Checklist $\geq$ 50	10.1 %	4.9 %
Unwin <sup>1698</sup>	5,177 U.K. vets	Selected questions from Mississippi Scale	13.2 %	4.1 %

Abbreviations: Mississippi Scale = Mississippi Scale for Combat-Related PTSD, CIDI = Composite International Diagnostic Interview, WRAIR = Walter Reed Army Institute of Research algorithm for determining PTSD

evaluated.<sup>142</sup> Similarly, the large population survey of British Gulf War veterans estimated PTSD prevalence at 13.2 percent<sup>1698</sup> based on questions selected from the Mississippi Scale. Later clinical evaluation of a subset of those veterans, however, identified a PTSD rate of only three percent in the most disabled subgroup and one percent in Gulf War veterans that were not disabled.<sup>699</sup>

It is important to point out, in this regard, that the validity of using screening tests such as the Mississippi Scale for PTSD and PTSD Checklist to identify PTSD rates in Gulf War veterans has been questioned.<sup>553,688</sup> A number of symptoms included in these instruments, such as sleep disturbances and memory problems, parallel symptoms associated with Gulf War illness. The number of PTSD cases identified using these checklists depends on the cut-off score used by investigators.<sup>1805</sup> Cut-off scores have varied in different studies, and no validation studies have determined the optimal use of PTSD screening instruments in Gulf War veterans.<sup>553,555,1805</sup> As a result, PTSD case ascertainment based on these checklists may overestimate PTSD rates, particularly in symptomatic Gulf War veterans who may or may not have problems resulting from intense psychological stressors.

Even in light of the potential for over diagnosing PTSD and the variability of prevalence estimates, identified rates of PTSD in Gulf War veterans are generally low—lower than rates reported in veterans of previous and current wars. The rate of PTSD in Gulf War veterans is more comparable to that in the U.S. adult population, reported to be five percent in males, and eight percent overall.<sup>799</sup> In studies of Vietnam veterans estimates of PTSD prevalence are also variable, as well as controversial,<sup>1008</sup> but have generally ranged between 15 and 30 percent.<sup>223,352,844,845,1159,1834</sup> Substantially higher PTSD rates are found in cohorts of combat veterans and former prisoners of war.<sup>384,1138,1517</sup>

Rates of PTSD and psychiatric illness are beginning to be reported for U.S. military personnel returning from current deployments in Iraq and Afghanistan. Studies have indicated that PTSD may not become apparent in veterans for months or even years after their return from the war zone, so actual rates may not be known for some time.<sup>127,530,1048,1456,1803</sup> Combat and traumatic experiences for U.S. personnel in the current Iraq War have been more widespread and more intense than in the 1991 Gulf War,<sup>447</sup> with one

survey indicating that 93 percent of U.S. veterans in combat units reported being shot at during deployment and 95 percent reported seeing dead bodies.<sup>614</sup> Not surprisingly, studies also indicate that psychiatric problems are more prevalent in returning veterans.<sup>447</sup> Recent studies have reported that 35 percent of Iraq War veterans accessed mental health services within a year of returning from the war, 17 percent of returning Army combat veterans have PTSD, and that between 20 and 42 percent of OIF personnel screened longitudinally are identified by clinicians as having a mental health problem.<sup>613,616,1048,1380</sup>

**Other psychiatric conditions affecting Gulf War veterans.** Research studies have also evaluated rates and population patterns of psychiatric disorders other than PTSD in Gulf War veterans. Several have reported that, like PTSD, rates of other psychiatric conditions are significantly associated with psychological stressors that occurred during deployment.<sup>139,674,1195,1728</sup> PTSD commonly co-occurs with conditions such as depression and generalized anxiety disorder.<sup>450,799,1156,1834</sup> Like PTSD, both depression and anxiety disorders occur at higher rates in Gulf War veterans than in nondeployed era veterans, with somewhat variable prevalence estimates. Low rates of both conditions were diagnosed in Gulf War veterans evaluated in the U.S. CCEP (3.0% depression, 0.4% anxiety disorder) and the U.K. MAP program (3% depression, 1% anxiety disorder).<sup>408,879</sup> Relatively low rates were also reported in the Ft. Devens cohort (6.6% depression, 0.8% anxiety disorder).<sup>1803</sup> Higher estimates for rates of depression and anxiety disorder, each from one study, come from national samples that used the CIDI structured interview to identify cases. The U.S. National Gulf War era study reported that eight percent of Gulf War veterans had major depression, and 21 percent had anxiety disorders.<sup>142</sup> Nearly reversed rates come from a second national sample that administered the CIDI by telephone interview (15% depression, 6% anxiety disorder).<sup>436</sup> Variability in these estimates may be a function of the measures used, since both studies that reported higher rates of these conditions in Gulf War veterans used the CIDI, and also found relatively high rates of psychiatric disorders in nondeployed era veterans.

**Relationship of postwar psychiatric illness to chronic symptoms and multisymptom illness.** There has been an extensive amount of scientific research conducted on the psychological sequelae of war, including factors associated with persistent psychiatric morbidity in some veterans.<sup>1518,1729</sup> It has long been observed that veterans and others with psychiatric conditions, particularly PTSD, experience somatic symptoms at higher rates than individuals with no psychiatric illness.<sup>616,1468,1710</sup> Conversely, people with chronic medical conditions are often reported to have higher rates of psychiatric illness than those who are medically well. For example, the prevalence of major depression in people age 15 to 54 in the U.S. was estimated to be seven percent in 2002.<sup>798</sup> Major depression is more common in patients with chronic illness, affecting about 15 percent of cancer patients,<sup>640</sup> 15-30 percent of patients with multiple sclerosis,<sup>249,1177</sup> and 20-40 percent of Parkinson's disease patients.<sup>300,1134,1423</sup>

This phenomenon has been well documented in studies of Gulf War veterans. Multiple studies have reported that Gulf War veterans with PTSD have higher rates of self-reported symptoms than veterans without PTSD.<sup>88,103,407,850,1741,1803</sup> For example, in a population-based sample of Iowa Gulf War era veterans, investigators report that veterans with PTSD endorse significantly more symptoms than veterans without PTSD in a broad range of categories. This occurred in both Gulf War and nondeployed era veterans with PTSD<sup>103</sup> and parallels what is known about veterans from other eras—that veterans with PTSD typically experience more symptoms than veterans with no psychiatric disorders.<sup>117,1834</sup> Several studies have also reported this association from the opposite perspective, that is, that Gulf War veterans with multisymptom illness have higher rates of PTSD and depression than veterans without multisymptom illness.<sup>142,449,699,1496</sup>

The largest national study of U.S. Gulf War veterans found that six percent of Gulf War veterans with multisymptom illness had PTSD, compared to two percent of Gulf War veterans without multisymptom illness.<sup>142</sup> This relative excess was also seen in nondeployed era veterans with multisymptom illness.

Other studies have reported both higher and lower rates of psychiatric diagnoses in Gulf War veterans with multisymptom conditions. For example, no cases of PTSD were identified among veterans with any of three defined symptom syndromes in the Texas study of Gulf War veterans from a Navy Seabees battalion.<sup>565</sup> In the Fort Devens cohort, Army veterans with the highest number of symptoms also had elevated rates of psychiatric disorders – 14 percent had PTSD and 15 percent had depression. Still, the large majority of the highly symptomatic veterans, 73 percent, had neither depression nor PTSD.<sup>1803</sup> Similarly, a clinical study of British Gulf War veterans indicated that, in the subset of veterans with the highest degree of disability, three percent had PTSD and 24 percent had any psychiatric disorder—findings similar to those for disabled veterans who had not deployed to the Gulf War. Seventy-six percent of ill Gulf War veterans in this population had no identifiable psychiatric disorder.<sup>699</sup>

Studies indicating that Gulf War veterans with multisymptom conditions have higher rates of psychiatric conditions and that veterans with psychiatric disorders report more symptoms are consistent with similar findings from other civilian and veteran populations affected by chronic illness. They are important in underscoring the need to identify subgroups of ill veterans with conditions that may benefit from established treatments. They do not, however, support assumptions that Gulf War illness was caused by deployment stressors or that Gulf War illness is a psychiatric disorder. Studies of Gulf War veterans consistently indicate that Gulf War illness was not caused by psychological stressors during the war. And, although some veterans with Gulf War illness also have psychiatric disorders, the large majority do not.

From a clinical perspective, it is important that those ill Gulf War veterans who have diagnosable psychiatric conditions are identified and appropriately treated.<sup>405,407</sup> There is little evidence, however, that standard treatments for mood disorders will benefit the broader range of symptoms associated with Gulf War illness.<sup>427,1072,1358</sup> And, given the consistency of findings that most veterans with Gulf War illness do not have psychiatric conditions, it is also extremely important that clinicians not assume that diverse undiagnosed symptoms affecting Gulf War veterans are primarily a psychiatric problem.

From a research perspective, the potential for confusion between undiagnosed multisymptom illness in Gulf War veterans and diagnosable psychiatric disorders emphasizes the need for careful study design and the use of rigorous methods in assigning psychiatric case status. It also underscores the need for careful data analysis that considers possible confounding effects of concurrent conditions associated with concurrent exposures during the war.

Epidemiologic studies consistently indicate that the etiology of Gulf War illness is very different from that of PTSD. It is likely that veterans with Gulf War illness are distinct in multiple ways from veterans with PTSD and other psychiatric conditions, as has been suggested by preliminary studies.<sup>435,502,864,1496</sup> To minimize confusing characteristics of Gulf War illness with those of psychiatric conditions, it is important that Gulf War illness research studies distinguish subsets of veteran participants who have psychiatric disorders, or limit study enrollment to Gulf War illness patients who do not have psychiatric disorders.

**Summary. Psychological stressors and the health of Gulf War veterans.** Although it is well recognized that excess rates of multisymptom illness resulted from service in the 1990-1991 Gulf War, the question of whether Gulf War illness was caused by hazardous exposures or psychological stressors has long been debated. Early views that Gulf War illness was likely the result of deployment-related stress were largely speculative, drawing on general information related to psychological and somatic effects of sustained or severe stressors. Research studies of Gulf War veterans have not supported these assumptions, however, consistently indicating that psychological stressors during deployment are *not* significantly associated with Gulf War illness. Neither intense stressors, such as serving in combat, nor less severe stressors evaluated in studies of Gulf War veterans are associated with higher rates of Gulf War illness, when effects of other deployment exposures are considered.

General research related to the effects of stress in humans provides useful insights about the potential for extreme and/or sustained stressors to precipitate short term somatic problems as well as sustained psychiatric illness. Animal studies also raise the possibility that stressors may alter or amplify effects of chemical exposures associated with Gulf War service. Some Gulf War veterans did experience trauma and the kinds of intense psychological stressors common to other wars—being in combat, coming under fire, witnessing death. Consequently, rates of posttraumatic stress disorder (PTSD) and other psychiatric conditions occur at higher rates in Gulf War veterans than era veterans who did not deploy to the Persian Gulf theater. But overall, the impact of wartime trauma and stress were less extensive in the Gulf War than in other wars and rates of PTSD and other psychiatric conditions are lower in Gulf War veterans than in veterans of other wars.

Studies indicate that the large majority of Gulf War veterans with chronic multisymptom illness do not have psychiatric disorders. It is therefore important that healthcare, research, and policy decisions concerning ill Gulf War veterans not be based on unsupported assumptions that Gulf War illness is primarily a psychiatric condition or that it was caused by psychological stressors during deployment. However, some veterans with Gulf War illness are also affected by psychiatric disorders, and it is important that those veterans are properly diagnosed and treated for those conditions.

## **Recommendation**

Evidence from multiple studies consistently indicates that Gulf War illness was not caused by psychological stressors during the war and the large majority of ill Gulf War veterans do not have psychiatric conditions. The Committee therefore recommends that federal funding for Gulf War illness research not be provided for studies of posttraumatic stress disorder or other psychiatric conditions, or studies that focus on psychological factors as the central cause of Gulf War illness.

## Kuwaiti Oil Well Fires and the Health of Gulf War Veterans

There were no less than three days when the smoke 'hugged' the ground, and turned the sunlit, bright day into a dark of night. Myself and others traveled the 'coastal highway' from Kuwait City down to Saudi Arabia on April 1<sup>st</sup>, 1991, and the petroleum-thickened air was so impregnated that we choked on oil while breathing through our doubled-up scarves and we were forced to stop and clear the raw petroleum off vehicle windshields and our goggles constantly. At some points on the highway the oil-thickened air was so thick our vehicle headlights could not penetrate the air further than 10-15 feet, and Marine escorts were needed to walk on foot ahead of the vehicles to keep us on the highway.

—Marine Corps Captain<sup>965</sup>

As the outcome of the U.S. and allied forces' campaign became increasingly evident in February of 1991, Iraqi forces set out to destroy Kuwait's oil infrastructure as they withdrew from the region. Valves were opened at the Sea Island oil terminal near Kuwait City, releasing large amounts of crude oil into the Gulf of Kuwait.<sup>1689</sup> Oil tankers moored in the area were ransacked and their cargo off-loaded into the waters. At the same time, over 600 Kuwaiti oil wells were damaged or ignited. By the end of February, at the peak of the oil well problem, an estimated 605 wells were on fire with another 46 gushing oil. Between four and six million barrels of oil per day were either burned or spewed onto the sand,<sup>1621</sup> creating plumes of smoke and lakes of crude oil collecting on the ground.

Throughout this time, images of plumes of dense black smoke pouring from the oil wells were prominent in newscasts, and medical and environmental scientists feared that exposure to the fires and smoke would result in catastrophic acute and chronic health effects for exposed military personnel.<sup>1461,1621</sup> After the ceasefire, U.S. and international teams quickly arrived in Kuwait to assist in extinguishing the fires and cleaning up the environmental disaster. The first oil well fire was extinguished by mid-June and, despite expert predictions that it would take 2-3 years to extinguish all fires, the last open well was capped on November 6, 1991.<sup>1621</sup>

Heavy exposure to smoke, oil, and other contaminants from the Kuwaiti oil well fires have long been suspected causes of the diverse chronic symptoms affecting Gulf War veterans. The oil fires are unique among Gulf War exposures, both with respect to their high public profile and because information is available on measured levels of oil fire-related pollutants in theater. These measures have been used to estimate the likely risk of diagnosed medical conditions resulting from oil fire smoke exposure but have done little to shed light on the extent to which the Kuwaiti oil fires might have caused or contributed to Gulf War illness.

### Exposure to Oil Well Fires and Smoke During Gulf War Deployment

It was a Monday, the sky was so dark it was like night. People's eyes were running with black tears, your saliva was black, you had to have a bandana over your nose to breathe.

- Army Sergeant<sup>1608</sup>

At the time the oil well fires were at their peak, between 550,000 and 600,000 U.S. troops were present in the Persian Gulf theater.<sup>1461</sup> Although most military personnel experienced exposure to smoke from the fires, the intensity and duration of exposure were highly variable. Many soldiers have reported that the smoke was at times so thick that a sunlit bright day was turned into the dark of night. At times, troops reported being soaked with unburned oil that rained from the sky. At other times, however, environmental conditions were reported to be less severe. During more favorable weather conditions,

winds helped to rapidly dissipate the smoke, and plumes rose above ground level where the smoke no longer posed noticeable difficulties for troops working in the area.<sup>1621</sup>

Epidemiologic studies indicate that 60-85 percent of U.S. and British Gulf War veterans report some exposure to smoke from oil well fires during deployment,<sup>241,692,751,988,1239,1698</sup> with exposure less common among Air Force and Navy personnel.<sup>241,1124</sup> The U.S. Army Environmental Hygiene Agency (USAEHA) estimated that over 40 percent of U.S. troops were, at some time, within one mile of a burning well.<sup>1586,1587</sup> In addition, nearly one-third of soldiers have reported eating food contaminated with oil or smoke.<sup>751</sup> For troops located in areas of precipitating crude oil and dense ground-level smoke, little was provided in the way of training or protective equipment. Protective measures for veterans in those areas consisted mostly of tying scarves or shirts over their noses and mouths, and rolling down their sleeves to cover exposed skin.<sup>1668,1669</sup>

**Oil fire pollutants of possible concern.** The hundreds of burning oil wells presented a complex mix of potentially hazardous substances to those covered with oil or breathing the heavy black smoke. The composition of crude oil varies by region and strata, but burning crude typically produces a smoke composed of a mixture of particulates and gases that include carbon dioxide (CO<sub>2</sub>), carbon monoxide (CO), sulfur dioxide (SO<sub>2</sub>), oxides of nitrogen (NO<sub>x</sub>), volatile organic compounds (VOCs), ozone (O<sub>3</sub>), various polycyclic aromatic hydrocarbons (PAHs), acid aerosols, and soot.<sup>1461</sup> Extensive analysis of the Kuwaiti oil fire smoke found that the smoke contained the expected mixture of pollutants. In addition, hydrogen sulfide (H<sub>2</sub>S), a major component of natural gas, was present at varying concentrations. The most visible components of the mix were the particulate matter and carbonized particles (soot) that formed the huge smoke plumes. The smoke contained other components, including small amounts of various heavy metals such as nickel, vanadium, iron, aluminum, beryllium, cadmium, calcium, chromium, arsenic, silicon, zinc, and lead, all present in crude oil as impurities.<sup>1621</sup>

Pollutants associated with combustion of crude oil have been the subject of extensive toxicological testing as part of established U.S. and international environment and occupational safety programs. For some, but not all pollutants, standards have been established that are intended to represent exposure levels that can be experienced without increased risk of identified adverse effects. When inhaled or ingested at sufficient concentrations and durations, many of these compounds have the potential to cause known health effects, primarily acute and chronic respiratory conditions and cancers. However, little occupational or animal research has been done to evaluate the potential for oil fire pollutants to cause a constellation of chronic symptoms resembling Gulf War illness. Oil fire-related compounds have been associated with some categories of chronic symptoms that affect Gulf War veterans. Particulate exposures can cause the development of chronic respiratory symptoms<sup>1663</sup> and VOCs and heavy metals have the potential to cause neurological symptoms.<sup>1661</sup> Carbon monoxide is highly toxic and exposure is associated with a variety of symptoms such as fatigue, headache, confusion, nausea, and impaired vision and coordination, some of which can persist for many years.<sup>1662</sup>

**Environmental monitoring and measured pollutants.** Widespread concern about the potential for serious health effects from the burning oil wells prompted environmental monitoring efforts by international agencies and organizations. Results of these monitoring efforts are summarized in Table 1. As shown, environmental samples were collected by multiple teams, testing for a wide range of potentially toxic pollutants. Early efforts to monitor air quality in the region were limited. During March 13-27, 1991, a U.S. Interagency Team measured particulates, SO<sub>2</sub>, PAHs, inorganic acids, VOCs, and metals in Kuwait and Saudi Arabia. These early assessments identified high particulate levels and SO<sub>2</sub> levels that exceeded 24 hour standards at the Burgan Oil Field.<sup>1660</sup> Later analyses determined that the portable samplers utilized in this monitoring effort tended to underestimate levels of particulates of inhalable size (10 micron diameter or smaller, or PM<sub>10</sub>).<sup>1337</sup> The most extensive monitoring program was undertaken by USAEHA, which was commissioned to assess levels of pollutants from oil fire emissions in areas where most U.S. troops would be affected. The USAEHA program analyzed samples for more

**Table 1. Measured Air Pollutants in Kuwait and Saudi Arabia, 1991**

<b>Monitoring Agency/Team</b>	<b>Monitoring Dates (1991)</b>	<b>Monitoring Locations</b>	<b>Pollutants Measured</b>	<b>Pollutants exceeding applicable standards</b>
Umwelt Bundesamt <sup>1692</sup>	Mar 3–Apr 27	Not described	SO <sub>2</sub>	None
U.S. Interagency Air Assessment Team <sup>1660</sup>	Mar 13–27	15 locations in Kuwait, 3 in Saudi Arabia	SO <sub>2</sub> , VOCs, TSPs, H <sub>2</sub> S, PAHs, metals, inorganic acids, formaldehyde	TSPs in 12 of 28 measurements; SO <sub>2</sub> at Burgan oil field
King Fahd University of Petroleum <sup>806</sup>	Mar – May	Dharan, Saudi Arabia	PM10, PAH, TSPs, lead, nickel, vanadium, cadmium, cobalt, copper	PM10; lead, cadmium, cobalt in inhalable particles
British Meteorological Office <sup>717</sup>	Mar 22-Apr 2	7 flights through smoke plume, 100 km from Kuwait	SO <sub>2</sub> , O <sub>3</sub> , NO <sub>x</sub>	Peak SO <sub>2</sub> levels
AIRPARIF <sup>1515</sup>	Mar 27-Apr 4	5 sites in and around Kuwait City, 3 in oil fields	SO <sub>2</sub> , CO, NO, NO <sub>2</sub> , PAHs, VOCs, O <sub>3</sub> , TSPs	Average SO <sub>2</sub> at 2 sites; TSPs
Kuwait Environment Protection Council <sup>849,1669</sup>	Apr–Jun	2 locations in Kuwait: Kuwait City and Rega	SO <sub>2</sub> , H <sub>2</sub> S, CO, NO <sub>2</sub> , O <sub>3</sub> , particulates	Particulates
Japan Environment Agency <sup>1145,1621</sup>	Apr 28-May 5	4 locations in Kuwait	SO <sub>2</sub> , NO <sub>2</sub>	Peak SO <sub>2</sub>
U.S. Army Environmental Hygiene Agency <sup>1586</sup>	May 5–Dec 3	6 locations in Kuwait, 4 in Saudi Arabia	VOCs, TSPs, PM10, metals, O <sub>3</sub> , PAHs, nitrates, SO <sub>4</sub> , NO, NO <sub>2</sub> , SO <sub>2</sub> , acidic gases	TSPs at all locations; PM10 in some locations
Norwegian Institute for Air Research <sup>1416</sup>	May 15-Jun 17	Umm Quasr, Iraq (100 km from largest oil field fires)	SO <sub>2</sub> , soot (particulates), PAHs	Soot
U.S. National Institute of Standards and Technology <sup>1083</sup>	May 15	Al Maqwa oil field in Kuwait	Particulates, PAHs	Particulates
National Toxics Campaign Fund <sup>1105</sup>	May 15-21	Al Jubayl, Saudi Arabia	1,4-dichlorobenzene, 1,2-dichlorobenzene, diethyl phthalate, dimethyl phthalate, naphthalene	1,4-dichlorobenzene in all samples
National Science Foundation <sup>1104</sup>	May 16-Jun 12	Flights through smoke plume	O <sub>3</sub> , NO <sub>x</sub> , CO, SO <sub>2</sub> , particulates	Particulates; SO <sub>2</sub> peak levels occasionally exceeded
U.S. Environmental Protection Agency, National Aeronautics and Space Administration <sup>1487,1669</sup>	Jul 28–Aug 8	Flights through plume, ground samples at Kuwait City and near Al Wafra, Al Burgan oil fields	SO <sub>2</sub> , SO <sub>4</sub> , VOCs, PAHs, CO <sub>2</sub> , CO, metals, particulates	None
Arabian Gulf University, Bahrain <sup>950</sup>	Jul 31-Aug 4	Bahrain	Particulates, 32 PAHs, heavy metals	Particulates, PAHs, metals elevated over usual levels

Abbreviations: VOCs = volatile organic compounds, TSPs = total suspended particulates, PM10 = particulate matter 10 microns or smaller, O<sub>3</sub> = ozone, PAHs = polycyclic aromatic hydrocarbons, CO<sub>x</sub> = oxides of carbon, NO<sub>x</sub> = oxides of nitrogen, SO<sub>x</sub> = oxides of sulfur

than 50 chemicals and compounds but, unfortunately, did not begin monitoring until May of 1991.<sup>1586</sup> By the time the USAEHA team arrived in theater, the “shamal” winds, strong northwesterly winds prevalent in the region during the spring and summer, had begun to blow and had helped to dissipate the smoke present at ground level.

Overall, results from environmental monitoring in the Kuwait theater provide a perspective in surprising contrast to the environmental conditions described by soldiers serving in areas where oil fires were burning. Measured levels of airborne particulates were excessive, but mean concentrations of VOCs, PAHs, metals, O<sub>3</sub>, CO, SO<sub>2</sub>, NO<sub>x</sub> and lead in collected samples were much lower than initially anticipated. Concentrations of these pollutants were consistent across studies, and maximum levels were found to be comparable to those in suburban areas in the U.S, lower than levels in large urban centers, and significantly lower than the U.S. recommended occupational exposure limits.<sup>1575,1587</sup> In contrast, airborne particulates were consistently found to be present at high levels at all monitoring sites. Particulate concentrations frequently exceeded EPA National Ambient Air Quality Standard limits, and were much higher than levels observed in the United States. In addition, several teams identified occasional excess SO<sub>2</sub> levels, and isolated findings of excess concentrations of heavy metals<sup>1337</sup> and 1,4 dichlorobenzene.<sup>1669</sup>

Information provided by air monitoring efforts in theater was limited, however, to the time periods and locations in which measurements were taken. For example, little information is available on measured levels of particulates and chemical toxins in areas close to the burning wells, particularly in February and March, before seasonal winds routinely dispersed the heavy black clouds of smoke near the ground. In order to estimate oil fire pollutants encountered by service members in areas where no measurements were taken, USAEHA utilized environmental monitoring data, meteorological data, and satellite imagery to generate models of pollutant concentrations in all areas of theater throughout the period that oil fires burned. Periods prior to the initiation of USAEHA monitoring were supplemented with monitoring data from other agencies. These exposure models, in conjunction with the Department of Defense's Gulf War troop location databases, have been used to estimate oil fire smoke exposures in epidemiologic studies, and for oil fire health risk assessments available to individual Gulf War veterans online at <https://gulfwarfires.apgea.army.mil>.

Two sets of health risk assessments were created by the U.S. Army's Center for Health Promotion and Preventive Medicine (USACHPPM, formerly referred to as USAEHA). One represented health risks associated with exposure to measured pollutant levels from all sources (including natural background particulates, industrial and vehicle pollution, etc.). The second used modeled pollutant levels and assessed risk only related to the excess pollution directly attributable to the burning oil fires.<sup>1575</sup> In addition, risk estimates were made for two broad categories of health outcomes: cancer and non-cancer risk. Overall, the final risk assessments concluded that the potential for significant long-term adverse health effects from the Kuwaiti oil fires was minimal, with exposures for all units below acceptable hazard index limits established by EPA.<sup>1575</sup> It is important to note, however, that this assessment relates to diagnosable medical conditions and does not provide information directly related to the risk of developing undiagnosed conditions, chronic symptoms, or symptom complexes. In addition, methods used to compute health risks considered only the subset of pollutants for which established toxicity coefficients were available.<sup>1575</sup> Consequently, the potential effects of exposure to high levels of particulates were not included in the health risk assessments. Oil exposure through ingestion of food or water was considered to be unlikely and also not included in the models.

A 1998 RAND Report commissioned by the Department of Defense<sup>1461</sup> also concluded that, even assuming a worst-case scenario, concentrations of pollutants were below levels likely to cause known health effects. Again, this assessment did not specifically address health questions related to Gulf War illness. Particulate levels were noted to be extremely high in the region and the report suggested that this might explain some of the respiratory complaints reported by veterans. The RAND report also pointed out that little is known about health effects of simultaneous exposure to multiple contaminants, and called for further investigation of this issue.<sup>1461</sup> The 2002 Environmental Exposure Report on Oil Well Fires from the Department of Defense generally concurred with conclusions of prior reports but identified three areas that required further study: particulate matter exposures and related health effects, health risks associated with dermal and inhalation exposures to "oil rain" during the Gulf War, and comprehensive health risk assessments that take into account all oil fire-related pollutants of concern.<sup>1621</sup>

## Health Effects of Kuwaiti Oil Fire-Related Exposures

No published studies have specifically evaluated Gulf War veterans who experienced the most extreme exposures to oil and smoke, that is, those in close proximity to burning oil wells in the early months of 1991. However, there are several reports on the health of U.S. civilian firefighters who came to Kuwait to assist in extinguishing the oil well fires.<sup>312,413,461</sup> These firefighters worked close-in for extended periods, at the base of the fires, and wore no protective equipment aside from the occasional use of particle masks.<sup>312,413,461</sup>

A 1992 study found that levels of DNA adducts, a biomarker for exposure to PAHs, were not elevated in civilian firefighters in Kuwait, but that some firefighters reported symptoms of eye, nose and throat irritation during their time in theater.<sup>312</sup> In a separate study, blood VOC levels—ethylbenzene, benzene, xylene, toluene, and styrene—were significantly higher in a group of 40 civilian firefighters in the Kuwaiti oil fields than in military personnel located twenty kilometers away.<sup>413</sup> None of the firefighters in the study required treatment for health conditions while working in the vicinity of the fires and there were no lost work days due to illness.<sup>312</sup> Dr. Gary Friedman, a Texas physician who evaluated a cohort of civilian firefighters after their return from Kuwait, reported to the Committee that his follow-up assessments through 1994 revealed no evidence of disease or illnesses with delayed onset, no indication of lost time due to illness, and no unexpected compensation claims filed among these workers.<sup>461</sup> In particular, he had seen no evidence of multisymptom illnesses resembling Gulf War illness among these firefighters.

The experience of professional firefighters working in the region is informative, but might not be wholly generalizable to Gulf War veterans for two reasons. First, the exposure milieu for military personnel in theater was distinct, involving exposure to oil fires in combination with other potentially hazardous substances, as described in this report. Second, a healthy worker effect likely exists among professional firefighters that would exclude individuals with particular susceptibilities to the types of exposures associated with the Kuwaiti oil fires. Although military personnel, in general, also exhibit a high degree of physical fitness, those serving in the region might have included individuals with greater vulnerability to effects of oil, smoke, and particulates.

Reports based on hospital and clinic records have suggested that local populations in areas affected by oil well fires may have experienced some adverse effects. For example, the number of visits to Kuwaiti health clinics and emergency rooms due to respiratory conditions increased over prewar rates in the months during and after the oil fires, peaking in April and declining thru September when many fires had been extinguished.<sup>1158</sup> No reports have provided information on the occurrence of symptoms or symptom complexes similar to Gulf War illness in local populations.

In 2002 scientists at the Harvard School of Public Health, in collaboration with an international team of investigators, initiated a project to assess the health effects of environmental exposures on the local Kuwaiti population during and after the 1991 oil fires. This project, “Monitoring and Assessment Program of Environmental Consequences of the Iraqi Aggression in Kuwait,” was commissioned by the government of Kuwait.<sup>591</sup> The project is ongoing, but investigators have reported that postwar mortality rates were 20 percent higher among Kuwaiti adults who remained in Kuwait during the conflict, compared to those who fled the region. Explanations for this mortality excess are unclear, and the Committee looks forward to reviewing additional information to be provided by this project.<sup>349,592</sup>

Animal studies have provided very limited information on the toxicity of exposures related to the Kuwaiti oil fires. One study compared pulmonary toxicity effects, in hamsters, of particulates collected downwind from the Kuwaiti oil fires to particulates from the St. Louis area and found the two to be comparable. Investigators concluded, however, that the substantially higher concentrations present in Kuwait remained a concern.<sup>165</sup> Another study evaluated respiratory tissues in feral cats collected in Kuwait eight months

after ignition of the oil wells. Accumulations of black sooty materials in 17 of 26 cats were described, and minor cellular changes in bronchial and tracheal tissues.<sup>1056</sup>

### **Occupational studies of the effects of exposure to smoke and fuel combustion products.**

Studies of health outcomes among individuals occupationally exposed to burning fires and fuel exhaust may also provide insights relating to health effects potentially resulting from the Kuwaiti oil fires. The direct applicability of such studies to the experiences of Gulf War veterans is limited by a number of factors, however. Occupational studies typically identify health effects resulting from exposures occurring over multiple years, as opposed to those lasting weeks or months as was the case for Gulf War veterans during deployment. In addition, the physical and chemical constituents of smoke and other exhaust products typically encountered by occupational cohorts would likely differ from those associated with the Kuwaiti oil well fires.

A 2005 report from the Institute of Medicine (IOM) reviewed, in some detail, evidence on health outcomes related to occupational exposure to combustion products such as fuel exhaust, wood smoke, and their chemical constituents.<sup>684</sup> The primary health outcomes considered were those commonly evaluated in occupational cohorts—cancers, nonmalignant respiratory diseases, cardiovascular diseases, and reproductive outcomes. The IOM panel concluded that there is sufficient evidence to indicate a positive association between exposure to combustion products and lung cancer and suggestive evidence of an association between combustion products and other respiratory cancers and bladder cancer. This represents one of the few conclusions from IOM's *Gulf War and Health* series indicating sufficient evidence of an association between any exposure and any health outcome. These conclusions do not specifically address whether exposure to the Kuwaiti oil fires are likely to be related to cancer outcomes in Gulf War veterans, for whom no elevation in cancers of the respiratory system or bladder have been identified. More importantly, the IOM review provides little information on the more immediate question of possible links between oil well fires and Gulf War illness, the health problem most prominently associated with Gulf War service.

The Research Advisory Committee, in its review of the occupational literature, also found few studies specifically relevant to the question of Gulf War illness. Studies of petroleum workers, potentially exposed to many of the chemicals found in uncombusted Kuwaiti crude, have found that these workers may be at increased risk for a number of cancer types, as previously described.<sup>541,542,898,1327,1354,1808</sup> Studies of urban firefighters have suggested that chronic exposure to smoke from burning structures may also be associated with some cancers including multiple myeloma, non-Hodgkin's lymphoma, and genitourinary cancers.<sup>100,108,341,539,882</sup> One small study of firefighters in India found these workers to experience significantly higher rates of transient memory loss, burning sensations in the extremities, tingling/numbness, and depression than a reference group, as well as elevated blood levels of epinephrine and norepinephrine.<sup>1260</sup>

### **Studies Evaluating the Health of Gulf War Veterans in Relation to the Kuwaiti Oil Fires**

At one point during the war, we were staying near the oil wells, and your uniform would be completely covered with black, like soot all over you. Your arms were exposed, your food, everything, your water where you took showers. It was constantly dark; there was no such thing as daylight.

- Army Gulf War veteran<sup>716</sup>

**Association of symptoms and multisymptom illness with oil fire exposure.** The largest study that evaluated Gulf War veterans' symptoms while they were still in theater was conducted by a team of Navy epidemiologists in March of 1991, while the oil well fires were still burning.<sup>1687</sup> That study

surveyed over 2,700 Marines in three groups, defined by the locations in which they served during the preceding months. The group closest to the oil well fires for the longest period of time (about five weeks) experienced significantly higher rates of respiratory symptoms (wheezing, cough, sore throat, runny nose) and gastrointestinal symptoms (diarrhea, stomach cramps, nausea, and vomiting) than groups more distant from the burning wells. An additional study evaluated symptoms among nearly 1,600 Army personnel before, during, and three months following their service near Doha after the end of Operation Desert Storm. Respiratory symptoms, rashes, and fatigue were generally increased in association with soldiers' proximity to the oil well fires during the time soldiers were in Kuwait. All symptoms except cough had resolved by one month post deployment.<sup>1203</sup>

Seventeen years after the war, the question of whether exposure to the Kuwaiti oil well fires is a likely cause of the persistent symptoms of Gulf War illness can best be addressed by considering evidence from studies of Gulf War veterans. Numerous epidemiologic studies have evaluated symptoms and multisymptom illness in relation to veterans' self-reported exposure to oil well fire smoke, although the amount of detail evaluated with respect to duration and intensity of smoke exposure is highly variable. Results of these studies are summarized in Appendix A-6. As shown, epidemiologic studies have commonly reported elevated illness rates in relation to oil fire exposures using preliminary or crude analyses, that is, analyses that do not account for effects of other exposures present in theater. Many studies reported results of this type, suggesting associations between oil fire smoke and increased risk for both symptoms<sup>524</sup> and multisymptom illness up to nine years after deployment.<sup>527,692,752,1124,1264,1466,1698,1804</sup> Several studies supported a possible dose-response effect, indicating that veterans who report more prolonged exposure to oil fire smoke had higher rates of Gulf War illness than veterans exposed more transiently.<sup>241,564,1466</sup> Also of note, the U.S. National Survey of Gulf War veterans found that veterans who reported consuming food contaminated with oil or smoke had a nearly 11-fold excess risk for the unique neurological symptom complex identified by this study.<sup>752</sup>

As previously described, in complex exposure scenarios like the Gulf War theater, exposure risk estimates based on unadjusted analyses often generate spurious results, due to the confounding effects of multiple concurrent exposures. More informative and reliable results require analyses that adjust for effects of other exposures in theater. The four studies that reported findings of this type in relation to oil fire exposure produced mixed results. Two found that self-reported exposure to oil fire smoke was associated with a significantly higher rate of symptoms and multisymptom illness,<sup>241,1804</sup> although the excess risk was modest. One of these studies also indicated a dose-response effect, with longer duration exposures associated with higher symptom scores.<sup>241</sup> In contrast, two studies reported that, after adjusting for other exposures, multisymptom illness was not significantly elevated among veterans who reported exposure to smoke from oil well fires.<sup>527,1124</sup>

Conflicting results from these studies cannot be conclusively explained. However, the dose-response effect demonstrated by several studies suggests that study populations that included a higher proportion of veterans who were closer to fires for longer durations would more likely have identified links between oil smoke exposure and chronic symptoms. In fact, the two studies that reported significant, albeit modest, associations between symptoms and oil fire exposure included predominantly Army personnel, while the two studies that did not find this association included only Air Force and Navy personnel. The most unexpected finding related to oil smoke exposure comes from the large Navy Seabees study. Using USACHPPM models to estimate exposure to oil fire-related pollutants, the study found that veterans with the highest modeled oil fire exposures had significantly *lower* rates of Gulf War illness.<sup>527</sup>

Taken together, epidemiologic studies do not provide consistent support for oil well fires as a prominent risk factor for Gulf War illness. Just two of the four studies providing fully adjusted analyses indicated that self-reported oil well smoke exposure was a statistically significant, but modest, risk factor for multisymptom illness. But several studies suggested that the Kuwaiti oil well fires may have contributed

to the risk of developing Gulf War illness for veterans who experienced longer duration exposures<sup>241,564,1466</sup> and/or veterans in close enough proximity to have eaten oil-contaminated food.<sup>752</sup>

**Diagnosed conditions potentially associated with oil well fire exposure.** In addition to Gulf War illness, several studies have indicated that Gulf War veterans, as a group, are significantly more likely to have symptoms of or report being diagnosed with respiratory conditions such as asthma and chronic bronchitis, compared to nondeployed era veterans.<sup>511,527,692,790,1476,1698</sup> Although these studies generally have found that less than 10 percent of all Gulf War veterans report these conditions, identified rates are consistently about twice as high in Gulf War veterans as in nondeployed era veterans. In the U.S. National Survey of Gulf War era veterans, Gulf War veterans did not report elevated asthma rates, but did report significantly higher rates of bronchitis, emphysema, and “other lung conditions.”<sup>751</sup> Clinical examination of a subset of study participants, however, did not find an excess of diagnosable lung disease among Gulf War veterans, when evaluated as a single group,<sup>393</sup> and results of pulmonary function tests were similar in Gulf War and nondeployed era veterans.<sup>755</sup>

The question most relevant to oil fire exposures, however, is whether Gulf War veterans have developed respiratory diseases at excess rates as a result of the Kuwaiti oil well fires. Several studies have addressed this question, using different methods to identify disease and degree of exposure, as summarized in Table 2. As shown, results of these studies are somewhat mixed, with two finding that asthma rates are significantly associated with self-reported exposure to oil well fire smoke and two indicating that modeled oil fire smoke exposure is not associated with symptoms suggestive of asthma/bronchitis or with hospitalization for these conditions.

**Table 2. Association of Oil Fire Exposure with Respiratory Diseases in U.S. Gulf War Veterans**

<i>Study</i>	<i>Study Population</i>	<i>Outcome Measures</i>	<i>Assessment of Oil Fire Exposure</i>	<i>Major Findings</i>
Cowan <sup>285</sup> 2002	873 asthma cases, 2,463 controls; Army CCEP participants	physician- diagnosed asthma	self reported  CHPPM models	Asthma sign. associated with self-reported exposure (OR = 1.6)  Asthma sign. associated with the number of high-exposure days and cumulative smoke exposure levels; sign dose/response effect
Lange <sup>866</sup> 2002	1,560 Iowa GW veterans	symptoms suggestive of asthma, bronchitis	self reported  CHPPM models	Asthma and bronchitis sign. associated with exposure (ORs = 1.8-2.8)  Neither associated with modeled exposures
Smith <sup>1434</sup> 2002	405,142 GW veterans	military hospitalizations, 1988-1999	CHPPM models	Hospitalizations for asthma, bronchitis were not sign. associated with modeled exposures

Abbreviations: CCEP = Comprehensive Clinical Evaluation Program, OR = odds ratio, CHPPM = U.S. Army Center for Health Promotion and Preventive Medicine, GW = Gulf War, sign. = statistically significant

The study of respiratory disease in relation to oil fire exposure that is strongest methodologically, in several respects, was the 2002 study led by Dr. David Cowan. It assessed asthma cases among Army veterans enrolled in the CCEP, and is likely to have provided the most accurate information. This study was unique among Gulf War studies in that it evaluated the rate of a medical condition that had been clinically diagnosed, in relation to modeled exposure levels. Case ascertainment and level of exposure in this study were therefore less susceptible to bias, and so presumably provide the most valid results. The

study found that asthma rates were significantly higher in Gulf War veterans exposed to higher levels of oil fire pollutants—both in terms of the number of days exposed and cumulative exposure levels. The study also identified a clear dose-response effect, with asthma risk increased about 20 percent in veterans with intermediate exposure levels, and 40 percent in veterans with highest exposure levels.<sup>285</sup>

There is evidence from other occupational groups to indicate that chronic exposure to petroleum combustion products is associated with increased risk for respiratory cancers, as previously described.<sup>684</sup> Although no studies have thus far identified excess rates of respiratory cancers in Gulf War veterans,<sup>892,943</sup> research in this area continues to be important, given the extended latency period required for many cancers to be diagnosed. The only information relating cancer rates specifically to the Kuwaiti oil fires comes from a study limited to data from military hospitalizations, which found no excess cancer hospitalizations in relation to modeled smoke exposure levels.<sup>1434</sup>

**Remaining questions.** Although an extensive amount of information is available from diverse sources concerning exposures associated with the Kuwaiti oil fires and their likely health effects, a number of questions specifically related to the health of Gulf War veterans remain unanswered. These include questions concerning levels of toxic exposures likely encountered by the subgroup of veterans who were very close to the burning wells for a prolonged period during February and March of 1991. Little information is available on health effects potentially resulting from prolonged inhalation of oily smoke, possibly combined with oil ingestion and dermal oil exposures. In addition, no information is available from epidemiologic or toxicology studies concerning the potential for oil fire exposures to act synergistically with other Gulf War-related exposures. Preliminary evidence indicates that oil fire exposure has not been associated with increased cancer rates, but may have contributed to increased asthma rates in Gulf War veterans. Additional studies are needed to provide more conclusive answers with respect to asthma and other chronic respiratory conditions in relation to oil fire exposures. Continued monitoring of cancer rates in Gulf War veterans is also important, in part to determine whether cancers with long latency periods may be associated with oil fire exposures in the Gulf War.

**Summary. Gulf War illness and the Kuwaiti oil well fires.** The roaring flames, darkened smoke-filled sky, and petroleum rain from the hundreds of Kuwaiti oil fires burning from February through November of 1991 are among the most vivid images of the Gulf War. Measurements taken by environmental assessment teams in theater, particularly after May of 1991, indicate that the primary oil fire-related pollutants of concern were high levels of particulates, but that chemical air pollutants were generally below established standards. Little information is available, however, on measured levels of oil fire-related pollutants in close proximity to the burning wells, particularly in the early months of 1991 before seasonal winds dissipated the heavy clouds of smoke at ground level.

The majority of Gulf War veterans encountered some level of smoke from the Kuwaiti oil well fires, although exposure was transient for many. Epidemiologic studies have routinely evaluated rates of Gulf War multisymptom illness in relation to oil fire exposure, using diverse assessment methods and providing mixed results. Overall, the lack of consistent findings relating oil well fires to Gulf War illness, particularly from the methodologically stronger studies, and the modest degree of risk identified by studies that found a significant association, indicate that the Kuwaiti oil well fires are not likely to have been the primary cause of Gulf War multisymptom illness for the majority of affected veterans. This general conclusion is qualified, however, by indications from several studies that more intense or sustained exposures may be associated with multisymptom illness, and the lack of information concerning the subset of veterans with particularly high exposures. In addition, one high-quality study has provided evidence that smoke exposure from the Kuwaiti oil fires is associated with an excess rate of asthma in the subset of Gulf War veterans with higher-level exposures.

## Recommendations

Based on available research and exposure information, the Committee finds that Kuwaiti oil well fires are not likely to be the primary cause of Gulf War illness for the majority of affected veterans. However, additional information is required to determine if higher level oil well fire exposures may have contributed to the risk of Gulf War illness or diagnosed medical conditions in identifiable subsets of Gulf War veterans. To address remaining questions related to long-term health effects of the Kuwaiti oil fires, the Committee recommends the following research:

- Analyze data collected from completed and ongoing epidemiologic studies to determine whether the subset of Gulf War veterans with the highest level exposures to smoke, oil, and particulates from the Kuwaiti oil well fires have elevated rates of Gulf War illness or other conditions. Such analyses should properly adjust for confounding effects of other Gulf War exposures.
- Conduct additional analyses of existing data from the U.S. national survey of Gulf War veterans and the Phase III clinical study to determine if rates of upper and lower respiratory conditions, pulmonary function abnormalities, or other medical conditions are significantly associated with modeled or self-reported levels of oil fire exposures.
- Continue monitoring cancer rates in Gulf War veterans, including assessment of cancer rates among subsets of veterans identified by modeled levels of oil fire exposures, self-reported oil fire exposure levels, and/or locations and time periods of deployment

## Depleted Uranium and the Health of Gulf War Veterans

After everything was over, we went back through the areas we had shot up and climbed all over the vehicles we had destroyed. We wanted to see the damage our tanks had done, and we were looking for souvenirs. I know of one guy who found a spent DU penetrator rod and kept it. I knew we were shooting DU rounds, but we were never told to stay away from vehicles that were hit by DU rounds. Now I know that we probably got DU dust all over us. But we didn't know any better, and we were dipping, smoking, and eating without having washed our hands. Right after the war we saw lots of guys from other units climbing on the vehicles we had shot with DU rounds. ... In April, 1991, while we were in Kuwait, I started getting diarrhea, nausea, stomach cramps, headaches, and tightness in my chest. My problems have gotten worse since then.

--Gulf War veteran, 2<sup>nd</sup> Armored Division<sup>425</sup>

The 1990-1991 Gulf War was the first conflict in which armaments containing depleted uranium, or DU, were widely used in a war zone. Depleted uranium is a dense, weakly radioactive metal with physical properties that make it particularly useful in weapons. Troops on the ground in the 1991 war were often unaware that the U.S. was firing DU munitions, that some U.S. tanks were shielded with DU armoring, or that precautions should be taken against possible health hazards related to this substance. After military personnel began reporting unexplained health problems in the aftermath of Desert Storm, questions have been raised concerning DU's possible role in causing or contributing to these conditions.

Like other potentially hazardous substances encountered in the Gulf War, no measurements or records exist that quantify the amount of DU to which individuals were exposed. Unlike other Gulf War-related exposures, however, there is relatively little information available from epidemiologic studies concerning veterans' exposure to DU and its possible link to Gulf War illness. To address some of the unknown factors related to DU exposure in the Gulf War, the U.S. Department of Defense (DOD) mounted an extensive effort to model and/or recreate DU exposure scenarios in order to estimate likely exposure levels under specific circumstances.<sup>1172,1620</sup> Such efforts have provided information on likely levels of DU exposures for some personnel who served in Desert Storm, particularly those involved in friendly fire incidents.<sup>1173</sup> Measured and modeled DU exposure levels have, in turn, been used to estimate the risks of specific health problems such as cancer and kidney damage that might be expected from those exposures. What has not been assessed to a meaningful degree by these models, however, is the extent to which the multisymptom illness affecting Gulf War veterans may be associated with DU exposures during deployment.

Depleted uranium is a byproduct of the process that converts natural uranium to enriched uranium for use in nuclear weapons and reactors. What remains, "depleted" uranium, is about 60 percent as radioactive as natural uranium.<sup>1620</sup> In addition to potential hazards associated with its radioactivity DU, a heavy metal, also presents a possible chemical hazard. It is its extreme density that makes DU exceptionally valuable in armor-piercing rounds and as an armoring material for tanks. The effectiveness of DU in weaponry was evidenced by the thousands of Iraqi tanks that were destroyed during the Gulf War by the 120 mm armor-piercing DU penetrators fired by Abrams tanks and the 25 and 30 mm DU rounds fired by the Air Force's A10 aircraft and the Marine Corps' AV-8B Harriers. DU was also remarkably effective as an armoring material. DOD reports indicate that no American tanks protected by DU armoring were penetrated by Iraqi fire.<sup>1620</sup>

In addition to its extreme density, DU has another property that enhances its effectiveness in weapons. Depleted uranium is pyrophoric, that is, DU rounds burst into flames when they hit their target, causing fire and frequently explosions when the targets' fuel tank or munitions are ignited. The resulting fire and exhaust contain DU dust and aerosol, which can be inhaled or ingested by personnel in the area, and absorbed onto their clothing and skin. This dust also settles on what is left of the target vehicle and in the surrounding area.

About 320 tons of DU was used during the Gulf War<sup>1620</sup> and much of that material is believed to still be present in the local environment. Since the 1990-1991 Gulf War, the U.S. and its allies have also used DU in conflicts in the Balkans and in operations in Afghanistan and Iraq. A number of agencies and groups have raised concerns about the potential for long-term environmental damage that may result from DU's persistence in soils and water in areas where it has been used in warfare.<sup>181</sup> International attention to this issue has resulted in a number of reports concerning DU's environmental and health effects.<sup>1325,1696,1811</sup> Questions related to environmental contamination associated with the use of DU will not be addressed by the present report, however, since they do not directly pertain to the Committee's charge of reviewing research on the health of Gulf War veterans.

Current military policy now directs soldiers who come into contact with spent DU munitions or areas contaminated by DU to wear protective clothing, to shower immediately following exposure, and to be medically evaluated.<sup>1598</sup> Because no such information or training was provided during the 1990-1991 Gulf War<sup>1671</sup> it is important to determine whether chronic health problems may have resulted from DU exposures.

### **Depleted Uranium Exposure in the Gulf War**

The largest number of military personnel exposed to DU during the Gulf War were the thousands who were in areas of and/or came into contact with destroyed Iraqi vehicles—those in or around burning or destroyed vehicles as part of their official duties and those just interested in these vehicles—climbing on them, getting inside, and taking souvenirs after the battle. DU exposures for the majority of those in the Gulf War, then, would have primarily been through inhalation, ingestion, and dermal contact.

The highest dosage DU exposures during the war, although they involved considerably fewer individuals, were those in which vehicles carrying U.S. troops were mistakenly hit by DU rounds in friendly fire incidents. These U.S. vehicles may or may not have themselves been loaded with DU munitions or DU armoring. American personnel in or on tanks hit by DU rounds would have experienced more concentrated levels of inhaled DU. Some individuals were actually hit by DU munitions or shrapnel, and may continue to carry DU fragments in their bodies to this day.

We were in a congested area with burning vehicles all around. Suddenly, the tank in front of us caught fire. The ammunition blew, but the blowout panel saved the lives of the crew. We saw DU penetrators flipping end over end over our heads. We immediately rushed to the tank to rescue the guys in it. We were breathing smoke from the burning ammo, but we had no concern about DU and took no protective measures. Afterwards, we stayed around that area for two or three hours but we were buttoned up due to exploding vehicles and ordnance around us.

—Gulf War veteran, 24<sup>th</sup> Infantry Division<sup>425</sup>

**The Camp Doha fire.** A major DU incident of concern involves a July, 1991, fire at a U.S. military base in Doha, Kuwait.<sup>1361</sup> The fire began in an M992 ammunition carrier loaded with artillery shells, then spread to stored munitions and vehicles loaded with ammunition. The scene has been described as a chaotic series of explosions and fires that scattered munitions and debris over a wide area, with vehicles and shells exploding for over six hours, and fires burning for a full 24 hours.<sup>425,1620</sup> The fire damaged or destroyed almost \$15 million in ammunition, over 100 vehicles, and over 20 buildings.<sup>1620</sup> When the fire was out, the area remained extremely hazardous due to the dispersion of massive amounts of debris containing live ordnance, and settling of oxidized DU dust in the area. Injuries and three deaths are reported to have resulted from unintentional detonations of the ordnance.<sup>1361</sup> Afterwards, the Army cleared the area and removed most of the contaminated soil. Tests conducted by the International Atomic Energy Agency (IAEA) in 2001 determined that high levels of DU were still present in soil removed from

the area during the 1991 clean up operation.<sup>691</sup> DOD reports indicate that as many as 4,000 people were in the area during the fire and that afterwards, over 600 individuals were directly involved in cleanup and decontamination.<sup>1620</sup> Cleanup efforts took months to complete, during summer temperatures that typically exceeded 110 degrees, with workers often engulfed by smoke from the burning oil well fires nearby.<sup>1620</sup> Recovery workers were reported not to have used protective measures during cleanup, with many unaware of the hazards potentially associated with DU.<sup>1361</sup>

Others who likely experienced higher levels of DU during deployment were personnel whose duties included disposing of or cleaning up enemy and U.S. vehicles damaged or destroyed during the war. This included members of a Battle Damage Assessment Team charged with evaluating U.S. vehicles hit by DU munitions and members of the 144<sup>th</sup> Service and Supply Company who processed damaged equipment, including vehicles hit by DU.<sup>1620</sup>

For three months after the fighting stopped, R. and his buddies in the 3<sup>rd</sup> Armored Division combat engineer squadron were ordered to crawl around in the black dust left over from successful shots of depleted uranium. He was ordered to live and breathe in it while finishing the job of destroying damaged Iraqi tanks and munitions, to make sure the enemy's equipment couldn't be used again. 'We actually slept underneath destroyed tanks and stuff because we figured they wouldn't fire at their own destroyed vehicles,' R said. For months, the black dust covered many of those vehicles, rubbing off on R's clothing, getting on his skin, and often into his food and water.

--Interview with Gulf War veteran, 3<sup>rd</sup> Armored Division<sup>415</sup>

**How many Gulf War veterans were exposed to DU during the war?** The IAEA has estimated that over 860,000 DU rounds were fired in the Gulf War.<sup>691</sup> Government reports have not provided information cataloguing specific sites where DU munitions were fired or individual units likely to have had the greatest exposures, as has been done in relation to oil well fires and low-level nerve agent exposure. An exposure analysis conducted by a veterans' group involved in the DU issue concluded that "several hundred thousand Gulf War veterans may have inhaled, ingested, or incurred wound contamination by depleted uranium dust"<sup>425</sup> but there are no official government estimates of the total number exposed. A DOD map provided to the Presidential Special Oversight Board in 1998 indicated that the highest concentration of DU munitions were fired in southern Iraq and Eastern Kuwait, within 100-200 kilometers of Iraqi borders with Kuwait and Saudi Arabia.<sup>1232,1612</sup> It is likely that the greatest concentration of DU-exposed military personnel would be those in locations where air assaults and ground battles took place. Epidemiologic studies have indicated that about 30 percent of Gulf War veterans participated in ground combat<sup>751</sup> and about 40 percent were in areas where combat took place.<sup>1476</sup>

In a 2000 Environmental Exposure Report, DOD's Office of the Special Assistant for Gulf War Illnesses classified DU exposure into three categories. The report estimated that up to 164 individuals experienced Level I exposures—the highest level—in association with friendly fire incidents. Over 700 more were estimated to have experienced Level II exposures in connection with processing of enemy and U.S. vehicles hit by DU munitions and with cleanup operations after the Doha fire. The report indicates that the number of personnel who experienced Level III exposures, those in areas of burning or destroyed vehicles, is "unknown."<sup>1620</sup>

## Health Effects of DU Exposure

Despite the large number of military personnel and civilians potentially exposed to DU during and since the 1991 Gulf War, relatively few studies have directly evaluated human health effects associated with DU exposure. Some scientists and commentators have concluded that DU exposure is a likely explanation for the multisymptom conditions affecting Gulf War veterans, given its potential for both

radiological and chemical effects.<sup>132,359,373,375,1303</sup> Yet the specific types of human health effects that have been described in relation to DU and uranium exposure have little apparent relationship to the pattern of chronic symptoms associated with Gulf War illness.

Uranium is a dense heavy metal that is ubiquitous in the natural environment, present in differing concentrations in different areas. Like other heavy metals, it can be taken into the body through inhalation, ingestion, or dermal exposure. Most uranium that enters the body is excreted through the digestive system and kidneys.<sup>183</sup> Scientific studies, as well as government and special panel reports have generally concluded that, at exposure levels encountered by most Gulf War veterans, the chemical effects of DU are of greater concern than the radiological effects.<sup>377,769,1235,1325,1326,1571</sup> The specific types of health hazards generally believed to be of greatest concern are those affecting tissues where DU accumulates in highest concentrations, cells that are most vulnerable to its effects, and biological processes known to be affected by metal and/or radiological toxicity. As a result, health and risk assessments have primarily focused on DU's effects on kidney function and on DU's potential for causing cancer, particularly lung and bone cancers.<sup>183,1000</sup>

**Research on DU-exposed populations.** News articles have reported that rates of cancer and birth defects in Iraq increased dramatically during the 1990s, specifically in regions where the greatest quantity of DU was used in the Gulf War.<sup>28,1309</sup> Conference reports describing an increased incidence of congenital anomalies in Basrah<sup>43</sup> and increased numbers of cancer cases, both in Iraqi military personnel who served in the war and in four Iraqi hospitals, lend some support to these contentions.<sup>38,931,1078</sup> Limitations in the data make clear interpretation of these reports impossible, however, and no formal studies have been conducted to clarify this issue.

About 14 tons of DU-containing munitions were used by U.S. forces in the Balkan conflicts during the 1990s.<sup>1624</sup> News reports of a perceived excess of leukemia among European soldiers who served in the Balkans raised concerns about a possible "Balkans Syndrome" resulting from DU exposure.<sup>373,454,859,1346</sup> Although no "Balkans Syndrome" issue has been raised among U.S. troops, one study reported that urine uranium levels were increased in a small cohort of U.S. soldiers during and after their deployment to Bosnia. The study did not provide information on symptoms or other health parameters, and uranium levels in this cohort remained below mean levels in the U.S. population.<sup>985</sup> In addition, British veterans who served in Bosnia were not found to have higher rates of symptoms or physical impairment than their nondeployed peers.<sup>642,1698</sup> Several research studies have assessed cancer rates among U.N. soldiers deployed to the Balkans but have not found excess rates of leukemia.<sup>547,1495</sup> One study has reported an excess of bone cancers among Danish troops who served in the region, based on four identified cases,<sup>1495</sup> and another study reported a slight increase in the rate of all cancers combined among Swedish troops who served in the region.<sup>547</sup>

Studies have also reported elevated rates of chromosomal and cellular abnormalities, particularly micronuclei formations, among individuals who live in areas where NATO forces used DU munitions in the Balkans.<sup>673,841,1029</sup> Health implications of these findings are unknown, since affected individuals were not reported to have any clinical indications of disease. An additional study found no post-war increase in the rates of childhood leukemia in Croatian counties in which DU was used during the war.<sup>854</sup> Studies of people living in the Sarajevo region during and after the war in Bosnia and Herzegovina indicate that rates of several types of cancer have increased in recent years, including lung and laryngeal cancer, breast cancer, bladder cancer, bone cancers, and malignant lymphomas. These increases were said by investigators to parallel those in other countries in Southeastern Europe over the same period. Researchers were unable to determine whether increased cancer rates in the Sarajevo region may have some relation to DU contamination, to other war-related nutritional, environmental, or psychological factors, or to other risk factors such as smoking, which is extremely prominent in the region.<sup>1108,1137</sup>

Depleted uranium munitions and armoring have also been used extensively in current conflicts in Iraq and Afghanistan. One study has reported elevated levels of excreted uranium in a small group of civilians living in an area of Afghanistan where DU munitions were used in 2002.<sup>375,376</sup> No information was provided concerning symptoms or medical conditions in relation to the presence/absence of uranium in these individuals, however. There have been no indications of a widespread problem with undiagnosed, multisymptom illness in military personnel returning from service in Iraq or Afghanistan.<sup>631</sup> Members of one U.S. Army National Guard police unit that served in Operation Iraqi Freedom (OIF) did report unexplained health problems after their return from the war in 2004, however.<sup>507,508</sup> This unit was not directly involved in combat but had been camped in a former train depot near Samawah, Iraq, with destroyed Iraqi tanks in the area. In news reports, veterans described the living environment in the camp as “disgusting. Oil, dirt, and bird droppings everywhere, insects crawling all around us.”<sup>507</sup> Believing their problems could be related to DU contamination, some members of the unit have been tested for DU levels by both the Army and a private laboratory, with contradictory results.<sup>508,803</sup> The specific cause or causes of the health problems in this unit have not been resolved.

Studies of workers occupationally exposed to uranium can also provide insights into possible effects of DU exposure. Uranium’s chemical properties are identical to those of DU and its radiological effects exceed those of DU. Studies of uranium miners and mill workers provide information on effects of exposure to uranium dust sustained over a prolonged period of time. Multiple studies have identified elevated rates of lung and laryngeal cancer among workers occupationally exposed to uranium<sup>58,184,371,848,1000,1342,1546</sup> and additional studies have indicated that uranium mining may be associated with increased rates of leukemia<sup>1057,1266</sup> and other cancers.<sup>372</sup> Recent reviews and government reports have concluded that the apparent association between occupational uranium exposure and cancer is questionable, due to multiple confounding factors.<sup>769,1571</sup> Most prominently, studies have indicated that the elevated rate of lung cancer in uranium miners is likely caused by radon exposure in uranium mines rather than from the uranium itself, except at very high exposure levels.<sup>1000,1571</sup> Kidney function has also long been a concern in relation to uranium exposure. Studies have documented impaired kidney function in uranium workers,<sup>1538</sup> although none have found an excess of mortality from renal disease.<sup>1000</sup>

Due to worldwide concern about possible long-term health and environmental effects resulting from the use of DU munitions, a number of scientific bodies and government agencies have sponsored scientific reviews to assess DU’s likely health effects. Key findings from these reports are summarized in Table 1. Overall, these reviews have consistently found that available evidence indicates that DU exposures, at levels experienced by the majority of Gulf War veterans, are not expected to produce long-term health effects, specifically in relation to excess cancer rates and chronic renal disease. Several of these reports indicated that there may be a minimal excess in cancer risk among the relatively few personnel with the highest level exposures—those involved in friendly fire incidents and those whose work included processing of DU-contaminated vehicles for extended periods. It is important to note, however, that risk assessments provided by all of these reports are based on toxicological and epidemiologic studies focused on specific health outcomes—primarily cancers and kidney disease. They do not provide information concerning risk associated with the development of chronic symptoms or symptom complexes.

Modeled risk assessments, while informative, do not supplant the need for research that directly and systematically evaluates health outcomes of interest in relation to uranium and DU exposure, particularly health outcomes not previously evaluated in occupational studies. Almost no information is available that directly supports or refutes a possible association between uranium exposure and chronic symptom complexes that resemble Gulf War illness. On one hand, there has been no mention in the medical literature of a multisymptom syndrome in workers occupationally exposed to uranium, as has been described for some other occupational groups exposed to neurotoxicants.<sup>735</sup> On the other, no studies were identified that specifically evaluated the occurrence of chronic symptoms in uranium-exposed populations. Several case reports have described neurological effects following extremely high levels of uranium exposure.<sup>495</sup> For example, workers accidentally exposed to a high dose of uranium aerosol

**Table 1. Health Effects of Depleted Uranium: Key Findings of U.S. and International Reports**

<i>Report</i>	<i>Year(s)</i>	<i>Key Findings</i>
RAND <sup>581</sup>	1999	Little concern related to radiological effects and cancer or other health outcomes. Chemical effects potentially associated with hematological and renal changes, but evidence does not suggest long-term excess morbidity or mortality.
Institute of Medicine <sup>679,690</sup>	2000 2008	Evidence is inadequate to determine whether there is an association between uranium exposure and lung cancer or other identified cancers. There is also insufficient evidence to determine whether uranium exposures is associated with nonmalignant renal diseases, respiratory disease, or reproductive effects.
USACHPPM <sup>1576</sup>	2000	In the Gulf War, Level I exposures may have exceeded radiation and chemical standards, warranting medical follow-up of individuals in friendly fire incidents; Levels II and III exposures are not likely to cause health effects.
DOD Environmental Exposure Report <sup>1620</sup>	2000	DU potentially poses a chemical hazard at very high levels, but Gulf War exposure levels are not expected to produce adverse health effects due to chemical or radiological effects.
World Health Organization <sup>1811</sup>	2001	DU may produce transient dose-related effects on renal function; Insoluble inhaled particles may cause radiological damage in lung tissues, dermal effects are unlikely. Environmental clean up operations are recommended in high exposure areas, but population screening is not necessary.
British Royal Society <sup>1325,1326</sup>	2002	Higher level DU exposures are potentially associated with increased rates of kidney damage, lung cancer. Excess risk associated with radiation, primarily for lung cancer, is extremely small. Chemical toxicity may cause acute kidney effects in relation to very high exposure.
International Atomic Energy Agency <sup>691</sup>	2003	Based on measurements taken of environmental samples at 11 sites in Kuwait in 2001, DU-related radiation exposure to the local population is low and does not present a health hazard.
Capstone Report <sup>1173</sup>	2004	Modeled health risks from DU inhalation, based on simulated friendly fire exposures, indicate that health effects from radiation are generally unlikely for personnel in, on, or near vehicles hit by DU munitions. Minimal increase in cancer risk and short-term kidney effects possible for personnel in unventilated Abrams tanks. Individuals working in DU contaminated vehicles for long periods may also exceed occupational exposure standards.
Sandia National Laboratories <sup>967</sup>	2005	Minimal excess cancer risk expected for DU-exposed veterans—too small to detect in veterans with less than Level I exposures, with most excess due to lung cancer. Renal effects are unlikely, but neurotoxic effects cannot be ruled out based on limited available evidence. Continued monitoring for long-term or unexpected health effects is recommended.

Abbreviations: DU = depleted uranium, USACHPPM = U.S. Army Center for Health Promotion and Preventive Medicine, DOD = Department of Defense

during World War II were reported to have “mental status changes believed to be in excess of what would be caused by a fear reaction” but no clinical effects were noted when two of the workers were reevaluated 38 years later.<sup>770</sup> A case report of long term effects of a massive skin exposure to uranium indicated that, seven years later, the patient continued to experience chronic tiredness, dizziness, and headache.<sup>1837</sup> In general, however, there is little reliable information concerning the presence or absence of chronic symptoms and neurological abnormalities in relation to uranium exposures.

Taken together, human research on the effects of uranium exposures indicate that the potential for DU to cause some cancers, particularly for those with higher-level exposures, cannot be ruled out. No excess of symptomatic illness has been reported in studies of workers occupationally exposed to uranium or people living in areas where DU has been used. However, there is also no indication that symptomatic health outcomes have been assessed in these populations. Overall, the extensive use of DU in current conflicts,

and the absence of a widespread “Gulf War illness”-type problem, argues against a major role for DU in the etiology of Gulf War illness. In addition, the types of diagnosed conditions that have been assessed in relation to uranium exposure, such as lung cancer and renal disease, have thus far not been associated with Gulf War service.

**Animal research on the effects of DU.** As with other potentially toxic exposures, ethical considerations prohibit experimental studies involving human exposure to DU. Information on specific biological effects of DU exposure is obtained, therefore, from animal studies and studies involving *in vitro* exposure of cells and tissues to uranium compounds. A large number of studies investigating biological effects of DU have been reported in the medical literature in recent years—nearly a hundred in the past decade. Uranium and DU toxicity depend on dosage and route of exposure, and on the chemical form of the uranium compound, particularly its level of solubility. Studies have evaluated effects of DU administered in diverse ways to different animals and tissues at varying dosage levels and durations.

DU effects potentially relevant to Gulf War illness. Gulf War illness and associated symptoms cannot specifically be evaluated in animal models, but recently-demonstrated biological effects of DU may have relevance to Gulf War illness. Kidneys and lungs have traditionally been considered the primary target organs for uranium toxicity, but animal studies have recently shown that uranium exposure can also target the brain.<sup>21,288,713,1168</sup> Early studies of uranium-exposed animals rarely evaluated effects on the central nervous system,<sup>873</sup> although several studies conducted prior to 1950 had indicated that very high uranium exposures can lead to muscle weakness and gait disturbances in cats and dogs<sup>383</sup> and cellular degeneration in the choroid plexi in dogs and rabbits.<sup>1246,1715</sup>

More recent studies, summarized in Table 2, indicate that uranium and/or DU can accumulate in the brain, where it can be associated with biological and behavioral effects. Neurological effects have been demonstrated in multiple studies, mostly in relation to prolonged exposure to soluble forms of DU, and also in relation to prolonged exposure to DU pellets implanted under the skin. Uranium appears to cross the blood brain barrier<sup>883,1192</sup> and accumulate differentially in specific brain regions, most consistently the hippocampus, cortex, midbrain, and cerebellum. Of particular relevance to the Gulf War experience, two studies<sup>610,896,1061</sup> have shown that inhaled uranium aerosols can access the brain directly, crossing the “nose-brain barrier,” in ways similar to those documented for other heavy metals<sup>356,357,897</sup> and independent of circulating uranium levels. Of particular interest are findings from an ongoing study at the University of New Mexico indicating that DU penetration into the brain through the nose is enhanced in the presence of nasal inflammation.<sup>896</sup>

DU and uranium have also been shown to affect learning and behavior in animal studies, in some cases at dosages below those associated with renal toxicity.<sup>12,97,174,647,890,1061</sup> In addition, one study has provided preliminary evidence that some neurological effects may result from uranium’s radiological, and not just its chemical properties. French researchers have reported that ingested enriched uranium accumulates in the hippocampus and hypothalamus at levels that exceed those of DU, and produces greater alterations in sleep patterns and behavior.<sup>647</sup>

Taken together, this group of studies indicates that DU and uranium can accumulate in the brain and can produce biochemical and behavioral alterations in animal models. It remains to be determined, however, if DU exposures like those encountered by the largest number of Gulf War veterans, that is, exposure to more insoluble forms of DU via inhalation or ingestion for more limited time periods, can produce chronic neurological or behavioral effects. The New Mexico study is an important example of a particularly relevant approach, involving dosage and exposure scenarios that parallel those of Gulf War veterans.<sup>896</sup> The Committee looks forward to reviewing final results from this project as they become available.

**Table 2. Brain and Behavioral Effects of Uranium and Depleted Uranium in Animals**

<b>Study</b>	<b>Model</b>	<b>Exposure</b>	<b>Major Finding(s)</b>
Pellmar <sup>1192</sup> 1999	rat	DU pellets implanted for 6,12, 18 months	Brain is a reservoir for DU; differential brain accumulation at 18 months, elevated in cortex, midbrain, vermis
Abou-Donia <sup>12</sup> 2002	rat	Uranyl acetate injected IM, 0.1 and 1mg/kg, 1x/day, 7 days	30 days post exposure, nitric oxide increased in midbrain and cortex, increased AChE activity in cortex, reduced neurobehavioral performance on inclined plane, grip time, beam walk
Briner <sup>173</sup> 2002	rat	Uranyl acetate in drinking water, varied doses for 2 weeks, 6 months	Time-dependent behavioral changes (line crossing, rearing)
Lewis <sup>610,896</sup> 2004	rat	Inhalation of uranium aerosols in dosages and durations to parallel Gulf War scenarios	Limited brain uptake of uranium evident in a fraction of animals, primarily in olfactory bulb. Evidence of neuroinflammation (glial fibrillary acidic protein) with more soluble forms and with concurrent nasal inflammation.
Barber <sup>98</sup> 2005	rat	Single uranyl acetate IP injection, 1mg/kg	Uranium entered brain rapidly, cleared slowly, distributed heterogeneously; elevated in cortex, hippocampus, cerebellum after 7 days; stress enhanced uranium clearance
Briner <sup>174</sup> 2005	rat	Uranyl acetate in drinking water, varied doses, 2 weeks or 6 months	Dose-dependent behavioral changes (increased line crossing, rearing), appeared earlier in males; increased brain lipid oxidation
Houpert <sup>647</sup> 2005	rat	Enriched (EU) or DU in drinking water, 1.5 months	Both accumulated in brain, particularly the striatum; EU also accumulated in hippocampus and hypothalamus; EU but not DU increased paradoxical sleep, reduced spatial working memory, increased anxiety-like behavior
Lestaevel <sup>890</sup> 2005	rat	Uranyl nitrate injected IP at 70, 144 ug/kg	Decreased food intake, reduced paradoxical sleep
Lestaevel <sup>889</sup> 2005	rat	Uranyl nitrate in drinking water (40 mg/l) for 90 days	EEG changes after 30 days: increased rapid eye movement sleep and theta band power during light period
Monleau <sup>1061</sup> 2005	rat	Inhalation of UO <sub>2</sub> aerosol for 30 min, 4 days/wk, 3 wks	Differential accumulation in brain: olfactory bulb > hippocampus > frontal cortex > cerebellum; increased locomotor and rearing activity, impaired spatial working memory
Bussy <sup>202</sup> 2006	rat	Uranyl nitrate in drinking water (40mg/l) up to 9 months	Uranium accumulated in striatum, hippocampus, frontal cortex; dopamine level decreased at 1.5 months in hypothalamus, AChE decreased in cerebellum after 6 months; decreases in dopamine, serotonin levels and turnover ratios in frontal cortex and striatum
Fitsanakis <sup>444</sup> 2006	rat	Implanted DU pellets, 3 or 6 months	DU accumulates in brain, significantly elevated in cortex, midbrain, and cerebellum at 6 months
Arfsten <sup>60</sup> 2007	rat	0-20 DU pellets, implanted 150 days	No evidence of significant neurobehavioral effects
Barber <sup>99</sup> 2007	rat	Single injection of uranyl acetate, varying doses (0.1-1.0 mg U/kg).	Brain levels of uranium remained elevated after serum levels normalized at 7 days. Highest dosage sign. reduced motor activity, grip strength. Striatal dopamine transiently reduced after highest dose. Effects modulated by stress prior to exposure.

Abbreviations: DU = depleted uranium, IP = intraperitoneal, IM = intramuscular, AChE = acetylcholinesterase, UO<sub>x</sub>= oxides of uranium

Additional DU studies that may also have relevance to Gulf War illness include those demonstrating that DU exposure can produce immunological changes, including macrophage apoptosis, increased production of proinflammatory cytokines, and indicators of oxidative stress in exposed cells and animal tissues.<sup>365,739,1061,1196,1751</sup> At sufficient doses DU exposure, like other heavy metals, may also affect the liver's ability to effectively process other toxic compounds.<sup>538,1222,1452</sup>

**Genotoxic and mutagenic effects of DU.** In addition to Gulf War illness, concerns have been raised about the potential for DU exposures to lead to increased rates of cancer, particularly cancers that develop over longer latency periods and might not yet have been detected in Gulf War veterans. Early animal studies had suggested that prolonged inhalation of uranium aerosol can lead to delayed development of lung tumors in dogs.<sup>873</sup> In recent years, multiple studies have shown that DU and uranium have genotoxic and mutagenic effects on cells, producing changes associated with tumor growth in animals, as summarized in Table 3. Much of this research has been conducted by scientists at the U.S. Armed Forces Radiobiology Research Institute (AFRRI). As shown, studies have addressed cancer-related questions on multiple levels using diverse models. Exposure of a variety of cultured cell lines to soluble and insoluble forms of DU has been shown to produce genotoxic effects, including increased frequencies of DNA strand breaks, adducts, micronuclei, chromosome aberrations, dicentrics, and sister chromatid exchanges.<sup>280,1031,1034,1040,1821</sup> One study reported that these effects can be carried through multiple cell generations,<sup>1034</sup> and two studies have indicated that genotoxic effects of inhaled uranium aerosols may be potentiated by repeat exposures.<sup>1062,1063</sup> Recent *in vitro* studies also suggest that genotoxic effects of lower-dose DU exposures are more likely to be reversible than higher dose exposures.<sup>1532</sup>

Additional studies have shown that soluble and insoluble forms of DU can cause mutagenic cellular changes and transformation, and that these transformed cells are highly tumorigenic.<sup>1031,1039,1040</sup> Of direct concern for Gulf War veterans who continue to carry DU-containing shrapnel fragments in their tissues, New Mexico investigators have found that animals with DU fragments implanted in their muscles develop soft tissue sarcomas at increased rates around those fragments.<sup>551</sup> In addition, rats with embedded DU pellets developed leukemia at a significantly elevated rate after being injected with hematopoietic cells.<sup>1032</sup> These studies indicate that continued concerns related to possible carcinogenic effects of DU are warranted, particularly in relation to embedded DU shrapnel fragments, and support continued monitoring of exposed populations.

Taken together, animal studies have indicated that DU and/or uranium, in different forms and by various exposure routes, is differentially distributed in organs and tissues, where it can have effects that have become known only in recent years.<sup>991,1036,1192</sup> Depleted uranium can accumulate differentially in brain tissues, where it has been associated with physiological, biochemical, and behavioral effects. In addition, a growing body of research indicates that uranium solutions and aerosols can cause genetic and cellular changes associated with tumor growth and that embedded DU fragments can be associated with the formation of tumors. It is important to note, however, that many of the recently-identified effects of DU developed after prolonged exposure to DU, at doses and in forms not encountered by most veterans during the Gulf War. Demonstration of the potential for DU, or other Gulf War-related exposures, to cause adverse effects is not equivalent to demonstrating that those exposures caused Gulf War illness or other adverse health outcomes in Gulf War veterans. It is important, therefore, to consider information from toxicology studies in animals in the context of findings from studies of human populations exposed to uranium and DU and, in particular, studies evaluating the health of Gulf War veterans.

**Table 3. Genotoxic, Mutagenic, and Tumorigenic Effects of Depleted Uranium and Uranium**

<b>Study</b>	<b>Model</b>	<b>Exposure</b>	<b>Major Finding(s)</b>
Lin <sup>905</sup> 1993	hamster ovary cells	Uranyl nitrate, varied doses	Increased frequency of micronuclei, chromosome aberrations, sister chromatid exchanges
Miller <sup>1031</sup> 1998	human osteo-sarcoma cells	DU-uranyl chloride	2-fold increase in sister chromatid exchanges; 9.6-fold increase in cell neoplastic transformation frequency; tumorigenic when injected into nude mice
Miller <sup>1035</sup> 1998	Ames reversion assay	Urine from DU-exposed rats	Dose/time-dependent increased mutagenesis
Miller <sup>1039</sup> 2001	human osteo-sarcoma cells	Insoluble DU-O <sub>2</sub>	Tumorigenic transformation, prevented by phenyl acetate
Miller <sup>1040</sup> 2002	human osteo-sarcoma cells	Insoluble DU-O <sub>2</sub>	25-fold increase in transformation frequency, tumorigenic in nude mice; genotoxicity (increased sister chromatid exchanges, micronuclei, DNA breaks); increased dicentric formations
Miller <sup>1037</sup> 2002	calf thymus DNA	DU-UO <sub>2</sub> (NO <sub>3</sub> ) <sub>2</sub> solution	Catalyzed oxidative DNA damage at pH 7 in absence of significant alpha decay
Miller <sup>1038</sup> 2002	human osteo-sarcoma cells	3 uranyl nitrate compounds, 50 uM, 24 hrs	Sign. more dicentric formations than nickel; neoplastic transformation increased with specific activity of uranyl nitrate
Hahn <sup>551</sup> 2002	rat	Implanted DU fragments, varied sizes	Fragment size-dependent increase in soft tissue sarcomas around DU fragments
Miller <sup>1034</sup> 2003	human osteo-sarcoma cells	DU-UO <sub>2</sub> NO <sub>2</sub> solution	Genomic instability in cell progeny (36 days, 30 doublings); delayed lethality, production of micronuclei up to 36 days post exposure
Yazzie <sup>1821</sup> 2003	pBluescript plasmid DNA	DU-uranyl acetate dehydrate in the presence of ascorbate	6-8-fold increase in DNA strand breaks vs. either UA or ascorbate alone; suggests uranyl ascorbate catalyzes DNA hydrolysis
Miller <sup>1033</sup> 2004	human liver carcinoma cells	Insoluble DU-O <sub>2</sub> , varied doses	Dose-dependent induction of gene promoters through multiple pathways
Miller <sup>1032</sup> 2005	mouse	Hematopoietic cells injected into mice with DU pellets	Leukemia developed in 76% of mice with DU pellets compared to 12% of controls
Monleau <sup>1063</sup> 2005	rat	Inhalation of UO <sub>2</sub> (insoluble) and UO <sub>4</sub> (soluble) aerosols	DNA strand breaks in bronchoalveolar cells, potentiated by repeat inhalations
Stearns <sup>1475</sup> 2005	hamster ovary cells	Uranyl acetate dihydrate, varied doses	Formation of U-DNA adducts and mutations; DNA strand breaks and cell death greater in EM9 than AA8 cells
Coryell <sup>280</sup> 2006	hamster ovary cells	Uranyl acetate, 200µM, 24 hours	Unique pattern of genetic mutations at hprt locus: fewer base deletions, more multiexon insertions and deletions
Monleau <sup>1062</sup> 2006	rat	Inhalation of UO <sub>2</sub> (insoluble) and UO <sub>4</sub> (soluble) aerosols	Repeated UO <sub>2</sub> preexposure increases genotoxic effects of UO <sub>4</sub> inhalation, no effect of UO <sub>4</sub> alone

Abbreviation: DU = depleted uranium, UO<sub>x</sub>= oxides of uranium, NO<sub>x</sub> = oxides of nitrogen

## Research on the Health of Gulf War Veterans in Relation to DU Exposure

**Laboratory assessment of DU and uranium levels in Gulf War veterans.** Several groups have evaluated DU and uranium levels detectable in Gulf War veterans since Desert Storm, using a variety of testing methods. One research team, using thermal ionization mass spectrometry to identify specific isotopes at low concentrations, evaluated urine uranium levels in 25 British, Canadian, and U.S. Gulf War veterans with inhalation exposure to DU, 8-9 years after the Gulf War.<sup>630</sup> No uranium was detected in 2 individuals, 11 had evidence of natural uranium, and 14 tested positive for DU, in varying proportions. A separate study evaluated genotoxicity in peripheral lymphocytes of British veterans who believed they had been exposed to DU—14 in the Gulf War and 3 in the Balkans. Analyses indicated an excess of chromosomal aberrations in this group, particularly dicentric and centric ring chromosomes, but no elevation in sister chromatid exchanges.<sup>1369</sup>

Since 1998, VA has sponsored a program to evaluate uranium levels in veterans who have concerns relating to DU exposure. Between 1998 and 2002, 446 samples were analyzed using 24 hour urine collections submitted to the Baltimore VA for analysis.<sup>993,999</sup> The large majority of samples contained no detectable uranium, but 22 (5%) were determined to have uranium levels in the “high” range (>0.05 ug/g creatinine), the upper limit of uranium distribution in the general population. Risk factors most strongly associated with elevated levels of uranium were having retained shrapnel in the body, being involved in a friendly fire incident, and being hit by enemy fire.

The Canadian Ministry of National Defence has also provided a testing program for personnel concerned about DU exposures. A 2002 report provided results for 104 veterans who had submitted 24 hour urine samples up to that time: 65 had served in the Gulf War, 25 served in Bosnia, and 14 had served in both. Hair samples were collected and a bone sample from a deceased Gulf War veteran was also tested. Values from all urine and hair samples were reported to be in the normal range and isotopic analyses indicated that the uranium present was consistent with natural uranium. Analysis of the bone sample from the deceased veteran indicated a higher-than-normal uranium concentration, but isotopic analysis results were also reported to be consistent with natural uranium.<sup>1162</sup> A later report indicated that all 227 Canadian veterans tested in the program had normal 24 hour urine uranium levels.<sup>1376</sup>

Reports on small groups of Gulf War veterans tested by private laboratories have reported elevated uranium levels more commonly than have been reported from government surveillance programs.<sup>374,375,1376</sup> While some differences may relate to the populations being evaluated, the lower rate of uranium detection in government programs has spurred discussion and disagreement concerning the most sensitive and most appropriate testing method to use.<sup>374,1469,1626</sup> Unfortunately, regardless of the methods used or the uranium levels detected, evaluations of this type have provided no direct insights into health effects of detected levels of DU or uranium. Similarly, identification of chromosome abnormalities in Gulf War veterans does not provide useful insights into DU’s health effects without data on symptoms or other health parameters and without suitable comparison groups.

### **Research studies evaluating the health of Gulf War veterans in relation to DU exposure.**

In 2006, the ombudsman for Canadian National Defence and Canadian Forces issued a special report related to health concerns raised by members of a Canadian combat engineer regiment that had been camped next to the U.S. compound at Camp Doha when it caught fire in July 1991. The report described the heroism of members of the unit who entered the compound during the fire to assist in controlling the damage, and the unit’s medical staff who worked into the night treating hundreds of injured U.S. troops under extremely hazardous conditions.<sup>1101</sup> The ombudsman indicated that soldiers from the unit have reported significant health problems since their return—severe headaches, respiratory problems, seizures, tumors—and that these concerns were poorly addressed by Canadian officials. The report was not intended to document the extent, nature, or causes of the veterans’ health concerns, focusing instead on how members of the unit had been treated. Yet it provides a compelling illustration not only of health

problems reported by Canadian Gulf War veterans, but also of the lack of systematic information on the extent to which those problems may have resulted from DU exposure.

**Symptom complexes and multisymptom illness.** Relatively little information is available from Gulf War epidemiologic studies concerning the relationship of symptomatic illness with DU exposure. As summarized in Appendix A-4, three U.S. studies, one Danish study, and one Australian study have evaluated symptom complexes in Gulf War veterans in relation to veteran-reported DU exposure. In unadjusted analyses, two of the U.S. studies identified significant associations between DU and symptomatic illness. In Danish Gulf War veterans, self-reported DU exposure was not significantly associated with persistent neurological or gastrointestinal symptoms, after controlling for effects of other exposures.<sup>1507</sup> Depleted uranium-related information from most of these studies is problematic, however, due to limitations in how veterans were asked about exposure. Over and above usual problems related to accurate recall of self-reported exposures during the Gulf War, Gulf War military personnel were frequently not aware of what DU was, when it was used, or if they had come into contact with it. As a result, results from studies that simply asked veterans whether or not they were exposed to DU during deployment are highly questionable.

As with several other Gulf War-related exposures, exposure to DU, would have been most common among personnel who served in battlefield areas. Two studies have reported that Gulf War illness and other health outcomes are most prevalent among veterans who reported being in Iraq or Kuwait during the war, as opposed to those who remained in areas more distant from battlefields.<sup>692,1476</sup>

**Other health outcomes in relation to DU exposure.** There is little information from Gulf War epidemiologic studies concerning associations between DU exposure and health outcomes other than Gulf War illness. A 2005 study of British Gulf War veterans reported that those who had reported DU exposure in earlier surveys had nearly twice the rate of disease-related deaths, overall, as other veterans. The observed excess was based on a relatively small number of deaths, however, and fell short of being statistically significant (MRR = 1.99, 95% C.I. = 0.98 – 4.04).<sup>944</sup> Evaluation of this same cohort between 1991 and 2002 had not identified any indication of excess cancer rates among Gulf War veterans who reported DU exposure.<sup>943</sup>

As previously described, media and conference reports have suggested that children born in Iraq in the 1990s, in regions where high concentrations of DU munitions were fired, have experienced excess rates of birth defects since the Gulf War. Several studies have also indicated that a limited number of birth defects have occurred at excess rates in children born to Gulf War veterans.<sup>57,361,747</sup> Although many have speculated that DU exposure causes elevated rates of birth defects, no research information is available that directly addresses this question. Specifically, no studies that have evaluated birth outcomes and birth defects among Gulf War veterans and their children have assessed whether there is any connection between reproductive outcomes and DU exposure in the Gulf War.

**VA longitudinal study of Gulf War veterans involved in friendly fire incidents.** Just one research project has directly evaluated the health of Gulf War veterans with known exposure to DU. In 1993 and 1994, VA and DOD initiated a program to monitor health parameters among U.S. personnel in friendly fire incidents involving DU munitions. Follow up evaluations have been conducted every 2-3 years since that time.<sup>1472</sup> In total, about 70 of the 100 individuals identified as eligible for the program have been evaluated at least once, with between 29 and 50 individuals participating in any given evaluation year. About one-fourth of study participants continue to carry embedded shrapnel fragments.<sup>992</sup> A variety of parameters have been assessed in veterans participating in the program. In the 1997 evaluation, 29 veterans involved in friendly fire incidents were compared to 38 Gulf War veterans with no identified DU exposure.<sup>997</sup> Later evaluations did not include an unexposed comparison group, but

**Table 4. Baltimore VA Longitudinal Evaluation of Gulf War Veterans in Friendly Fire Incidents: Summary of Findings in Veterans with High (vs. Low) Levels of Excreted Uranium**

<i>Measure</i>	<i>Findings (by evaluation year)</i>
Urine uranium	1994, 1997, 1998, 1999, 2001, 2003, 2005: Elevated levels detected in veterans with embedded shrapnel
Renal function	1999: Serum calcium sign. higher, urine creatinine ns lower 2001: Serum creatinine sign. lower; urine total protein and retinol binding protein ns higher 2003: Serum phosphorous sign. higher; retinol binding protein ns higher 2005: Serum uric acid ns lower
Neurocognitive function	1997: Poorer accuracy on automated performance tests sign. corr with higher uranium levels 2001: Poorer accuracy on automated performance tests ns corr with higher uranium levels 2003: Poorer accuracy on automated performance tests ns corr with higher uranium levels
Serum measures	
Hematological	1994: White cells, neutrophils sign. higher; lymphocytes, monocytes sign. lower 1997: Eosinophils ns higher 1999: Neutrophils, monocytes sign. higher; lymphocytes sign. lower 2001: CD4+ T cells, monocytes sign. higher; CD8+ T cells sign. lower; hematocrit and hemoglobin sign. lower
Endocrine	1997: Prolactin sign. higher 2001: Prolactin ns lower; free thyroxine sign. lower
Other	1999: Lactate dehydrogenase sign. lower 2001: Lactate dehydrogenase sign. lower 2003: Glutamic oxaloacetic transaminase ns lower
Genotoxicity measures	1997: Sister chromatid exchanges ns lower 1999: Sister chromatid exchanges sign. higher 2001: Chromosomal aberrations sign. higher; HPRT mutations ns higher; sister chromatid exchanges ns lower 2003: HPRT mutations ns higher 2005: In mutation frequencies sign. higher; total number chromosomal abnormalities ns higher
Sperm measures	1997: Sperm concentration sign. higher 1999: Sperm count sign. higher, sperm concentration ns higher 2001: Sperm count and concentration ns higher 2003: Sperm count and concentration ns higher

Sources: McDiarmid <sup>992-998</sup>

Abbreviations: sign. = statistically significant (p<0.05), ns = borderline statistical significance (0.05<p<0.10), corr = correlated, HPRT = hypoxanthine-guanine phosphoribosyl transferase

instead compared health measures between subgroups of DU-exposed veterans with lower (< 0.10 ug/g creatine) vs. higher (≥ 0.10 ug/g creatine) urinary levels of uranium. A number of differences between these subgroups have been identified, which are summarized in Table 4.

The most prominent finding from this series of evaluations is that veterans with embedded shrapnel have continued to excrete elevated levels of uranium throughout the follow up period, levels that have been fairly consistent over time.<sup>628,998</sup> This indicates that these veterans have had a continuous systemic exposure to uranium as it is mobilized from the fragments and/or a storage depot in the body, and that excretion has not significantly lowered the body burden of circulating uranium over time.

The significance of identified differences between veterans with higher vs. lower excreted uranium levels shown in Table 4 is unclear. A number of differences in specific measures have been inconsistent from year to year. It is not known whether this is because these differences were artifactual or transient, or because different individuals were in the high and low uranium subgroups in different years. For

example, prolactin levels were significantly higher in the high uranium subgroup in 1997, but significantly higher in the *low* uranium subgroup in 2001, with levels outside the normal range. From one perspective, this might be interpreted to indicate that the findings are contradictory and not likely to be important. Conversely, it might indicate that, overall, prolactin perturbations in this small cohort of DU-exposed veterans may reflect time-related changes associated with circulating uranium levels. In general, study investigators have characterized identified differences as having no clinical significance.

One of the more consistent findings over time relates to indications of poorer accuracy on automated neurocognitive performance tests in 1997, 2001, and 2003 that correlated with urinary uranium levels. Investigators indicated that these differences were primarily attributable to a subset of individuals with embedded shrapnel who were affected by severe complications of their combat injuries. Investigators later reported that veterans with higher urine uranium levels had worse (but not significantly lower) scores on a summary measure of cognitive function—the Index of Cognitive Efficiency—in 2005, the first year this summary measure was reported.<sup>994</sup>

The 2001 evaluation was the first to identify renal function differences between high and low uranium-excreting subgroups, which investigators suggested may represent changes in proximal tubule function.<sup>992</sup> The 2003 evaluation found indications of changes in glomerular and tubular function in both the high and low uranium subgroups, but indicated that these were not sufficient to cause clinically significant problems. In all years through 2003, seminal fluid sperm concentrations were higher in veterans with higher circulating levels of uranium, but the biological significance of this finding is unknown. In addition, indicators of genotoxicity were observed in the high uranium-excreting subgroup in 1999, 2001, 2003, and 2005.

A lack of significant differences for any given parameter is also difficult to interpret since, with the exception of the 1997 comparison group, all veterans in the program experienced a significant DU exposure in 1991. Further, the study's comparisons between veterans excreting high vs. low levels of uranium have little power to identify significant differences, given the small number in each subgroup. In the 2003 evaluation, for example, measures were compared between 13 DU-exposed veterans in the high uranium-excreting subgroup and 19 veterans in the low-excreting subgroup.<sup>995</sup>

Parameters not specifically followed or reported over the years include a 1997 finding that five of the 17 DU-exposed veterans tested had detectable uranium levels in their sperm.<sup>997</sup> No subsequent measures of uranium in sperm have been reported. In addition, reports on this cohort have provided little information on chronic symptoms or symptom complexes. In 1997, the only evaluation that included a Gulf War comparison group not involved in friendly fire incidents, 90 percent of veterans in the friendly fire cohort and 71 percent of comparison group veterans were said to have at least one medical problem.<sup>997</sup> Some of the DU-exposed veterans were dealing with the aftermath of severe trauma and injuries—burns, wounds, and loss of limbs—resulting from the friendly fire incidents in which they were involved.<sup>628,997</sup> Investigators categorized medical problems into groups, and reported that the 38 veterans *not* involved in friendly fire incidents more often reported “nervous system” and “other” problems than the 29 veterans in the friendly fire cohort. Thereafter, no differences in “medical problems” were found between subgroups of DU-exposed veterans excreting high vs. low levels of uranium. It is not clear whether specific assessments were ever made to determine the frequency and severity of the symptoms commonly associated with Gulf War service.

Longitudinal reports on this cohort have provided little or no mention of tumors, although the Committee is aware of two veterans in the assessed group who developed cancer and a benign tumor. The discussion section of the 1999 follow-up report briefly mentioned that the “other” category of health problems included one veteran diagnosed with Hodgkin’s lymphoma.<sup>998</sup> The Committee was informed that another veteran evaluated in this cohort had developed a nonmalignant bone tumor. Both cases were confirmed by the principal investigator of the study. Failure to mention these cases in most scientific reports on this

cohort is puzzling.<sup>996,1472</sup> The study director indicated to the Committee that these cases were not included because they were not believed to be the result of DU exposure.

Reports on this cohort are often cited to indicate that there are no likely long-term effects of DU exposure, yet the limited types of information provided and the small number of veterans evaluated leave important questions unanswered. Most prominently, the study provides no information on possible associations between DU exposure and the chronic symptom complexes associated with Gulf War illness. And investigators have not reported on the occurrence of other health outcomes not previously expected to relate to DU exposure. Given the small size of this cohort, all health outcomes are of interest, even if they occur as single cases. But the small size of the cohort and lack of an unexposed comparison group mean the project cannot determine whether DU exposure is associated with common or uncommon diagnosed conditions of concern such as cancer. As a result, although this longitudinal project has provided useful information in relation to laboratory parameters in the small number of Gulf War veterans with embedded shrapnel, it does not provide answers to important questions concerning health effects that may be associated more generally with DU exposures in the Gulf War.

Taken together, results of epidemiologic studies of Gulf War veterans provide very limited information concerning possible associations between DU and the health of Gulf War veterans. Risk assessments and studies indicating that Gulf War veterans should have few concerns related to kidney disease or lung cancer stemming from DU exposure are reassuring, but provide no insights into possible increases in the development of chronic symptom complexes or other unexpected health outcomes. The lack of clear information related to questions of primary concern for Gulf War veterans underscores the need for additional, focused research studies more capable of providing direct answers to these questions.

**Summary. The health of Gulf War veterans in relation to depleted uranium.** The 1990-1991 Gulf War was the first conflict in which munitions containing DU were widely used, and the possible role of DU in causing or contributing to Gulf War-related multisymptom illness has long been the subject of debate and controversy. About 320 tons of DU were used during the Gulf War and a substantial number of Gulf War personnel were potentially exposed to DU at lower levels, particularly troops who came into contact with vehicles damaged by DU munitions. The Department of Defense has indicated that at least 900 U.S. personnel were involved in incidents or activities associated with higher-level DU exposures. Health risk assessments indicate that DU exposures at levels encountered by the majority of Gulf War veterans are not likely to result in increased rates of kidney disease or lung cancer, but have not provided insights directly related to questions concerning persistent symptomatic illness.

Recent animal studies indicate that DU exposure, particularly longer term exposure to soluble forms of DU, can have adverse effects on the brain and behavior. Research in animal models has also demonstrated mutagenic and tumorigenic effects of DU that raise concerns, particularly in connection with sustained DU exposures. Studies of Gulf War veterans have provided limited information concerning associations between DU and multisymptom illness and other health outcomes of interest. The extensive use of DU in current Middle East conflicts, in the absence of a widespread “Gulf War illness”-type problem in returning veterans, suggests that DU is not likely a primary cause of Gulf War illness for most Gulf War veterans. Questions remain, however, concerning long-term effects of DU in relation to other health outcomes, particularly among individuals with higher level DU exposures. These questions indicate the need for epidemiologic research to more comprehensively assess effects of DU exposure in Gulf War veterans.

## Recommendations

Preliminary evidence from animal studies that DU accumulates in the brain and can cause adverse physiological and behavioral effects is of interest and potentially of great importance. However, the Committee finds that specifically with respect to the health of Gulf War veterans, the primary issues of concern are whether DU is a cause or contributor to Gulf War multisymptom illness, cancer, or mortality. Therefore, prior to making recommendations related to animal/toxicological studies that evaluate biological effects of DU, additional research is needed to determine whether rates of Gulf War illness, or other health outcomes, are associated with DU exposure in an expanded cohort of personnel exposed to DU during the Gulf War.

To address priority questions concerning health effects related to DU exposures in the Gulf War, the Committee recommends the following research:

- Conduct an epidemiologic investigation to evaluate health outcomes in Gulf War veterans who had the greatest exposure to DU during deployment and an unexposed comparison group. The exposed cohort should include Gulf War veterans exposed to DU via inhalation, ingestion, dermal contact, or embedded fragments as a result of friendly fire incidents, veterans who served in units tasked with processing Iraqi or Coalition vehicles struck by DU munitions, and in relation to the Camp Doha fire and subsequent cleanup activities. Evaluated health outcomes should include detailed information on symptoms, Gulf War illness, functional status, diagnosed medical conditions, and reproductive outcomes.
- In current and future studies of Gulf War veterans, assess possible DU exposure by querying veterans in detail about experiences most likely to have resulted in DU exposures, including veterans' involvement in friendly fire incidents and the extent of their exposure to vehicles destroyed by U.S. munitions.
- Continue monitoring cancer rates and mortality in Gulf War veterans, including assessment of cancer and mortality rates among subsets of veterans identified as being exposed to DU and veterans who served in areas where the highest concentrations of DU munitions were fired.

## Vaccines and Gulf War Illness

Vaccines given to troops for the Gulf War have been among the most prominent, and controversial, suspected causes of Gulf War illness. Most military personnel who served in the Gulf War received multiple vaccinations in preparation for deployment, and many received additional shots in theater. Two of the vaccines used during the war were intended to protect troops from serious disease, and possible death, in the event of exposure to biological weapons—anthrax and botulinum toxin—that Iraq was believed to possess. Since the war, reported adverse reactions to the anthrax vaccine, and quality control issues related to its production, have given it a particularly high profile as a possible cause of Gulf War illness. There is relatively little scientific research, however, that has provided clear information on the potential for the anthrax vaccine, or other vaccinations received by Gulf War veterans, to produce chronic symptoms similar to those of Gulf War illness. Receipt of multiple vaccines over a brief time period, prior to and during deployment, has also been suspected as a possible contributor to Gulf War illness. But relatively little research has specifically assessed the development of chronic symptoms following receipt of numerous vaccines, particularly the specific shots received by Gulf War personnel.

The Committee has reviewed diverse types of evidence relating to multiple questions concerning the potential for vaccines—individually or collectively—to have contributed to Gulf War illness. The Committee's 2004 report, in a preliminary assessment of the issue, pointed out that several epidemiologic studies had identified associations between Gulf War illness and vaccines received for deployment. The Committee recommended both prospective and retrospective assessments of individuals who received the type of anthrax vaccine used during the Gulf War to determine the degree to which recipients developed symptom complexes like those affecting Gulf War veterans.

### Vaccines Given to Gulf War Military Personnel

**Routine and predeployment immunizations.** Vaccines are an important component of military force health protection and readiness in both peacetime and in war. Vaccines routinely administered to military personnel at the time of the Gulf War are shown in Table 1. New recruits are given a series of vaccinations to protect them from infectious diseases that are common in the U.S., and also from diseases of greater concern for military populations. At the time of the Gulf War, new recruits received as many as 17 antigens during the first two weeks of basic training.<sup>1523</sup>

Throughout their military service, personnel continue to receive vaccines and boosters to maintain immunity to pathogens of concern. Additional vaccines are given to specific occupational groups, such as medical personnel, as protection against risks associated with their job duties. Still other vaccines are routinely given for overseas deployment, as dictated by circumstances specific to the region.<sup>1523</sup> Policies regarding specific vaccines and schedules are established by each service branch. The Department of Defense reports that these policies are developed in compliance with U.S. Public Health Service guidelines and in accordance with the U.S. Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices, in consultation with the Armed Forces Epidemiological Board and Armed Forces Medical Intelligence Center.<sup>1622</sup>

The specific vaccines received by individual U.S. troops before and during the Gulf War varied, depending on shots they had previously received, required boosters, branch of service, and their military occupation. In addition to the requirement for all personnel to update required vaccines and boosters, U.S. Central Command (CENTCOM) recommended additional vaccines for deployment to the Gulf War theater, including meningococcal, typhoid, and yellow fever vaccines, and immune globulin to protect against hepatitis A.<sup>1622</sup> Smallpox, plague, cholera, and rabies shots were not generally recommended.

**Table 1. Vaccines Routinely Given to U.S. Military Personnel at the Time of the Gulf War**

<b>Vaccine</b>	<b>Personnel Directed to Receive Vaccine</b>	<b>Schedule</b>
Adenovirus	all recruits	1 oral dose
Influenza	all recruits and active duty	annual shot
Measles	all recruits	1 shot
Meningococcal	all recruits, active duty as required	1 <sup>st</sup> shot, then booster every 3-5 years
Plague	all Marines; Army and Navy special forces, others in at-risk occupations or deploying to high risk areas	5 shots over 12 months, then booster every 1-2 years
Polio	all recruits	1 oral dose
Rabies	special forces, at-risk occupations	3 shot series
Rubella	all recruits	1 shot
Smallpox	vaccine or booster to new recruits through the late 1980s	1 dose
Tetanus-diphtheria	all recruits, active duty, and reserve	booster every 10 years
Typhoid	Army and Air Force alert forces and for deployment to high risk areas	2 doses in 2 months, then booster every 3 years
Yellow fever	all Navy and Marine Corps, Army and Air Force alert forces and for deployment to high risk areas	1 <sup>st</sup> shot, then booster every 10 years

Sources: Takafuji,<sup>1523</sup> U.S. Department of Defense<sup>1622</sup>

Vaccines administered during the war, and the proportions of U.S. and U.K. veterans who reported receiving those vaccines, are listed in Table 2. The Iowa survey indicated that nearly all Gulf War veterans reported getting at least one vaccine for deployment: 70 percent reported receiving more than five vaccines, and 30 percent received more than 10.<sup>692</sup>

CENTCOM's Gulf War-specific vaccine recommendations were modified by the different service branches, most often by the Army. For example, CENTCOM recommended the meningococcal vaccine be given to individuals that hadn't received it for at least five years and were likely to have prolonged contact with local populations. The Army modified this to recommend meningococcal shots for all deploying personnel.<sup>1622</sup> DOD has reported that there were shortages of the meningococcal vaccine, immune globulin, and influenza vaccine prior to the war, and that some troops may have received some of these shots in theater.<sup>1622</sup>

**Vaccines against biological warfare agents.** Prior to the war, intelligence reports indicated that Iraq had weaponized two biological agents, anthrax and botulinum toxin, and military officials believed they posed a possible threat to U.S. troops. Vaccines against both agents were available. The U.S. anthrax vaccine had been licensed since 1970, and had primarily been used by occupational groups at risk for anthrax, for example, veterinarians and those working with animal hides. A pentavalent botulinum toxoid (BT) was developed in the 1950s and, although not licensed, had investigational new drug (IND) status with the U.S. Food and Drug Administration (FDA). In light of the potential risk posed by these

**Table 2. Vaccines Given to U.S. Military Personnel Specifically for Gulf War Deployment**

<i>Vaccine/ Prophylactic Measure</i>	<i>U.S. Personnel Recommended to Receive Vaccine</i>	<i>Recommended Schedule for Gulf War</i>	<i>Proportion of Veterans Reporting They Received the Vaccine</i>		
			<i>U.S. National Survey<sup>751</sup></i>	<i>U.S. Navy Seabees<sup>527</sup></i>	<i>U.K. National Survey<sup>1698</sup></i>
Anthrax	fixed units, rear deployed	2 shots, 2 weeks apart	41%	30%	57%
Botulinum toxoid	fixed units, forward deployed	2 shots, 2 weeks apart; 3 <sup>rd</sup> shot 10 weeks later	12%	8%	
Immune globulin	all troops, dose varied by branch and length of deployment	1 dose (some received 2 <sup>nd</sup> dose)	60%	41%	
Meningococcal	all Army; personnel in other branches who had not received it in 5 years and would have close contact with locals	1 shot	14%	2%	
Typhoid	all Army; personnel in other branches who had not received it in 3 years	2 initial doses or 1 booster	59%	50%	12%
Yellow fever	all Marines, Navy, Air Force; Army special forces	1 shot			14%

Sources: U.S. Department of Defense,<sup>1622</sup> and studies indicated

two agents, the Assistant Secretary of Defense for Health Affairs, in September 1990, recommended instituting a program of immunization against anthrax and botulinum toxin, with the support of the Surgeons General of all branches of the armed forces.<sup>1622,1635</sup>

The immunization protocol for the U.S. anthrax vaccine required a series of six injections over a period of 18 months, with annual boosters thereafter. Adequate supplies of anthrax vaccine were not available to protect all deploying troops with the six-shot regimen, however.<sup>1635</sup> Nor was there enough time to fully immunize troops in the time frame expected for the war to get underway. At the time of the Gulf War, the U.S. anthrax vaccine was exclusively produced by the Michigan Department of Public Health (MDPH). Attempts were made in the fall of 1990 to identify additional sources of the vaccine. According to DOD, these attempts were unsuccessful,<sup>1675</sup> and only MDPH-produced anthrax and BT were ultimately used during the war.<sup>1622</sup> CENTCOM developed a policy for using available supplies, and plans for additional distribution as more vaccine became available.

Department of Defense reports indicate that 310,680 doses of anthrax vaccine were delivered in theater and that approximately 150,000 troops received one or more anthrax shots. The U.S. Gulf War biological warfare vaccine program was terminated in March of 1991, when CENTCOM indicated that individuals who had begun anthrax or BT vaccine series need not complete them.<sup>1622</sup>

Policies for distribution of biological warfare vaccines to U.S. troops were established in December, 1990, after available supplies were ascertained. A report from DOD indicates that CENTCOM based its policy for use of the anthrax vaccine on the expectation that, since anthrax takes several days to develop, it would most likely be used against troops who were not forward deployed.<sup>1622</sup> The policy directed that anthrax vaccine be given to troops in fixed ground units in areas specified by CENTCOM, listed in Table 3. It was not to be given to transient or shipboard personnel, with the exception of pathologists and laboratory workers.<sup>1636</sup> The majority of Gulf War troops vaccinated against anthrax received one or two

shots in theater, in January and February 1991.<sup>1622</sup> In addition, some Army special operations forces are reported to have received anthrax vaccine prior to their deployment in August of 1990, with a second shot given in October or November of 1990.<sup>1623</sup>

GD oversaw the immunization of more than 14,000 troops against anthrax in one 72-hour marathon completed just a few days shy of the U.N.'s January 15<sup>th</sup> deadline for Iraq to pull out of Kuwait. The Army gave the 129<sup>th</sup> a special commendation for this achievement. But what really sticks out in GD's mind are the extra precautions he and his 'shot teams' took in giving troops the injections—precautions that, even today, strike him as peculiar. 'Each soldier had to read a classified sheet of instructions, stating that he, or she, was receiving a secret shot, and that this was for reasons of national security. You don't want to tell the enemy you're getting protection against one of his weapons.'

...'Our battalion commander also told us there wasn't enough anthrax vaccine to go around. Only combat support troops were getting the shot; we were supposed to keep quiet about it so the front line guys didn't get upset about not getting the vaccine. It was a morale issue.'

--Report on Gulf War Army Reservist<sup>977</sup>

Which individual Gulf War veterans actually received the anthrax vaccine is not known, however. According to DOD, units were directed to keep a low profile when administering both anthrax and botulinum vaccines, for operational security purposes. Shots were not to be given in open areas and no media or photographs were allowed.<sup>1636</sup> Personnel were commonly not told what the shots were, or told not to discuss with others that they had received them. Although vaccines administered by the military are typically entered into individuals' shot records, receipt of anthrax and botulinum vaccines during the Gulf War were often not recorded, or entered with notations like "Vac A" and "Vac A-2" for the first and second doses of anthrax vaccine and "Vac B" for the botulinum vaccine. Units sometimes used rosters to indicate who had received the shots. The DOD Office of the Special Assistant for Gulf War Illnesses (OSAGWI) reported that it collected a large number of such rosters, but that some did not provide clear information.<sup>1622</sup>

Military planners also believed that Iraq had developed the deadly botulinum toxin as a bioweapon and that it posed a possible danger for troops in theater. The investigational botulinum toxoid (BT) vaccine had been available for decades and had been used by some high-risk occupational groups, but limited supplies were available. Due to the perceived threat, DOD petitioned FDA for permission to administer BT to troops in theater, without informed consent. On December 21, 1990, an interim ruling was jointly issued by FDA and the Secretary of Health and Human Services, allowing BT to be given to troops in the Gulf War without informed consent. This interim ruling applied in the limited military situation in which there was an imminent threat of combat, informed consent was not feasible, and withholding the treatment (vaccine) would not be in the best interest of personnel.<sup>1275</sup>

According to DOD, CENTCOM policy for BT distribution in theater was based on the assumption that, because serious illness develops rapidly after exposure to botulinum toxin, this weapon would most likely be used against forward deployed troops.<sup>1622</sup> As shown in Table 3, personnel in the VII Army Corps and the 1<sup>st</sup> Marines Expeditionary Force were designated to receive BT. The recommended protocol in the Gulf War called for two shots to be given, 14 days apart, with a third dose given 10 weeks later.<sup>1637</sup> Due to limited supplies, the vaccine was to be administered on a voluntary basis. Although several thousand troops are reported to have declined the vaccine, it appears that troops were not always aware that the vaccine was voluntary. In all, DOD estimates that 137,850 BT doses were delivered in theater, and that 8,000 individuals received at least one BT shot.<sup>246,1622</sup> Like the anthrax vaccine, administration of BT was directed to be carried out under a low profile, and little information is now available concerning which individuals received it.

**Table 3. U.S. Troops Designated by CENTCOM to Receive Biological Warfare Vaccines in January 1991**

Anthrax Vaccine	Botulinum Toxoid
personnel in Riyadh	Army VII Corps
personnel in Dharan-Damman areas	1 <sup>st</sup> Marine Expeditionary Force
personnel at King Khalid Military City	
personnel at Logistic Bases A,B,C,D,E	
personnel at Army VII Corps HQ	
personnel at Army XVIII Airborne Corps HQ	
personnel in Bahrain	
1 <sup>st</sup> Cavalry Division	

Source: U.S. Department of Defense<sup>1622</sup>  
 Abbreviations: CENTCOM = U.S. Central Command, HQ = headquarters

**Vaccines received by Coalition forces.** Other countries in the allied Coalition adopted different policies with respect to vaccines and measures taken against the threat of biowarfare agents.<sup>1679</sup> British troops were routinely immunized against yellow fever, tetanus, typhoid, and polio. Some troops also received the cholera vaccine, and medical personnel were given hepatitis B shots or “jabs.”<sup>666</sup> The U.K. also provided vaccines against biological agents in the Gulf War, in a program also carried out under a veil of secrecy.<sup>1567,1622</sup> The anthrax vaccine used in the U.K. differed from the U.S. vaccine, and was available in sufficient quantities to provide to all troops. Pertussis vaccine was given as an adjuvant, to boost the immune response to the anthrax vaccine. Although British troops were not required to take the anthrax shots, it was administered without explicit informed consent.<sup>1087,1567</sup> The British Ministry of Defence estimated that up to 75 percent of Gulf War personnel received at least one dose of the anthrax/pertussis vaccine combination, with rates falling off for subsequent shots in the series.<sup>1567</sup> British troops did not receive BT, but were given plague vaccine.

Among other Coalition troops, some Canadian and Australian personnel are reported to have received anthrax and plague vaccines on a limited basis.<sup>75,511</sup> No other Coalition troops are believed to have received vaccines against bioweapons on a widespread basis.

### Health Effects of Vaccines Given to Gulf War Troops

One sick veteran who testified, Air Policeman JG of the Air Force, with orders to ship out to the Gulf War from Germany, had taken the vaccines and PB tabs and become sick. His orders were canceled at the last moment. ‘I signed up for the VA Health Registry in 1994. They sent me to the VA hospital for an exam. The doctor asked me what was wrong and to describe the symptoms. I was ... referred to the mental health clinic for stress-related problems. Seems awful funny to me that my illness is stress and I was not even in theater.’

--1997 Congressional report, testimony of Air Force veteran<sup>1684</sup>

The central question related to vaccines for Gulf War veterans is whether any of the vaccines they received, or some combination of those vaccines, contributed to the development of Gulf War illness or other chronic health problems. Although Gulf War personnel received many vaccines, attention has focused overwhelmingly on the anthrax vaccine. Questions have also been raised about possible adverse

effects from receiving multiple vaccines in a short time period, as opposed to reactions to any single vaccine. There have also been concerns related to reports of health problems among individuals who received vaccines in preparation for Gulf War deployment, but did not actually deploy.<sup>69,1476</sup>

All vaccines are known to produce, in some individuals, transient, local reactions such as redness or swelling at the injection site. Less commonly, vaccines can produce systemic and/or prolonged effects. Very serious reactions can also occur, usually in a very small number of individuals who have an atypical reaction to some component of a vaccine. In the U.S., the Vaccine Adverse Effect Reporting System (VAERS) was established in 1990 as a nationwide reporting system for adverse reactions to vaccines. Co-administered by FDA and CDC, it provides a passive surveillance system that is useful for flagging unexpected events. The VAERS cannot be used to accurately determine rates of adverse events, since it depends on reports submitted by healthcare providers, vaccine manufacturers, and patients. Since 1995, the Department of Defense has required that all adverse reactions to military vaccinations be reported to VAERS. This includes any event requiring hospitalization or that causes the recipient to miss more than 24 hours from duty.<sup>1010,1622</sup>

Federal agencies have commissioned multiple reports to evaluate available evidence on health effects potentially related to vaccines received by Gulf War veterans. The U.S. Army commissioned the 1996 Institute of Medicine (IOM) report *Interactions of Drugs, Biologics, and Chemicals in U.S. Military Forces*.<sup>677</sup> The IOM committee indicated there was little information describing health effects of the many combinations of multiple vaccines, drugs, and chemicals to which military personnel are exposed. The panel recommended a strategy for categorizing known and unknown interactions, and a graded approach for monitoring and studying their effects.<sup>677</sup> In 2000, Volume One of the IOM *Gulf War and Health* series of reports reviewed research information on effects of the anthrax vaccine, botulinum toxoid, and multiple vaccinations. The report concluded that, while evidence clearly indicated that vaccines are associated with transient adverse effects, there was insufficient evidence to determine whether the vaccines considered, or multiple vaccinations, are associated with long-term adverse health effects.<sup>679</sup> The Department of Defense also commissioned the RAND Corporation to conduct a review of scientific information related to vaccines administered to Gulf War veterans, a report that has not yet been published.

## **Anthrax Vaccine**

The anthrax vaccine has been the focus of intense controversy and debate on multiple fronts. Concerns have been raised about the vaccine's efficacy against inhalational anthrax, quality control issues in its production, short and long-term side effects, vaccine components and adjuvants, and military policies requiring mandatory vaccination. These issues have been addressed by government investigations and reports, expert panel reviews, scientific studies, court cases, and editorial commentaries.<sup>514,680,773,1046,1096,1112,1406,1674,1684,1690</sup> With current concerns about the use of biological weapons against both military and civilian targets, it is vitally important that the full scope of issues regarding the safety and efficacy of the anthrax vaccine be fully considered in the public arena.

In keeping with its charge, however, the Committee is concerned primarily with evidence related to associations between the anthrax vaccine given to Gulf War personnel and the development of Gulf War illness or other chronic health problems. This limited our primary focus to questions about the safety of the anthrax vaccine, and more precisely, about the potential for the anthrax vaccine administered to Gulf War veterans to produce persistent health effects. Such questions are complicated by indications that the anthrax vaccine has not been a constant or uniform entity. Most obviously, the vaccine given to U.S. Gulf War troops differed substantially from that given to British personnel. But the U.S. vaccine also differed, in some ways, from the vaccine licensed for use in 1970 and perhaps also from the vaccine distributed to U.S. military personnel today.

Although media stories describing Gulf War veterans' unexplained health problems began to appear soon after the war, concern about a possible role for anthrax vaccine did not become prominent until six years later. In 1997, a series of stories in *Insight* magazine reported that Gulf War veterans were made ill by unlicensed adjuvants added to vaccines they received for the war.<sup>1299</sup> Vaccine concerns were heightened by reports that multiple safety violations had been identified in the production facilities of the government's sole anthrax vaccine supplier. Adding to the controversy, in December 1997, DOD announced plans to implement a program of mandatory anthrax vaccination of all U.S. military personnel.

In March 1998, DOD initiated the Anthrax Vaccine Immunization Program (AVIP), a massive effort to vaccinate all personnel against anthrax using the six-shot, 18 month protocol. This program has been controversial since its inception, associated with high profile media reports of serious illness, even death, following receipt of the anthrax vaccine.<sup>416,417,1247</sup> Some personnel refused to be vaccinated and some refusers were punished—fined, dishonorably discharged, or court marshaled.<sup>418,623,1069</sup> Reservists and National Guardsmen were reported to be leaving the military or changing their duty status to avoid taking the vaccine.<sup>231,1680</sup> The issue has been fought in court cases for nearly a decade, resulting in the vaccine moving back and forth between mandatory and voluntary status.<sup>382,1773</sup> An often cited reason for questioning the safety of the anthrax vaccine has been its putative role as a cause of Gulf War illness. But a detailed consideration of available evidence that supports or refutes this assertion has not generally been provided in the debate.

**Characteristics of the anthrax vaccine used in the Gulf War.** The anthrax vaccine licensed for use in the U.S. was developed in the 1950s. The U.S. vaccine, referred to as anthrax vaccine adsorbed (AVA), is a cell-free filtrate of an unencapsulated strain of anthrax, adsorbed onto aluminum hydroxide. Its immunogenic component is protective antigen (PA), one of three proteins produced by the anthrax bacillus that contribute to its toxic effects. Aluminum hydroxide acts as an adjuvant to boost the body's immune response to the vaccine. Although disputed by nonmilitary observers,<sup>977</sup> the Department of Defense has consistently maintained that all anthrax vaccine used in the Gulf War was manufactured and supplied by the Michigan Department of Public Health (MDPH), which had been producing AVA since 1970. In 1995, the vaccine manufacturing division of MDPH became known as the Michigan Biological Products Institute (MBPI). MBPI was sold in 1998 to the private company, Bioport. Bioport is currently a subsidiary of Emergent Biosolutions, which continues to manufacture AVA for the U.S. military under the trade name BioThrax.

It has been necessary for the Committee to distinguish the large amount of information now available on the anthrax vaccine—pro and con—from the more limited amount of information specifically relevant to anthrax vaccine and the health of Gulf War veterans. An important first question, which the Committee was not able to fully answer, concerns the extent to which research on adverse effects of the U.S. anthrax vaccine, largely conducted prior to 1972 and again after 1998, can be applied to the anthrax vaccine given to Gulf War veterans. There are many unknowns surrounding the anthrax vaccine provided at the time of the Gulf War. This includes a number of indications that AVA has not been an unvarying product with a risk profile that can be assumed to be the same before, during, and after the Gulf War.

The anthrax vaccine used during the Gulf War was the general type developed and tested in the 1950s, but modifications were made in vaccine components and production methods over the years, including major changes made between the 1950s efficacy trial and vaccine licensure in 1970.<sup>1009,1678</sup> Specific changes in the manufacturing process were also made by MDPH in 1990, just prior to the Gulf War, to meet the military's increased demand. At that time, MDPH changed from glass to stainless steel fermenters and substituted nylon filters for the ceramic filters previously used.<sup>680,1678</sup> The changes sped up processing time and increased production volume for a given lot, allowing more vaccine to be produced in a shorter time period.<sup>1678</sup> No information is available from testing done by MDPH at the time of these changes, however, to determine possible effects on the vaccine. An investigation by the General

Accounting Office (GAO, now the Government Accountability Office) suggested that the filter changes could result in higher levels of proteins in the vaccines, and that MDPH did not test for anthrax proteins edema factor (EF) or lethal factor (LF). The GAO also reported that results of an unpublished Army study, conducted in October 1990, found as much as a 100-fold increase in the level of PA in the vaccine after the filter change.<sup>1678</sup>

It is likely that some of the vaccine lots distributed in the Gulf War were manufactured prior to the 1990 production changes, and some after, raising the possibility of differences among lots given to Gulf War military personnel. Earlier studies, for example, had indicated that AVA lots produced in the 1980s contained detectable amounts of LF and EF.<sup>513,915</sup> The type of filters used in the Michigan production plant were again changed in 1997, to a polyvinylidene filter.<sup>1678</sup> Therefore, vaccine lots produced in the late 1980s and after the 1990 filter changes might both have differed from vaccine produced after the 1997 filter changes and also from lots produced after extensive changes were made in the Michigan production facility in 1998 and 1999.

Several reports have indicated that acute reaction rates to the Michigan-produced anthrax vaccine did vary between lots. For example, data collected by CDC between 1967 and 1972 in support of AVA licensure identified significant lot-to-lot variation in rates of acute reactogenicity.<sup>680,1009</sup> Similarly, adverse reactions reported by 1,583 workers who received anthrax vaccine at Fort Detrick between 1973 and 1999 also varied significantly by lot.<sup>1213</sup> Of the 32 anthrax vaccine lots used over the 26 year period, highest injection site reaction rates were reported for lots numbered 10, FAV001, FAV004, FAV006 and FAV008. This is of particular interest, since anthrax vaccine lots FAV001, FAV004, and FAV006 were also given to Gulf War troops during the war, and lot FAV008 was manufactured at about the same time as lots given to Gulf War troops.<sup>589,1622</sup>

There are other distinctions potentially applicable to Gulf War-era anthrax vaccine. The vaccine is temperature sensitive, and must be kept between two and eight degrees Celsius.<sup>138</sup> Reports have described the challenges involved in maintaining a high-quality system for packaging and transporting the vaccine to ensure it is maintained at proper temperatures.<sup>453,1676</sup> After the 1991 Gulf War cease fire, for example, DOD reports that all unused anthrax vaccine stocks were stored at an Army medical supply facility in Dhahran, Saudi Arabia. Refrigeration malfunctions at the facility in April and May 1991 prompted Army officials to recommend that the vaccine be disposed of, rather than returned to the U.S.<sup>1622</sup> In 1999, DOD had to destroy a shipment of 20,000 vials of anthrax vaccine delivered to a U.S. base in Germany because of vaccine degradation caused in shipment. Since that time, an improved system for packaging and transporting AVA was jointly developed by DOD and Bioport.<sup>1676</sup> But during the Gulf War, it is possible that some vaccine was affected by problems during shipment, storage, or distribution under the difficult circumstances of wartime, mass inoculations, and the harsh desert environment.

Although there are many sources of *possible* variability in the anthrax vaccine used in the Gulf War, there is little reliable information to indicate whether or how the anthrax vaccine given to Gulf War veterans was actually affected by any of these circumstances. So the question of whether effects of AVA received in the Gulf War can reliably be deduced from studies of vaccine produced in the years before the war, or in more recent years, remains open. If the anthrax vaccine given to Gulf War troops varied in important ways from AVA produced in recent years, adverse effects data from recent studies would tell us little about adverse effects of anthrax vaccine given to Gulf War veterans. If there were problems with specific shipments or lots of the vaccine used during the war, Gulf War veterans or other subgroups who received those lots might be affected by problems not typical of vaccine recipients overall, problems that could go undetected when all Gulf War veterans are assessed as a single group.

**Quality control issues related to vaccine production at the Michigan facility.** U.S. FDA regulations require any vaccine lot approved for distribution to pass specific tests that demonstrate the

lot's purity, potency, sterility, and safety. The anthrax vaccine has a three year shelf life, but the manufacturer may request three year extensions of the expiration date, after retesting and demonstrating the lot's potency.<sup>1676</sup> As mentioned, FDA identified multiple violations and problems in MBPI/Bioport's production facility in the late 1990s. But little quality control information is available on anthrax vaccine produced by MDPH at the time of the Gulf War. There were no FDA inspections of the MDPH anthrax vaccine production facility prior to 1993. Department of Defense inspections, however, identified multiple problems in the MDPH anthrax vaccine production process in 1992, including a lack of stability studies.<sup>1674</sup>

In 1993 and 1995, FDA inspections at MBPI revealed a number of problems and violations in product lines unrelated to anthrax vaccine.<sup>680</sup> Additional problems were noted between 1996 and 1998, some of which did relate to anthrax vaccine production and testing. For example, 1998 FDA inspections identified significant violations related to stability testing, potency testing, assigning expiration dates, and justification for redating expired anthrax vaccine lots that resulted in MBPI quarantining several lots. FDA issued warnings during this period, and a 1997 notice to revoke MBPI's license.<sup>680,1665</sup>

MBPI voluntarily ceased vaccine production in January 1998 to undergo extensive plant renovations that had been previously planned. The facility transferred ownership to Bioport in September 1998. After renovations were completed, the production facility and newly produced vaccine were required to undergo detailed testing and FDA review before full production could resume, and before newly-manufactured vaccine was released for distribution. All plans, processes, and facilities related to production of the anthrax vaccine received final FDA approval in January, 2002.<sup>680</sup>

Production changes in the U.S. anthrax vaccine before and at the time of the Gulf War, lot-to-lot variation documented before and after the Gulf War, production violations after the Gulf War, and extensive improvements in the manufacturing process since 1998 all contribute to the Committee's observation that health effects potentially related to AVA given to Gulf War veterans may not be reflected by vaccine studies conducted prior to 1972 and, again, after 1998. However, any identified patterns of health problems that relate to AVA more generally, over different periods of time, may be informative about the potential for anthrax vaccine to have contributed to ill health in Gulf War veterans. Therefore, the Committee reviewed available research concerning acute reactogenicity and longer-term health effects of the anthrax vaccine.

**Short and long-term health effects of AVA.** Unwanted side effects of vaccines can be due to antigens used in the vaccine or to other vaccine components such as adjuvants, preservatives, or contaminants. Since the military implemented its anthrax vaccination program, a growing number of studies and monitoring efforts have provided data on acute adverse reactions associated with the anthrax vaccine. There has also been more information available related to longer-term health outcomes in AVA recipients. Thus far, however, longer-term studies have focused primarily on large health services datasets that provide information on hospitalizations, clinic visits, and disability for diagnosed conditions. While these represent an important step forward in understanding possible longer-term health effects of the anthrax vaccine, such studies provide few insights concerning symptom rates and undiagnosed multisymptom conditions.

Until recent years, the only controlled clinical trial of AVA was a study conducted between 1955 and 1959 that compared rates of anthrax among 1,249 vaccinated and unvaccinated workers in four goat hair mills.<sup>162</sup> Investigators reported that 35 percent of vaccine recipients had acute, local reactions to the vaccine over the course of the vaccination series, with less than three percent characterized as severe. The U.S. Centers for Disease Control and Prevention (CDC) also provided unpublished data in support of licensure of the anthrax vaccine in 1970. Those data, described in a 2002 IOM report, indicate that among the nearly 7,000 people vaccinated, eight percent had mild reactions and 0.2 percent had severe

**Table 4. Studies Identifying Rates of Acute Adverse Reactions to the U.S. Anthrax Vaccine**

Study	Follow up	Injection Site Reactions			Systemic Reactions				
			% All	% Women	% Men	% All	% Women	% Men	
Clinical trial of 1,249 mill workers, 1955-1959 <sup>162</sup>	Active, 48 hours	any red < 5 cm red > 5 cm	35% 30% 5%			any	0.2%		
CDC surveillance of 6,895 AVA recipients 1967-1972 <sup>138,680</sup>	Active, 48 hours	any mild moderate severe	10% 9% 1% <0.2%			any	<0.06%		
Reanalysis of CDC data on 1,749 AVA recipients 1967-1972 <sup>1009</sup>	Active, 48 hours	any mild moderate severe	28% 24% 3% 0.2%	48%*	16%*	any fever headache	0.6% 0.3% 0.2%		
1,583 Fort Detrick lab workers who received AVA 1973-1999 <sup>1213</sup>	Passive, "short term"	any induration erythema tenderness	3.6% 2.8% 2.5% 1.7%	6.4% 6.3% 3.6%	2.0% 1.7% 1.3%	any headache fever	1% 0.4% 0.1%	0.7% 0.2%	0.3% <0.1%
Fort Bragg booster study, 452 men received AVA and BT boosters 1992-1994 <sup>1214</sup>	Active, 1 month	any	26%			any myalgia rash headache	45% 31% 17% 17%		
Fort Detrick dosing study, 101 volunteers received 1-3 doses AVA subQ 1998 <sup>1214,1215</sup>	Active, 1 month	tenderness nodule erythema	70% 38% 36%	84% 63% 63%	63% 24% 22%	headache malaise myalgia		11% 8% 7%	9% 10% 3%
GAO survey of 311 Air Guard and reservists in 2000 who received AVA <sup>1680</sup>	Active, duration not specified	any burning knot red > 2.5 in	76% 60% 55% 19%			any joint pain fatigue fever	24% 16% 12% 8%		
2,824 Army personnel in Korea, 1998-1999 <sup>612</sup>	Active, symptoms recorded at next dose	any* knot red > 5 cm		68% 58% 11%	40% 28% 4%	pain malaise fever		19% 15% 2%	10% 6% 1%
Tripler Army Medical Center, 601 healthcare personnel 1998-2000 <sup>1754</sup>	Active, 1-2 weeks	lump* soreness red > 5 cm		90% 80% 41%	64% 66% 17%	myalgia fatigue headache		47% 36% 33%	41% 22% 17%
48 Fort Lewis ROTC cadets, received standard dose AVA in 2000 <sup>543</sup>	Active, "few days"	sore arm* lump swelling	83% 42% 42%			fever tiredness headache	8% 0% 0%		

Abbreviations: AVA=anthrax vaccine adsorbed; BT = botulinum toxoid; subQ = subcutaneous  
 Note: \*reaction rates after initial dose

reactions.<sup>680</sup> Recently, CDC investigators reanalyzed a subset of those data, using original reporting forms for 1,749 individuals, and found that local, mostly mild reactions had occurred with 28 percent of the doses, and that women were nearly three times as likely as men to have had adverse reactions.<sup>1009</sup>

The Committee reviewed these, and more recent studies to evaluate rates of acute reactions to the anthrax vaccine, as summarized in Table 4. Although such studies rarely provide information on vaccine reactions that persisted longer than a few days, acute reactions may be relevant to chronic health problems affecting Gulf War veterans. A direct connection is suggested by two Gulf War studies indicating that veterans who experienced acute reactions to deployment-related vaccines were more likely to be in poor health years after the war.<sup>1374,1698</sup>

As shown in Table 4, reported rates of both local and systemic reactions were markedly higher among vaccine recipients evaluated after 1998 than groups evaluated in the 1950s-1970s. The only exception is the study of laboratory workers at Fort Detrick, which relied on passive surveillance rather than actively querying individuals about vaccine reactions, and included some individuals who received anthrax vaccine produced in the 1960s or 1970s. Studies of AVA recipients have consistently reported that significantly higher proportions of women than men have localized reactions to AVA. Several studies have also reported higher rates of systemic reactions in women.<sup>612,1213,1754</sup>

Overall, local reaction rates in post-1998 vaccine studies were extremely high, generally affecting 70-80 percent of recipients. Systemic reactions were also much higher than in early studies. Pre-1972 reports had indicated that fewer than one percent of AVA recipients experienced systemic reactions. Post 1998 studies, however, typically reported that 10-40 percent of vaccine recipients experienced systemic reactions. It is not clear why adverse reactions have been reported at dramatically higher rates in recent studies. It could be that the current AVA is more reactogenic than formulations used in the 1960s and 1970s. Alternatively, the differences may relate to how data were collected, that is, the recent use of interviews or questionnaires that proactively query vaccine recipients about specific problems, rather than a passive process that requires individuals to come forward to identify complaints.

The 2002 IOM report on AVA provides data from a commissioned report summarizing rates of adverse reactions identified in clinical trials of other vaccines, for comparison to adverse reactions reported for AVA.<sup>680</sup> The IOM report concluded that rates of acute adverse reactions to AVA appeared comparable to other vaccines. As shown in Table 4, however, recently published studies indicate that AVA is associated with extremely high rates of acute, local reactions, higher than is typical of other vaccines.

Earlier committee reports often observed that no studies had provided information on long-term health outcomes in relation to receipt of AVA or other vaccines. But in recent years, military studies have begun to address this issue, largely through research involving the use of large military health services datasets. Studies providing information on longer-term health outcomes in relation to receipt of anthrax vaccine are summarized in Table 5. Studies that specifically evaluated the health of Gulf War veterans in relation to receipt of the anthrax vaccine are discussed in a later section.

As shown in Table 5, data linkage studies that evaluated hospitalizations, outpatient visits, and disability claims for diagnosed conditions six weeks to four years after vaccination have found few differences between anthrax vaccine recipients and nonrecipients. In considering results of these large data linkage studies, however, it is important to keep in mind potentially important biases. These include: (1) the generally better fitness level of “combat ready” personnel most likely to have received the anthrax vaccine and likelihood that those with identified disabilities would not have received AVA, (2) the inclusion of only military hospitalizations, and (3) follow-up periods that were insufficient to detect conditions associated with long latency.<sup>680,1370,1514,1760</sup> No studies have actively assessed rates of symptoms or multisymptom illness months or years after receipt of the anthrax vaccine.

**Table 5. Studies Assessing Longer-term Health Outcomes Following Receipt of U.S. Anthrax Vaccine**

<b>Study</b>	<b>Follow up</b>	<b>Outcomes</b>
Long-term follow up of 155 Fort Detrick workers who received multiple vaccines 1943-1969, including multiple doses of AVA, compared to 265 community controls <sup>1212</sup>	Up to 43 years	No differences in diagnosed medical conditions. Significantly more AVA recipients reported fatigue and had abnormal lab values for several measures, including a higher proportion (12% vs. 4%) with monoclonal gammopathies.
Comparison of outpatient visits among 4,045 AVA recipients at Langley AFB to 1,132 unvaccinated personnel deployed to southwest Asia 1998-1999 <sup>1263</sup>	6 month period after return from deployment	No differences in total number of outpatient diagnoses or any specific diagnoses in vaccinated vs. unvaccinated.
1998 military hospitalizations among 159,386 active duty AVA recipients compared to nonrecipients <sup>1355</sup>	0-42 days after vaccination	Vaccinated personnel sign. less likely to be hospitalized overall, and for multiple diagnostic categories.
Retrospective medical chart review of 403 Canadian military personnel who received AVA in 1998, compared to 445 who did not <sup>655</sup>	8 month period after vaccine received	Overall, groups similar in total number of symptoms and diagnoses; minor increases in symptoms and diagnoses post-deployment in both groups.
Comparison of general health status and healthcare visits among 301 AVA recipients and 639 unvaccinated personnel at Tripler Army base in 2000 <sup>1754</sup>	Up to 2 years following receipt of 1 <sup>st</sup> vaccine	Most outcomes similar in vaccinated and unvaccinated. Vaccinated women were 4 times as likely to report general health as fair or poor (6.6% vs. 1.5%); sign. fewer mental health visits in vaccinated.
CDC study of postal and government workers who received antibiotics only (n=948) or antibiotics with AVA (n=165) following possible exposure to anthrax in 2001 <sup>973,1541</sup>	2 months active, then passive	43-46% of AVA recipients reported at least one adverse event, similar for those who did/did not receive AVA. Four conditions sign. lower in AVA group. No serious adverse events reported by AVA recipients.
Case control study of AVA as a risk factor in 1,131 cases of optic neuritis, using DMSS data 1998-2003 <sup>1180</sup>	6-18 weeks after vaccination	No association between optic neuritis and receiving AVA or number of doses of AVA.
Comparison of DMSS data on outpatient visits and hospitalizations for 843 diagnoses among 2 million individuals in "prevaccination" and "postvaccination" cohorts; 23% received AVA during 3 year observation period <sup>865</sup>	1 day-21 months after vaccination	Overall, fewer hospitalizations and outpatient visits in post-vaccination cohort. Higher number of postvaccination hospitalizations for 17 diagnoses and outpatient visits for 34 diagnoses—fewer than expected by chance, partially explained by confounding.
Comparison of disability claims for AVA recipients and nonrecipients among 716,833 Army personnel; 22% received AVA <sup>1514</sup>	1 day-4 years after vaccination	Overall, rate of disability evaluations similar for vaccinated and unvaccinated. No sign. differences related to neurological or musculoskeletal conditions. Older AVA lots associated with slightly higher disability than newer lots.
Post-vaccination military hospitalizations among 170,723 active duty AVA recipients deployed 1998-2001, compared to pre-vaccination hospitalizations <sup>1760</sup>	0-42 days after vaccination	Overall, vaccinated personnel sign. less likely to be hospitalized than unvaccinated for any cause; no increases in any diagnostic categories.
Health status and hospitalizations among 67,796 military personnel enrolled in the Millennium Cohort Study <sup>1427</sup>	Time after receipt of AVA not specified	AVA recipients and nonrecipients were similar on all SF36 measures and rates of hospitalization for any cause.

Abbreviations: AVA = anthrax vaccine adsorbed, DMSS = Defense Medical Surveillance System, sign. = statistically significantly

One data linkage study utilized the Defense Medical Surveillance System (DMSS) to evaluate hospitalizations and outpatient visits 1998-2000 in military medical facilities worldwide in personnel who received AVA, compared with a “prevaccination cohort” of personnel who had not yet been vaccinated.<sup>865</sup> Overall hospitalization and clinic visit rates were higher in the prevaccination cohort, reflecting generally better health among personnel who receive immunizations and deploy overseas. Of the 843 diagnoses evaluated, significantly higher post-vaccination hospitalization rates were identified for 17 conditions, fewer than the number expected by chance.<sup>680</sup> Some differences were explainable by confounding, for example, higher rates of malaria identified after vaccination, reflecting AVA received prior to deployment to regions where personnel were at increased risk for malaria. None of the 40 diagnoses reported to VAERS after receipt of AVA were associated with significantly higher hospitalization rates. However, the post vaccination cohort had a nonsignificant increase in hospitalization for multiple sclerosis (RR=1.3) Unpublished data provided to the IOM anthrax vaccine committee indicated that this elevation was limited to women AVA recipients, an observation the panel considered a preliminary “signal” that warranted continued monitoring.<sup>680</sup>

The military’s current policy is not to give the vaccine to pregnant women, based on early indications of a possible increase in birth defects among women who received AVA in the first trimester of pregnancy.<sup>138,221,680</sup> A large study has recently been reported by the U.S. Naval Health Research Center that used computerized records to identify all birth defects identified in the first year of life among over 115,000 live births to women service members between 1998 and 2004. Women who received AVA in the first trimester of pregnancy had a significant 20 percent greater risk for having children with birth defects, compared to those who had not received the vaccine.<sup>1335</sup> Atrial septal defects were the only specific birth defect category significantly associated with first trimester receipt of the vaccine. Smaller studies have found no association between receipt of AVA and number of pregnancies, birth outcomes, or male fertility measures.<sup>217,1785</sup>

**Individual cases and VAERS reports.** Several published case reports have described medical conditions that developed in individuals after they received the anthrax vaccine. These have included immediate and delayed hypersensitivity reactions,<sup>533,971,1521,1544</sup> rheumatoid arthritis,<sup>1711</sup> optic neuritis,<sup>797</sup> lymphocytic vasculitis,<sup>1085</sup> and oral pemphigus vulgaris, an autoimmune condition associated with oral blisters and ulcers.<sup>1080</sup>

As previously described, the military requires that all serious adverse reactions to vaccines, specifically those requiring hospitalization or those resulting in lost duty for more than 24 hours, be reported to VAERS. It appears that vaccine reactions are sometimes not reported to VAERS, however, for reasons that include reticence of military personnel to identify health problems and lack of familiarity with the reporting process.<sup>1680</sup> Among the 600 healthcare personnel evaluated in the Tripler Army survey after receiving the anthrax vaccine, five events were reported to VAERS. This included one female with MRI indications of demyelinating disease within one week of her fourth shot who was eventually diagnosed with multiple sclerosis.<sup>1754</sup> Two studies have provided summary analyses of VAERS data in relation to AVA, and found more adverse reactions involving joint symptoms and gastrointestinal problems than have been reported for other vaccines.<sup>477,478</sup>

Determining whether the anthrax vaccine is the primary cause of conditions that develop in temporal proximity to receipt of the vaccine can be difficult, however.<sup>571,1392</sup> At the request of the Army Surgeon General, the Department of Health and Human Services appointed an advisory panel of civilian physicians and scientists, the Anthrax Vaccine Expert Committee (AVEC), to advise on the likelihood that individual adverse events reported to VAERS were caused by the anthrax vaccine.<sup>1391</sup> Over the first four years of the AVIP program, after 500,000 military personnel had received the anthrax vaccine, the AVEC reported that 1,841 reports involving 3,991 adverse events had been submitted to VAERS.<sup>1390</sup> The most commonly reported problems involved extended areas of inflammation and redness at the injection site, rash elsewhere on the body, malaise/fatigue, arthralgia, and headache. Forty-four reports described

an arthralgia-related multisymptom illness, defined as including arthralgia and two or more of the following: malaise/fatigue, paresthesia, memory loss, sleep disorder, and altered mentation. One hundred forty-seven events were classified as serious or medically important. These included five cases of an anaphylactic-type reaction, four cases of Guillain-Barré syndrome, three cases of multiple sclerosis, two cases each of seizure, diabetes, and Hashimoto's thyroiditis, and one case each of lupus, rheumatoid arthritis, and fibromyalgia. Of the 147 serious/medically important events, 26 were identified as possibly, probably, or certainly the result of the vaccine. Others were identified as unlikely, unrelated, or unclassifiable. Of the six deaths reported, four were identified as unrelated to the vaccine, and two were unclassifiable. The AVEC concluded that the evidence indicates that AVA was not associated with an unusually high rate of serious adverse events and identified no pattern of problems with specific lots.

All cases of serious medical conditions that develop after receipt of the anthrax vaccine, are, of course, of great concern. Individuals who develop disease as a result of vaccines received for military service are entitled to have their condition acknowledged and their health needs addressed by DOD and/or VA. But there is no indication from research studies conducted thus far that anthrax vaccine is associated with an increased risk of any specific chronic medical condition—diagnosed or undiagnosed. Given the limitations of studies conducted to date, however, it cannot be said with certainty whether or not AVA is associated with excess rates of undiagnosed multisymptom conditions or with serious diagnosed diseases of longer latency periods that would not be detected in short-term studies of military hospitalizations and clinic visits. Therefore, it is still important that individuals who received AVA be monitored for an extended period to carefully ascertain rates of both multisymptom illness and diagnosed diseases.

**Ongoing anthrax vaccine research.** Government officials have generally considered the U.S. anthrax vaccine to be both safe and effective.<sup>459,514</sup> But the extended dosing schedule required, and concerns about the vaccine's reactogenicity have prompted efforts to develop improved anthrax vaccines, as well as alternate dosing methods and schedules for the current vaccine.<sup>679,914,968,1213</sup> Multiple projects have been funded by the military, as well as by other agencies in connection with Project Bioshield. Studies to ascertain safety and immunogenicity of a next-generation recombinant PA anthrax vaccine continue, despite recent contract and production problems.<sup>1334</sup> The U.S. Centers for Disease Control is currently sponsoring a multifaceted program to evaluate AVA effectiveness, adverse effects, and optimal dosing/scheduling. The program includes a human trial to determine reactogenicity and immunogenicity resulting from current and alternate dosing methods, a primate trial to determine vaccine immunogenicity, and laboratory studies to determine biological processes associated with the development of anthrax. Additional objectives include long-term follow-up of previously immunized populations.<sup>681</sup>

### **Other Vaccines Given to Gulf War Troops**

Although the anthrax vaccine has been the primary vaccine-related issue raised in connection with Gulf War illness, Gulf War veterans received many other immunizations prior to and during deployment. There is little or no documented evidence regarding associations between any of these vaccines and long-term health outcomes, including symptom complexes like those affecting Gulf War veterans.

**Botulinum toxoid (BT).** Seven different toxins are produced by strains of the bacterium *Clostridium botulinum*. These extremely toxic substances affect peripheral nerves at extremely low doses, causing death by paralysis and respiratory failure. Animal studies have assessed the effectiveness of different individual and combination toxoid vaccines, but as is generally the case, provide limited information on adverse reactions and no information on long-term effects. The pentavalent BT vaccine used in the Gulf War contains aluminum phosphate as an adjuvant. It requires three injections, given over 12 weeks, with annual boosters thereafter. This vaccine has still not been licensed, and is still designated by FDA as investigational. In studies of the efficacy of this and other pentavalent BT vaccines conducted in the 1960s, investigators reported there were few problems with acute, local reactions and no problems with

systemic or severe reactions.<sup>439,440</sup> The IOM report on vaccines also describes an unpublished study, conducted by the Army, of two BT vaccine formulations given to 36 individuals.<sup>679</sup> Both formulations, containing different levels of formaldehyde, produced similar rates of local reactions (15-18%), and no severe reactions. CDC monitoring data for BT recipients reportedly found that seven percent of the nearly 17,000 doses administered prior to 1997 were associated with a moderate local reaction and 0.4 percent with a severe reaction. These events were described as being of limited duration.<sup>679</sup>

The agreement that allowed BT to be given to personnel in the Gulf War stipulated that records be kept of who received the vaccine and that side effects be monitored, but neither were effectively carried out.<sup>462</sup> A 1995 IOM report provided results of a postcard survey of 123 Marines at Camp Pendleton who had received BT during the Gulf War. Of the 121 Marines who responded, 12 percent reported they had had a mild local reaction to the vaccine, 14 percent reported pain that temporarily limited the use of the vaccinated arm, and 2.5 percent reported some type of systemic reaction. No reactions were associated with serious problems or limited duty.<sup>675</sup>

**Additional vaccines given to military personnel.** As shown in Tables 1 and 2, Gulf War veterans received many different types of vaccines before and during deployment. Little concern has been raised about vaccines other than anthrax and BT, however. Most vaccines administered at the time of the Gulf War had been in use for many years, by both military and civilian populations. For example, yellow fever vaccine has been widely used by the military and by civilians in endemic areas for decades, and is considered to have an acceptable safety profile.<sup>445,1060</sup> Reactions to this vaccine are generally mild (headache, low-grade fever, and myalgia) and can affect up to 25 percent of recipients.<sup>964</sup> In recent years, neurological conditions have been reported to VAERS in relation to receipt of the yellow fever vaccine, including four cases of encephalitis, four cases of Guillain-Barré syndrome, and three cases of demyelinating disease reported between 2001 and 2006.<sup>964</sup>

Other vaccines used in the war are also associated with transient, local effects, and with rare cases of serious systemic and/or chronic effects.<sup>550</sup> Similarly, immune globulin injections, used to prevent hepatitis A in the Gulf War, can produce transient local effects and, infrequently, more serious effects.<sup>219</sup> Although widely considered to be safe, little research information is available concerning long term effects of these vaccines, individually or in combination.

## Vaccine Adjuvants

The presence of anti-squalene antibodies in ill people and the absence of the antibodies in healthy people is the first hard laboratory evidence that Gulf War illness is what some might refer to as a 'real disease.' It is also the first evidence that an abnormal immunological response is under way in Gulf War illness patients.

-- Dr. Robert Garry, statement for 2002 Congressional hearing <sup>474</sup>

Adjuvants are substances added to vaccines to enhance the immune response triggered by the vaccine. Although only aluminum-based adjuvants are licensed for use in the U.S., many types of adjuvants have been developed and tested. Different adjuvants produce different types and strengths of immune stimulation, and have different adverse reaction profiles.<sup>548,963</sup> In 1997, a series of magazine articles reported that Gulf War illness had been linked to autoimmune abnormalities caused by the use of an unlicensed adjuvant containing squalene in a vaccine given to military personnel.<sup>1299</sup> The reporter described evidence provided by Dr. Pamela Asa, a Tennessee immunologist in private practice, who had tested the blood of a number of ill veterans and found high levels of antibodies to squalene. These reports spurred a major controversy, and the squalene theory of Gulf War illness became the subject of government inquiries, scientific articles, panel reviews, and a high profile book published by an investigative journalist.<sup>679,977,1675,1690</sup>

The squalene controversy has been multifaceted, raising such diverse questions as whether the government illegally used an experimental vaccine adjuvant during the Gulf War, whether squalene adjuvants cause the types of symptoms seen in Gulf War veterans, and whether the tests used to detect squalene antibodies are reliable. The Committee reviewed available evidence concerning these and other questions. For the Committee's purposes, however, a single question is primary, that is, whether there is evidence that symptomatic Gulf War veterans have abnormally high levels of circulating squalene antibodies. Despite the attention given to the squalene issue over the past decade by scientists and government agencies, no clear answer to this question has emerged.

**Squalene antibodies in ill veterans.** Although Dr. Asa is reported to first have broached the subject of adjuvant-induced illness in Gulf War veterans with military officials in 1994,<sup>977,1675</sup> the first study that addressed the issue was published in 2000. In the study, Dr. Asa and colleagues at Tulane University tested for IgG antibodies to squalene in two Gulf War veteran groups, using an assay developed at Tulane. In the first group, blinded analyses were conducted on sera from 38 sick and 12 healthy Gulf War veterans. Symptomatic Gulf War veterans in the study all met the CDC definition of chronic multisymptom illness, but more than a third also had serious diagnosed conditions such as ALS, lupus, and multiple sclerosis.<sup>69</sup> Results indicated that 36 of the 38 sick veterans (95%) tested positive for squalene antibodies, but none of the 12 healthy veterans tested positive. An additional six symptomatic Gulf War era veterans who had received vaccines for deployment, but had not actually deployed, also tested positive.

The second set of analyses were not blinded. The samples tested included 86 Gulf War veterans of undetermined health status and 48 blood donors from the general population. Sixty-nine percent of the Gulf War veterans tested positive for squalene antibodies, but only five percent of the community blood donors were positive. By comparison, few patients from separate groups of lupus patients and breast implant recipients tested positive for squalene antibodies.<sup>69</sup>

In a second paper, Dr. Asa and her Tulane collaborators reported elevated levels of squalene antibodies among military personnel who had received the anthrax vaccine after 1997, as part of DOD's anthrax vaccine immunization program (AVIP). About half of the 25 vaccine recipients in the sample were symptomatic, although case status was not explicitly defined. Thirty-two percent of vaccine recipients tested positive for squalene antibodies, compared to only 16 percent of matched, nonmilitary controls. Further analyses indicated that all individuals with squalene antibodies had received anthrax vaccine from one of five specific lots. Among the 17 individuals who received vaccine from those lots, 76 percent were symptomatic and 47 percent had squalene antibodies. None of the eight veterans vaccinated with other lots were symptomatic or had squalene antibodies.<sup>70</sup>

These studies were reported to have been done with no external funding and, in a number of ways, were not optimally designed.<sup>1572</sup> Samples were small, self-selected, and poorly defined. For example, some Gulf War multisymptom illness cases in the first study had concurrent autoimmune diseases, while some controls had fibromyalgia or chronic fatigue; some findings came from unblinded analyses of sera obtained from poorly characterized patients. Still, study results were intriguing and raised a hypothesis that could be further evaluated in more definitive studies. Identification of an objective test that distinguished a sizable proportion of symptomatic from healthy Gulf War veterans was potentially of great importance as a diagnostic tool, and for providing possible insights concerning pathophysiological processes and even treatments for ill veterans.

**Squalene antibody research at Walter Reed Army Institute of Research (WRAIR).** After its publication, the Asa/Tulane squalene antibody research was criticized by government scientists and panels.<sup>45,679,1572</sup> Critics questioned the idea that squalene, when injected, acted as an antigen, and whether the assay used had actually detected antibodies to squalene. Within months, however, investigators at Walter Reed Army Institute of Research (WRAIR) published research showing that squalene can act as

an antigen and that antibodies could be detected in a model system.<sup>981</sup> A WRAIR high throughput squalene antibody assay was developed by 2002,<sup>979</sup> and subsequently used to evaluate squalene antibodies in mice and humans. Human blood samples from three populations were evaluated: (1) retired laboratory workers from Fort Detrick who had received multiple vaccines, including AVA, over many years, (2) similarly aged community controls who had never received AVA, and (3) samples from an Army blood center at Fort Knox, which primarily contained serum from young recruits.<sup>980</sup>

Squalene antibodies were detected in all of the groups tested. IgM antibodies were found in about one third of both the Fort Detrick and community cohorts (37%, 32% respectively), but in significantly fewer blood center samples (19%). IgG antibodies were found less frequently in the Fort Detrick and community samples (7% and 15%, respectively), and were not detected at all in the Army blood center samples. Investigators suggested that the prevalence of squalene antibodies increases with age, since the mean age of Fort Detrick volunteers was 68, and the blood center samples were predominantly from individuals 18-21 years of age. This was supported by studies in mice demonstrating a significant increase in circulating squalene antibodies with age.<sup>980</sup>

The WRAIR studies have been extremely useful, developing a well-validated assay and demonstrating that squalene antibodies are detectable in human serum at rates that may increase with age. However, this research did not address the core issue raised by the Asa/Tulane studies concerning Gulf War illness. That is, the WRAIR studies did not measure IgG squalene antibodies in individuals who received vaccines postulated to contain squalene. Nor did they compare squalene antibody levels in symptomatic versus healthy Gulf War veterans. It is important to note, also, that the WRAIR and Asa/Tulane studies provided comparable results concerning “background” rates of squalene IgG antibodies in humans. The WRAIR study identified IgG antibodies in 7-15 percent of individuals in the Fort Detrick and community samples, similar to the 5-16 percent range identified in control populations in the two Asa studies.

**Did anthrax vaccine used in the Gulf War contain a squalene adjuvant?** Both DOD and NIH have sponsored multiple animal studies and human trials of vaccines with experimental adjuvants containing squalene and squalane, a hydrogenated variant of squalene. This includes DOD-sponsored animal studies of anthrax vaccine formulations with squalene-containing adjuvants begun in 1987, and two small DOD-sponsored human trials of a malaria vaccine that were underway before the Gulf War.<sup>1675</sup>

It has been argued that, given the deadly threat posed by anthrax, the addition of a potent adjuvant to AVA at the time of the Gulf War might have been considered a responsible decision, to enhance the immunogenicity provided by the vaccine in the limited time available in the run up to the war. Facing similar time constraints, British officials opted to use the pertussis vaccine to adjuvanate the U.K. anthrax vaccine. But U.S. government reports have consistently maintained that DOD officials decided against using novel adjuvants with the anthrax vaccine because of restrictions and delays required for FDA licensure of an altered vaccine formulation.<sup>1622,1675</sup>

Still, given the concern surrounding the issue, several investigations were undertaken to determine whether or not there was squalene in the U.S. anthrax vaccine. The Department of Defense commissioned Stanford Research Institute International (SRI) to develop an assay capable of detecting squalene in anthrax vaccine. The initial assay could detect squalene at levels of 140 parts per billion, equal to 70 ng. of squalene per 0.5 ml. AVA dose. SRI then tested samples from 17 lots of AVA, including the five lots identified in the 2002 Asa study as being associated with excess levels of squalene antibodies. No squalene was found in any of the lots tested.<sup>1459</sup>

In 2000, however, U.S. Food and Drug Administration (FDA) officials announced that, using a more sensitive assay, they had detected “trace” amounts of squalene, ranging from 10 to 83 parts per billion, in each of five lots of anthrax vaccine tested, and also in lots of tetanus and diphtheria vaccines.<sup>984</sup> The FDA report verified that manufacturing records did not indicate that squalene had been added to the anthrax

vaccine formulation, and concluded that the low levels detected were likely related to natural occurrence or low-level contamination.<sup>1665</sup> Subsequently, SRI developed a more sensitive assay, capable of identifying squalene at the level of 1 ng. per 0.5 ml. dose of vaccine, and tested samples from 38 lots of AVA, including seven lots reported to have been used during the Gulf War. All lots tested had been produced by MDPH or Bioport, with expiration dates between 1982 and 2001. No squalene was detected in 43 of the 44 lots tested, but an extremely low level was detected in three samples from lot FAV008 (1-9 ng. per ml.).<sup>1458</sup> In contrast to the FDA findings, none of the suspect lots identified in the Asa/Tulane studies were found to contain squalene.

Reports indicate that, when squalene-containing adjuvants are used as part of a vaccine formulation, squalene is present at a concentration of 0.2 – 5.0 percent, or 1-25 mg. in a 0.5 ml. dose of vaccine.<sup>1458,1665</sup> This is more than a million times the level of squalene detected in anthrax vaccines by FDA and SRI testing. Whatever the source of the detected squalene, the FDA and SRI studies support the government's assertion that squalene-containing adjuvants were not added to the tested vaccine lots at levels generally used for adjuvants. Some have speculated that even these very minute levels of squalene, less than the level normally found in human blood, might be capable of stimulating reactions,<sup>977</sup> but no studies have evaluated this contention.

**Health effects of squalene.** Squalene is an oily substance that naturally occurs in plants and animals. It is found in a variety of foods, lotions, and cosmetics. It is also used as a food supplement and has been postulated to provide therapeutic benefits.<sup>225,787</sup> In humans, squalene is synthesized by the liver as a precursor to cholesterol, and circulates in the blood. Many substances that are ingested or found in the blood, however, cannot be safely injected. Squalene, when injected, stimulates a nonspecific immune response, making it a useful component of vaccine adjuvants.<sup>41,1218</sup> The original theory relating anthrax vaccine and squalene adjuvant to Gulf War illness suggested that veterans' symptoms were autoimmune in nature, that is, they were associated with autoantibodies stimulated by receipt of the vaccine. Associations between autoimmune conditions and vaccines have long been postulated, including vaccines against diphtheria, tetanus, polio, and hepatitis B.<sup>1148,1404</sup> In animal models, squalene has been used to induce antibodies and precipitate diseases that simulate human autoimmune conditions, including lupus<sup>847,1356</sup> rheumatoid arthritis,<sup>213,618</sup> and multiple sclerosis.<sup>114</sup>

No squalene-containing adjuvants are licensed for use in the U.S., but a number have been evaluated in clinical studies. These include trials of vaccines for influenza, herpes simplex, and HIV.<sup>92,518,867,972,1675</sup> MF59, an oil-in-water microemulsion, is the most widely used squalene-containing adjuvant. An influenza vaccine containing MF59 has been licensed for use in European countries since 1997 and is considered to have a good safety record.<sup>1217</sup>

A recent collaborative study between Italian and U.S. investigators suggests that receipt of squalene-containing adjuvants may not stimulate elevated levels of squalene antibodies in humans.<sup>328</sup> Using an ELISA squalene antibody assay, investigators identified low-levels of squalene IgG antibodies in 79 percent of a sample of U.S. adults, and 26 percent of European adults who had not received vaccines containing squalene. IgG antibodies to squalene were also detected at low levels in 94-100 percent of European adults 65 years of age and over who participated in influenza vaccine trials, whether or not the vaccine received in the trial contained MF59. Investigators concluded that low levels of circulating squalene antibodies are commonly found in adults, and that squalene antibody levels are not affected by receipt of vaccines containing squalene. Although interesting, these findings raise more questions than they answer. No clear explanation is offered, for example, for the substantial differences in rates of squalene antibody positivity in the three cohorts evaluated. Nor is there any explanation for why results differed so dramatically from the two previous U.S. studies, which found IgG antibodies in fewer than 20 percent of adults studied.<sup>69,980</sup>

**Conclusions of special committees.** Previous government committees and scientific panels have focused on different aspects of the squalene issue. The theory was sometimes dismissed without detailed consideration, based on DOD assertions that squalene was not added to the anthrax vaccine.<sup>1227,1690</sup> Little published research was available to earlier panels, so conclusions were usually based on commonsense observations. The Presidential Special Oversight Board pointed out, for example, that low levels of squalene had been found in diphtheria and tetanus vaccines, but no “Gulf War syndrome” issues had been raised in relation to these vaccines.<sup>1232</sup> An Institute of Medicine panel pointed out shortcomings in the Asa/Tulane squalene antibody studies, and concluded they did not provide persuasive evidence that squalene antibodies had been detected.<sup>679</sup> The World Health Organization issued a statement on the safety of squalene-containing adjuvants, citing the safety record of the 22 million doses of the Italian influenza vaccine distributed since 1997.<sup>1812</sup>

**Other adjuvants in Gulf War vaccines.** Adjuvant issues relating to the anthrax vaccine have also made headlines in the U.K. The British MOD acknowledged, in 1997, that pertussis vaccine had been used to adjuvinate the anthrax vaccine given to British Gulf War troops, a decision that has also been controversial.<sup>203,1551,1756</sup> MOD officials have maintained that no vaccines containing squalene were given to British troops. Tests conducted by an independent laboratory in 2001, sponsored by MOD, found no squalene in 11 lots of the U.K. anthrax vaccine, nor in other types of vaccines given to British troops during the Gulf War.<sup>1568</sup>

The U.S. Department of Defense has consistently maintained that all adjuvants in vaccines used during the Gulf War were aluminum-based and FDA approved. Immunizations given to Gulf War veterans that contained aluminum adjuvants included anthrax, BT, and tetanus-diphtheria vaccines.<sup>1622</sup> Aluminum adjuvants have been used in vaccines for over 60 years, and are considered to have a good safety record.<sup>711,909</sup> Vaccines containing aluminum adjuvants have been extensively studied in humans and animals for both effectiveness and adverse effects, but very little research has specifically looked at neurological effects of vaccine adjuvants, an area of particular interest in relation to Gulf War illness.

A recent Canadian study evaluated long-term effects of both squalene and aluminum hydroxide adjuvants on behavior and central nervous system tissues in a mouse model.<sup>1202</sup> Using dosages comparable to those used in human vaccines, animals received two injections, two weeks apart, of one of the adjuvants, both adjuvants combined, or placebo. They were then evaluated using a variety of neurobehavioral tests over a six month period, followed by histochemical analyses of brain and spinal cord tissues. Anti-squalene antibodies were found in 20% of animals injected with placebo, 27% of those injected with aluminum, 40% of those injected with squalene, but only 10% of those injected with both adjuvants. Overall, the aluminum adjuvant produced more adverse effects than placebo, squalene, or the combined adjuvants. After six months, mice injected with the aluminum adjuvant exhibited significant declines in muscle strength and endurance, and increased indicators of anxiety, compared to placebo. Aluminum adjuvant was also associated with indicators of increased central nervous system inflammation and motor neuron loss, as reflected by a significant increase (350%) in the number of reactive astrocytes in the lumbar spinal cord and neuronal apoptosis in the motor cortex and spinal cord. Investigators concluded that their findings were consistent with an association between aluminum adjuvants and neurological deficits, including ALS. By contrast, squalene adjuvant was associated with fewer changes in brain and behavior, none of which were statistically significant.

Vaccines containing aluminum hydroxide adjuvant have also been associated with the development of macrophagic myofasciitis.<sup>486</sup> This recently-identified condition is characterized by macrophage infiltration of muscle tissue after receipt of vaccines.<sup>239,485</sup> Patients develop arthromyalgias and fatigue, among other symptoms, with one report indicating that about half of macrophagic myofasciitis patients meet criteria for chronic fatigue syndrome.<sup>76</sup>

Although squalene has been the primary adjuvant issue raised in relation to Gulf War veterans, no studies have specifically linked receipt of squalene-containing adjuvants to biological processes or chronic symptoms that parallel those affecting Gulf War veterans. In contrast, there are preliminary indicators, from both human and animal studies, that aluminum hydroxide adjuvant may be associated with neurological damage and chronic symptoms potentially relevant to the health of Gulf War veterans.

**Primary Gulf War squalene antibody question unanswered.** Eleven years after the squalene controversy was first publicly raised, studies have addressed several related questions. Two laboratories have assessed levels of squalene in selected lots of the U.S. anthrax vaccine, both yielding results that support government assertions that a squalene-containing adjuvant was not added to those lots. Additional studies have provided insights on detection of antibodies to squalene in humans and animals, but have provided little indication that receipt of squalene-containing adjuvants results in chronic production of squalene antibodies.

The observation from the Asa/Tulane studies that is most relevant to the health of Gulf War veterans, however, has not been further evaluated. Their initial study, reported in 2000, indicated that symptomatic Gulf War veterans had detectable levels of IgG antibodies to squalene, but that healthy veterans did not. This raised a testable hypothesis concerning an objective measure of an immunological abnormality that distinguished ill from healthy veterans. The Asa/Tulane studies may have correctly identified excess rates of squalene antibodies in ill veterans, whether or not they were caused by vaccines, by vaccine contamination, or by clandestine use of an unapproved adjuvant. It is important to determine whether the observed association between squalene antibodies and Gulf War illness is supported, or refuted, by more definitive research.

## Health Effects of Receiving Multiple Vaccines

Most studies conducted to establish vaccine safety in humans evaluate vaccines individually. Studies that evaluate receipt of more than one vaccine at the same time are generally concerned with changes in vaccine effectiveness, but may also report on short term adverse effects. The Committee identified little research that provides information on long-term effects of specific vaccine combinations, or numerous vaccines received in a brief time span.<sup>512,675</sup> Receipt of multiple vaccines together is fairly common, however. Multiple immunizations are routinely given to infants and young children. Adults traveling overseas also commonly receive multiple immunizations. Studies have assessed short term side effects related to receipt of vaccine combinations in childhood and have generally reported little or no increase in short-term reactogenicity.<sup>236,1453,1540</sup> In civilians traveling to foreign countries, receipt of multiple vaccines has also been reported as being well-tolerated, although the number who experience acute side effects increases with the number of vaccines received.<sup>156,426</sup> For many years, multiple vaccinations have also been given to new military recruits and to troops preparing for overseas deployment.<sup>1523</sup> Surprisingly little information is available, either from studies or from monitoring programs, that quantifies short or long-term adverse effects resulting from specific combinations of vaccines, or a large number of vaccines received concurrently.

Some insights regarding effects of multiple vaccines received over a prolonged period of time have been provided by a series of follow-up evaluations of laboratory workers at Fort Detrick, Maryland. These workers received multiple immunizations as participants in vaccine studies conducted for the U.S. biological weapons development and countermeasures program between 1943 and 1969.<sup>1211</sup> The first three assessments were conducted in 1958, 1965, and 1974. No abnormal excess of diagnosed diseases affected the workers, but several indicators of a chronic inflammatory process were identified. These included increased rates of leukocytosis and lymphocytosis, alterations in ratios of alpha and beta globulins, and higher mean serum levels of hexosamine.<sup>1189,1190,1770</sup>

The most recent assessment, reported in 2004, evaluated 155 former workers who participated in a Fort Detrick laboratory alumni gathering in 1996, and 265 age and gender-matched controls.<sup>1212</sup> Fort Detrick participants were evaluated an average of 43 years after their first program immunization. Individuals had received different types and numbers of vaccines—a median of 154 each—during their years in the program. For example, 142 of the 155 Fort Detrick workers had received multiple doses of anthrax vaccine, an average of 23 doses per subject. Results indicated no differences in clinically diagnosed diseases between workers and community controls. Fort Detrick workers reported their overall health status to be slightly worse, however, and a higher proportion reported being fatigued. Several serum parameters also differed between the groups. Most significantly, unspecified monoclonal proteins were detected at elevated rates in the Fort Detrick workers. These gammopathies were not further characterized and were not associated with identifiable disease, but have been linked in other studies with the development of serious conditions, including multiple myeloma.<sup>851,852</sup>

The Fort Detrick studies provide an interesting look at the long-term health of selected individuals many years after receiving a large number of vaccines. Overall, the studies indicate that receipt of repeated doses of multiple vaccines over an extended period of time was not associated with identifiable disease, but may produce persistent immune alterations in a subset of individuals. For several reasons, however, these studies have limited relevance for understanding effects of multiple vaccines received for Gulf War deployment. Of the over 3,000 original participants in the Fort Detrick program, those evaluated in follow-up studies were a select group of volunteers. They would not have included, for example, individuals who did not tolerate multiple vaccinations and withdrew from the program, those who had died, or those not healthy enough to attend a social gathering many years after retirement.<sup>1211,1212</sup> Unlike the Fort Detrick program, Gulf War veterans received multiple vaccines over a brief period of time, vaccines that differed from those given to Fort Detrick workers in the 1940s, 1950s, and 1960s.

**Animal studies of effects of vaccines combined with other Gulf War exposures.** As part of its Gulf War research effort, the British Ministry of Defence (MOD) sponsored a series of studies that evaluated effects of multiple vaccines given to U.K. military personnel in the Gulf War, combined with pyridostigmine bromide (PB), in several animal models. A number of abnormalities resulting from these exposures were identified, which differed according to the study design and animal model used. Relatively high-dose combinations of anthrax and pertussis vaccines produced observable illness and weight loss in mice, with milder effects associated with more dilute vaccines. Toxicity effects in the mouse model were attributed mainly to the pertussis vaccine.<sup>1285</sup> A separate study found that PB, given at levels comparable to those used in the Gulf War, had no effect on humoral immunity in mice.<sup>535</sup> A second series of experiments evaluated effects of 10 vaccines, given at various doses, alone and with PB, in a guinea pig model. After 72 days, all animals appeared generally healthy. The only observable effect was slight weight loss in the animals who received the highest-dose vaccine regimen.

The most comprehensive series of studies evaluated diverse health parameters in the marmoset, a small primate, following receipt of vaccines and/or PB. Evaluations included effects on general health, cognitive function, muscle function, sleep patterns, electroencephalograms (EEGs), immune function, and adrenal function. Animals received one-fifth the human dose of all 10 vaccines, along with boosters, over a 51 day period, and were infused for 28 days with PB at the dose required to reduce serum cholinesterase levels by 30 percent. Outcomes were monitored over a 21 month period. The marmosets exhibited no obvious behavioral or health changes over that time, and no differences in weight or muscle function.

Animals that received PB and/or vaccines, however, had significantly higher error rates on two of the eight measures of cognitive function (new learning and compound reversal) that lessened over the period of observation.<sup>1486</sup> Animals treated with PB exhibited significantly reduced EEG alpha wave activity early in the study, and reduced beta 2 waves at various times over the observation period. Pyridostigmine bromide was also associated with reduced levels of rapid eye movement (REM) sleep and fewer REM periods. In contrast, animals who received multiple vaccines, had fewer waking periods early in the

observation period, with improved sleep efficiency and more REM periods.<sup>1789</sup> Urinary cortisol levels did not vary by treatment group and there were no indicators of compromised immunity following treatment with multiple vaccines and/or PB.<sup>632</sup>

Overall, the U.K. studies found no interactive or synergistic effects between PB and receipt of multiple vaccines on any of the parameters studied. Individually, receipt of multiple vaccines, as well as PB, produced a limited number of significant neurobehavioral effects. Both also produced significant, but different, effects on sleep patterns. But neither PB nor multiple vaccines had detectable effects on muscle function, peripheral immune response, or cortisol levels.

Results from the marmoset studies have parallel observations in Gulf War veterans—both in what was found and in what was not found. A large British epidemiologic study reported no significant interaction between PB and receipt of multiple vaccinations in relation to Gulf War illness.<sup>1698</sup> Gulf War veterans have also been reported to be similar to controls with respect to resting cortisol levels,<sup>502</sup> and *in vitro* tests of cellular and humoral immunity.<sup>422</sup> Gulf War veterans commonly report sleep and cognitive difficulties, and studies have identified several domains of measurable cognitive impairment in subsets of symptomatic veterans.<sup>1709,1779</sup>

As will be described in a separate section, the Committee has reviewed evidence suggesting that immune alterations related to veterans' persistent symptoms might more likely be found in the brain than in the peripheral circulation. A study conducted by investigators at Boston University School of Medicine provides a preliminary indication that combined exposure to vaccines, stress, and PB may affect brain processes associated with central immune activation and inflammation.<sup>917,1752</sup> Immune stimulation by KLH, used as a vaccine analog in the Boston study, significantly enhanced and prolonged the production of stress-activated kinases regionally in the mouse brain. This effect was further enhanced and prolonged by PB. Investigators suggested that vaccines and PB may act synergistically to dysregulate processes normally associated with immune activation and inflammation in the brain, processes that mediate neuronal damage following exposure to stress and toxic chemicals.

## **Studies Evaluating the Health of Gulf War Veterans in Relation to Vaccines**

**Association of Gulf War illness with individual vaccines.** As detailed in Appendix A-12a, Gulf War studies have frequently reported significant associations between Gulf War illness and receipt of individual vaccines (e.g., BT, meningococcal, anthrax, plague, typhoid) using analyses that did not take into account effects of other exposures in theater. This includes novel findings from a large study of British Gulf War veterans that tetanus and cholera vaccines were not associated with Gulf War illness if veterans received them before deployment, but were problematic for veterans who received them during deployment.<sup>641</sup> It is not possible to reliably interpret these findings, however, in light of confounding potentially introduced by concurrent exposures, as previously described.

Only two Gulf War studies have assessed effects of individual vaccines while adjusting for the effects of other exposures in theater. The large U.S. study of Navy Seabees queried veterans about their receipt of five vaccines and immune globulin. All were significantly associated with Gulf War illness in unadjusted analyses. After controlling for effects of other exposures, however, only meningococcal vaccine was associated with Gulf War illness, presenting a significant, but only slightly elevated risk (OR = 1.3).<sup>527</sup> In the Fort Devens cohort, receipt of the anthrax vaccine was a significant risk factor for Gulf War illness after adjusting for other exposures in theater. The increased risk for anthrax vaccine was also modest (OR = 1.5) and the study did not assess contributions of other vaccines.<sup>1804</sup>

Health effects of anthrax vaccine in Gulf War veterans. Although it has often been suggested that anthrax vaccine is a cause of Gulf War illness there is relatively little reliable evidence to support this

view. No efforts were made during the Gulf War to monitor short or long-term health problems following receipt of AVA. Epidemiologic studies have generally not identified the anthrax vaccine to be a prominent risk factor for Gulf War illness. As indicated, anthrax vaccine has been associated with increased rates of symptoms, Gulf War illness, and poor health status in several studies, using analyses that did not take into account effects of other exposures in theater.<sup>161,511,1371,1374,1698</sup> The magnitude of risk identified for the anthrax vaccine in these studies, however, was similar to that for most other vaccines, and lower than for other types of exposures in theater. But more informative research on this issue is extremely limited. Only two studies have evaluated the association of anthrax vaccine with Gulf War illness, adjusting for effects of other exposures. Anthrax vaccine was identified as a significant, albeit modest, risk factor in one of those studies.<sup>1804</sup>

There has been some concern that, since many Gulf War veterans might not have known if they received the anthrax vaccine, inaccurate reporting could markedly affect studies evaluating effects of the anthrax vaccine. Two studies have compared health outcomes in Gulf War veterans with self-reported versus documented receipt of the vaccine. In a large study of U.K. Gulf War veterans, associations between anthrax vaccine and health outcomes were similar in individuals who did and did not have their vaccine records, as well as for anthrax vaccine received prior to and after deployment.<sup>641,1698</sup> In all subgroups, receipt of the anthrax vaccine was associated with a 1.3 to 1.5 times greater risk of Gulf War illness, with no adjustments made for other types of exposures in theater.

The U.S. DOD has identified over 7,000 Gulf War veterans who are known to have received the anthrax vaccine, based on available documents. Investigators from the Washington, DC, VAMC identified 352 of those individuals among the 11,441 Gulf War veterans previously interviewed for the U.S. national survey of Gulf War veterans.<sup>957</sup> Gulf War veterans documented to have received the anthrax vaccine reported a number of medical conditions and symptoms at higher rates than veterans who said they did not receive the anthrax vaccine. These included significantly higher rates of dermatitis, gastritis, diarrhea, joint pain, fatigue, mood changes, sleep abnormalities, and indigestion. A still greater number of symptoms and health problems were significantly associated with self-reported, but undocumented, receipt of the anthrax vaccine. These results indicate that, while the anthrax vaccine is potentially associated with excess symptoms in Gulf War veterans, self-reported data introduced a bias that led to an overestimate of the vaccine's adverse effects.

**Gulf War illness and receipt of multiple vaccines.** An additional vaccine-related question of importance is whether receipt of multiple vaccinations together, rather than any single vaccine alone, contributed to the development of Gulf War illness. This issue has been of particular interest in the U.K. and has been investigated in studies of British and Australian Gulf War veterans, but not U.S. veterans. In 1997, Professors Rook and Zumla of University College in London hypothesized that receipt of multiple vaccines for the Gulf War could have precipitated an immunological shift that resulted in an unbalanced production of Th2-type cytokines (associated with humoral immunity) relative to Th1-type cytokines (associated with cell-mediated immunity).<sup>1306</sup> They suggested that this shift may have resulted from the many TH2-inducing vaccines given to Gulf War personnel, exacerbated by stress and perhaps also by pesticide exposures. This idea, referred to as the Rook hypothesis, provided a testable theory for explaining veterans' diverse symptoms.

In 1999, investigators from King's College in London reported that Gulf War veterans who received the largest number of vaccines for the war had significantly worse health, on multiple measures, than veterans who received fewer vaccines.<sup>1698</sup> Additional analyses among the 923 study veterans with vaccination records appeared, initially, to indicate that receipt of multiple vaccines *before* deployment was not problematic. However, veterans who received five or more vaccines *during* deployment had a significantly elevated rate of Gulf War illness (OR = 5).<sup>641</sup> Commentators identified possible explanations for this difference, pointing out, for example, that the types of vaccines received in theater

differed from those administered prior to deployment.<sup>153,638,679</sup> The study investigators suggested that the difference was attributable to receiving multiple vaccines in conjunction with the stress of deployment.<sup>641</sup>

Further analyses, however, indicated that receiving multiple vaccines in theater was not more problematic than multiple vaccines received before deployment. In response to suggestions from scientific colleagues, the King's College investigators revised their analytic approach and found no significant differences between effects of multiple vaccines administered before and during deployment.<sup>638</sup> Their final conclusion, then, was that their data supported an overall association between multiple vaccines and ill health in Gulf War veterans that was not specific to post-deployment vaccines.<sup>638</sup> A study of Australian Gulf War veterans also reported higher symptom rates among those who received the largest number of immunizations for the Gulf War.<sup>789</sup> Results of both the King's College and Australian studies are difficult to interpret, however, since neither study assessed effects of multiple vaccines, adjusted for other types of exposures in theater.

A second British study provides a more informative look at this issue. Controlling for effects of multiple exposures during deployment, investigators at the University of Manchester reported that the number of inoculations received by British Gulf War veterans was significantly correlated with overall symptom severity, and with symptoms of peripheral neuropathy.<sup>241</sup> The Manchester study also indicated that there were no differences between effects of vaccines received prior to and during deployment. No specific information was provided, however, on types of vaccines or vaccine combinations linked to veterans' ill health.

There are two components of the original Rook hypothesis. The first is that receipt of multiple vaccinations contributed to veterans' persistent symptoms after the war. This has not been evaluated in U.S. veterans, but is supported by one well-analyzed study of British veterans, with suggestive evidence provided by two additional studies. The other component of the Rook hypothesis is that veterans' ill health resulted from a Th1-Th2 shift in cytokine production. Several studies have tested this directly by assessing Th1 and Th2-related immune parameters in Gulf War veterans.<sup>1420,1835</sup> As will be described in more detail in a later section of the report, findings have not supported a bias towards production of Th2-type cytokines in ill Gulf War veterans. It is not possible to know if such a shift occurred, temporarily, at the time of the war, but a Th1-Th2 shift is not evident in veterans evaluated years after their return from theater.<sup>1182</sup>

**Other health effects of vaccines received during the Gulf War.** Very few other Gulf War-related health outcomes have been assessed in relation to vaccines. Two studies have identified significant associations between acute adverse reactions to vaccines received for deployment and poor health outcomes after the war.<sup>1374,1698</sup> Military hospitalization records indicate that there were 58 hospitalizations in theater for adverse reactions to vaccines. The largest number of cases attributed to one vaccine was tetanus. One hospital admission, for seizures, was attributed to receipt of the anthrax vaccine.<sup>1622</sup> A report on U.S. military personnel who participated in DOD's Gulf War registry program, the CCEP, indicated that veterans who reported receiving BT, but not anthrax, had a significantly higher rate of hospitalization after the war.<sup>1435</sup> In studies of British Gulf War veterans, cancer rates were not associated with receiving biological warfare vaccines (anthrax, pertussis, plague).<sup>943</sup> Self-reported receipt of the anthrax vaccine was associated with a small, nonsignificant, increase in overall mortality among British veterans (mortality rate ratio = 1.2).<sup>944</sup>

**Vaccines and the health of veterans who did not serve in the Gulf War.** Epidemiologic studies have generally assessed Gulf War-related health outcomes by comparing the health of Gulf War veterans to personnel who served in the military during the war, but did not deploy to the Gulf War theater. A potential problem of using nondeployed Gulf War era veterans as a comparison group is that they may have received some or all of the vaccines given to Gulf War veterans. There are several reports

of military personnel with symptoms that resemble Gulf War illness who received vaccines in preparation for service in the Gulf War, but did not actually deploy.<sup>69,918,1684</sup>

Very little research has assessed health problems in relation to vaccines received by Gulf War-era veterans who did not serve in the Gulf War. The Kansas study asked nondeployed Gulf War-era veterans if they had received any vaccines during the time of the Gulf War. Nondeployed veterans who reported getting vaccines during that time had significantly higher rates of symptoms in several domains (chronic somatic pain, neurological, and gastrointestinal problems) and a nearly four-fold higher rate of Gulf War illness than nondeployed veterans who did not receive vaccines. Veterans who served in theater, by comparison, had Gulf War illness symptoms at 11 times the rate of nondeployed veterans who did not receive vaccines.<sup>1476</sup> These findings provide support for the idea that military vaccines contributed to the development of chronic symptoms in Gulf War era veterans. But the findings are preliminary and are nonspecific, that is, no information is provided on the types or number of vaccines received by nondeployed personnel.

Findings from the King's College study of U.K. veterans may also have relevance to this issue. The study compared the health of U.K. Gulf War veterans with Bosnia veterans, and asked both groups about vaccines they had received. Few Bosnia veterans reported receiving biological warfare vaccines: anthrax, pertussis, or plague. The total number of vaccines received was significantly associated with multisymptom illness in Gulf War veterans, but not in Bosnia veterans.<sup>1698</sup> Information provided did not allow for a clear interpretation of these findings, however. They could indicate that the multiple vaccine effect observed in British Gulf War veterans is related to specific vaccines given to Gulf War, but not Bosnia, personnel. Alternatively, they could indicate that the multiple vaccine effect resulted from confounding by other risk factors associated with Gulf War service. For example, the large Manchester study of British Gulf War veterans found that the number of vaccines received by Gulf War veterans was significantly correlated with other exposures in theater, such as the number of days PB was used.<sup>241</sup>

**Accuracy of self-reported vaccine data.** Most Gulf War studies have assessed veterans' health in relation to vaccines based on veterans' own reports of immunizations they received for the war. Self-reported information on the number and types of vaccines received for Gulf War deployment is potentially more problematic than for some other self-reported exposures. In addition to usual problems related to accurate recall, veterans might not have known what vaccines they received at the time they received them, as has been reported for anthrax and BT vaccines. Several studies have provided useful insights related to the accuracy of vaccine reporting by veterans. Department of Veterans Affairs investigators were able to evaluate the accuracy of veterans' self-reported receipt of the anthrax vaccine in 352 veterans interviewed for the U.S. national Gulf War survey. When questioned, three-fourths of the 352 veterans with DOD-documented receipt of the anthrax vaccine reported that they had, in fact, received it. Only 10 percent reported they did not receive the anthrax vaccine and 16 percent didn't know.<sup>957</sup>

Two studies of U.K. Gulf War veterans found that veterans who used their shot records in reporting immunizations tended to report more vaccines than veterans who did not have shot records.<sup>241,1698</sup> But misreporting and underreporting of vaccines appears to have had little effect on health findings related to vaccines. Both large national studies of British Gulf War veterans found that associations between vaccines and health outcomes were similar in veterans who did have vaccine records compared to veterans who did not have their records.<sup>241,1698</sup>

**Summary. Vaccines and Gulf War illness.** Gulf War veterans received multiple immunizations for deployment. These included the anthrax vaccine, which was given to a large number of military personnel for the first time during the Gulf War. Diverse issues have been raised in relation to the anthrax vaccine's potential for causing adverse health effects. Due to changes in production methods and quality control measures between 1990 and 2001, it is not known if the safety profile of the anthrax vaccine in

current use is the same as that of the vaccine given to Gulf War personnel. Recent studies have indicated that the current anthrax vaccine is associated with high rates of acute adverse reactions, particularly in women. No information is available on rates of persistent symptoms or multisymptom illness following receipt of the anthrax vaccine. Studies have not identified excess hospitalizations or outpatient visits for diagnosed diseases in the weeks and months following receipt of the vaccine. Limitations in the types of information provided by these studies, however, indicate a continued need for long-term follow up, to determine whether excess rates of diagnosed or undiagnosed conditions occur in anthrax vaccine recipients.

An excess of circulating antibodies to the natural substance squalene was reported in symptomatic Gulf War veterans in 2000, and investigators suggested this could have been caused by an unapproved vaccine adjuvant in the anthrax vaccine. Testing of potentially suspect vaccine lots by two laboratories identified only trace amounts of squalene, far below levels usually used for vaccine adjuvants. The observed association between Gulf War illness and elevated levels of squalene antibodies was not contingent on anthrax vaccine being the source of this abnormality, however, and has not yet been independently evaluated.

Gulf War epidemiologic studies have not identified any individual vaccine, including the anthrax vaccine, to be a prominent risk factor for Gulf War illness. Several studies have provided indications that personnel who received a larger number of vaccines for deployment have had higher rates of persistent symptoms since the war. Few Gulf War studies have adequately analyzed data collected in relation to vaccines received for deployment, however, to determine whether individual vaccines or combinations of vaccines are independent risk factors for persistent health problems in Gulf War veterans.

## Recommendations

Diverse concerns have been raised in relation to vaccines received for the Gulf War, but relatively little reliable information has implicated individual vaccines as prominent risk factors for Gulf War illness. Several issues related to vaccines received by Gulf War veterans have not been adequately addressed by existing research. These include the need for more thorough evaluation of vaccines as risk factors for chronic health problems in epidemiologic studies, a definitive study to conclusively evaluate the previously-observed association between squalene antibodies and Gulf War illness, and the need for longer-term evaluation of symptoms and diagnosed diseases following receipt of the anthrax vaccine.

The Committee therefore recommends the following research:

- In previously-conducted and future epidemiologic studies of Gulf War veterans, analyze associations between Gulf War illness and individual vaccines, combinations of vaccines, and total number of vaccines received using methods that control for potential confounding by other Gulf War-related exposures.
- Commission a case-control study to provide clear answers concerning possible associations between Gulf War illness and squalene antibodies. The study should, at minimum, analyze blinded samples from well-characterized symptomatic and healthy Gulf War veterans for the presence of squalene antibodies using each of the assays developed for this purpose. It should also assess whether there is an identifiable link between levels of squalene antibodies in ill Gulf War veterans and receipt of the anthrax vaccine or vaccines more generally. The project should be organized and overseen by qualified investigators not affiliated with the federal government or civilian scientists whose initial work raised the squalene issue in relation to Gulf War illness.
- Evaluate the association of anthrax vaccine adsorbed (AVA) with chronic symptoms, Gulf War illness, and diagnosed diseases in personnel known to have received the anthrax vaccine during the Gulf War. These health outcomes should also be assessed at least five years after vaccination in deployment and era subgroups of personnel in the Millenium Cohort study as well as other groups vaccinated in association with the military's anthrax vaccine immunization program and federal anthrax vaccine trials.

## **Cholinergic and Related Neurotoxicants: Pyridostigmine Bromide, Pesticides, and Nerve Agents**

Vesser [Acting Special Assistant to the Secretary of Defense for Gulf War illnesses LTG Dale Vesser] remarked that although Saddam Hussein didn't use nuclear, biological, or chemical agents against coalition forces during the war, 'it never dawned on us ... that we may have done it to ourselves.'

... 'We know that at least 40,000 American troops may have been overexposed to pesticides,' Vesser said, adding that more than 250,000 American troops took the small, white pyridostigmine bromide pills. .... Both of these substances may cause symptoms that are consistent with the symptoms that some Gulf War veterans have.'

--Armed Forces Press Service, 2001<sup>491</sup>

Many classes of chemicals are neurotoxicants, that is, exposure to these compounds can have adverse biological and physical effects on the nervous system. Three types of neurotoxicant exposures encountered by Gulf War military personnel during deployment are chemically related. They include chemical nerve agents, many of the pesticides used during the Gulf War, and pyridostigmine bromide (PB), the drug given to troops as a protective measure in the event of nerve gas attack. In its 2004 report, the Committee provided an overview of information concerning veterans' exposures to these toxicants, what was known about their health effects, and what had been learned from studies of Gulf War veterans. The report concluded that available evidence supported a probable link between Gulf War illness and exposure to these compounds.

Chemical nerve agents, PB, and many of the pesticides to which Gulf War veterans were exposed belong to a class of chemicals known as acetylcholinesterase (AChE) inhibitors. They share a common toxic mechanism of action, that is, they inactivate the enzyme AChE, which is essential for breaking down the nerve signaling chemical (or neurotransmitter) acetylcholine. Inhibition of AChE leads to the buildup of acetylcholine in the brain and peripheral nerve endings, and over stimulation of cholinergic nerve receptors. Acetylcholinesterase-inhibiting medications and pesticides can be used safely at recommended levels. Adverse effects can occur with excessive exposure, and are also seen at lower doses in individuals who are particularly sensitive to these compounds.

The acute symptoms of excess exposure to AChE inhibitors relate to the different types of cholinergic receptors affected by acetylcholine buildup. Excess cholinergic stimulation of muscarinic receptors of the parasympathetic autonomic nervous system results in increased salivation and respiratory secretions, nausea, abdominal cramping, diarrhea, and excess sweating. Effects on autonomic nicotinic receptors include increased heart rate and blood pressure. Excess stimulation of nicotinic receptors in skeletal muscles leads to muscle twitching, cramps, weakness, tremors, and paralysis. Excess stimulation of acetylcholine receptors in the brain produces fatigue, mental confusion, headache, poor concentration and general weakness and, at higher exposures, convulsions and coma.<sup>387</sup> At sufficient doses, exposure to AChE inhibiting chemicals can result in respiratory arrest and death.

This section of the report provides information on what is known about Gulf War veterans' exposure to these chemicals, what is known about their health effects overall, and what has been learned about their effects from studies of Gulf War veterans. It also includes information on additional pesticides of concern that are not AChE inhibitors and information from research on effects of exposure to combinations of PB, pesticides, and nerve agents.

## Exposure to Cholinergic and Related Neurotoxicants During Gulf War Deployment

My unit arrived in the Gulf the day before the air war started. We first spent about a month in Dhahran in Saudi Arabia. Our chemical alarms went off several times during that month, and we had to go to MOPP-level four, which meant we had to put on chemical suits, masks, gloves, and boots. While we were still in Dhahran, we started taking pyridostigmine bromide pills, which were supposed to protect us against exposures to nerve gas. About three days after I started taking the pills, my eyes were jittery, my vision was jumping, and I was seeing double, and I was nauseated. By the fourth day, I was vomiting a little blood, so I went to sick-call. They told me to cut the dose in half and said there was nothing to worry about. At least I no longer vomited blood after I reduced the dosage. Many other people in the unit reported having similar vision problems.

--SSgt PB, Gulf War veteran<sup>716</sup>

Military personnel serving in the 1990-1991 Gulf War were exposed to a variety of substances that have the potential to adversely affect the central nervous system. These include multiple types of anticholinesterase compounds—pyridostigmine bromide (PB) pills, pesticides, and for some veterans, low-level exposure to chemical nerve agents. But not all personnel were exposed to the same compounds at the same dosages and in the same combinations. Although records are not available that document individual exposures to these compounds, government investigations have provided considerable information on the extent and patterns of use of PB and pesticides, and have modeled nerve agent exposures in relation to the largest verified nerve agent release incident.

**Table 1. Veteran-Reported Exposures to Neurotoxicants During Gulf War Deployment**

	<i>U.S. National Survey</i> <sup>751</sup>	<i>U.S. Army Veterans</i> <sup>1804</sup>	<i>U.S. Navy Seabees</i> <sup>524</sup>	<i>U.K. National Survey</i> <sup>1698</sup>
Took pyridostigmine bromide pills	49 %	66 %	33 %	82 %
Used personal pesticides	48 %	46 %	35 %	69 %
Exposed to nerve gas/chemical agents	10 %	19 %	3 %	9 %

Population-based surveys of Gulf War veterans have also provided consistent information on veteran-reported exposures during deployment. Table 1 summarizes responses to survey questions from studies of Gulf War veterans in the U.S. and U.K. concerning their use of PB and pesticides, and whether they thought they were exposed to chemical weapons. About half of all U.S. Gulf War veterans, and a higher proportion of U.K. Gulf War veterans, report using PB and pesticides during deployment. Nearly two out of three Gulf War veterans in the U.S. national survey reported that they had heard chemical alarms sound or put on their MOPP gear (mission oriented protective posture, protective garments worn in a possible chemical event) during deployment,<sup>751</sup> but only 10 percent believed that they were exposed to nerve agents or other chemical weapons in theater. Overall, Army veterans report greater exposure to PB, pesticides, and nerve agents than Navy veterans. A large survey of British Gulf War veterans also found that PB and pesticide use were reported by more U.K. Army personnel than those in the Royal Air Force or Navy.<sup>241</sup>

## Pyridostigmine bromide (PB) use in the Gulf War

Pyridostigmine bromide (PB) is a compound that reversibly binds to, and temporarily inactivates, AChE. It is the active ingredient in the nerve agent pyridostigmine pretreatment (NAPP) pills that were distributed to military personnel in the Gulf War as part of a three drug regimen to protect troops from poisoning by nerve agents. The small white PB pills were intended for use *before* a nerve gas attack, to establish blood levels adequate to temporarily bind about 30 percent of circulating AChE. If exposed to nerve agents, soldiers were to inject themselves (or their buddy) with two antidotes, atropine and 2-pralidoxime chloride (2-PAM), using prepackaged autoinjectors. These measures were intended to protect cholinergic receptors from excess acetylcholine buildup, and “rescue” AChE in order to restabilize cholinergic nerve transmission after the attack. Orders for initiating PB pretreatment were issued by unit commanders. The NAPPs were contained in blister packs of 21 pills, 30 mg. each. Each pack provided the number of pills needed for one week at the recommended dosage of one 30 mg. pill every eight hours.<sup>951,1604</sup>

The 1990-1991 Gulf War was the first time the U.S. military had used PB on a widespread basis as a nerve agent pretreatment. In 1990, PB was not licensed for this purpose by the U.S. Food and Drug Administration (FDA) but had been approved, since 1955, for treatment of myasthenia gravis. As a nerve agent protective measure, PB was considered an investigational new drug (IND). At the request of DOD, FDA granted a temporary waiver, in December 1990, that allowed use of PB in theater, in situations involving combat or the threat of combat, without the usual IND requirement for informed consent.<sup>1275</sup> The waiver was granted in light of the threat posed by Iraqi chemical weapons and the long history of PB safety in the treatment of myasthenia gravis.<sup>781,951,1275,1604,1667</sup> A number of problems occurred in implementation of the use of PB under this agreement, however, which prominently included insufficient information provided to troops in theater, and failure to keep adequate records of PB distribution and use.<sup>462,1275,1604,1667</sup>

Pyridostigmine bromide has now been approved by FDA for use as a pretreatment measure against exposure to the nerve agent soman.<sup>1664</sup> Research in animal models indicates that PB pretreatment enhances the effectiveness of the two antidotes that are used after exposure to soman, which permanently inactivates AChE within minutes. Pyridostigmine is not useful as a pretreatment in the event of sarin exposure, since sarin’s effects on AChE can be mitigated by the post exposure antidotes over a period of several hours.<sup>504,830,951,1793,1810</sup> There have been no reports indicating that soman was present in theater during the 1990-1991 Gulf War, however. Available documents suggest that during the war, PB pretreatment was directed in anticipation of nerve agent exposure more generally, rather than specifically in relation to soman.<sup>781,1588,1604,1690</sup>

Epidemiologic studies indicate that about half of U.S. Gulf War veterans report using PB during deployment,<sup>692,751</sup> with greatest use among Army personnel.<sup>458,1804</sup> The DOD Office of the Special Assistant for Gulf War Illnesses (OSAGWI) commissioned the RAND National Defense Research Institute to undertake an in-depth evaluation of pesticide and PB use patterns by ground troops during the Gulf War.<sup>458</sup> Investigators conducted detailed interviews of over 2,000 Gulf War veterans. Results indicated that slightly more than half of Army and Navy/Marine Corps personnel serving on the ground used PB, but only 23 percent of Air Force personnel used PB. Among individuals who used PB, the number of pills taken was highly variable, with an average of 26 pills used in a given month. Most individuals reported taking three or fewer pills per day for 30 days or less, but a small percentage reported taking substantially more.<sup>458</sup> Overall, troops living in the open desert took PB at twice the rate of troops in tent cities, who in turn took PB at twice the rate of personnel living in buildings.<sup>458</sup> Results from the population-based Iowa study also suggested that active duty personnel took more pills, overall, than reservists.<sup>692</sup>

## Pesticide use and exposures in the Gulf War

On a nightly basis, we would spray our uniforms with pesticides. There was a chemical spray that they gave us to spray our uniforms. We had to hang them outside so that the excess spray would dissipate in the air, I guess. We weren't supposed to put them on immediately after spraying them. The sand fleas were a problem. We used to put flea collars around the legs of our cots or we would put flea powder on the floor around our cots to try to keep the sand fleas away from us while we were sleeping. We slept with nets over us to keep the flies off. The flies were ungodly.

--SSgt TS, Gulf War veteran<sup>716</sup>

The desert environment was home to large numbers of flying and biting insects, and other pests, which posed a risk of disease to troops in theater. Control of disease-carrying pests is an important part of force protection and readiness during military deployments. Troops serving in the region in earlier campaigns had been affected by high rates of pest-borne diseases<sup>475,596,1632</sup> and the U.S. military implemented extensive measures to limit this problem in the Gulf War. Individuals were issued pesticide creams, liquids, and sprays, to use on their skin, their uniforms, and their bedding, and pest strips, bait, and sprays to use in their living quarters. Military preventive medicine specialists and field sanitation teams also conducted extensive operations to control pests in areas where people lived, ate, and worked with environmental fogging and surface spraying. These efforts were largely successful, as demonstrated by the low rate of vector-transmitted infections identified during the war.<sup>664,1632</sup>

Similar to other exposures in the Gulf War, no records were kept in relation to pesticide use or exposure for different areas, units, or individuals. After the war, when concerns were raised about the possible contribution of pesticides to veterans' unexplained illness, DOD undertook a number of assessments to determine the types of pesticides to which Gulf War veterans were exposed, the amounts used in theater, and patterns of pesticide use among individuals in the general military population and by pest control personnel.

In its final Environmental Exposure Report on pesticide use in the Gulf War, issued in 2003, DOD reported that U.S. personnel serving in the Gulf War used or had available for use, at least 64 pesticides and related products, containing 37 active ingredients.<sup>1632</sup> Of these, 15 were identified as "pesticides of potential concern" based on what was known about the use and toxic effects of these compounds. The 15 pesticides are listed in Table 2, and include seven organophosphates, three carbamates, two pyrethroids, one organochlorine, and two forms of the insect repellent DEET.

The most commonly used personal repellants were DEET, which was primarily to be used on the skin, and permethrin, which was to be sprayed onto uniforms. Some personnel are known to have acquired personal use pesticides in addition to those supplied by the military, including the commercial product OFF, citronella products, and flea collars. Military environmental pesticide control measures included surface spraying and environmental fogging using the organophosphates chlorpyrifos, diazinon, and malathion, in varying concentrations, as well as the carbamates propoxur and bendiocarb. The organochlorine lindane powder was used by military police and other personnel for delousing in the processing of the more than 87,000 enemy prisoners captured in the war. Lindane was also issued to troops for their personal use, primarily to Army personnel.<sup>1632</sup> In addition, environmental pest control was commonly provided by local pest control services in host nations, either under contract with the military, or supplied by health departments of local Saudi Arabian municipalities. Relatively little information is available concerning the types of compounds used or the frequency and patterns of spraying done by local pesticide services.<sup>1632</sup>

Gulf War epidemiologic studies queried veterans about pesticide use in theater in diverse ways that ranged from a simple question about whether or not the veteran had used "pesticides" during deployment, to more detailed questions about specific types used and the extent of their use. The U.S. national survey

**Table 2. Pesticides and Insect Repellants Identified as Pesticides of Potential Concern by the Deployment Health Support Directorate**

<i>Compound</i>	<i>Use</i>	<i>Chemical Class</i>	<i>Purpose</i>	<i>Application</i>
<i>Pesticides and Repellants Used by the General Military Population</i>				
DEET, 33% cream, stick	Personal use repellent	Dialkylamide	Repel flies and mosquitoes	By hand to skin
DEET, 75% liquid	Personal use repellent	Dialkylamide	Repel flies and mosquitoes	By hand to skin, uniform, netting
Permethrin, 0.5% spray	Personal use repellent	Pyrethroid	Repel flies and mosquitoes	Sprayed on uniforms
d-Phenothrin, 0.2% aerosol	Area use repellent	Pyrethroid	Knock down, kill flies and mosquitoes	Sprayed in tents, other enclosed areas
Methomyl 1% crystals	Fly bait	Carbamate	Attract and kill flies	Placed in pans outside latrines, tents
Azamethiphos, 1% crystals	Fly bait	Organophosphate	Attract and kill flies	Placed in pans outside latrines, tents
Dichlorvos, 20% pest strip	Pest strip	Organophosphate	Attract and kill mosquitoes	Hung in tents, working areas, dumpsters
<i>Pesticides Used by Pesticide Applicators</i>				
Chlorpyrifos, 45% liquid	Sprayed liquid	Organophosphate	Kill flies, mosquitoes, flying insects	Sprayed in corners, cracks, crevices
Diazinon, 48% liquid	Sprayed liquid	Organophosphate	Kill flies, mosquitoes, flying insects	Sprayed in corners, cracks, crevices
Malathion, 57% liquid	Sprayed liquid	Organophosphate	Kill flies, mosquitoes, flying insects	Sprayed in corners, cracks, crevices
Propoxur, 14.7% liquid	Sprayed liquid	Carbamate	Kill flies, mosquitoes, flying insects	Sprayed in corners, cracks, crevices
Bendiocarb, 19% liquid	Sprayed powder	Carbamate	Kill flies, mosquitoes, flying insects	Sprayed in corners, cracks, crevices
Chlorpyrifos, 19% liquid	Fog	Organophosphate	Kill flies, mosquitoes	Large area fogging
Malathion, 91% liquid	Fog	Organophosphate	Kill flies, mosquitoes	Large area fogging
<i>Delousing Pesticide</i>				
Lindane, 1% powder	Delouser	Organochlorine	Kill lice, other insects	Dusted on prisoners, also for personal use

Source: DOD Environmental Exposure Report: Pesticides (2003)<sup>1632</sup>

indicated that about half of all Gulf War veterans reported using personal pesticides,<sup>751</sup> with additional studies suggesting that pesticide use was more common in Army than Navy personnel.<sup>524,1782</sup> The Iowa study also indicated that reservists reported pesticide use more commonly (63%) than active duty personnel (44%).<sup>692</sup>

The RAND investigation of pesticide use among ground troops during the Gulf War reported considerable diversity in patterns of pesticide use in theater. Survey respondents were often unable to recall the specific chemicals used during deployment, but could identify the form of pesticides used (e.g., spray, liquid, powder) and how it was used (e.g., on clothing, skin, in tent), from which investigators imputed the most likely compound.<sup>458</sup> Personnel living in the desert used more pesticide sprays and liquids than those who lived in buildings. Officers reported less use of pesticide lotions and flea collars than enlisted personnel, and senior enlisted personnel reported greatest use of pesticide sprays and powders.

Overall, 62 percent of ground troops interviewed reported some form of pesticide use. Forty-four percent used pesticide sprays, a median of 30 times per month, and 26 percent used pesticide lotions a median of 20 times per month. Investigators estimated that the most commonly used compound was DEET, used by half of all personnel, a median of 30 times per month. Permethrin was used by fewer personnel<sup>458,1632</sup> but was used an average of almost 30 times per month. This raises concerns, since the permethrin label indicated that uniforms were to be sprayed only once every six weeks, or after six launderings. In contrast, DOD reports indicate that guidance issued to some Army personnel directed them to “apply a light coat of permethrin every four or five days.”<sup>1632</sup>

The RAND investigation indicates that overuse of pesticides was most apparent for permethrin, d-phenothrin, lindane, and flea collars, although fewer individuals used these than the more commonly used DEET. No-pest strips were also frequently used in greater density than recommended, particularly in eating areas and latrines. Some pesticide overuse was extreme. About 13 percent of veterans reported using pesticide sprays more than 50 times per month, and about five percent reported using pesticide liquids or lotions more than 100 times in a given month, or more than three times per day.<sup>458</sup>

It also seems reasonable that people in environments with large numbers of insects, such as in the Persian Gulf, would be tempted to use whatever means was available to remove the pests, including using products in ways that were not recommended.

--RAND National Defense Research Institute, *Pesticide Use During the Gulf War*<sup>458</sup>

RAND investigators reported that personnel who reported frequent use of one type of personal pesticide were also more likely to report frequent use of multiple pesticides, suggesting exposure to a “cocktail of pesticides.”<sup>458</sup> Use of personal pesticides was also significantly correlated with the number of PB pills taken in a given month. Over one in four veterans serving on the ground reported they had applied pesticides from 51 to over 120 times in a given month, and had also used an average of 15-19 PB pills in the same month.<sup>458</sup> By comparison, ground troops who reported no use of pesticides took, on average, only six PB pills in a given month.

The DOD final environmental exposure report on pesticides in the Gulf War included a health risk assessment that relied on information from the RAND survey, as well as interviews conducted with preventive medicine personnel knowledgeable about field pesticide use. The report concluded that “at least 41,000 Gulf War service members may have been overexposed to pesticides” and that “overexposure to pesticides, particularly organophosphates and carbamates, may have contributed to the unexplained illnesses reported by some Gulf War veterans.” The figure of 41,000 was provided as a minimum figure, and did not consider effects of “overexposure” potentially resulting from combinations of organophosphate and carbamate pesticides with concurrent exposures to DEET, permethrin, PB, or low-level nerve agents or pesticide exposures resulting from pest control services provide by host nations.<sup>1632</sup>

Although comprehensive information on pesticide use in current deployments to Iraq and Afghanistan has not yet been reported, it appears that improved pesticide use and oversight have been among the important lessons learned from the 1991 Gulf War.<sup>36</sup> In 1993, the Deputy Undersecretary of Defense issued three pest management “Measures of Merit” that established objectives for improved pest management planning, a 50 percent reduction in the amount of pesticides used on military installations, and improved training and certification of pesticide applicators.<sup>442</sup> The military has now established improved standards and practices that include expanded use of trained preventive medicine field teams that monitor environmental hazards, training and printed materials for military personnel on the need for proper use of pesticides and insect repellants, as well as some changes in the specific pesticide products used.<sup>1074,1583,1632</sup>

There are multiple indications that pesticide usage in Operation Iraqi Freedom has differed from that in the 1990-1991 Gulf War. DEET formulations currently provided by the military contain 20-33 percent DEET; the 75 percent DEET liquid issued during the Gulf War is no longer in use.<sup>62</sup> Lindane, the organochlorine issued for delousing prisoners and for personal use during the Gulf War is no longer used for either purpose by the military.<sup>63</sup> In addition, troops in current deployments have had access to uniforms that were pretreated with permethrin, and permethrin treatment kits that reduce risks associated with uniform spraying, and sometimes over spraying, as occurred in the Gulf War.<sup>62,1771</sup>

Reports indicate that Iraq War troops were more educated about pesticides,<sup>36</sup> but sometimes did not have sufficient access to repellants, at least in the first years of the war.<sup>399,1771</sup> A survey of 870 service members at camps in Kuwait in 2004 indicated that most personnel had received medical briefings on why and how insect repellants were to be properly used. However, only 36 percent had been issued any DEET product and 48 percent had received permethrin products.<sup>1771</sup> A substantially larger number of cutaneous leishmaniasis cases have occurred among Iraq War troops, compared to the 1991 Gulf War,<sup>399</sup> which a National Defense University report suggests may be related to reduced used of pesticides.<sup>1537</sup>

Therefore it appears that pesticide usage by troops in Operation Iraqi Freedom is decreased, or from another perspective, improved and more judicious, compared to pesticide usage in the 1991 Gulf War. This can be attributed to a number of factors, including improved pest management policies, improved education of pesticide applicators and the general military population, expanded placement of preventive medicine field sanitation teams, differences in living conditions, discontinued use of lindane and 75 percent DEET, and, in some cases, inadequate supplies of repellant products.

## **Exposure to chemical weapons in the Gulf War**

In late January 1991, while assigned to an area between Rafha and Naryian about six miles south of the Iraqi border, BM recorded in his journal and on videotape that chemical ‘false alarms’ were going off almost every day. At first, according to BM, the alarms were explained as being caused by vapors coming off the sand. Later, since the alarms kept going off and troops no longer believed they were being caused by vapors, BM said he was informed by both his battalion commander and the battalion NBC NCO that the alarms were sounding because of ‘minute’ quantities of nerve agent in the air, released by the coalition bombing of Iraqi chemical weapons facilities. The troops were assured that there was no danger.

--1994 Senate Committee report on Gulf War veteran, 18<sup>th</sup> Airborne Corps<sup>1688</sup>

Among the many challenging issues related to understanding levels and effects of hazardous exposures in the Gulf War, those surrounding troop exposures to chemical weapons in theater are the most complex and controversial. Multiple accounts of chemical alerts during the war, positive readings on chemical detection tests, and incidents involving unusual vapors and unexplained symptoms were reported in the

media and documented in Congressional reports. Seventeen years after the war, after numerous government and special committee investigations, research studies, and reports, significant questions remain about the extent to which military personnel were exposed to low levels of chemical warfare agents during the Gulf War.

For the first five years after Desert Storm, DOD maintained that no troops had been exposed to chemical agents. The Iraqis were known to have chemical weapons and to have used them against Iranians and their own citizens in the 1980s. The Department of Defense consistently affirmed, however, that Iraq had not used chemical weapons offensively in the Gulf War and that none had been positioned in areas of Iraq that were penetrated by Coalition forces. In preparing for the Gulf War air offensive, U.S. military planners had identified multiple Iraqi targets where chemical weapons were believed to be manufactured or stored.<sup>1748</sup> Most of these chemical targets had been successfully destroyed during the air campaign.<sup>320</sup> But DOD indicated that any chemical agents released with the bombing of Iraqi targets had occurred a great distance from Coalition troop locations, too far away to have affected U.S. or allied personnel.

In June of 1996, DOD announced that U.S. troops had potentially been exposed to low levels of nerve agents after the cease fire in March of 1991, when Army personnel detonated large caches of munitions stored at a massive compound near Khamisiyah, in southeastern Iraq. This announcement proved to be a turning point in the federal response to Gulf War health issues. It triggered an expanded effort to analyze and address Gulf War health issues overall, stimulated multiple investigations into chemical weapons exposures in theater, and led to a military research program aimed at better understanding effects of low-dose exposure to chemical warfare agents.<sup>1102</sup>

**Chemical warfare agent exposure and detection in the Gulf War theater.** Understanding the likely extent of chemical agent exposures in the Gulf War has been complicated by a number of factors. These include long-time official denials that chemical releases and exposures had occurred in theater, the postwar disappearance of the U.S. Central Command's records of reported chemical events during the Gulf War, the limited capabilities of chemical monitoring equipment in theater, controversy surrounding government conclusions about chemical releases at Khamisiyah and other locations, and the limited degree to which military personnel could have known if they had been exposed to low levels of chemical agents.

There are multiple scenarios in which chemical agent exposures could potentially have occurred. These include Iraqi offensive use of chemical weapons, downwind drift of chemical agents released by Coalition aerial bombing of Iraqi targets, local exposure and downwind drift following ground destruction of chemical munitions, and exposure of individuals who entered bunkers or other areas contaminated by chemical weapons. The Department of Defense has maintained that there was no offensive use of chemical weapons in theater, and has only verified that troops were exposed to nerve agents in one case, as a result of the ground destruction of chemical weapons at Khamisiyah. Multiple reports of chemical detections and other incidents that potentially involved chemical exposures have long fueled speculation, however, that additional exposures may have occurred, exposures that were either not identified or not verified by DOD.<sup>388,1560,1683,1685,1688</sup>

In the years since the war, an extensive number of reports from DOD, the U.S. Central Intelligence Agency (CIA), the United Nations, and other sources have provided information on the types and amounts of chemical agents stored, deployed, and destroyed in different locations in the Gulf War theater. Previous advisory panels, government agencies, and Congressional committees have been tasked with reviewing available information on these issues. Their reports have identified a variety of different issues and produced different, sometimes contradictory, findings.<sup>1231,1232,1595,1683,1688,1690</sup> Detailed analysis of the many intelligence reports, modeling protocols, incident reports, and investigations related to possible chemical releases and exposures in theater was beyond the scope of the present report. Instead, the

Committee broadly reviewed information provided by government investigations and issues raised by earlier panels to determine what has been learned about chemical agent exposures during the Gulf War.

It is important to note that there have been no reports during or after the war of high-level chemical exposure incidents in which large numbers of personnel experienced clear signs and symptoms of chemical agent poisoning. Available information indicates that the major unanswered questions about exposure to chemical weapons during the Gulf War relate to: (1) whether more limited or lower level chemical agent exposures occurred in theater that were undetected, unreported, or unverified by the government, and (2) if modeled plume estimates for the Khamisiyah demolitions usefully reflect chemical exposures that resulted from releases at that site.

**Limitations and problems in detecting chemical warfare agents.** At the most fundamental level, identifying chemical agent exposures during the Gulf War depended on reliable detection of those agents. Concerns about the inability of chemical monitoring systems used in the Gulf War to detect lower levels of chemical agents in the field were raised in 1994 by the Senate Banking Committee, and again in 1996 and 1997 by the Presidential Advisory Committee on Gulf War Veterans' Illnesses.<sup>1227,1231,1690</sup>

During the Gulf War, the U.S. military used a multilevel system for detecting and verifying chemical agents. With an initial detection, an alarm alerted personnel to the possible presence of a chemical agent and troops donned protective gear until results from a second type of test either verified a positive detection or permitted an "all clear" notification. The primary early warning system for airborne chemical agents was the M8A1 chemical alarm. These alarms could be placed upwind from the unit's position to monitor for VX and G series nerve agents, including sarin. The M8A1 could only detect nerve agents at levels that can also cause symptoms, and could not detect blister agents such as mustard gas at any level.<sup>1231,1595,1605,1690</sup> Handheld chemical agent monitors (CAMs) could detect airborne vapors of both nerve and blister agents but were not primarily used as an open air warning device. They were more commonly used to determine if personnel or surfaces had been contaminated, by assessing and roughly quantifying vapors emanating from liquid agent.<sup>961,1595</sup> Liquid chemical agent hazards could also be detected by M8 and M9 papers, issued to individual service members, and by a specialized kit (M272) used by NBC (nuclear, biological, chemical) personnel to identify chemical agents in water.<sup>1595</sup>

The most widely used system for verifying airborne chemical agents was the M256A1 Chemical Agent Detector Kit. Testing was conducted by trained NBC personnel and involved a sequence of steps that required 20-25 minutes to complete.<sup>1595,1613</sup> Although not useful as an early warning monitor, the M256A1 kits were more sensitive to nerve agents than the alarms, and less prone to false positives.

The U.S. military also fielded 60 armored FOX NBC Reconnaissance vehicles, provided by Germany during Operation Desert Shield.<sup>1606</sup> The Fox vehicles were considered the most technologically advanced chemical equipment used by the U.S. in the Gulf War. This mobile unit could conduct chemical and radiation reconnaissance in different settings, with capabilities to sample for, detect, and verify chemical agents. Fox vehicles were equipped with the M43A1 chemical agent detector and an MM-1 mobile mass spectrometer. They were designed primarily to identify ground contaminated areas and were most sensitive and specific for detecting liquid chemical agents. The Fox was not considered a suitable first warning device when used in air sampling mode, since a relatively high concentration of nerve or blister agent vapor was required for detection.<sup>1231,1595,1606,1628,1690</sup> The MM-1 spectrometer provided detailed chemical agent verification capability, but identified only the compound present at the highest concentration.<sup>1228,1628</sup> If, for example, nerve agent was present, but at a lower concentration than a compound in oil fire smoke, only the oil fire compound would be identified.

The multilevel chemical agent detection system used by the military during the Gulf War was intended to detect chemical agents at levels that could cause acute harm to troops in the field, and provide warning to allow them to take protective action. This was consistent with the understanding at the time that subacute

**Table 3. Chemical Agent Vapor Detection Capabilities of Equipment Used in the Gulf War, and Current Chemical Weapons Air Exposure Guidelines and Standards**

	<i>Sarin</i>	<i>Mustard</i>
<i>Vapor Detection Capabilities of Chemical Detection Equipment Used by the U.S. Military in the Gulf War</i>		
M8A1 chemical alarms	0.1 – 0.2 mg/m <sup>3</sup>	no capability
Portable chemical agent monitors	≤ 0.1 mg/m <sup>3</sup>	≤ 0.1 mg/m <sup>3</sup>
M256A1 detector kits	0.005 mg/m <sup>3</sup>	2 mg/m <sup>3</sup>
Fox vehicle M43A1 alarm	0.2 mg/m <sup>3</sup>	no capability
Fox vehicle MM-1 mass spectrometer monitor	62 – 100 mg/m <sup>3</sup>	
<i>Chemical Weapons Air Standards and Guidelines Currently Used by the U.S. Military</i>		
Air exposure limits:		
Immediate danger to life and health (1 time exposure)	0.1 mg/m <sup>3</sup>	0.7 mg/m <sup>3</sup>
Short term exposure limit (occasional 15 minute exposure)	0.0001 mg/m <sup>3</sup>	0.003 mg/m <sup>3</sup>
Acute exposure guideline levels (1 time exposure)		
Level 1 (potential for noticeable effects, minor discomfort)		
- 10 minutes	0.0069 mg/m <sup>3</sup>	0.400 mg/m <sup>3</sup>
- 1 hour	0.0028 mg/m <sup>3</sup>	0.067 mg/m <sup>3</sup>
Level 2 (more obvious effects, potential impact on function)		
- 10 minutes	0.087 mg/m <sup>3</sup>	0.600 mg/m <sup>3</sup>
- 1 hour	0.035 mg/m <sup>3</sup>	0.100 mg/m <sup>3</sup>
Level 3 (potentially life threatening)		
- 10 minutes	0.38 mg/m <sup>3</sup>	3.900 mg/m <sup>3</sup>
- 1 hour	0.13 mg/m <sup>3</sup>	2.100 mg/m <sup>3</sup>

Chemical Agent Detection Capabilities Sources: Defense Science Board Task Force on Persian Gulf War Health Effects,<sup>1597</sup>

National Research Council,<sup>1007</sup> U.S. Department of Defense<sup>1605,1606,1613</sup>

Air Standards and Guidelines Source: U.S. Army Center for Health Promotion and Preventive Medicine<sup>1581,1582</sup>

exposure to chemical agents did not pose a serious health threat. In recent years, growing concern about possible adverse effects of lower level exposures have prompted federal agencies, including DOD, to revise chemical agent exposure standards and adopt guidelines that are more conservative than those in place during the Gulf War, that is, standards that consider lower exposure levels to be potentially problematic.<sup>1574,1755</sup> The Department of Defense has also replaced the M8A1 alarms with next generation alarms that have expanded capabilities and are less prone to false alarm.<sup>1605</sup>

Information on detection capabilities of equipment used by the U.S. in the Gulf War for airborne sarin and mustard is provided in Table 3. The table also provides current toxicity standards and guidelines used by the military for exposure to these agents. Because the toxicity of chemical agents varies with the concentration and duration of exposure,<sup>86</sup> limits are provided for immediate and short term exposures, and guidelines identify levels at which mild, more serious, and life threatening health effects may acutely occur.<sup>1581,1582</sup> As shown, the M8A1 alarms could have detected sarin at levels that pose an immediate danger to life and health with a one time exposure. The alarms would not have detected sarin present at levels capable of producing limited symptoms after only 10 minutes exposure, identified as a Level 1 exposure in the table. The M8A1 alarms also might not have detected a Level 2 exposure, associated with

more significant symptoms and signs with 10 minutes exposure. The M256A1 detection kits could potentially have identified chemical agents at considerably lower levels, but would not likely have been used in the absence of an initial warning alarm.

Overall, monitoring capabilities for chemical agent vapors were insufficient to detect levels that could cause limited symptoms with relatively brief exposures, or more pronounced problems with sustained exposures. And, as previously indicated, the M8A1/M43A1 alarm systems would not have detected nerve agents at levels too low to cause any symptoms, or blister agents at any level.

From the Saudi berm north, the air was heavy with oil smoke. This smoke deposited an oily residue on the alarms' paddles which tripped the alarms. On the average, the alarms activated every 20 to 30 minutes. ... The M8A1s were useless in the smoky, dusty desert environment.

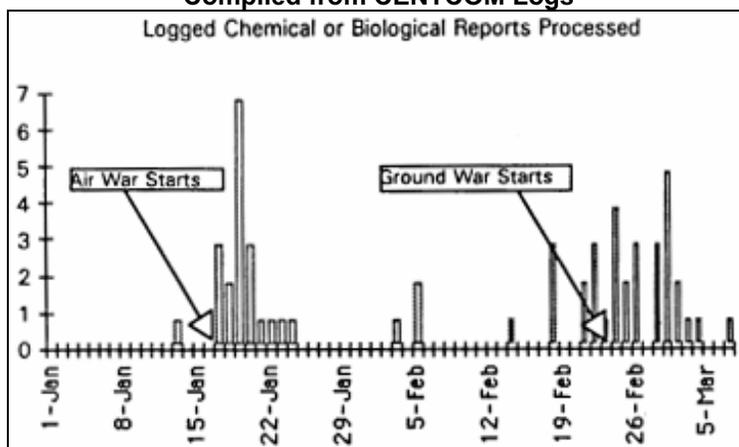
--March 1991 memo, 2<sup>nd</sup> Light Armored Infantry Battalion<sup>1381</sup>

Another major concern related to chemical detections were problems caused by the repeated sounding of alarms deemed to be false. Department of Defense reports indicate that M8A1 alarms were widely used in theater, and that false alarms were triggered by factors such as fuel vapors and engine exhaust, oily smoke, blowing sand, and low batteries on the units.<sup>961,1605</sup> Surveys of Gulf War veterans consistently report that most ground troops heard chemical alarms one or more times during deployment, indicating that a very large number of alarms sounded in theater. But overall, it is not known how many chemical alarms sounded over the course of the war, in what areas they occurred, or how many were followed up with additional testing. Repeated false alarms in some locations led some units to ignore or disable their alarms.<sup>1228,1684</sup> Such problems might have led some personnel to believe they were exposed to chemical agents when they had not been, or others to believe they had not been exposed when they might have been.

Chemical incidents during the war that were communicated to Central Command (CENTCOM) forward headquarters in Riyadh, Saudi Arabia, were recorded in logs maintained by NBC desk officers. In 1996, DOD announced that the NBC logs on which chemical incidents had been recorded during Operations Desert Shield and Desert Storm were missing. The Pentagon's Office of the Inspector General (IG) investigated the logs' disappearance and issued its report in 1997. The IG report indicated that the NBC logs had initially been generated in hard copy, entered into computer files, and backed up on portable disks by the NBC desk in Riyadh.<sup>1602</sup> After the war, hard copies, laptop computers, and disks containing the logs were shipped to CENTCOM Headquarters in Tampa, Florida, and stored in safes. It was never determined with certainty what happened to them, but the IG report found it likely that, contrary to DOD policy, they had inadvertently been disposed of when the NBC office was relocated in 1994. Duplicate disks had also been sent to Aberdeen Proving Ground after the war, but were also not locatable.

The loss of the NBC logs made it impossible to ascertain what chemical incidents had been reported to CENTCOM and what determinations had been made. It also raised a great deal of public skepticism concerning the reliability of DOD reporting on chemical exposures in theater. The IG report indicated that copies of 32 of the approximately 150 pages of the missing NBC logs had been provided to assist the Defense Science Board Task Force on Persian Gulf War Health Effects in 1993, whose 1994 report contained information compiled from those pages. The graph in Figure 1 is taken from the 1994 report, and depicts an unspecified group of chemical reports logged by CENTCOM between January 1 and March 7, 1991. The largest number were recorded in the early days after the air war began, and again in the days surrounding the ground war.

**Figure 1. Logged Chemical or Biological Reports Processed:  
Compiled from CENTCOM Logs**



Source: Defense Science Board Task Force on Persian Gulf War Health Effects<sup>1595</sup>

As previously described, verification of a chemical agent detection required that an initial detection be retested and confirmed by a second type of test that used different technology. The Presidential Advisory Committee pointed out that verification of chemical detections using the Fox vehicle was often not possible on the battlefield, as described below:

Doctrine required that following an initial alarm for CW [chemical warfare] agent(s), the Fox vehicle's full spectrum capability should be engaged. To complete the full spectrum analysis, however, required that U.S. military personnel stop the Fox vehicle, return to the site where the MM-1 alarmed, and then perform a 20-minute process. Fox vehicle personnel recognized the danger that stopping in the midst of battle would pose to themselves and their fellow service members, and so they did not. As a consequence, full spectrum analyses rarely were performed during the Gulf War. Yet doctrine is clear it is impossible to confirm a detection without a full spectrum. Because doctrine did not accommodate the actual conditions of use, a post-incident evaluation of an incident that lacks a full spectrum cannot be validated.

--Presidential Advisory Committee on Gulf War Veterans' Illnesses, 1997<sup>1231</sup>

The Department of Defense has consistently maintained that no U.S. chemical agent detections during the Gulf War were verified as positive. This is commonly interpreted to mean that all alarms that sounded in theater were false alarms, and that troops were not exposed to chemical agents, except in relation to the Khamisiyah demolitions. But there are limitations in what can and cannot be determined from chemical alarm detections. It can only be said that DOD has not verified any U.S. chemical detections based on its own criteria which, at a minimum, required evidence of positive detections using two types of tests.<sup>1230</sup> As indicated, blister agents and lower level exposures to nerve agents would not have been detected by M8A1 alarms or the M43A1 alarm used on Fox vehicles. And detections that did trigger alarms were not always followed up with additional testing.

It is relevant to note that at least one chemical alarm sounded on March 4, 1991, during the first munitions demolitions at Khamisiyah. Initial follow up tests with M256A1 kits were inconclusive or negative, and repeat tests were negative, leading NBC personnel to conclude that the alarm had been false, and that no chemical agents were present. Therefore, no additional actions were taken and no chemical incident report was submitted up the chain of command.<sup>1638</sup> Years later, DOD confirmed that there were multiple definite releases at the site and that about 100,000 troops may have been exposed to low levels of nerve

agent as a result. But based on routine field criteria, even at close proximity to the chemical agent release, the alarm was determined to be a false alarm, and the detection not credible.

**Exposure to nerve agents in relation to the Khamisiyah demolitions.** In early March of 1991, just days after the U.S. declared a cease fire, U.S. soldiers began operations to destroy enemy munitions at a large weapons compound near Khamisiyah, about 100 km. from the Kuwaiti border in southeastern Iraq. The Khamisiyah Ammunition Supply Point was a massive Iraqi weapons storage area, covering nearly 40 square km., which included approximately 100 ammunition storage bunkers, 88 ammunition storage warehouses, and many additional buildings.<sup>1630</sup> It is now known that chemical agents were located at this site and were destroyed and scattered during the demolitions operations, potentially exposing large numbers of U.S. personnel to low levels of sarin and cyclosarin. An enormous amount has been written about these events, including details of the demolitions operations, dissemination of intelligence on chemical agents to units responsible for destroying munitions, and efforts to determine who may have been exposed to chemical agents, and at what levels.<sup>1590,1630</sup>

Although attention has focused on demolition events at Khamisiyah following the cease fire, there was considerable activity at the site during the Coalition air and ground offensives. A 2002 DOD report indicates that during the period of active hostilities, Coalition aircraft made 40 air strikes against Khamisiyah on six different dates between January 19 and February 25, 1991. These attacks reportedly destroyed 45 warehouses and at least four bunkers.<sup>1630</sup> Units of the XVIII Airborne Corps had attacked and occupied the sector of Iraq in which Khamisiyah was located during the ground war. On February 26, 1991, the XVIII Airborne Tactical Operations Center sent a message that they may have hit chemical munitions near a site referred to as Objective Gold, a primary target of the ground offensive that was located about five km. from Khamisiyah.<sup>1590,1630</sup> No further investigations have been reported concerning possible chemical releases during the air and ground wars either at Khamisiyah or at Objective Gold. The 24<sup>th</sup> Infantry Division is reported to have pushed through the Khamisiyah weapons site on February 26, but not to have occupied the site at that time.

Before the ground war began in February, 1991, Army Central Command had directed the XVIII Airborne and VII Corps to destroy all enemy munitions within their respective sectors, in an effort to eliminate Iraq's military capabilities.<sup>1630</sup> After the ceasefire, units in the XVIII Airborne's 82<sup>nd</sup> Airborne Division, along with supporting units, conducted their initial reconnaissance in and around Khamisiyah. Troops wore protective MOPP gear and had M8A1 alarms and M256A1 test kits when they entered the bunkers to survey the site, and chemical officers later reported that no chemical weapons had been detected. Army directives available to the XVIII Airborne at that time indicated that Iraqi chemical weapons could be identified by certain characteristic markings. Later information that munitions carrying chemical agents were not clearly or consistently marked was not provided until after the demolitions.<sup>1590,1630</sup>

After their initial survey of the site, combat engineering units set charges in preparation for the initial large-scale demolitions on March 4, 1991. All personnel and civilians were cleared from the area. The troops conducting the demolitions moved back, at least three miles from the site, to observe the explosions when the charges were detonated. Reports indicate that the massive explosions were visible for miles around, with debris flying out to great distances, some dropping in areas where demolitions personnel were observing the explosions. M8A1 alarms were operational during this time, and at least one is reported to have sounded from an observation location, causing unit members to go into MOPP4. Confirmation tests using M256 detection kits were negative, and the alarm or alarms were determined to be false. Explosions continued for hours after the detonations.<sup>1630,1638</sup>

Additional large-scale demolitions were conducted on March 10, when bunkers, warehouses, and stacks of crated rockets in an area known as "the Pit" were destroyed. On March 20, more than 400 earth berm

bunkers located at Khamisiyah Storage Depot South were destroyed. Units from VII Corps came into the area on March 24, and continued demolitions on remaining bunkers at Khamisiyah through early April.

The United Nations Special Commission on Iraq (UNSCOM) was created in April 1991 to identify and destroy Iraq's remaining chemical and biological capabilities. On May 16, 1991, Iraq declared to UNSCOM that chemical weapons had been present at Khamisiyah before and during the Gulf War.<sup>1630</sup> UNSCOM inspectors visited the site in October, 1991, and confirmed that both nerve and blister agents had been in the area. Government reports later blamed confusion over different names used for the site by the intelligence community and the military—in reports and memos transmitted before, during, and after the war—as the reason that it did not become clear until several years later that chemical weapons had been present at Khamisiyah.<sup>1590,1630</sup>

It was not until June 21, 1996, that DOD publicly announced that U.S. forces had destroyed bunkers containing chemical agents at Khamisiyah.<sup>1600</sup> In the wake of the announcement, DOD and CIA initiated activities to investigate events at the site, to characterize the release of chemical agents, and to evaluate its possible association with the health problems affecting Gulf War veterans.<sup>1589</sup> In October 1996, DOD announced it would contact the 20,000 veterans in units who had been within 50 km. of Khamisiyah to notify them of the nerve agent release. In November, 1996, Dr. Bernard Rostker was named to head the newly established Office of the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses (OSAGWI).<sup>1630</sup>

In the months and years that followed, OSAGWI mounted extensive investigations of events and exposures during the Gulf War. This included several detailed efforts to model chemical release and exposure scenarios resulting from the Khamisiyah demolitions, in cooperation with CIA. Modeling efforts were complex, and involved estimates of the number and types of rockets destroyed in different areas of Khamisiyah, the amount of agent in each rocket, the degree of purity of the agents and ratio of sarin to cyclosarin, demolition simulations conducted at Dugway Proving Ground, and determinations of wind speed and direction at different times over multiple days.<sup>1630,1631</sup> The modeling approaches used were sophisticated, but necessarily involved major assumptions and uncertainties. Alongside these efforts, DOD developed unit location databases to determine where each unit had been located in theater for each day in question, to assist in identifying individuals in areas potentially affected by chemical releases at Khamisiyah.

After initially determining that 20,000 veterans had been located within 50 km. of the Khamisiyah demolitions, DOD and CIA announced, in July 1997, results of a modeling effort developed to more accurately characterize troop exposures between March 10 and March 13, 1991. The models for the four day period, derived from a composite of four modeling approaches, indicated that no troops had been in areas where exposures would have been predicted to immediately produce noticeable symptoms. This was consistent with earlier reports from medical officers who had not observed symptoms of chemical agent exposure at the time of the demolitions.<sup>1638</sup> However, lower-level exposures were possible for 98,910 soldiers who had been in the modeled “low level hazard area,” where exposures below those that cause immediate symptoms may have occurred.<sup>1630</sup>

Results of a second detailed modeling effort were released in early 2000. Overall, the 2000 models indicated that 101,752 troops were in locations within the “potential hazard” area. This included areas where exposures were estimated to exceed the “general population limit” threshold for a sustained four day exposure. Exposures within this hazard area would therefore have ranged from extremely low levels with no noticeable effects to levels that could potentially cause observable symptoms. The specific geographical area identified by the 2000 hazard area differed markedly from the 1997 hazard area. As a result, nearly a third of the troops identified as potentially exposed by the 1997 models were no longer in the hazard area identified by the 2000 models, and over 30,000 additional troops were newly identified as potentially exposed to low level nerve agents.<sup>1630</sup>

Questions about Khamisiyah models and exposure estimates. Because of the many uncertainty factors and assumptions used in generating both the 1997 and 2000 Khamisiyah models, it is not surprising that both the methods used and the conclusions drawn from these efforts have been challenged. In its 1998 report, the Senate Special Investigation Unit on Gulf War Illnesses (SIU) raised far-reaching criticisms of the 1997 models. The committee favored an alternate approach, supported by an independent consultant, that utilized weather data and plume diffusion modeling from the Air Force Technical Assistance Center (AFTAC). Preliminary modeling conducted by AFTAC had described an alternate plume that moved south and east after the detonations, extending further into Kuwait.<sup>1690</sup>

The U.S. General Accounting Office (GAO) also conducted an in-depth investigation of Khamisiyah modeling efforts and provided its findings in a detailed report issued in June 2004.<sup>1683</sup> The report sharply criticized the DOD/CIA Khamisiyah models, and concluded that estimated troop exposure levels were highly questionable because the models on which they were based were not reliable. Specific problems were identified on many levels, beginning with the initial data on which the models were based—information on agent quantity, purity, and concentration, and on weather and wind patterns. The report further indicated that assumptions used to construct models were often inaccurate or contradictory and that modeling procedures were not validated for estimating long-range environmental fallout. The GAO report concluded that the actual extent of chemical agent exposures resulting from the Khamisiyah demolitions could not be determined. Further, because the data required for accurate modeling were not available, additional modeling efforts were not likely to be any more useful than DOD models had been.

It is likely that if fully developed and validated models and more realistic data for source term were included in the modeling, particularly plume height and exposure duration, the exposure footprints would be much larger and most likely to cover most of the areas where U.S. and other coalition forces were deployed.

--U.S. General Accounting Office, 2003<sup>1681</sup>

In addition, GAO cautioned that research findings based on the Khamisiyah models could not, with confidence, be considered valid.<sup>1681</sup> Use of the models to identify veterans who had been “exposed” or “not exposed” to nerve agents was problematic for two reasons. The first related to inaccuracies specific to the Khamisiyah models, spelled out in detail. The second related to the possibility that military personnel had been exposed to chemical agents at other times and locations.<sup>1683</sup> Both factors could potentially contribute to extensive classification errors in determining which veterans had been exposed to nerve agents. Due to the many unknown factors associated with chemical agent exposure in theater, GAO recommended that no additional epidemiologic research be based on nerve agent exposures estimated by the DOD Khamisiyah models.

The Department of Defense responded to issues raised by GAO, defending the modeling techniques employed as state-of-the-art. The DOD response also pointed out a number of factual errors in GAO’s assertions, and indicated that changes made in the 2000 models had addressed some of the concerns raised.<sup>1683</sup> Although DOD did not concur with GAO’s recommendation on epidemiologic research, it did concur that no additional modeling efforts should be conducted.

The many detailed issues raised by GAO concerning the Khamisiyah models, at minimum, indicate the need for caution in assuming that the models accurately represent nerve agent exposures resulting from the demolitions. Additional issues related to Khamisiyah that were not raised by GAO or SIU include questions about possible chemical releases at the site during the air and ground offensives. There is also minimal support in DOD reports for their including only nerve agent releases from a single day, March 10, 1991, in the Khamisiyah models, although demolitions occurred there on multiple occasions over a five week period. The GAO report also raises a second issue of importance, that is, the potential for Gulf War personnel to have been exposed to chemical agents in other locations.<sup>1683</sup>

**The possibility of other chemical agent exposures.** There are numerous reports from government and private sources, and personal stories from individual veterans, that describe incidents suggesting possible chemical agent exposures during the war.<sup>388,521,579,961,1231,1558,1688</sup> Many are anecdotal, undocumented by any type of evidence. Others are associated with some level of evidence such as a positive chemical detection, but government investigations have found the available evidence too limited to verify the detection. Reports commonly indicate that troops believed that positive detections had been the result of chemicals drifting south from where Coalition troops had bombed chemical facilities in Iraq. Iraq's chemical production and storage facilities had been high priority targets in the early days of the air offensive.<sup>320,1284,1690</sup>

The measures we took to eliminate the enemy's chemical and biological threat were both active and passive. The active measures were the destruction of known storage and production sites in the earliest stages of the strategic air campaign.

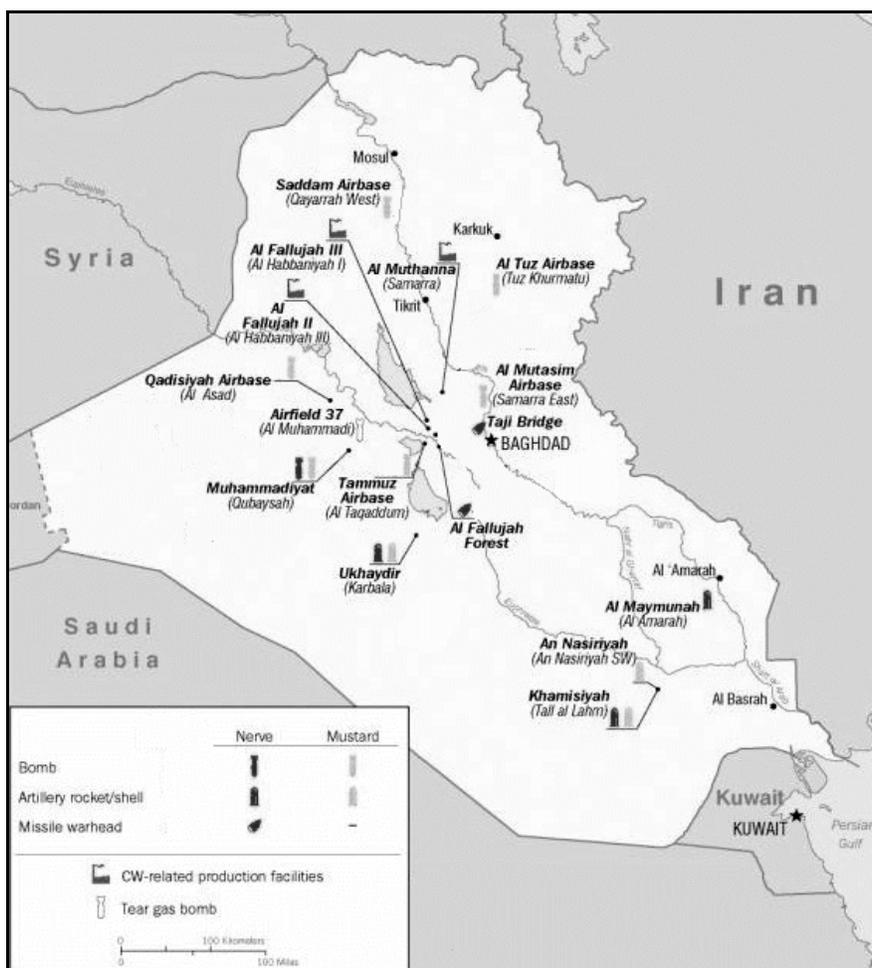
--General Norman Schwarzkopf, 1997 Senate Testimony<sup>1690</sup>

After the war, in connection with the work done by UNSCOM, additional information became available on locations where Iraq had produced, stored, and deployed chemical agents during the war. These sites are shown in Figure 2. Multiple additional sites were identified where Iraq had deployed binary nerve agent weapons, that is, weapons that contained compounds that could be converted to nerve agents by adding a second ingredient before firing. Many suspected chemical agent release and exposure events have since been evaluated by DOD and CIA, leading to two types of findings: (1) determinations of whether a chemical release is likely to have occurred, and (2) determinations of whether U.S. personnel were likely to have been exposed to chemical agents. This distinction is important, since there are a number of sites in Iraq where CIA and DOD have reported massive releases of nerve and blister agents as a result of Coalition bombing. For example, a 1996 CIA report indicated that during the air campaign, 17 metric tons of sarin were released at Iraq's primary chemical weapons and storage facility, Al Muthanna, and 15 metric tons of mustard and 2.9 metric tons of sarin were released at the Muhammadiyat munitions storage site.<sup>1589</sup> Both targets were in central Iraq, hundreds of kilometers from the nearest U.S. troop locations, and CIA's dispersion models indicated that troops would not have been exposed to chemicals as a result of these releases. A later CIA report revised sarin release estimates dramatically downward from the 1996 estimates, and increased estimated levels of mustard released, but continued to assert that the chemicals had not reached U.S. troops.<sup>1591,1629</sup>

In 2002, CIA reported its findings related to 20 suspected chemical agent *releases* during the Gulf War.<sup>1591</sup> Twelve of the scenarios investigated were found to have resulted in a "definite" chemical agent release, one as a "likely" release, six as "suspect" releases, and one as "unlikely." Of the 20 chemical agent releases evaluated, only Khamisiyah was found to have resulted in a "likely" chemical exposure to U.S. troops. In addition, DOD has conducted investigations of many suspected chemical exposure events, some of which overlap with the releases evaluated by CIA. The DOD findings are provided in 20 "Case Narrative" reports, which sometimes encompass multiple chemical detection incidents by certain units or in certain areas.<sup>1603</sup> Again, only events at Khamisiyah were found to have resulted in "likely" U.S. troop exposures to chemical agents.<sup>1630</sup> Exposures were found to be "unlikely" for most of the remaining events,<sup>1609,1627,1628</sup> although a chemical agent detection by Czech chemical specialists was identified as "valid" in one report, and several other detections were judged to be "indeterminate."<sup>1610,1614,1617,1629</sup>

Because our Committee has not conducted detailed investigations of the many reported chemical events during the Gulf War, we cannot offer independent judgments about whether specific exposures did or did not occur. Our review of DOD and CIA reports does indicate, however, that conclusions related to specific incidents are often less conclusive than might be suggested by summary findings of "likely" or "unlikely." For example DOD findings frequently depend on whether or not the presence of a chemical

**Figure 2. Iraqi Chemical Weapons Facilities and Declared Sites Where Chemical Agent-Filled Munitions Were Deployed During Desert Storm**



Source: U.S. Central Intelligence Agency<sup>1591</sup>

agent was *verified* based on two confirmed tests using different analytic methods. As a result, situations in which two tests were done but records not retained, or where two different types of tests were not done, or where putative exposures occurred below levels detectable by monitoring equipment would not have been verified by *post-hoc* evaluations.

A compelling example is provided in a 2004 GAO report that detailed 20 positive chemical agent detections between January 17 and 23, 1991, by U.S., Czech, French, and British units.<sup>1683</sup> On some days during that period, multiple detections of the same type of agent were reported by different units from different nations, in close proximity. For example, U.S., French, and Czech units all reported detecting sarin or an unknown nerve agent near King Khalid Military City (KKMC) in northern Saudi Arabia on January 20, 1991. The January 17-23 period coincides with the initiation of Coalition air bombing in Iraq. The GAO report and testimony provided to a Congressional committee also indicate that this period coincided with a stationary weather pattern identified by meteorological satellite imagery in areas where troops were located in northern Saudi Arabia.<sup>1683,1684</sup>

A thermal plume rose into the atmosphere over the largest Iraqi chemical warfare agent research, production, and storage facility at Muthanna after Coalition aircraft and missile bombardment. Seventeen metric tons of Sarin were reportedly destroyed during these attacks, which began on January 17, 1991. These thermal and visual plumes extended directly toward the areas where those same chemical warfare agents were detected and confirmed by Czechoslovak chemical specialists.

--Jim Tuite, 1997 Congressional Testimony<sup>1684</sup>

Taken together, this information suggests that Coalition bombing in the early days of the air war resulted in one or more releases from chemical weapons production or storage sites in central Iraq that, aided by weather patterns, drifted over the Saudi border. There, chemical agents were detected by different units over a period of several days. But both DOD and CIA have investigated many of the events described and have concluded that this did not occur, that is, that chemical agents released with Coalition air bombing did not drift far enough south to have been detected in northern Saudi Arabia.

The Department of Defense originally reported findings from an investigation of Czech chemical agent detections in November, 1993.<sup>1601</sup> At that time, the Secretary of Defense announced that Czech chemical specialists had reported very low levels of sarin and mustard on several dates and that DOD experts had found the detections to be credible. Czech chemical units had the most sophisticated chemical capabilities available during the Gulf War, with detection systems that were highly sensitive for both nerve and blister agents.<sup>1610</sup>

In 1998, an OSAGWI Case Narrative described a series of Czech nerve agent detections on January 19, 1991.<sup>1610</sup> That morning, two separate teams of Czech chemical specialists reported near-simultaneous detections of low-level sarin about a mile apart near Hafir Al-Batin, in northern Saudi Arabia. Thirty minutes later, a third detection was reported by another unit about 30 miles away. In each case, the initial detections were retested with a second type of detector and also found to be positive. An air sample collected for further testing at a laboratory in KKMC also tested positive for sarin. The detected levels of nerve agents were below the sensitivity thresholds of equipment used by other Coalition partners. U.S. specialists who arrived in the area four hours later did not detect sarin using U.S. equipment. Still, DOD concluded that the detections had been valid and credible, although the source of the sarin was not ascertained.<sup>1610</sup> In 2002, CIA released a report that included findings on the Czech January 19 chemical detections. CIA officials had earlier identified these detections as credible,<sup>276,1610</sup> but the 2002 report concluded that the detections that day were “unlikely,” based on CIA’s inability to identify a plausible source for sarin in the area, and newly raised questions about the reliability of the detections.<sup>1591</sup>

Although an extensive amount of information has been reported on these events, the lines of evidence that either favor or discount the presence of chemical agent that day are less-than-definitive. It can only be concluded that low levels of nerve agent *might* have been present in the northern part of Saudi Arabia on January 19, 1991. Even if detections were accepted as valid, it is not known the extent to which U.S. troops might have been exposed as a result.

The challenges and conflicting conclusions described with respect to this particular incident on this single day illustrate the difficulties inherent in determining if and where military personnel might have been exposed to low level chemical agents during the Gulf War. Other reported incidents, including additional Czech detections, are also associated with both supporting and negative indicators.<sup>1610,1614,1627</sup> As a result, the extent of exposure to low level chemical agents in theater remains an open question.

**Recent information concerning Iraq’s intended use of chemical weapons.** In the years following the Gulf War, several investigations suggested that Iraq had prepared to use chemical weapons during the Gulf War, and that some limited use may have occurred.<sup>388,1560,1688</sup> Both DOD and CIA have consistently maintained that, based on their investigations, there is no credible evidence of Iraqi offensive

use of chemical agents during the Gulf War.<sup>1284,1589-1591</sup> This issue was raised again in recent years, with findings from a comprehensive investigation, conducted by the Iraq Survey Group (ISG), of Iraq's weapons of mass destruction (WMD) capabilities prior to the 2003 Iraq War.<sup>693</sup> The ISG report provides additional information about Iraq's deployment of chemical weapons during the 1991 Gulf War, and evidence that Saddam Hussein had authorized their use against Coalition forces. It also documents Iraqi attempts to use sarin against the Shia population in southern Iraq in March of 1991, to quell an uprising after the U.S.-declared ceasefire. Iraq's attempt to bomb the Shia with sarin was not successful, however. This was thought to be because the sarin-filled bombs had not detonated when released from low-flying helicopters, the only aircraft Iraq could utilize under terms of the ceasefire. As an alternative, the Iraqi military dropped large aerial bombs filled with CS (tear gas) in the areas of Karbala and Najaf, an estimated 200 bombs over a two week period. CS is not technically classified as a chemical warfare agent, but is nonetheless a toxic chemical that can cause acute tearing, respiratory problems, and burning and blistering of the skin.

The U.S. military was well familiar with Iraq's brutal attacks in areas of Southern Iraq during this period. A defense intelligence bulletin in early March of 1991 had warned that Iraq might resort to the use of chemical weapons to quash the Shia rebellion.<sup>1617</sup> Refugees, some of them seriously injured, had streamed into U.S. controlled areas after the attacks began. U.S. forces provided humanitarian support, and medical teams treated large numbers of wounded civilians.<sup>1617</sup> Rev. Joel Graves, a Committee member and Gulf War veteran, reported that on March 15, members of his unit, stationed south of Basra, had become acutely ill in the evening and that chemical alarms had sounded nearby. The next day, his commander informed him that mustard gas was thought to have been used in Iraqi attacks against the Shia in Basra, and may have drifted towards U.S. troop locations with the strong southerly winds.<sup>521</sup> A joint staff message of March 28, 1991, indicated that Shia refugees had reported Iraqi attacks on Basra with both mustard and white phosphorous in mid March.<sup>1599</sup> Although the ISG report indicates that nerve agents were unsuccessfully deployed, the events described by the Iraq Survey Group provide a sobering indication of Saddam Hussein's willingness to attack with chemicals, even when Iraq was occupied by Coalition forces.

**Summary. Exposure to chemical weapons in the Gulf War.** During the Gulf War, military defenses against chemical weapons emphasized detection and response to high level, acutely dangerous exposures, to protect troops from potentially dire consequences. There are no indications that U.S. or Coalition forces encountered large scale, high dosage exposures to chemical weapons during the Gulf War. Since the war, however, concerns have emerged about possible effects of lower level chemical agent exposures and their association with the health problems affecting Gulf War veterans.

Despite extensive government efforts, substantial questions remain about the extent to which Gulf War military personnel were exposed to low-level chemical agents in theater. Uncertainties are associated with several factors. First, it is unlikely that low levels of airborne chemical agents would generally have been identified or documented by military personnel. Monitoring systems had little capacity to detect chemical agents at levels that do not cause immediate symptoms. Second, although the Department of Defense estimates that about 100,000 personnel may have been exposed to low levels of sarin and cyclosarin nerve agents as a result of weapons demolitions at Khamisiyah, serious questions have been raised about the accuracy of government models used to determine who was exposed, and at what levels. Third, unanswered questions and limited information related to other reported chemical events leave open the possibility that additional chemical exposures might have occurred during and after the Gulf War, in locations other than those affected by the Khamisiyah demolitions.

## Health Effects of Cholinergic and Related Neurotoxicants

A neurotoxic response to a single large dose of a substance often predicts neither the existence nor the type of response seen in animals repeatedly exposed to lower levels of the same agent.

-- *Biological Principles of Chemical Neurotoxicity*, 2000<sup>1463</sup>

### Health effects of pyridostigmine bromide

Information concerning biological and health effects of PB is available from both animal research and human studies. Pyridostigmine is a carbamate compound that temporarily, and reversibly, binds AChE. A comprehensive review of the available literature was provided in a 1999 RAND report, which identified several mechanisms whereby PB could plausibly contribute to veterans' chronic symptoms.<sup>504</sup> These included chronic dysregulation of acetylcholine and persistent damaging effects on peripheral neuromuscular junctions. The RAND report concluded that PB could not be ruled out as a possible cause or contributor to Gulf War illness.

**Pyridostigmine research in animals.** Pyridostigmine normally does not cross the blood brain barrier in significant amounts, due to a positively charged quaternary ammonium group. This confers an important advantage for using PB as a nerve agent pretreatment over other reversible AChE inhibitors, since direct effects on the central nervous system would be expected to be minimal. The importance of brain penetration in determining some effects of PB is demonstrated by recent research from the Lovelace Respiratory Research Institute, which evaluated effects of anticholinesterase compounds on the immune response and hypothalamic-pituitary-adrenal (HPA) function. Pyridostigmine administered subcutaneously had no effect on antibody response or corticosteroid levels. But when injected directly into the brain, PB significantly inhibited antibody response and reduced circulating corticosteroid levels in the same way as physostigmine, an anticholinesterase drug that readily crosses the blood brain barrier.<sup>868</sup>

Animal studies conducted since the 1980s have demonstrated that PB can adversely affect peripheral nerve function and structure,<sup>25,364,651</sup> and can also have central and behavioral effects, especially when given at higher doses.<sup>144,366,648,916,1401,1443,1793,1807</sup> Research in animal models has also described acute adverse effects on gastrointestinal function with relatively low doses of PB,<sup>816</sup> and autonomic, immune, respiratory, and cardiovascular effects at moderate-to-high doses.<sup>129,771,1188,1379,1439,1814</sup>

Although multiple studies have evaluated biological effects of PB in animal models in recent years, most have focused on effects of PB in combination with other Gulf War-related exposures and with stress. These have included assessments of PB in combination with low-level sarin, pesticides and insect repellants, caffeine, and vaccines, as will be described in a later section.

**Effects of low-level pyridostigmine on brain and behavior.** It has long been observed that PB can produce significant, acute effects on the brain and behavior when given in high doses.<sup>144,366,916,1401</sup> In recent years, multiple studies have also identified significant central nervous system effects resulting from low-dose exposure to PB. Dutch investigators have reported that primates exhibited significant EEG abnormalities after receiving low dose PB for four days.<sup>1706</sup> Five studies conducted in rodent models since 2000 have reported that low-to-moderate doses of PB, administered by gavage on a schedule of repeated exposures over time, produced significant deficits on a variety of tests of learning and behavior.<sup>10,11,14,1704,1705</sup> Animals exposed to PB in these studies are described as exhibiting no overt signs of cholinergic toxicity or ill health.

A consistent feature of the behavioral studies is that repeat, low and moderate dose exposure to PB, over a period of days to weeks, produced central effects not reported from studies using single, brief exposures,

even at higher doses. Additional effects of repeated PB dosing on the central nervous system have been demonstrated by researchers from Purdue University and the East Orange, New Jersey VAMC. Purdue investigators reported that repeated, low-to-moderate doses of PB, administered over a four day period produced only a limited decrease in brain AChE activity, but yielded extensive neuronal apoptosis in the cortex, striatum, and hippocampus of treated rats, in a dose-response pattern. The effect was sustained in the cortex over a 30 day period following cessation of PB treatment. Investigators suggested that the repeated dosing schedule enabled PB to cross the blood brain barrier and act directly on brain cells.<sup>900</sup>

In addition, New Jersey researchers have reported delayed central effects of low-to-high doses of PB, administered in drinking water over a seven day period. In exposed rats, a persistently exaggerated acoustic startle response first appeared 15 days after PB treatment had been completed.<sup>1387</sup> The delayed effect was only observed in a strain of rats (WKY) with low activity of the PB-scavenging enzyme butyrylcholinesterase (BChE).<sup>1388</sup> Investigators suggested that individuals with low BChE activity may have increased sensitivity to delayed, central effects of PB.

**Pyridostigmine and stress.** Widespread interest in the potential for PB to interact synergistically with stress was stimulated by a 1996 Israeli study indicating that central nervous system effects of PB were markedly enhanced, in animal models, by an intense stressor—forced swimming. Investigators suggested that conditions of extreme stress rendered the blood brain barrier more permeable to PB.<sup>460</sup> This initial observation was not supported by subsequent findings from different laboratories, which found that stressors of various types did not enhance levels of PB in the brain or lead to marked decreases in whole brain AChE activity.<sup>519,857,1394,1414,1444,1539</sup> Several studies did report, however, that PB exposure alone reduced brain levels of AChE to a limited degree, independent of whether animals had been stressed or not.<sup>85,900,1414</sup>

Recent studies have reported findings of other types that do suggest interactive effects between PB and stress, however. Investigators at Wright State University found that PB, alone, had no effect on heart rate or blood pressure in mice. But in combination with a relatively mild stressor (intermittent shaker stress), PB produced significant autonomic alterations, specifically, increased low frequency heart rate variability and baroreflex sensitivity.<sup>714</sup> Researchers from the East Orange, New Jersey, VA reported that administering an intense stressor to rats prior to PB exposure resulted in reduced AChE levels in the basal forebrain/striatum but not in other brain areas.<sup>115</sup> And French investigators have reported that PB, in conjunction with stress, produced increased levels of the serotonin metabolite 5-HIAA in multiple regions of the brain, and increased dopamine levels in the striatum/hippocampus.<sup>1528</sup> Pyridostigmine has also been shown to interact synergistically with physical stress in peripheral tissues. Research from Southern Illinois University indicates that low-dose PB, when given concurrently with an exercise stressor, resulted in significantly reduced levels of AChE and increased indicators of muscle tension and oxidative stress in skeletal muscle, effects not seen with either PB or exercise alone.<sup>703,1442,1713</sup>

In assessing the literature on stress/PB interactions in animal models, the most important distinctions appear to relate to the specific outcomes assessed and exposure protocols used. Overall, studies that did *not* identify interactive effects between PB and stress focused on whether the combination increased central AChE activity and permeability of the blood brain barrier. Most of these studies also assessed acute effects, following single doses of PB at low-to-high levels. In contrast, nearly all studies that *did* identify stress/PB interactions assessed effects of low-dose, repeat exposure to PB over a period of five to 14 days. In addition, these studies assessed outcomes other than changes in central AChE activity and blood brain barrier permeability. Taken together, these studies suggest that interactive effects between PB and stress may occur, but are not reflected by a general reduction in central AChE activity or a general increase in blood brain barrier permeability, and are also not observable as acute effects following single exposures. It is not possible to determine from these studies, however, whether central effects were due to PB acting directly in the brain, or indirectly, through effects stimulated in the periphery.<sup>85,116,1528,1704</sup>

**Human studies of the effects of PB.** Short-term effects of PB have been evaluated in a relatively large number of human studies in relation to its military use as a nerve agent pretreatment, its use as a treatment for myasthenia gravis, its use in testing for growth hormone (GH) abnormalities, and other applications. In the early 1990s, multiple studies conducted by the U.S. and Israeli militaries evaluated health and performance effects of PB, taken over a brief time period, in small samples of healthy human volunteers, usually military personnel. Health parameters were assessed under a variety of conditions, including flight simulation, exercise, and heat stress. Under conditions of heat and exercise stress, PB taken over several days produced significant reductions in heart rate, blood pressure, and handgrip strength compared to placebo.<sup>271,1762,1763</sup> But overall, few significant differences were identified, and there were no indications that PB impaired work performance.<sup>53,271,410,411,476,700,1296,1762,1788</sup> A more recent study, in fact, identified improved reaction time on tests of memory and attention in healthy subjects taking PB, perhaps due to effects of AChE inhibition on neuromuscular synaptic efficiency.<sup>273</sup>

Multiple studies conducted in clinical settings have documented rates and types of acute side effects associated with PB. Milder effects include abdominal and digestive discomfort, runny nose, and excess salivation and sweating, while more severe reactions can include diarrhea, muscle weakness and spasms, and vomiting. Pyridostigmine also stimulates GH secretion, and this effect is used to test for GH abnormalities in different clinical conditions.<sup>347,487</sup> Acute side effects reported in conjunction with a single use of PB in GH testing are similar to those seen in other clinical studies of PB. Gastrointestinal symptoms (e.g., nausea, cramping, flatulence, diarrhea) are most common.<sup>679</sup> Side effects appear to be more frequent with higher PB dosages,<sup>1819</sup> but are generally tolerable and transient.

A detailed clinical study that evaluated symptoms reported by healthy subjects who used PB over several days, at the level recommended for use in the Gulf War, also indicated that gastrointestinal side effects were most common. Few side effects were reported in the first day of dosing but more side effects, overall, were reported by subjects taking PB than those taking placebo. Symptoms were generally mild and short lived, more frequently reported by women than men, and more pronounced with higher doses of PB.<sup>272</sup> Several studies have also reported rates of acute side effects from PB use by military personnel during the Gulf War. Studies indicate that use of PB during the Gulf War was associated with higher rates of side effects than has commonly been observed in clinical settings,<sup>781,1396</sup> and suggest that side effects may relate to longer term illness, as will be described in a later section.

In both clinical and war zone settings, a subset of individuals who take PB develop side effects from taking relatively low doses of PB. The factors that determine who does or does not react to PB are not well understood, however. There are indications from two reports that symptoms associated with PB use are not related to the degree of peripheral cholinesterase inhibition.<sup>272,1396</sup> One case report of an Israeli soldier who suffered severe side effects after taking PB during the Gulf War indicated that he was a rare homozygous carrier of the atypical A allele for the butyrylcholinesterase (BChE) gene. BChE is a circulating enzyme that serves as a scavenger that irreversibly binds cholinesterase inhibitors, thus sparing AChE. The Israeli soldier's BChE was found to have very poor affinity for binding PB, leading authors to suggest that some individuals may be more genetically susceptible to adverse effects of PB.<sup>929</sup> This hypothesis has been further explored in relation to Gulf War illness, as will be described in a later section.

No human studies have evaluated long-term effects that might develop or persist over an extended period after short term use of PB. Information on side effects from long-term, high-dosage use of PB is available from studies of myasthenia gravis patients,<sup>119,627</sup> who typically use between 300 and 1200 mg. of PB per day over many years.<sup>52,169</sup> Effects of PB in myasthenia gravis patients cannot be directly compared to effects expected in healthy soldiers, however. Myasthenia gravis is associated with severely reduced cholinergic activity, and PB treatment is used specifically to increase acetylcholine in order to bring patients' neuromuscular function to a more normal state. Reports indicate that the most common side effects of PB treatment for myasthenia gravis patients include diarrhea, increased salivary secretions, and

sweating. Symptoms are reported by 34 - 54 percent of myasthenia gravis patients, are more problematic with higher PB dosages, but are seldom severe enough to cause discontinuation of treatment.<sup>119,627</sup>

Pyridostigmine bromide has been associated with autonomic alterations in several human studies. A single low dose of PB has been shown to reduce cardiovascular response to physical and mental exertion.<sup>1347,1386</sup> Four 30 mg. doses of PB, taken at eight hour intervals over a 24 hour period, produced significantly lower heart rate and significant increases in time domain measures of heart rate variability, compared to placebo.<sup>1129</sup> Research conducted by Midwest Research Institute identified more pronounced autonomic alterations with somewhat longer PB use. After four to five days of taking either 30 mg. or 60 mg. of PB every eight hours, healthy subjects exhibited slower heart rates, significantly reduced heart rate variability in the high frequency range, and significantly increased variability in the low frequency range compared to subjects who had taken placebo.<sup>273</sup> Reduced high frequency power was substantial, averaging 21 percent at the 30 mg. dose, and was significantly correlated with the degree to which PB inhibited AChE and BChE activity. Findings suggest a central nervous system effect of PB. Investigators pointed out, however, that this central effect might not require PB to have crossed the blood brain barrier, since vagal control centers are reciprocally innervated by the medullary *area postrema*, which lies outside the blood brain barrier.<sup>273</sup>

Pyridostigmine bromide has been suggested to provide some clinical benefits for patients with autonomic irregularities and patients with multisymptom illnesses. It has recently been investigated as a treatment for neurogenic orthostatic hypotension, a condition associated with impaired autonomic regulation of blood pressure. Initial reports suggest that PB improves standing blood pressure, without adversely affecting supine blood pressure.<sup>472,1412</sup> In a six month, placebo-controlled trial of 165 fibromyalgia patients, PB was found to provide significant improvements in sleep and anxiety measures, but no improvement in pain.<sup>723</sup> A case series report has also described substantial symptomatic improvement in three chronic fatigue syndrome patients treated with PB.<sup>777</sup>

Overall, diverse studies of the effects of PB in humans have indicated that PB has a low risk profile for acute adverse side effects when taken by healthy subjects over brief time periods in clinical settings. Little information is available concerning long-term effects of PB used by healthy subjects, although side effects described in clinical settings are described as transient. Several studies have indicated that PB, given to soldiers in wartime, induces a higher level of acute side effects than is typically observed in clinical studies. Animal studies indicate that PB, even at relatively low doses, can affect the brain and that repeated dosing schedule over an extended period of time produces central nervous system effects not observed with single doses. Animal studies have also reported limited interactive effects between stress and PB, although the majority of studies indicate that stress does not enhance PB passage into the brain. Both animal and human studies have demonstrated effects of low dose PB on autonomic nervous system function, at dosages too low to cause serious symptoms or excessive peripheral AChE inhibition. It is not known, however, how long these effects are sustained.

## Health effects of pesticides and insect repellants used in the Gulf War

Overexposure to pesticides, particularly organophosphates and carbamates, may have contributed to the unexplained illnesses reported by some Gulf War veterans.

--*Environmental Exposure Report: Pesticides*, U.S. Department of Defense, 2003<sup>1632</sup>

Chemical pesticides and insect repellants have been in widespread use since the middle of the last century. Many pesticides are neurotoxic by design, that is, they are developed to kill insects by attacking their nervous systems. Thousands of compounds have been developed for use against different insects and other pests, for application in different settings. The Department of Defense estimates that 64 different pesticide and insect repellent products, with 37 different active ingredients, were used by military personnel during the Gulf War. The 15 pesticide products identified by DOD as being the pesticide products of greatest concern in relation to the health of Gulf War veterans are listed in Table 2. Although these 15 products represent a diverse mix of chemical compounds, the majority fall into two chemical classes—organophosphates and carbamates—both of which are AChE inhibitors. The list also includes two pyrethroid compounds, one organochlorine, and two DEET products.

Many thousands of research studies have evaluated biological effects of pesticides in animal models and health effects in human populations. Detailed information from this large literature is compiled in comprehensive textbooks on pesticide toxicology. New findings related to toxicological effects of pesticides and insect repellants continue to emerge at a rapid pace. In recent years, this research has provided important insights into health effects of lower-level and chronic pesticide exposures in human populations, including associations with persistent symptomatic illness. The U.S. government has launched a number of important research initiatives to better understand effects of pesticides on human health. This includes the Agricultural Health Study, a large interagency project to characterize acute and long term health effects in nearly 90,000 Americans who work with pesticides, and their family members.<sup>1686</sup> This longitudinal, multi-state project is evaluating diverse health parameters and has produced important research findings, some of which have relevance to issues considered in this report.

In the last several years, major reports have been released internationally by government and scientific panels concerning effects of pesticide exposures on the public health. These reports have raised awareness of recent findings on potential associations between pesticides and a broad spectrum of human diseases, including difficult-to-diagnose multisymptom conditions. This includes a review of the scientific literature on health effects of pesticides from the Ontario College of Family Physicians, which concluded that “there is a high level of consistency in results to indicate a wide range of pesticide-related clinical and subclinical health effects” and that “exposure to all the commonly used pesticides—phenoxyherbicides, organophosphates, carbamates, and pyrethrins—has shown positive associations with adverse health effects.”<sup>1155</sup> The report urges physicians to become more aware of health effects of pesticides in order to better educate the community and treat their patients. A 2005 report on human health affects of agricultural pesticides from the British Royal Commission on Environmental Pollution described the complex issue of discerning chronic health effects resulting from unmeasured and varying combinations of pesticide exposures. The Commission noted that “the clinical awareness of general practitioners and specialists needs to be improved in order to improve the investigation of people with chronic, ill-defined health effects.”<sup>1324</sup>

A number of reports describing toxicological issues and potential health effects specifically related to pesticide use in the Gulf War have also been published. In addition to the detailed investigation of pesticide use by Gulf War military personnel, DOD commissioned RAND to review scientific research related to potential health effects of pesticide use in the Gulf War.<sup>218</sup> The 2000 RAND report provided information pertaining to each of the major classes of pesticides and insect repellants of greatest concern used by military personnel in theater. It pointed out that understanding effects of pesticides on the health of Gulf War veterans is complicated by a number of factors, including variation in individual

vulnerability to adverse effects of neurotoxicants, differences in the degree to which pesticides used by veterans were absorbed into their skin and circulation, and unknown effects of combinations of multiple pesticides or pesticides in combination with other exposures in theater. The RAND report concluded that pesticides, specifically AChE inhibitors, could be among the agents that contributed to the development of veterans' multisymptom illness and called for additional research to investigate the association.

The Institute of Medicine (IOM) conducted a detailed review of human studies related to health effects of pesticide exposures as part of the *Gulf War and Health* series of reports.<sup>682</sup> The report focused primarily on effects of pesticides in relation to multiple types of cancer, with some information on effects of pesticides on diagnosed neurological diseases and reproductive outcomes. No conclusions were provided concerning possible associations between pesticide exposures in theater and Gulf War multisymptom illness.

Information concerning health effects of the major classes of pesticides and insect repellants used during the Gulf War is briefly summarized below, with attention to health issues relevant to Gulf War veterans. Most scientific research on pesticides has evaluated effects of individual chemicals that develop over a relatively brief time period. Human research has historically focused primarily on effects of high-level exposures associated with pesticide poisoning. However, a growing body of research has evaluated human health effects of lower-level exposures and exposures experienced over longer periods of time. Nearly all studies that have evaluated effects of combinations of pesticides and repellants used in the Gulf War have been conducted in the past 12 years, using animal models, in connection with the federal Gulf War research effort. This research will be described in a later section that addresses effects of combinations of Gulf War exposures.

**Organophosphate pesticides.** Organophosphate pesticides (OPs) constitute the largest number of chemicals identified as pesticides of potential concern used during the Gulf War. These include chlorpyrifos, diazinon, and malathion, used in different concentrations by pesticide applicators as area fogs and surface sprays. They also include dichlorvos-containing pest strips, issued for personal use to the general military population, and azamethiphos crystals used as fly bait, which was purchased locally.<sup>1632</sup>

Organophosphate compounds are a large and diverse family of chemicals that include hundreds of different pesticides, as well as several types of chemical warfare agents.<sup>387,932</sup> They are among the most extensively studied of any chemicals in toxicology. Acute effects of excess exposure to OP pesticides are those previously described for AChE inhibiting chemicals generally, and include effects on the central nervous system, autonomic nervous system, and skeletal muscles. There are also a growing number of indicators that OPs can exert neurotoxic effects through mechanisms other than AChE inhibition.<sup>216,982,1166,1436,1553</sup> In addition, recent studies in animal models have demonstrated that repeated exposures to OP pesticides, even at relatively low doses, can produce persistent neurochemical and behavioral alterations that do not occur with single exposures at similar or higher doses.<sup>29,775,823,1226,1251,1530,1531,1553</sup>

Symptoms that result from acute OP poisoning usually develop within minutes to hours and resolve in hours to a few days, but there are exceptions. A delayed reaction to poisoning by malathion or diazinon has been described in some individuals, a condition known as "intermediate syndrome." This condition develops between one and four days after OP exposure and is associated with severe muscle weakness. Serious cases can lead to respiratory arrest but if respiration is maintained, recovery generally takes several weeks.<sup>754</sup>

Poisoning by some OP compounds can also produce, in a minority of cases, a chronic condition known as organophosphate induced delayed neuropathy (OPIDN). Onset of OPIDN varies with the specific compound and dosage of exposure, but ranges from 10 days to five weeks after OP poisoning. Symptoms

usually begin with cramping muscle pain in the lower extremities, followed by numbness, parasthesia, and progressive muscle weakness. More severe cases can also involve the upper extremities. The condition results from inhibition not of AChE, but of a second enzyme, neuropathy target esterase (NTE), which is not affected by all OP compounds.<sup>718,934</sup> Only two compounds widely used in the Gulf War, chlorpyrifos and dichlorvos, have been associated with OPIDN, and only following poisoning episodes involving extremely high doses.

Persistent neurological and cognitive symptoms have long been described in some individuals following recovery from acute OP poisoning, and also in relation to long term OP exposure in the absence of poisoning.<sup>9,344,483,1313</sup> Neurotoxicologists from the U.S. and the U.K. have proposed the existence of a long-term OP-associated neurotoxic syndrome that develops with chronic low-level OP exposure or persists after substantial recovery from acute OP poisoning.<sup>9,316,705</sup> Persistent central nervous system effects are notable in the proposed condition, as opposed to the prominent peripheral effects associated with OPIDN. Based on his and other research teams' investigations in animal models, Dr. Mohamed Abou-Donia of Duke University has suggested these persistent symptoms are associated with neuronal oxidative injury and apoptotic cell death in multiple brain regions following OP exposure.<sup>9</sup>

The issue of persistent central nervous system effects following lower-level OP exposures has been controversial,<sup>197,387,932</sup> as have questions related to chronic subclinical encephalopathies associated with other neurotoxicants.<sup>31,532,1781</sup> In IOM's *Gulf War and Health* report on pesticides, the review panel concluded there is sufficient evidence that OP poisoning is associated with long-term, measurable neurobehavioral deficits but did not reach consensus on whether measurable deficits were associated with OP exposures in the absence of earlier poisoning.<sup>682</sup> Aside from questions related to measured neurobehavioral deficits, a growing number of epidemiologic studies in diverse populations have consistently identified elevated rates of chronic symptoms and multisymptom illness in relation to long term, low-level pesticide exposure.

**Carbamate pesticides.** Carbamates are chemically distinct from OPs, but also exert neurotoxic effects by inhibiting the enzyme AChE. There are about 25 different types of carbamate pesticides currently in use.<sup>387</sup> Three—bendiocarb, propoxur, and methomyl—have been identified as pesticides of potential concern in relation to the Gulf War. Bendiocarb and propoxur were sprayed on surfaces and in cracks and crevices by pesticide applicators to kill flies, mosquitoes, and flying insects. In addition, fly baits containing the carbamate methomyl were issued by the military and also purchased locally, and used both by trained pesticide personnel and by individual service members.<sup>1632</sup>

Effects of acute overexposure to carbamate pesticides are similar to those described for other anticholinesterase compounds, and result from the buildup of acetylcholine at cholinergic nerve terminals. Central nervous system pathology and neurobehavioral effects from higher-dose carbamates exposure have been described in animal models. Reported cases of carbamate poisoning in humans have included large incidents involving ingestion of contaminated food and water, and accidental exposure from aerial crop spraying. The severity of symptoms is dependent on the specific compound and dosage received.<sup>386</sup> Unlike OP pesticides, the chemical process by which carbamates inactivate AChE is reversible, and AChE enzyme activity is reestablished within hours after exposure. A persistent condition similar to OPIDN has not been described following poisoning by carbamate pesticides, but a limited number of single case reports of prolonged neurotoxicity have been described following massive exposures.<sup>386</sup>

**DEET insect repellent.** DEET is the acronym used for the chemical compound n,n-diethyl-m-toluamide, a broad spectrum insect repellent that has a long history of use worldwide. The RAND pesticide study identified DEET as the “pesticide” product most frequently used by military personnel in the Gulf War. As listed in Table 2, personnel were issued creams and sticks that contained 33 percent DEET, and a high concentration liquid that contained 75 percent DEET. DEET was intended for use on areas of exposed skin, although it appears that it may have also been used on uniforms.

Civilian use DEET formulations typically contain 10-25 percent DEET<sup>1464</sup> and have a good safety record when used as directed.<sup>774,1157,1248</sup> DEET works as an insect repellent, that is, it reduces the number of insect bites by discouraging insects from landing on the skin. The chemical mechanism by which this occurs is not known, however.<sup>1076,1509</sup> There is relatively little systematic research on effects of DEET in humans. It appears to be a neurotoxicant, with a limited number of case reports of overexposure associated with encephalopathy and seizures.<sup>170,390,573,1157,1438</sup> Dermatitis has also been reported.<sup>1276</sup> Studies indicate that in animals given extremely high doses, DEET accumulates at high levels in the brain, adrenal glands, and lungs<sup>1297</sup> and produces marked effects on central and peripheral nerves, including edema in the myelin and a patchy spongiform myelinopathy.<sup>1720</sup> Lower doses have been associated with limited adverse effects in rodents,<sup>1365</sup> but with tremor, hyperactivity, excess salivation, and vomiting in dogs.<sup>1366</sup> DEET has not been shown to inhibit AChE activity, but DEET toxicity in cats has been associated with symptoms similar to those associated with AChE inhibition—hypersalivation, tremors, seizures.<sup>1464</sup> There is some indication that synergistic effects between DEET and AChE compounds occur through pathways other than AChE inhibition.<sup>1076</sup>

DEET has been considered a useful compound for enhancing dermal absorption of other compounds through the skin,<sup>1795</sup> although this has been called into question by more recent studies.<sup>110</sup> DEET applied to the skin can accumulate and remain in deeper skin layers for an extended time period—weeks or months.<sup>1276,1464</sup> Studies indicate that up to 17 percent is absorbed into the circulation<sup>428,1297,1384</sup> and can be retained in the body for an extended period, with one study indicating that about half of absorbed DEET is excreted over a five day period.<sup>1297</sup> Absorption of DEET is enhanced when it is provided in ethanol solution,<sup>1241,1384,1490</sup> and can also be enhanced by coadministration of sunscreen.<sup>573,1314</sup> Additional research on synergistic effects of DEET with other Gulf War exposures is described in a later section.

**Pyrethroid insecticides.** Synthetic pyrethroids are a class of compounds derived from pyrethrins, naturally occurring chemicals found in chrysanthemums. They include permethrin, a compound issued as a spray to treat uniforms and bedding in the Gulf War, and d-phenothrin, a compound sprayed in tents and other enclosed areas to knock down and kill flying insects. These compounds act both as insect repellants and as insecticides.<sup>1722</sup> Permethrin is a particularly effective long-term repellent product for fabrics because it retains its potency for an extended period after application. The 0.5 % permethrin sprayed onto uniforms in the Gulf War and still used by the military retains its repellent activity for six weeks, and through six launderings.<sup>62</sup> Absorption of pyrethroids through the skin varies by species, with the specific formulation used, and with the area of the body to which it is applied.<sup>1407,1768</sup> Once absorbed, pyrethroids are widely dispersed throughout different tissues and metabolized by carboxylesterases in the liver.<sup>1316,1722</sup>

Pyrethroids are neurotoxicants and, at very high doses, can have adverse effects on both the central and peripheral nervous systems. Their best known mechanism of action involves effects on voltage-gated sodium channels that result in alterations in nerve cell excitability.<sup>163,1258,1722</sup> Multiple studies have also described additional pyrethroid targets and effects that include enhanced release of acetylcholine and alterations in other neurotransmitter systems.<sup>351,392,400,637,1026,1255,1258,1547</sup>

Although highly toxic to insects, pyrethroids have long been considered relatively safe for mammals. In animal studies, extremely high doses of non-cyano pyrethroids such as permethrin produce symptoms of aggressive behavior and increased sensitivity to external stimuli, followed by extensive tremors. More subtle neurobehavioral effects have been observed at lower doses that produce no overt signs of toxicity.<sup>149,297,1798</sup>

In humans who have been exposed occupationally or by accident to high doses of pyrethroids, symptoms have included nausea, facial tingling, dizziness, headache, fatigue, burning and itching of the skin, eye irritation, and respiratory symptoms.<sup>163,237,826,827,1836</sup> At extremely high doses, convulsions and loss of consciousness can occur.<sup>598</sup> Permethrin-containing products are also used as topical treatments for

scabies and head lice in humans. In clinical trials, side effects have primarily included transitory skin reactions, and infrequent allergic reactions.<sup>1722</sup>

**Organochlorine insecticide.** Organochlorines are a diverse class of insecticides that include DDT, chlordane, and dieldrin. DOD has identified one organochlorine compound, lindane, as a pesticide of potential concern during the Gulf War. During the war, lindane powder was used as a delousing agent by military police units and others involved in processing Iraqi prisoners of war. Two ounce bottles of lindane powder were also issued to individual troops in theater, primarily Army personnel, for their personal use.<sup>1632</sup>

Lindane is a neurotoxicant that blocks the action of the neurotransmitter gamma aminobutyric acid (GABA) by altering the flow of ions through neuronal membranes.<sup>732,1093</sup> This leads to a persistent hyperexcitation of post synaptic membranes, primarily in the central nervous system.<sup>387</sup> Release of other neurotransmitters can also be affected, including alterations in levels of dopamine, serotonin, and norepinephrine.<sup>68,290,731,1292</sup> Animals given high doses of lindane develop behavioral changes, loss of balance, and seizures.<sup>1738</sup> Effects vary both with the dosage and with the dosing schedule. Behavioral and neurochemical effects of a single exposure to lindane have been shown to differ from those of repeated, lower-dose exposures.<sup>489,1291</sup> Lindane is also associated with chemical kindling, the phenomenon by which chemical exposures potentiate a persistent increase in the sensitivity of brain cells to electrical stimuli and seizures.<sup>34,489,490,730</sup>

Human overexposure to lindane is also associated with tremors, ataxia, and seizures, and several deaths have been attributed to lindane poisoning.<sup>318,387,1132,1360,1508</sup> In addition, studies of brain tissues of Parkinson's disease patients, at autopsy, have demonstrated significantly elevated levels of lindane and dieldrin, compared to controls.<sup>278,446</sup>

**Association of chronic disease with lower-level pesticide exposure.** In the past decade, a growing number of epidemiologic studies have identified human health effects associated with pesticide exposures at levels that do not cause acute signs and symptoms or any indication of poisoning. These prominently include: (1) links between pesticide exposure and chronic neurodegenerative diseases, and (2) associations between pesticide exposure and elevated rates of chronic symptoms and multisymptom illness. In addition, a large number of toxicological studies in animal models have explored biological processes that potentially link lower-level pesticide exposure to the development of persistent neurological sequelae.

The extensive literature implicating pesticide exposure in the development of chronic neurological conditions has been reviewed and summarized in several publications.<sup>179,343,705,742,1075,1259</sup> Human populations evaluated in these studies have often been exposed to multiple pesticides over an extended period of time, in different combinations and at different levels, the specifics of which usually are not precisely known. Findings from studies of this type can therefore be affected by many of the problems described in relation to Gulf War illness research, that is, potential inaccuracies in identifying "exposed" vs. "unexposed" groups, the lack of useful biomarkers of exposure, and individual variability in specific exposures and vulnerability to those exposures. Given such limitations, it is important that this literature be considered broadly, taking into account patterns of associations across multiple studies and populations.

**Pesticide exposure and chronic neurodegenerative disease.** The largest number of studies have evaluated links between Parkinson's disease and pesticide exposure.<sup>180,343,396,899</sup> These have included diverse types of toxicological studies using animal models, occupational studies of farmers and agricultural workers, and epidemiologic studies of residents living in areas of high pesticide use.<sup>575,742</sup> The British Medical Research Council recently reviewed this literature in detail and concluded that there is a general consistency from human population research supporting an association between Parkinson's

disease and exposure to pesticides generically, but insufficient evidence to implicate any specific pesticide or combination of pesticides.<sup>180</sup> Some epidemiologic studies have also linked chronic pesticide exposure to increased risk for both ALS and Alzheimer's disease, although research has been more limited and results more mixed than those related to Parkinson's disease.<sup>91,742,1001,1066,1348</sup> In addition, several studies have provided evidence of a gene-environment interaction in the risk for both ALS and Parkinson's disease. Both conditions have been found to occur at higher rates in individuals with genetic variants of the paraoxonase (PON1) gene, which may cause them to be more vulnerable to adverse effects from certain pesticides.<sup>126,1426,1840</sup>

**Pesticide exposure in relation to chronic symptoms and multisymptom illness.** In community and occupational studies, chronic low-level exposure to pesticides has frequently been associated with increased rates of symptoms and multisymptom illness similar to those affecting Gulf War veterans.<sup>742</sup> The majority of studies have focused on effects of exposure to pesticides in general or effects of organophosphate pesticides. Compared to unexposed controls, populations chronically exposed to pesticides, either in relation to their occupation or where they live, have consistently been shown to report higher rates of symptoms that include memory problems, difficulty concentrating, headache, fatigue, difficulty sleeping, nausea, respiratory problems, and mood alterations.<sup>316,506,702,741,742,930,1283,1479</sup>

In addition to elevated symptom rates, there are a number of other parallels between ill Gulf War veterans and populations chronically exposed to pesticides. Multiple studies have demonstrated associations between chronic pesticide exposure and poorer performance on measures of cognition, affect, and behavior.<sup>682,742</sup> Most have identified reduced performance on a limited number of tests, with different studies reporting decrements on different measures.<sup>1302,1320,1479,1484</sup> In addition, workers chronically exposed to organophosphate pesticides are reported to have a significantly increased risk of death due to motor vehicle accidents compared to unexposed individuals, but no excess of disease-related mortality.<sup>880</sup> There is also limited evidence that PON1 polymorphisms are associated with poorer cognitive performance, neurological alterations, and increased symptoms in individuals chronically exposed to pesticides.<sup>182,1005</sup> Although symptoms associated with chronic pesticide exposure include muscle weakness and tingling in the extremities, few studies have identified objective indicators of peripheral nerve conduction or sensory abnormalities in pesticide-exposed populations.<sup>32,805,933,1479,1493</sup>

A multisymptom condition sometimes referred to as sheep dippers syndrome has been described in a subgroup of British sheep farmers. Since 1984, sheep farmers in the United Kingdom have been required to periodically immerse their animals in a pesticide dip to control the spread of a serious parasitic disease. Since use of the organochlorine pesticide dieldrin was banned in the U.K., the sheep bath has consisted largely of OP chemicals, prominently diazinon.<sup>1471</sup> The constellation of symptoms reported by this subgroup of sheep farmers is similar to the multisymptom illness affecting Gulf War veterans, and includes chronic headache, memory and concentration problems, gastrointestinal difficulties, mood alterations, and fatigue. Farmers have also commonly indicated that their symptoms continue long after they have quit working with sheep and are no longer exposed to sheep dip.<sup>242,1471</sup>

Research studies conducted since the mid 1990s consistently indicate that exposed sheep farmers have significantly more symptoms than unexposed controls.<sup>112,1209,1441,1483,1522</sup> Sheep dip-exposed farmers also exhibit significantly poorer performance on measures of attention and information processing,<sup>1483</sup> but only limited abnormalities on standard neurological examinations or tests of peripheral neuropathy.<sup>112,706,1209</sup> Symptomatic sheep farmers have also been found to have a significantly higher rate of PON1 polymorphisms that provide poorer hydrolysis of diazinon, compared to nonsymptomatic sheep farmers.<sup>242,946,1223</sup>

Another multisymptom condition, multiple chemical sensitivity (MCS), occurs sporadically in the general population and is often attributed by patients to exposure to neurotoxic chemicals, including pesticides.<sup>212,1044</sup> The syndrome is associated with diverse symptoms similar to those that affect Gulf War

veterans—cognitive impairment, sleep abnormalities, digestive difficulties, headache, fatigue, and mood alterations—symptoms that are exacerbated by low-level exposure to chemicals. This condition has been assessed in multiple studies of Gulf War veterans, as will be described in a later section of the report.

Patients with MCS report that minimizing their exposure to chemicals is the most useful way to limit the severity of their symptomatic illness.<sup>488</sup> The Committee has discussed suggestions from clinicians and members of the public that veterans be advised to limit their exposure to pesticides and other chemicals. Anecdotal reports have suggested that some veterans' symptoms were triggered or worsened by exposure to pesticides after they returned from the Gulf War.<sup>716</sup> Clinicians have also provided testimony and case reports indicating that chemical avoidance can be useful in improving veterans' health.<sup>1115,1399</sup> There is currently no scientific research, however, to indicate whether veterans' exposure to chemicals since their return from the Gulf War is associated with chronic ill health, nor whether chemical avoidance provides symptomatic relief. It is hoped that insights into this question will be provided by a recently-funded study of a multimodal treatment for Gulf War illness that includes reduction of chemical exposures.<sup>1013</sup>

### **Health effects of low-level sarin exposure**

The organophosphate compound sarin was developed as a chemical warfare agent by German scientists in the 1930s. Sarin is highly toxic and when used in warfare at militarily effective doses causes serious symptoms and death as a result of acute cholinergic toxicity. Relatively little was known about biological effects of lower-level sarin exposures until recent years, particularly with respect to persistent or delayed effects of low-level exposures.<sup>86</sup> In the past decade research in these areas has expanded as a result of several factors. These include questions raised about effects of low-level sarin exposure in the Gulf War following DOD's 1996 announcement that nerve agents had been released in theater, exposure of a large number of Japanese citizens to sublethal doses of sarin in terrorist attacks during the 1990s, and increased concern in the U.S. and elsewhere about use of chemical agents on civilian populations. Recent research has provided important insights into effects of sublethal exposure to sarin and longer-term effects of low dose sarin exposure, the issue most relevant to the health of Gulf War veterans.

In the late 1990s, both DOD and VA commissioned reviews of the available scientific literature to provide information on possible health consequences of nerve agent exposure in the Gulf War. A 2000 report from the RAND National Defense Research Institute detailed the challenges of determining whether or not Gulf War veterans had developed acute symptoms in connection with low-level chemical agent exposures in theater.<sup>74</sup> The RAND report pointed out that symptoms of low level exposure to nerve agents are nonspecific and might, at the time of exposure, be attributed by a soldier to a common headache, gastrointestinal condition, or respiratory problem. It also described research suggesting that expected symptoms of low-level sarin in theater might have been attenuated by veterans' use of PB, or as a result of tolerance that developed with repeat exposures to AChE inhibitors. The RAND report concluded that there were no indications of serious symptoms suggestive of a large dose chemical agent exposure in Gulf War personnel. Milder symptoms associated with low dose exposures might have been overlooked or misinterpreted, however, so could not be ruled out. The report also found that it was not possible, based on the limited literature available at the time, to rule out the possibility that low level exposures could produce chronic health effects, and identified research needed to investigate this issue.

In response to a Congressional directive, VA commissioned the Institute of Medicine (IOM) to conduct a series of research reviews to assist the Secretary in making decisions about veterans' disability compensation, as previously described. Volume One of the resulting IOM *Gulf War and Health* series was published in 2000 and included a literature review on the effects of sarin. Based on its review, the IOM committee concluded that "there is sufficient evidence of a causal relationship between exposure to sarin and a dose-dependent acute cholinergic syndrome that is evident seconds to hours subsequent to sarin exposure and resolves in days to months"<sup>679</sup> an effect that has been well recognized for decades.

The IOM committee also found that evidence from human studies to determine if subsymptomatic exposure to sarin led to long term health effects. Based on studies of nonhuman primates and humans exposed to low levels of other OPs, the committee added that “it is reasonable to hypothesize the occurrence of long-term adverse health effects from exposure to low levels of sarin.”<sup>679</sup>

Within several years of the IOM report’s publication, multiple studies emerged that identified effects of low-level sarin exposure in animal models. As a result, the Secretary of Veterans Affairs asked IOM to revisit the question of long-term effects of low-dose sarin exposure. In response, IOM published an “Updated Literature Review of Sarin” in 2004. The conclusions of this second IOM report were essentially unchanged from those of the first.<sup>683</sup> Similar to the prior IOM report, the second panel did not consider findings from toxicological research in animals or studies evaluating risk factors for multisymptom illness in Gulf War veterans to determine the strength of evidence relating low-level sarin exposure to health outcomes. This omission was striking, since the new animal studies had been the reason the Secretary requested the updated report.<sup>1641</sup>

Research on the effects of low-level sarin exposure considered for the present report includes studies on health outcomes in humans, as well as biological effects observed in animal models. Because the Committee is charged specifically with reviewing research related to the health of Gulf War veterans, this review focused most specifically on studies that have evaluated longer-term effects of lower-level sarin exposures. Results from studies that have specifically evaluated health outcomes in Gulf War veterans in relation to nerve agent exposure is considered in detail in a later section, along with similar research related to PB and pesticide exposures in the Gulf War.

### **Animal research on effects of sarin exposure**

Repeated exposures to levels of sarin that would not be noticed clinically resulted in delayed development of brain alterations that could be associated with memory loss and cognitive dysfunction.

--R. Henderson, “Response of Rats to Low Levels of Sarin”<sup>601</sup>

A large number of studies have evaluated effects of sarin in different animal models. In reviewing this literature, several key parameters were important to differentiate in characterizing research findings. In addition to potential effect differences in different animal species, key study parameters relate to whether the study evaluated effects of higher doses that caused serious signs of cholinergic toxicity or death in exposed animals, intermediate doses that caused milder effects in a subset of animals, or effects of lower-dose exposures that caused minimal or no observable signs of toxicity. In addition to dose levels, the route of exposure (e.g., inhalation, injection, intravenous infusion) and the dosing pattern (e.g., single doses or repeated dosing, of brief or sustained duration) appeared to make a difference in some cases. An additional issue of importance related to how long animals were observed after exposure—hours, days, weeks, or months—to determine the duration of identified effects or the development of delayed effects. As will be described below, animal studies have included different combinations of these key elements, evaluating high or medium or low dose exposures given once or multiple times by inhalation or injection, with outcomes evaluated at time points that range from immediately after exposure to periods more than one year later.

**Acute effects of sarin exposure in animals.** Acute effects of high dose sarin exposure in both humans and animals result from cholinergic toxicity—evidenced by symptoms that include miosis, salivation, tremors, nausea and vomiting, seizures, coma, and respiratory arrest—which vary in severity with the level and duration of exposure.<sup>51,133,1051</sup> Research in animal models has also demonstrated additional acute effects of moderate to high dose sarin exposure that include behavioral effects, autonomic effects, renal and neuroinflammatory effects, and alterations in gene

expression.<sup>145,230,304,307,860,869,895</sup> In addition, animal studies have identified longer term effects in surviving animals following high dose sarin exposure, including persistent changes in behavior, central inflammatory processes, cardiac function, and gene expression profiles.<sup>42,308,520,652</sup> Sarin exposure at lower doses often produces limited or no overt effects that are apparent by simple observation. A large number of animal studies, however, have described both acute and chronic biological effects associated with low-dose sarin exposure, often in the absence of observable signs or symptoms. Understanding effects that may develop or persist over an extended time period after low-dose exposures is of greatest relevance to the health of Gulf War veterans, as will be described below. In addition, many studies have described short-term effects of low level sarin exposures. In these studies, animals were observed for only a limited time after exposure, so it is generally unknown how long identified biological effects might have lasted had animals been observed for longer periods. In addition to alterations in cholinesterase activity, low-to-moderate doses of sarin have been shown to produce short-term neurological effects that include neurobehavioral alterations,<sup>652,761,1120,1402,1415,1806</sup> spinal cord lesions and swelling,<sup>656,659</sup> and increased expression of genes associated with neuronal degeneration and apoptosis.<sup>1383</sup> Several studies have also described acute immune alterations with low-level sarin exposure.<sup>740,762-764</sup>

**Evaluation of persistent or delayed effects of low-level sarin exposure in animals.** As described in the Committee's 2004 report, a growing number of animal studies have, since 2000, assessed biological effects of lower-level sarin exposure, effects that develop or persist over an extended time period. Results from these studies are summarized in Table 4. As shown, this research includes a wide variety of study designs and exposure models. It includes studies in both rodent and primate models, sarin exposure by inhalation or injection at levels that range from extremely low doses to those that cause limited symptoms in some animals, and follow-up periods that range from 17 days to more than one year after exposure. Findings are also diverse, and include effects that are detectable immediately after exposure and persist through the last observation point, effects that are not apparent until some time after exposure, changes that normalize over time, and effects that vary with time (for example, a biological measure that is initially increased, but later decreased).

As with other areas of research considered by the Committee, studies related to persistent effects of low-level sarin exposure vary with respect to strength of study design, investigators' conclusions, and reliability of publication source. Because of limitations related to individual studies and sources, the Committee again adopted an inclusive approach in reviewing this literature, considering all relevant studies and drawing on the breadth of results to inform general conclusions, rather than relying on any single study or source.

**Brain and behavioral effects.** The largest number of studies have evaluated long-term effects of low-level sarin exposure on the brain and behavior. The earliest published study of this type, from 1976, reported that monkeys exposed to either a single high dose or repeated low doses of sarin developed electroencephalogram (EEG) abnormalities that persisted at least one year after exposure.<sup>195</sup> A 1999 study identified only minimal long term EEG effects following a single, somewhat higher-level exposure to sarin in marmosets.<sup>1183</sup> A more recent study from the Netherlands,<sup>1706</sup> like the initial EEG study, reported long term EEG effects in monkeys who received a sustained, low-dose sarin exposure by inhalation. In the 2004 study, Dutch investigators reported that EEG readings were an order of magnitude more sensitive than pupil measures for detecting low-dose sarin exposure and that exposed monkeys continued to exhibit significant EEG alterations one year after exposure.

Studies listed in Table 4 indicate that central effects of sarin vary with exposure method, dose, and duration and also may vary between species. Results from several studies also suggest that the persistent effects of sarin exposure can differ with the pattern of exposure. That is, repeated low dose exposures can produce effects that differ from those of single exposures, even at similar or higher doses. For example, Duke investigators reported that after injecting rats once with sarin at doses that ranged from very low to

**Table 4. Studies Evaluating Persistent and/or Delayed Effects of Low Level Sarin Exposure in Animals**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
Burchfiel <sup>195</sup> 1976	Monkeys injected with sarin IV with single, sublethal large dose or 1 low dose/week for 10 weeks	1 year following exposure, EEG alterations, prominently increased beta activity, persisted in monkeys exposed both to single, high dose exposure and multiple, low-dose exposures. Low dose exposure generated biphasic response, with early increase in delta and theta, which shifted to increase in beta by 1 year post exposure.
Pearce <sup>1183</sup> 1999	Marmosets given single, moderate dose injection	No sign. EEG alterations observed over 15 months, ns (p=0.07) increase in beta amplitude. No sign. cognitive deficits observed.
Jones <sup>724</sup> 2000	Rats injected IM with single 0.01, 0.1, 0.5, or 1.0 LD <sub>50</sub> dose of sarin	90 days post exposure, blood brain barrier permeability sign. decreased, AChE activity sign. increased, M2 receptors sign. increased in brainstem only after 1.0 LD <sub>50</sub> dose. M2 receptors sign. reduced in cortex after 0.5 and 1.0 LD <sub>50</sub> dose.
Kassa <sup>768</sup> 2000	Rats given 1 of 3 levels of sarin by inhalation for 60 min, mid level exposure given 1x or 3x within 1 week	3 months post exposure, DNA replication and synthesis in the liver was sign. decreased with all single doses, but not with repeat exposure. 6 months post exposure, DNA content and total protein sign. reduced with all doses. Minimal differences at 12 months post exposure.
Kassa <sup>766</sup> 2000	Rats given 1 of 3 levels of sarin by inhalation for 60 min, mid level exposure given 1x or 3x within 1 week	12 months post exposure, sarin repeated dose sign. increased lymphoproliferation, while single dose at same and lower level sign. reduced it. Repeat dose sign. decreased macrophage activity, while single dose at same and higher level sign. increased it. No sign. difference in immune measures 3 months post exposure, limited differences at 6 months.
Kassa <sup>767</sup> 2001	Rats given 1 of 3 levels of sarin by inhalation for 60 min, mid level exposure given 1x or 3x within 1 week	3 months after exposure, rats that received repeat sarin exposure had sign. locomotor, gait, and behavioral abnormalities, and sign. greater CNS excitability. Behavioral deficits, but not enhanced CNS excitability, also with single higher, nonconvulsive dose.
Kassa <sup>758</sup> 2001	Rats given 1 of 3 levels of sarin by inhalation for 60 minutes, mid level exposure given 1x or 3x within 1 week	1 day after exposure, rats with mid and higher level sarin exposure showed sign. deficits in spatial memory performance on T maze. Differences no longer sign. at one week or 3 months post exposure. No sign. difference between single and repeat dosing.
Kassa <sup>759</sup> 2001	Rats given 1 of 3 levels of sarin by inhalation for 60 minutes, mid level exposure given 1x or 3x within 1 week	Single low and mid level doses produced only brief (< 1 day) reduced spatial memory performance on Y maze. Repeat dosing or single higher dose produced sign. impairment for 3 weeks, which normalized at 4-5 weeks.
Kassa <sup>757</sup> 2001	Rats given 1 of 3 levels of sarin by inhalation for 60 min, mid level exposure given 1x or 3x within 1 week	Gait abnormalities, sign. decreases in automated measures of motor activity, and increased CNS excitability 3 months after exposure. Sign. increased exploratory activity and hind limb grip strength 6 months after exposure.
Conn <sup>267</sup> 2002	Rats exposed to subclinical levels of sarin by inhalation 1 hour/day for 1,5, or 10 days with/without heat stress	Low-dose, single or repeated sarin exposure had no acute or delayed effects on body temperature or locomotor activity with or without heat stress.
Hender-son <sup>601</sup> 2002	Rats exposed to subclinical levels of sarin by inhalation 1 hour/day for 1,5, or 10 days with/without heat stress	1 day after exposure, M1 cholinergic receptors were unchanged. After 30 days, sarin alone sign. reduced M1 receptors in olfactory tubercle; sarin+heat stress sign. reduced M1 receptors in frontal cortex, hippocampus, and olfactory nucleus. Sarin+heat stress also sign. increased M3 receptors in frontal cortex, olfactory tubercle, anterior nucleus, and striatum 1 day and 30 days post exposure. Sarin sign. increased brain mRNA for IL-1beta, TNF-alpha, and IL-6. No apoptosis or brain lesions identified on histopathology.

**Table 4. (cont.) Studies Evaluating Persistent and/or Delayed Effects of Low Level Sarin Exposure in Animals**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
Scremin <sup>1377</sup> 2003	0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	2 weeks post exposure, acoustic startle response was sign. increased and exploratory behavior decreased, indicating cholinergic hyperactivity. At 16 weeks post exposure, habituation was sign. decreased. Muscarinic receptor binding was sign. decreased in multiple brain regions at 2 weeks, sign. increased in cortex at 4 weeks, with no sign. differences at 16 weeks.
Husain <sup>657,658</sup> 2003, 2004	10 weeks exercise, with low-dose sarin subQ daily during weeks 5-6 in mice	4 weeks post exposure, sarin sign. decreased peripheral BChE and AChE, AChE in striatum, NTE peripherally and in cortex, striatum, and spinal cord, and increased MDA (indicator of lipid peroxidation) in spinal cord and sciatic nerve.
Kassa <sup>765</sup> 2004	Rats given low and moderate doses of sarin by inhalation for 60 minutes, infected with tularemia 7 days after exposure	24 hours after infection, sarin at both levels caused sign. decrease in IgM and IgA antibodies, sign. increase in lymphoproliferation. Higher dose associated with sign. more IgM antibodies after 7 days. Both doses sign. decreased lymphoproliferation at 21 days.
Van Helden <sup>1706</sup> 2004	Monkeys exposed to sarin for 5 hours by inhalation at 5 subclinical doses	During exposure, EEG readings were 10x more sensitive than pupil miosis to low level sarin. 1 year after exposure, sarin exposure associated with sign. EEG abnormalities on multiple bands, and sign. more alpha frequency bursts than at baseline.
Scremin <sup>1378</sup> 2005	0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	4 weeks after exposure, sarin exposure associated with sign. increased cerebral blood flow in multiple areas. Few sign. differences remained at 16 weeks.
Shih <sup>1403</sup> 2006	0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	Brain acetylcholine levels were sign. increased at 4 weeks post exposure, but not at 16 weeks.
Scremin <sup>1379</sup> 2006	0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	2 and 4 weeks post exposure, sarin associated with sign. decreased heart rate at different times over 24 hour period. Low frequency HRV at midnight was sign. reduced at 2 but not 4 or 16 weeks post exposure.
Genovese <sup>480</sup> 2007	Monkeys injected IM with single moderate dose of sarin	Sarin exposure was not associated with sign. deficits on cognitive performance (serial probe recognition tasks) assessed up to 10 weeks post exposure.
Morris <sup>1071</sup> 2007	Rats injected subQ with 0.05 LD <sub>50</sub> sarin on 2 consecutive days	Low dose sarin produced biphasic autonomic modulation, with sign. increase in HRV (pulse interval, low and high frequency) 1 week post exposure, followed by a sign. decrease at 10 weeks. Tyrosine hydroxylase mRNA sign. increased in areas of brainstem 10 weeks post exposure.
Pena-Philippides <sup>1193</sup> 2007	Rats exposed to low dose sarin by inhalation 1 hour/day for 1 or 5 days	Sarin sign. reduced serum corticosterone and ACTH levels, which persisted through last observation (8 weeks corticosteroid, 4 weeks ACTH). 5 day repeat exposure sign. reduced antibody forming cell response, which was autonomically mediated, and normalized 2-4 weeks post exposure.
Dave <sup>314</sup> 2007	Guinea pigs injected subQ with 0.1, 0.2, or 0.4 LD <sub>50</sub> 1x/day for 10 days	Repeat low dose sarin produced sign. increase in DNA fragmentation in neurons and leukocytes at 0 and 3 days post exposure, but not at 17 days.
Mach <sup>945</sup> 2008	Mice injected subQ with 0.4 LD <sub>50</sub> sarin on 3 consecutive days, with/without intermittent stress	3 weeks post exposure, sarin alone produced sign. reduced motor activity on open field testing, no interaction with stress. Sarin+stress produced delayed behavior alterations (increased grooming behavior) at 7 weeks post exposure, and sign. increased size and reduced catecholamine concentrations in adrenal glands.

Abbreviations: IV = intravenous, IM = intramuscular, subQ = subcutaneous, EEG = electroencephalogram, LD<sub>50</sub> = dose that is lethal to half of exposed animals, M1 or M2 or M3 = subtypes of acetylcholine muscarinic receptors, CNS = central nervous system, AChE = acetylcholinesterase, BChE = butyrylcholinesterase, NTE = neurotoxic esterase, MDA malondialdehyde, ACTH = adrenocorticotropic hormone, min = minutes, sign. = statistically significant

very high, only rats with the high dose exposure exhibited persistent regional alterations in brain AChE activity.<sup>724</sup> In contrast, several studies have indicated that repeated, low dose sarin exposures over periods up to two weeks produce persistent regional alterations in central AChE activity.<sup>601,657,658</sup>

Studies have reported a variety of changes in the brain following repeat, low dose sarin exposure. A 2002 study from Lovelace Respiratory Research Institute reported both persistent and delayed effects on the brain following repeated inhalation exposures to low dose sarin over periods from one day to two weeks.<sup>601</sup> Some effects were delayed, that is, they were not observed the first day following exposure but were identified 30 days after exposure. Some effects occurred only with the combination of sarin exposure and heat stress. Overall, 30 days after repeat low dose sarin exposure, cholinergic M1 receptors were significantly reduced in several brain regions, including the hippocampus, frontal cortex, and olfactory areas. With heat stress, M3 receptors were significantly enhanced in striatum, frontal cortex, and olfactory areas. Increased levels of proinflammatory cytokines were also found in the brain, although no brain lesions were identified. Research from the Los Angeles VAMC also reported alterations in central muscarinic receptors after repeated, higher doses of sarin over a longer time period, although specific receptor subtypes were not distinguished. Overall, muscarinic receptors were significantly decreased in several brain areas two weeks after exposure, increased in the cortex at four weeks, but no longer differed significantly from controls at 16 weeks.<sup>1377</sup>

Multiple studies have reported persistent behavioral effects of low dose sarin exposure, with findings varying with dosage level, the duration of follow-up, and the type of motor or cognitive function assessed. Some studies identified no behavioral effects<sup>267,480,1183</sup> or only transient effects.<sup>758</sup> Several studies have reported that behavioral alterations were more pronounced with repeat exposures than with single exposures at the same dosage.<sup>759,760,767</sup> One of the earliest reports on sustained behavioral effects indicated that three repeated, low dose sarin exposures given over one week, but not just one dose, resulted in significant locomotor, gait, and behavioral abnormalities three months after exposure, and significantly increased sensitivity to drug-stimulated seizures.<sup>767</sup> Additional studies have reported significant reductions in acoustic startle response, motor activity, grooming behavior, and habituation, changes that persisted from two to sixteen weeks after repeat doses of sarin.<sup>945,1377</sup>

In many cases, it is not known how long identified central effects of low dose sarin exposure persist, since many effects were reported to continue through the final observation point of the study. Other changes appeared to normalize within the follow-up period of the study, usually over several weeks or months. These included sarin-related cognitive changes observed in two studies,<sup>758,759</sup> alterations in cerebral blood flow<sup>1378</sup> and changes in brain levels of acetylcholine.<sup>1403</sup>

**Autonomic effects of low-dose sarin.** Low level sarin exposure has been associated with alterations in autonomic function in several animal studies. Investigators from Wright State University identified a biphasic autonomic response following extremely low-dose sarin exposure, given each of two days. One week after exposure, heart rate variability was significantly *elevated* in both the low and high frequency ranges. By 10 weeks, however, heart rate variability was significantly *reduced* in sarin-exposed rats.<sup>1070,1071</sup> A second study reported that higher-dose sarin, given over a more sustained period, produced significant alterations in heart rate variability in the low frequency range. These differences were observed two weeks after exposure, but not at four or 16 weeks after exposure.<sup>1379</sup> In addition, immune suppressive effects of low-dose sarin exposure have been shown to be autonomically mediated, and did not occur when sarin-exposed animals were pretreated with a ganglionic blocker.<sup>740,1193</sup>

**Neuroendocrine effects of low-dose sarin.** An unexpected effect of low-dose sarin has been reported by two studies from Lovelace Respiratory Research Institute. Investigators found that low-dose sarin exposure resulted in immune suppression, but that this effect was not the result of elevated levels of corticosteroid, the adrenal stress hormone. Instead, study findings indicated that low-dose sarin exposure significantly *decreased* serum corticosteroid levels.<sup>740</sup> A follow-up study indicated that both

corticosteroid and adrenal corticotrophic hormone (ACTH), the pituitary hormone that stimulates corticosteroid production, were significantly reduced by low-dose sarin, and that this suppression persisted for as long as animals were observed, four-to-eight weeks.<sup>1193</sup> A similar effect was also associated with other centrally-acting AChE inhibitors.<sup>868</sup>

Additional neuroendocrine alterations reported in response to low-dose sarin exposure include a persistent increase in brainstem mRNA for tyrosine hydroxylase, the rate limiting enzyme for synthesis of dopamine and related neurohormones.<sup>1071</sup> Low dose sarin exposure has also been reported to produce significant adrenal gland enlargement and reduced adrenal catecholamine concentrations, in combination with an intermittent stress.<sup>945</sup>

**Immune effects of low-dose sarin.** Several studies have reported that low-level sarin exposure can significantly alter the immune response, producing a number of effects that differ over time. Long-term alterations in lymphoproliferation have been demonstrated in several studies.<sup>763,766,767</sup> The first, from Czech investigators, reported that no sarin-related immune changes were observed three months after exposure, and very limited differences six months after exposure. Twelve months after exposure, however, rats who had received repeated, low dose inhalation exposures to sarin had significantly decreased macrophage activity and significantly increased lymphoproliferation. At the same time, rats who had received a single dose of sarin, at the same concentration, also had significant changes in both measures, but in the opposite directions.<sup>766</sup> Other studies have identified temporary suppression of antibody responses following low-dose sarin exposure. Significant reductions in T cell mitogenesis and antibody forming cells, observed shortly after low dose sarin exposure, were reported to normalize between two and four weeks after exposure.<sup>1193</sup> Czech investigators have also reported a temporary suppression of antibody response to infection one week after low or moderate dose sarin exposure.<sup>765</sup> More recently, a study from Walter Reed Army Institute of Research found that low-level, repeat sarin exposure produced a significant, but temporary, increase in DNA fragmentation in leukocytes, an effect observed at three days, but not 17 days after exposure.<sup>314</sup>

## Effects of sublethal and low-level sarin exposure in humans

Interest and research on the effects of chemical nerve agents has historically focused on acute symptoms and signs, and on lethal effects of acute exposure. It was widely believed, for many years, that there are no long term effects of sarin following recovery from sublethal exposure, although research on long-term human health effects of sarin was limited. Experimental studies conducted by government agencies in chemical warfare programs did not evaluate long term effects, and there were few opportunities for systematic observational research, since human populations had rarely been exposed to sarin. In the past 25 years, unfortunately, humans have been exposed to chemical weapons, including sarin, in connection with several situations and incidents. As a result, scientists and clinicians have learned more about immediate, short term, and long term effects of sublethal exposure to chemical warfare agents on humans.

Prior to more recent exposure events, there was limited information on the potential for lower-level exposure to chemical agents, including sarin, to produce long term effects. As described in the Committee's 2004 report, reports emerged, in the 1950s, of a multisymptom condition affecting a group of individuals who had worked in the German military's munitions factories in the 1930s and 1940s, factories that produced sarin and other chemical agents. A 1963 medical report described a "cerebro-organic delayed effect syndrome" in these workers that was characterized by lowered vitality, defective autonomic regulation, headache and gastrointestinal symptoms, and cognitive impairment.<sup>1467,1491</sup> A case series report, published in 1969, described symptoms of impaired memory, difficulty concentrating, and mood alterations, as well as an excess of slow wave activity on electroencephalograms (EEG) in 25 industrial workers in the U.S. who had been exposed to sarin in the 1950s and 1960s.<sup>1025</sup>

In 1979, investigators from Harvard Medical School and collaborating institutions reported results of a study of 77 government workers with histories of accidental exposures to sarin, and 38 healthy controls.<sup>368</sup> Researchers explained that they undertook the study because of reports that a number of civilian government employees working with or around sarin had complained of a variety of symptoms that included memory loss, trouble concentrating, and excessive dreaming.<sup>194</sup> Forty-one of the workers evaluated in the 1979 study had been exposed to sarin three or more times within the six years prior to evaluation, but none of the workers in the study had been exposed in the year prior to the study. Sarin-exposed workers had normal erythrocyte AChE activity, but differed significantly from controls on both waking and sleeping EEG, with most marked increases in higher frequency beta activity. Similar persistent alterations in beta activity had previously been demonstrated in primates one year after sarin exposure.<sup>195</sup>

Both the U.S. and British governments have supported chemical weapons research and development programs that included use of human subjects.<sup>780,1652</sup> A 2003 report described results of a follow-up survey of 2,478 men who, as military volunteers, had participated in the U.S. program between 1955 and 1975.<sup>1164</sup> The DOD-sponsored study compared the health of 855 men who had been exposed to cholinergic agents (sarin, VX, and eserine), 871 men exposed to other chemical agents (e.g. blister agents, LSD), and 752 men not exposed to chemical agents. Overall, no differences were reported in rates of diagnosed diseases and only minimal differences on general health measures. Individuals exposed to cholinergic agents in the program had a slightly lower overall death rate than men not exposed to chemical agents. This report is reassuring, providing a general indication that military personnel exposed to chemical agents were not, overall, affected by excessive long-term health problems many years later. Important limitations include the lack of information on health outcomes in relation to specific nerve agents, dosages, or duration of exposure, and the lack of information on the health of individuals whose program participation was limited due to short term difficulties with chemical exposures.

The British Medical Research Council has commissioned a series of projects to evaluate health outcomes among the thousands of military personnel who participated in research programs at the British chemical research facility at Porton Down. An initial report on an evaluation of 289 members of a Porton Down veterans' support group was published in 2006. Multiple symptoms, including fatigue, sleep, and mood difficulties, were reported to have occurred in the first five years after program participation, and continued to be problematic in the years that followed.<sup>40</sup> This preliminary project did not have an unexposed comparison group of veterans, but did report that SF36 measures of function and health-related quality of life were significantly lower in the Porton Down veterans than in comparably aged men in the general population. These findings do not provide information on whether Porton Down veterans have excess problems due to their program participation, since veterans in the support group are not likely representative of all program participants. But the report does provide a preliminary indication that a selected subgroup of program participants are in worse health than the general population.

Chemical weapons, both nerve and blister agents, were used in the Iran-Iraq War during the 1980s.<sup>178,693</sup> Blister agents are said to have been used the most extensively by Iraq. Reports indicate that as many as 100,000 Iranians may have been exposed to sulfur mustard and that tens of thousands still suffer long term health effects that include respiratory disorders and eye and skin abnormalities.<sup>90,484</sup> In 1988, the Kurdish town of Halabja, near the Iranian border in Northern Iraq, was bombarded with what is believed to be a mix of chemical agents—mustard gas and nerve agents that included sarin, tabun, and VX.<sup>509,1566</sup> The attack lasted several days and had tragic and lasting consequences, reportedly killing 5,000 people and producing an additional untold number of serious casualties.<sup>496</sup> No scientific or systematic reports have provided information on the extent and types of injury and disease caused by this attack, nor on rates of medical conditions or persistent symptomatic illness in the years since the attack. Reports from clinicians and the media have described increased rates of cancers, respiratory conditions, psychiatric disorders, and birth defects among survivors.<sup>496,509,597</sup> Because of the mixed effects of multiple, high

dosage exposures in these attacks, it is not known whether any long-term effects can be attributed to effects of OP nerve agents.

**Survivors of 1990s terrorist incidents in Japan.** The most extensively studied sarin-exposed populations are Japanese citizens who were exposed to sarin in two terrorist incidents in the 1990s. The first attack occurred in 1994 when sarin was released in the middle of the night in a residential area of the city of Matsumoto, Japan. Area residents, rescue workers, and clinical staff exposed to sarin when victims were brought into hospitals exhibited acute cholinergic symptoms of exposure. In all, 600 people were poisoned, 58 were hospitalized, and seven died.<sup>1068,1092,1133</sup> The following year, a religious cult released sarin on three different lines in the Tokyo subway system during Monday morning rush hour. About 5,500 people are reported to have been poisoned, and 12 died.<sup>1147,1818,1825</sup>

Initial clinical reports focused on exposed individuals who sought evaluation and treatment, most of whom had acute signs and symptoms of cholinergic toxicity—pupil miosis, headache, nausea and vomiting, rhinorea, and fatigue.<sup>1818</sup> In the years since, a large number of studies have evaluated multiple health parameters in these populations, with most focused on neurological and psychiatric sequelae of the exposure events.<sup>1825</sup> For many of those exposed, acute symptoms resolved in a matter of weeks. Some individuals, however, exhibited persistent symptoms when evaluated years after exposure. Three years after the Matsumoto incident, a substantial number of victims continued to report symptoms that included eye weakness (24%), fatigue (15%), and headache, at rates significantly higher than controls.<sup>1091</sup> Persistent symptoms reported by Tokyo survivors five years after exposure included eye fatigue (39%), visual abnormalities (21%), general fatigue (16%), muscle stiffness (15%), and headache (10%), as well as psychological symptoms including flashbacks (13%) and depressed mood (13%).<sup>778</sup>

Six to eight months after the Tokyo subway attack, exposed individuals who no longer exhibited clinical signs of poisoning, were shown to have a variety of subtle central nervous system alterations, including poorer performance on neurobehavioral tests, prolonged auditory and visual evoked potentials, and postural sway abnormalities.<sup>1826-1829</sup> Heart rate variability, assessed six to eight months after exposure, was significantly correlated with the degree of AChE reduction measured at the time of exposure.<sup>1086</sup> Studies conducted in the years that followed the Tokyo attack continued to identify psychomotor and memory alterations in individuals exposed to sarin, three years<sup>1128</sup> and seven years<sup>1054</sup> after exposure. Some individuals also continued to have symptoms of posttraumatic stress disorder (PTSD). Studies indicated that some neurobehavioral measures were significantly associated with PTSD symptoms in those individuals. Others were significantly associated with sarin exposure, after controlling for effects of PTSD.<sup>1128,1828</sup> Investigators concluded that some survivors exhibited persistent or delayed central nervous system effects resulting from sarin exposure, in addition to persistent psychological effects resulting from trauma.<sup>1828</sup>

Neuroimaging studies have identified persistent brain structure abnormalities in relation to sarin exposure. Five to six years after the Tokyo attacks, a study of 38 individuals exposed to sarin found them to have significantly smaller regional grey matter volume in the right insular and temporal cortex, smaller white matter volume in the temporal stem near the insular cortex, and smaller left hippocampus volume, compared to matched controls.<sup>1816</sup> White matter reductions were significantly correlated both with the severity of somatic symptoms at the time of the study and with the degree of AChE reduction years earlier, on the day of sarin exposure. No associations were identified between brain volume and measures of psychological stress. Study results therefore supported direct links between sarin exposure, persistent symptoms, and brain structure alterations.<sup>1816</sup> A small study had previously reported that nine individuals with PTSD following sarin exposure in the Tokyo subway showed a significant reduction in grey matter in the left anterior cingulate cortex.<sup>1817</sup>

Overall, follow up evaluations of individuals exposed to sarin in Japanese terrorist events indicate that sarin exposure, at levels sufficient to cause acute symptoms, is associated with persistent symptoms and

central nervous system effects, in a subset of those exposed. These findings contrast with earlier assumptions that sublethal exposure to sarin does not lead to long-term health sequelae following recovery from acute effects of exposure. This research does not indicate whether low-level sarin exposure that does not produce acute symptoms can lead to persistent central nervous system effects, however. Studies have not evaluated the health of individuals who were located near areas where sarin was released in the Japanese events and potentially exposed to lower levels of sarin, but did not exhibit acute symptoms at the time.<sup>1146</sup>

**Summary. Chronic health effects of low-level sarin exposure.** Acute toxic effects of high dose exposure to the organophosphate nerve agent sarin have been characterized for many years in both humans and animals. Recent studies have provided important insights into long term effects of lower-dose sarin exposure and indicate that, contrary to earlier assumptions, exposure to sarin at relatively low doses can result in long-term biological effects. Animal studies have identified multiple central nervous system effects of low-dose exposure that include persistent EEG abnormalities, cognitive and behavioral changes, and alterations in regional expression of cholinergic receptors in the brain. Persistent or delayed autonomic effects have also been described in animal studies, as well as neuroendocrine and immune effects of low-level sarin exposure. Identified effects of low-dose sarin exposure in animal models have varied, in some cases, over the duration of follow up, as well as with the dose, route, and pattern of exposure. Humans exposed to sarin at levels sufficient to cause short-term symptoms have also been shown to have persistent EEG abnormalities and subtle neurobehavioral decrements years after exposure. Studies have also identified brain volume differences in several areas, audiovestibular abnormalities, and elevated rates of symptoms such as vision problems, headache, fatigue, and mood disturbances that persist for months or years in some individuals after exposure to symptomatic doses of sarin.

## Effects of Combinations of Gulf War Neurotoxicant Exposures

It seems prudent to recommend avoidance when possible of untoward levels of simultaneous exposure to incompletely studied combinations such as PB, permethrin, and DEET while at the same time realizing that currently available evidence is insufficient to warrant abandoning current doctrinal guidance concerning the military use of these compounds.

--U.S. Army Medical Research Institute of Chemical Defense, 2003<sup>951</sup>

As described throughout this report, military personnel serving in the Gulf War experienced a uniquely complex mix of exposures in theater. In its 2004 report, the Committee pointed out the potential for the diverse exposures encountered during the Gulf War, particularly those associated with neurotoxicity, to have interactive effects that differed from those expected from individual exposures. The report included a table that described the results of 28 animal studies that assessed effects of combinations of Gulf War-related exposures in a variety of models, most of which identified significant effects. More recent studies have continued to report on effects of combinations of Gulf War exposures, providing more detailed information on specific combinations and persistent effects. Results indicate that some, but not all combinations of Gulf War exposures can act synergistically, and that specific effects vary with the specific chemicals assessed and with the dosage, route, and pattern of exposures.

An extensive number of scientific studies and government-sponsored investigations has provided diverse types of evidence related to health effects of individual Gulf War exposures. By comparison, information on health effects of combinations of exposures encountered by military personnel in theater is quite limited. Synergistic effects of mixtures of anticholinesterase pesticides have been described in the medical literature for over 50 years.<sup>455</sup> But most research on combined effects of the specific chemicals

associated with Gulf War service has been conducted in recent years, as part of the federal Gulf War research effort. Nearly all information on combined effects of Gulf War exposures comes from animal models. Ethical considerations generally prohibit exposing humans to combinations of toxicants for purposes of understanding their synergistic effects, and observational studies of exposures in human populations have generally focused on individual chemicals. Very little information on effects of combinations of exposures has been provided by Gulf War epidemiologic studies, although such analyses can and should be done. The few Gulf War studies that statistically evaluated interactions between two selected exposures did not take into account effects of other prominent exposures, and so have provided little useful information on synergistic effects of multiple exposures.

Available information from Gulf War studies and government reports, however, indicates that combined effects of exposures in theater are potentially an important concern. Gulf War studies have consistently indicated that exposures in theater were highly correlated. That is, veterans' exposures during deployment were "grouped" in identifiable ways, as opposed to being randomly experienced.<sup>241,458,1466</sup> Important examples were identified in the RAND pesticide investigation, which found that Gulf War personnel who used a large amount of one type of pesticide were also significantly more likely to use other types of pesticides, and that individuals who used the most pesticides also used the most PB.<sup>458</sup>

Interactive effects of potentially hazardous chemicals can occur in different ways. Compounds can affect the degree to which other chemicals are taken into the body or the efficiency with which they are neutralized and eliminated from the body. Both processes can directly affect the dose of chemical delivered to target organs, and can also affect the duration of the delivered exposure. Once in the body, compounds can also interact with one another biologically, altering effects of one another on specific biochemical processes in the brain or the periphery.

#### Dermal absorption of combined exposures.

Significantly, systemic exposure to certain chemicals such as pyridostigmine and DFP can modulate the percutaneous absorption of an unrelated chemical. This scenario is not usually assumed to be relevant to dermal risk assessment, and further supports the contention that risk assessment of chemical mixtures cannot be based solely on individual chemical studies.  
--J. Riviere, 2003<sup>1294</sup>

Several studies have assessed the degree to which different mixtures of Gulf War exposures alter absorption of insecticides and repellants, and their dermal effects. Those studies are summarized in Table 5. Findings from these studies demonstrated that skin absorption of repellants, and their penetration through dermal layers, varies with the type of carrier used in the chemical preparation. Overall, results indicated that permethrin absorption, alone, was generally minimal and that combined skin exposure to both DEET and permethrin did not enhance absorption of either compound. Neither was absorption of DEET or permethrin enhanced by topical exposure to PB or the organophosphate DFP, an exposure used to simulate nerve agent exposure. Topical exposure to JP-8 fuel did, however, significantly increase absorption of permethrin.

The major finding from these studies was somewhat unexpected. In contrast to topical applications, PB in the circulation significantly increased both dermal absorption and skin penetration of permethrin. In addition, the combination of circulating PB and DFP further enhanced absorption of both permethrin and DEET, increasing permethrin absorption by nearly six-fold. Pyridostigmine also significantly attenuated the dermal inflammatory response that normally develops in response to topically applied DEET and PB. This group of studies therefore indicates that systemic PB increases the absorption and bioavailability of permethrin. In combination with DFP, PB further enhances absorption of both permethrin and DEET. In addition, circulating PB inhibits the protective inflammatory response normally stimulated by topical exposure to either permethrin or DEET.

**Table 5. Effects of Combined Gulf War-related Exposures on Dermal Absorption and Response to Pesticides and Insect Repellants**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
Baynes <sup>110</sup> 1997	DEET, permethrin, carbaryl applied to rodent skin and perfused porcine skin	Absorption and penetration of each compound varied with carrier. DEET did not enhance dermal absorption of permethrin or carbaryl.
Baynes <sup>111</sup> 2002	Permethrin applied to perfused porcine skin and an <i>in vitro</i> model, with or without PB, DFP, and DEET.	Intrararterial perfusion of PB and/or DFP sign. enhanced dermal absorption and deposition of permethrin; DFP+PB yielded a 6-fold increase. Topical DEET and topical DFP reduced permethrin absorption.
Riviere <sup>1295</sup> 2002	Permethrin, DEET, and JP-8 jet fuel applied to perfused porcine skin	JP-8 enhanced permethrin absorption and penetration. DEET did not affect absorption.
Riviere <sup>1294</sup> 2003	DEET applied to perfused porcine skin and an <i>in vitro</i> model, with or without PB, DEET, and permethrin	Intrararterial perfusion of PB and DFP sign. enhanced dermal absorption and deposition of DEET. Topical DFP or permethrin had no effect on DEET absorption.
Monteiro- Riviere <sup>1064</sup> 2003	Permethrin and DEET applied to perfused porcine skin and an <i>in vitro</i> model, with or without PB and DFP.	Permethrin and DEET produced time-related increases in IL-8, prostaglandin E <sub>2</sub> and TNF alpha. Intrararterial perfusion of PB sign. suppressed release of IL-8 and prostaglandin. TNF alpha effects differed with different combinations and vehicles.

Abbreviations: DEET = diethyl-m-toluamide, PB = pyridostigmine bromide, DFP =diisopropyl fluorophosphate, an organophosphate used as a nerve agent stimulant, sign. = statistically significant

**Metabolic interactions of Gulf War-related toxicants.** After potentially hazardous chemicals enter the circulation, their adverse effects can be reduced or eliminated through biological mechanisms that protect the body from chemical toxins. This involves a cascade of biological processes that bind and metabolize the chemical, convert it to a form that is less toxic, and excrete it from the body. Metabolic processes can also convert relatively harmless chemicals that enter the body into more toxic forms. Toxicant metabolism is therefore an important determinant of the degree to which chemical exposures produce adverse effects.

Investigators who first identified synergistic effects of combined exposure to PB and pesticides hypothesized that the increased toxicity observed was due, in part, to competitive alterations in the capacity for liver and plasma hydrolyzing enzymes to effectively neutralize the chemicals.<sup>16,17</sup> Only limited information was available at that time, however, concerning the specific chemical processes involved in human detoxification of pesticides and related compounds.<sup>1440</sup> Since then, a growing body of research has provided important insights into how concurrent exposure to multiple chemicals can alter metabolism of toxic substances.

Human enzymes involved in metabolizing toxic chemicals differ from those of rodents and other species commonly used in toxicological research.<sup>1440,1525</sup> Research sponsored by DOD in recent years has begun to provide detailed information concerning the complex biochemical processes involved in the metabolism of Gulf War-related chemicals in models that utilize human liver cell fractions. Much of this work has been conducted by investigators at North Carolina State University. Initial studies have characterized details of metabolism of PB, DEET, permethrin, chlorpyrifos, and other pesticides by multiple cytochrome p450 enzyme isoforms, esterases, and other hydrolyzing enzymes. Results consistently demonstrate that the effectiveness of liver hydrolysis of chemical toxicants depends on the specific amounts and types of the different enzymes involved in metabolizing each compound, which can vary significantly between individuals.<sup>305,611,1525</sup>

These studies have also identified diverse types of interactions that result in one chemical inhibiting the metabolism of another. For example, the first step of permethrin metabolism involves ester hydrolysis, a process that is inhibited by chlorpyrifos. Incubation of liver microsome or cytosol fractions with chlorpyrifos prior to addition of permethrin results in dramatic inhibition of permethrin metabolism.<sup>1312</sup> A second type of interaction is illustrated by the observation that both chlorpyrifos and carbaryl are hydrolyzed by the same cytochrome p450 isoform. Coincubation of these two compounds in human liver microsomes yields significant inhibition of carbaryl metabolism, even at low doses.<sup>1312</sup>

Overall, these studies have most consistently demonstrated that chlorpyrifos can markedly inhibit, *in vitro*, metabolism of several other compounds associated with Gulf War service, including permethrin, DEET and carbaryl. Several other compounds can also modulate metabolism of one another.<sup>245</sup> For example, PB, permethrin, and chlorpyrifos can either stimulate or inhibit DEET metabolism, in different combinations.<sup>611,1701</sup> Investigators from Duke University recently reported that, using *in vitro* models, PB and permethrin both inhibited metabolism of one another in plasma. DEET did not affect metabolism of either PB or permethrin, but both PB and permethrin significantly inhibited DEET metabolism.<sup>22</sup>

Overall, research in this area provides evidence that metabolic interactions between combinations of anticholinesterase compounds and insect repellants can significantly affect the degree to which these compounds are effectively neutralized by the body. The extent to which such interactions contributed to adverse effects of Gulf War exposures and the development of Gulf War illness can not be deduced from studies of this type. But this information provides extremely useful insights into specific biochemical processes potentially involved in interactions between combinations of Gulf War exposures. Information from this research can also improve assessments that extrapolate findings on biological effects of Gulf War exposures from animal studies to humans.

Scientific understanding of the specific biological effects of combinations of chemical exposures on human health is relatively limited. But as described in the Committee's 2004 report, a relatively large number of studies have been conducted in recent years, as part of the federal Gulf War research effort, to evaluate biological effects of combinations of Gulf War-related exposures in animal models. These studies have demonstrated diverse effects resulting from combinations of neurotoxicant exposures, which differ from those of individual chemicals.

Effects of mixtures of PB and Gulf War-related pesticides and repellants. The largest number of federally-sponsored studies evaluating combined effects of Gulf War-related neurotoxicants have assessed effects of mixtures of PB, pesticides, and insect repellants on a variety of central nervous system and behavioral parameters. Findings from these studies are summarized in Table 6. As shown, the earliest studies of this type were conducted in the middle and late 1990s, and used exposure protocols that differed in important ways from Gulf War-related exposures. These studies were important, however, for providing a first look at the potential for synergistic effects of combinations of Gulf War-related exposures on the central nervous system.

Since 2001, multiple studies have used animal exposure models that provided a closer approximation to the types and levels of exposures experienced by Gulf War military personnel. Many of those studies have been conducted by Duke University investigators, and are noteworthy for two important reasons. First, the exposure models used were specifically developed to parallel exposures during the Gulf War. For example, permethrin and DEET were administered topically to the skin and PB was given orally at doses, calibrated by body weight, comparable to those of veterans. Second, many of the Duke studies evaluated effects that developed after an extended exposure period. Rats were typically given PB and pesticides in a repeated dosing schedule for 15-30 days,

**Table 6. Animal Studies Evaluating Combined Effects of PB, Pesticides, and Insect Repellants Used in the Gulf War on the Brain and Behavior**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
Abou-Donia <sup>16</sup> 1996	High doses of oral PB, subQ DEET, subQ chlorpyrifos to hens for 2 months	All combinations of 2 compounds produced multiple signs of toxicity (cholinergic symptoms, locomotor dysfunction, spinal cord swelling) that sign. exceeded single compounds, especially with PB+chlorpyrifos combination. Three chemicals combined yielded sign. greater toxicity than 2 chemicals combined.
Abou-Donia <sup>17</sup> 1996	High doses of oral PB, subQ DEET, subQ permethrin to hens for 2 months	Combinations of 2 compounds produced multiple signs of toxicity (gait abnormalities, weakness, tremors, decreased locomotor activity) that sign. exceeded single compounds. Combination of all 3 chemicals yielded sign. greater toxicity, spinal cord abnormalities than 2 chemicals combined.
Bucholz <sup>185</sup> 1997	Moderate dose of oral PB, very low dose of subQ permethrin to rats for 10 days	PB sign. decreased the amount of permethrin in the brain.
Chaney <sup>228</sup> 1999	High doses of PB and DEET given once IP to mice	Combination produced seizures and death by mechanisms that differed from single compounds. Effects were not altered by preadministration of anticonvulsant drugs.
Chaney <sup>229</sup> 2000	High dose DEET and varying doses of PB given once IP to rats	1 hour post exposure, DEET alone had no effect on AChE activity, PB alone did not affect brain AChE activity. High dose PB+DEET produced 40% reduction in whole brain AChE activity.
Hoy <sup>649</sup> 2000	High dose PB, DEET by gavage, permethrin IP given once to rats	2 hours post exposure, single compounds had minimal effects. Permethrin combined with PB or DEET sign reduced locomotor speed in males but not females. Serum levels of permethrin increased with coadministration of PB.
Hoy <sup>650</sup> 2000	High dose PB, DEET by gavage, permethrin IP given daily for 7 days to rats	24 hours after last dosing, no effects with single compounds. PB+DEET produced sign. reduced locomotor speed; permethrin + DEET sign. increased speed in male rats only.
Van Haaren <sup>1704</sup> 2000	GW-relevant dose of PB by gavage, high dose of permethrin IP given for 7 days to rats	Serum permethrin levels sign. greater in rats given PB, sign. greater in female than male rats. PB alone caused sign. learning deficits that were not affected by permethrin.
Abou-Donia <sup>13</sup> 2001	GW-relevant doses (also 0.1x, 10x GW doses) of DEET and permethrin dermally applied for 60 days to rats	DEET alone reduced blood brain barrier permeability in brainstem, DEET+ permethrin decreased permeability in cortex. 30-60 days after exposures initiated, all single compounds produced sign. reductions in sensorimotor performance; some deficits increased with time and dosage, and were sign. greater with combined exposures at highest doses.
Abou-Donia <sup>14</sup> 2001	GW-relevant doses of PB by gavage for 15 days, dermally applied DEET, permethrin daily for 45 days to rats	Locomotor performance on different tests was sign. reduced for each compound alone, with deficits increasing over time. Greatest deficits with PB; no interactive motor effects between compounds. PB alone produced 40% decline in midbrain AChE activity. DEET produced sign. increase in brainstem AChE activity, and permethrin produced sign. increase in cortical AChE activity. PB + DEET and/or permethrin produced sign. decrease in brainstem AChE.
Abu-Qare <sup>20</sup> 2001	GW-relevant doses of permethrin and high dose of DEET dermally applied once to rats	Brain mitochondria assessed at multiple time points 0.5 – 72 hours after exposures. Starting 24 hours after exposure, rats exposed to both DEET and permethrin had sign. increased release of brain mitochondrial cytochrome c. No effect with single exposures.

**Table 6. (cont.) Animal Studies Evaluating Combined Effects of PB, Pesticides, and Insect Repellants Used in the Gulf War on the Brain and Behavior**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
Abdel-Rahman <sup>5</sup> 2001	GW-relevant doses of DEET and permethrin dermally applied for 60 days to rats	DEET and permethrin, individually and combined, produced hypertrophy of astrocytes and sign. increased GFAP expression in hippocampus and cerebellum. All treatments resulted in sign. neuronal cell death in motor cortex, hippocampus, and dentate gyrus. Neuronal effects were attenuated with combination of DEET and permethrin.
Van Haaren <sup>1705</sup> 2001	Variable doses of PB and DEET by gavage, high doses of permethrin IP in rats	With PB treatment, rats had sign. decreased behavioral responses in dose-response manner. Only highest exposures to DEET and permethrin sign. reduced behavioral responses. Synergistic responses observed only with low dose PB combined with low dose DEET or permethrin. Some effects differed in male vs. female rats.
Vogel <sup>1727</sup> 2002	Assessment of DFP binding, in combination with varying low dose PB and permethrin, given in feed to mice	Outcomes observed 48 hours after dosing. Permethrin produced sign. (25-30%) increase in DFP binding in the brain. PB reduced DFP binding in plasma, red blood cells, muscle, and brain.
Abdel-Rahman <sup>6</sup> 2002	GW-relevant doses of PB by gavage for 15 days, dermally applied DEET, permethrin given daily to rats for 28 days with/without 5 min restraint stress to rats	All chemicals together, plus stress, produced disruption of blood brain barrier in cingulate cortex, dentate gyrus, thalamus, and hypothalamus but not in other brain regions. Neuronal death and increased GFAP were observed in those four brain regions. Exposures plus stress also sign. reduced AChE activity and m2 receptors in the forebrain. Minimal effects of combined chemicals alone or stress alone.
Abdel-Rahman <sup>3</sup> 2004	GW-relevant doses of PB by gavage, dermally applied DEET and permethrin given daily to rats for 28 days with/without 5 min restraint stress	Following up above study, evaluated changes in brain regions in which no disruption of blood brain barrier occurred. Combination of chemicals and stress yielded sign. decreased AChE activity in midbrain, brainstem, and cerebellum, and decreased m2 cholinergic receptor binding in midbrain and cerebellum. Stress plus chemicals also produced sign. neuronal death and increased GFAP in cerebral cortex and hippocampus. These changes not seen with stress or combined chemicals alone.
Abdel-Rahman <sup>4</sup> 2004	GW-relevant doses of dermally applied malthion, DEET and permethrin given daily to rats for 30 days	24 hours after last treatment, all behavioral tests (beam walk time and score, inclined plane, forepaw grip) showed sign. impairment with all single and combined exposures. DEET combined with either malthion or permethrin produced sign. increase in plasma BChE activity. Permethrin plus either malthion or DEET produced sign. reduced midbrain AChE, while DEET and permethrin alone sign. increased cortical AChE. Treatments also associated with reduced neuron density in several brain regions.
Abou-Donia <sup>10</sup> 2004	GW-relevant doses of PB by gavage for 15 days, dermally applied DEET, permethrin (also 0.1x, 10x GW doses) given daily for 60 days to rats	24 hours after last treatment, PB alone, DEET+ permethrin produced sign. locomotor and behavioral deficits (beam walk score and time, incline plane, forepaw grip). PB alone slightly reduced plasma BChE activity, but PB + DEET or permethrin sign. increased plasma BChE activity. DEET + permethrin sign. increased brainstem AChE activity. PB+DEET+permethrin sign. reduced AChE activity in midbrain. Results similar at different doses.

Abbreviations: DEET = diethyl-m-toluamide, PB = pyridostigmine bromide, DFP =diisopropyl fluorophosphate, an organophosphate used as a nerve agent simulant, subQ = subcutaneous, IP = intraperitoneal administration, GW = Gulf War, GFAP = glial fibrillary acidic protein, AChE = acetylcholinesterase, BChE = butyrylcholinesterase, sign. = statistically significant

and up to 60 days in different studies, an exposure profile that parallels that experienced by many Gulf War veterans. As a result, these studies have been extremely valuable not only for describing synergistic effects of multiple exposures, but also for characterizing central nervous system effects of single exposures, delivered orally and to the skin using a repeated dosing schedule over an extended period of time. As summarized in Table 6, these studies have produced an extensive number of detailed findings.

Effects of high dose exposures, evaluated by earlier studies, consistently indicated that different combinations of PB, DEET, permethrin, and chlorpyrifos yielded significantly greater neurotoxicity than single exposures. Synergistic neurotoxic effects were reflected by overt clinical signs of ill health, tissue damage in brain and spinal cord, behavioral changes, and reduced levels of AChE activity in the brain. These studies also suggested that moderate-to-high exposure to PB can effect levels of permethrin, increasing it in serum<sup>649,1704</sup> and decreasing it in the brain.<sup>185</sup> Two studies also suggested that immediate effects of high-dose exposures differ from effects that develop shortly thereafter. Male rats exposed to both permethrin and DEET (but neither compound alone) had significantly reduced locomotor speed after two hours,<sup>649</sup> but significantly increased speed after 24 hours.<sup>650</sup>

Later studies that used more Gulf War-relevant exposure protocols and doses identified diverse central nervous system effects following both individual and combined exposures. Some of the most noteworthy findings from these studies were effects observed from individual exposures to PB and insect repellants, effects not observed in previous studies that used single high dose and/or short term exposures. Identified changes resulting from a repeated dosing schedule were most pronounced, and most consistently demonstrated with PB. All four studies that evaluated behavioral measures following Gulf War-relevant doses of PB given orally to animals in a repeated and extended dosing pattern identified significant alterations in learning and/or locomotor activity.<sup>10,14,1704,1705</sup> Additional central nervous system effects of exposures to PB, permethrin, and DEET alone were noted in relation to low-dose, repeated administration, effects not observed in earlier studies that evaluated effects of higher dose, single dose, and short-term exposures. As summarized in Table 6, these effects included alterations in blood brain barrier permeability, regional alterations in brain AChE activity, and behavioral effects.

In addition, studies utilizing Gulf War-relevant protocols have identified diverse interactions between different mixtures of cholinergic neurotoxicants and insect repellants used in the Gulf War. It is important to note that different studies have evaluated different exposure combinations and durations, and that the majority of synergistic effects reported have been identified by only one or two studies, usually from the same team of investigators. These studies are generally consistent in showing that combined exposures can produce synergistic effects. However, many of the specific effects identified can only be considered preliminary, pending additional investigation. It is also important to note that relatively few three-way interactions were identified in these studies. That is, few synergistic effects resulting from combinations of three compounds were identified that differed from those observed with only two of the compounds.

As detailed in Table 6, a variety of synergistic effects have been reported in relation to combined exposure to PB and DEET in rat models, which differ from those observed with PB or DEET individually. These are generally similar to effects reported with combined exposure to PB and permethrin, and include significantly decreased AChE activity in brainstem,<sup>14</sup> increased plasma levels of BChE,<sup>10</sup> and behavioral deficits at low-dose exposures that were not observed with higher doses.<sup>1705</sup> Synergistic effects resulting from combined exposure to DEET and permethrin in rat models include reduced permeability of the blood brain barrier in the cortex,<sup>13</sup> reduced AChE activity in the midbrain,<sup>4</sup> increased AChE activity in brainstem,<sup>10</sup> and increased production of brain mitochondrial cytochrome c.<sup>20</sup> The combination of DEET and permethrin was also reported to

attenuate the degree of neuronal cell death observed in the hippocampus and cerebellum following exposure to either DEET or permethrin alone.<sup>5</sup>

Two studies have reported significant interactive effects between exposure to three chemicals together—PB, DEET, and permethrin—and a mild stressor. This combination produced significant increases in blood brain barrier permeability in four regions—the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus.<sup>3,6</sup> Investigators also reported glial fibrillary acidic protein (GFAP) staining in those regions, an indicator of astrocytic response to underlying neural injury. This response was consistent with reported indicators of neuronal cell death in those regions, as well as in the cerebral cortex and hippocampus.<sup>3</sup> None of these changes was observed with exposure to the three chemicals without the stressor, or with the stressor alone.

Findings indicative of neuronal cell death in these studies have been challenged by a suggestion that the dark neurons described as indicating cell death in exposed animals may be an experimental artifact that can be produced by a number of experimental conditions.<sup>726</sup> The Committee was not in a position to determine the validity of this concern, but notes that the neurons in question were observed only in some subgroups of exposed animals and not in unexposed animals, and were accompanied by other indicators of neurotoxicity, such as astrocyte hypertrophy and increased GFAP levels.<sup>3,5,6</sup>

In addition to the published animal studies summarized in Table 6, a DOD report on a project conducted by the U.S. Air Force Research Laboratory indicates that combined exposure to low doses of PB, DEET, JP-4 jet fuel, and stress produced significant neurobehavioral deficits and increased levels of serotonin in multiple brain areas, increases that were sustained at least 88 days after exposure.<sup>948</sup>

A limited number of animal studies have also evaluated combined effects of pesticides and PB on outcomes not directly related to neurological function and behavior. Increased urinary excretion of markers of oxidative stress and DNA damage have been reported in rats after combined low dose exposure to PB, DEET, and permethrin.<sup>18,19</sup> Apoptosis in testicular germ cells and spermatocytes have also been reported in rats following low dose, combined exposure to PB, DEET, and permethrin, an effect that were significantly enhanced by a moderate stressor.<sup>15</sup> A series of animal studies sponsored by the British Ministry of Defence generally found no interactive effects between PB and receipt of multiple vaccines given to British troops in the Gulf War, as detailed in the earlier discussion of vaccines. Combined exposure to DEET, PB, and JP-8 jet fuel in a mouse model produced only limited effects on the immune response.<sup>1187</sup> Higher level exposures to combinations of PB, permethrin, and DEET have been shown to significantly increase the lethality of each compound.<sup>986,1076</sup> Caffeine and adrenergic drugs have also been shown to potentiate the lethality of PB.<sup>227</sup>

Preliminary insights concerning the potential for biological interactions between Gulf War-related pesticides have also been provided by cell culture studies. Combinations of lindane, malathion, and permethrin have been reported to act synergistically to increase markers of oxidative stress, stimulate increased levels of antioxidant enzymes, and produce necrotic and apoptotic cell death in thymocytes.<sup>1151,1152</sup> And, using a novel *in vitro* screen for neurotoxicity, significant interactive effects have also been demonstrated when chlorpyrifos was combined with pyrethrum or with a solvent commonly used in pesticide formulations.<sup>77</sup>

Just one human study has specifically evaluated effects of combined exposure to DEET, permethrin, and PB. Investigators from the U.S. Uniformed Services University of the Health Sciences conducted a placebo-controlled crossover trial to assess effects of short term, low level exposure to PB, DEET, permethrin, and stress in 64 healthy, mostly military, volunteers.<sup>1322,1323</sup> During one and a half days in a

clinical research unit, subjects wearing untreated or permethrin-treated uniforms took a total of four 30 mg. PB tablets, or placebo, at eight hour intervals. They also applied a measured amount of 32 percent DEET cream, or placebo, three times to their neck, face, and legs, with gloved hands, at 12 hour intervals. Following the last use of DEET and PB, subjects were given a one hour rest session or a one hour stress session that involved marching on a treadmill with a weighted backpack. During the treadmill session, subjects watched a video depicting battle scenes from popular movies, and also performed mental arithmetic stress tests. The trial identified few differences between treatment and placebo groups on measures of neurobehavioral function, physical performance, or blood hormone levels.

The study was useful in showing that brief use of these products, at levels similar to or below those directed by current military policy, does not produce acute, observable adverse effects in military personnel. It provides only limited information directly relevant to the Gulf War scenario, however, in light of the types of DEET, permethrin, and stress applications evaluated in comparison to what is known about types and patterns of pesticide and repellent use during the Gulf War.

Interactive effects of PB with sarin. As previously described, the 1990-1991 Gulf War was the first time the military had used PB on a wide scale as a preventive measure in the event of nerve gas exposure. Since the war, questions have been raised about the potential for PB to have interacted with low-level sarin exposure to produce long-term adverse effects. Multiple studies have specifically assessed combined effects of exposure to PB and sarin, as summarized in Table 7. As shown, these studies have utilized a variety of designs and dosing methods to evaluate the potential for mixtures of PB and sarin to produce short and long-term effects.

Most of the studies listed in Table 7 identified significant effects resulting from exposure to sarin or PB, individually. These included effects on the brain and behavior, on autonomic function, and on peripheral metabolizing enzymes and muscle function. In addition, a number of interactive effects were reported that exceeded effects of PB and sarin individually. These include acute and long-term EEG alterations,<sup>1706</sup> increased levels of cholinergic M2 receptors in the cortex and brain stem,<sup>11</sup> increased startle threshold and locomotor activity,<sup>1377</sup> time-limited increases in regional cerebral blood flow<sup>1378</sup> and autonomic alterations in heart rate variability,<sup>1379</sup> and alterations in brain levels of acetylcholine.<sup>1403</sup> No studies identified interactive effects between PB and sarin on AChE levels in the brain.

It is important to note that many of the significant PB/sarin interactive effects identified in these studies were initially observed days or weeks after dosing ended. Studies also identified a number of effects that changed over time. Some alterations were most pronounced two or four weeks after exposure, with values similar to unexposed controls at later time points. Findings therefore provide some answers to questions concerning potential interactions between sarin and PB, but raise others. Most importantly, it is unknown whether time-related effects identified by some studies persisted or changed further at time points beyond those included in the study. Longer-term effects appear to be plausible, in light of long-term effects described following exposure to sarin alone, as well as results of some of the sarin/PB studies listed in Table 7.

For example, the 2003 study from researchers at the Army Medical Research Institute of Chemical Defense and the Los Angeles VA identified delayed behavioral changes that potentially reflect a hypercholinergic state, after exposure to sarin and PB. These changes were first observed 16 weeks after exposure, the latest time point evaluated, so it is not known if they were sustained for a longer time.<sup>1377</sup> A separate study, using a similar dosing protocol, evaluated choline and acetylcholine levels following exposure to PB and sarin. Exposure to AChE inhibitors, in general, leads to an acute *increase* in acetylcholine. In the Army study, rats exposed to sarin had significantly elevated cerebral acetylcholine levels four weeks after exposure.<sup>1403</sup> In comparison, rats exposed to both sarin and PB had significantly *reduced* levels of acetylcholine between 2 and 4 weeks after exposure.

**Table 7. Animal Studies Evaluating Combined Effects of Sarin and Pyridostigmine Bromide**

<b>Study</b>	<b>Exposure Model</b>	<b>Key Findings</b>
<i>Central and behavioral effects</i>		
Abou-Donia <sup>11</sup> 2002	GW-relevant oral dose of PB for 15 days, and single low-to-high sarin dose IM on day 15 in rats	At 7 and 15 days post exposure, sarin and PB individually produced sign. sensorimotor deficits. Sarin+PB together produced sign. sensorimotor deficits that worsened with time, sign. increase in m2 cholinergic receptor binding.
Scremin <sup>1377</sup> 2003	PB given in drinking water, 0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	Effects varied over time. Interactive effects of PB+sarin first observed at 16 weeks post exposure (sign. increased nociceptive threshold, increased startle threshold, increased locomotor activity, increased habituation). Sarin alone produced increased startle response and down regulated muscarinic receptors in several brain regions 2 weeks post exposure. No effects on brain AChE levels.
Van Helden <sup>1706</sup> 2004	PB given subQ to marmosets, prior to varying doses of sarin (5 hours in air)	PB+sarin treated animals exhibited EEG abnormalities at lower sarin doses than animals exposed to sarin alone. One year after exposure, PB+sarin exposure associated with sign. more EEG alpha frequency bursts than sarin alone.
Scremin <sup>1378</sup> 2005	PB given in drinking water, 0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	Effects varied over time. At 2 weeks post exposure, PB+sarin produced sign. increased cerebral blood flow in several areas. Similar patterns with sarin only at 4 weeks. Few differences remained at 16 weeks.
Scremin <sup>1379</sup> 2006	PB given in drinking water, 0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	2 weeks post exposure, heart rate sign. reduced in single and combined exposed animals. Sarin+PB produced sign. decrease in low frequency HRV at midnight and early morning, and sign increase in total power. Minimal HRV differences at 4 and 16 weeks. No differences in locomotor measures between groups.
Shih <sup>1403</sup> 2006	PB given in drinking water, 0.5 LD <sub>50</sub> sarin dose subQ, 3x/week for 3 weeks in rats	Sign. regional differences in brain levels of choline and acetylcholine at 2, 4, and 16 weeks post treatment. Overall, acetylcholine levels were sign. lower with sarin+PB than with sarin alone at 2 and 4 weeks, but not at 16 weeks.
<i>Peripheral effects</i>		
Abu-Qare <sup>19</sup> 2001	Single moderately high oral dose of PB and moderately high sarin dose IM in rats	48 hours after exposure, rats who received PB+sarin excreted sign. elevated levels of 2 markers of oxidative stress in urine. No oxidative stress markers with either PB or sarin alone.
Husain <sup>657,658</sup> 2003, 2004	10 weeks exercise, with GW-relevant doses of oral PB and low-dose sarin subQ at weeks 5-6 in mice	Four weeks after exposure, exercise+sarin and exercise+PB yielded sign. decreased respiratory exchange, plasma BChE, peripheral and central AChE activity, and increased plasma CK activity. Little indication of 2-way interaction of PB+sarin or 3-way interaction of exercise+PB+sarin.
Dabisch <sup>303</sup> 2006	GW-relevant doses of PB injected in rats IM 2x/day for 8 days, followed by sarin inhalation	Pupil miotic response to PB decreased over the treatment period, indicating increased tolerance to PB. PB pretreatment did not affect initial pupil response to sarin, but shortened pupil recovery time.

Abbreviations: GW = Gulf War, PB = pyridostigmine bromide, IM = intramuscular, AChE = acetylcholinesterase, BChE = butyrylcholinesterase, EEG = electroencephalogram, HRV = heart rate variability, LD<sub>50</sub> = dose that is lethal to half of exposed animals, sign. = statistically significant

At 16 weeks, brain acetylcholine levels had “rebounded” in rats exposed to both compounds, and were nonsignificantly *higher* than levels in rats exposed to sarin alone. These findings are unique, and suggest an unexpected course for time-related changes in brain acetylcholine levels following combined exposure to PB and sarin. It is unknown, however, if brain acetylcholine levels continued to increase in rats exposed to both sarin and PB after 16 weeks.

It is also not known the extent to which alterations in brain chemistry sustained over a limited period of time, such as the 2-16 week time frame in most of the PB/sarin studies, can lead to other, downstream biological effects that have not been assessed in studies focused on immediate outcomes. In the real-world situation of the Gulf War, neurochemical alterations sustained over a period of days or weeks might potentially have been the first in a cascade of additional effects triggered by the initial exposures. Alternatively, changes that occur within a limited time frame might alter the impact of other exposures encountered during that time frame, exposures that might not normally have produced adverse effects. Therefore, although a number of synergistic effects have been described following repeat, low-level exposure to sarin and PB, the long-term implications of those effects remain to be more fully elucidated.

**Summary. Health effects of combinations of Gulf War exposures.** Gulf War veterans were exposed to unique mixtures of neurotoxicants during deployment, and possible health effects resulting from those mixtures are an important concern. Studies indicate that veterans exposed to one type of neurotoxicant, for example, PB or a certain class of pesticide, were usually exposed to others. Little information on health effects of combined exposures is available from studies of Gulf War veterans or other human populations. Animal studies have demonstrated that combinations of Gulf War-related exposures can interact at different stages of exposure, and that some combinations produce effects that differ from those of individual exposures. Studies have indicated, for example, that pyridostigmine in the circulation significantly increases absorption of permethrin through the skin, but topically applied DEET does not. Recent research has also described mechanisms through which toxicants inhibit metabolism of other toxicants in liver cells and consistently indicate that the organophosphate pesticide chlorpyrifos significantly inhibits the breakdown of other compounds, including permethrin and DEET.

The largest number of studies has evaluated combined effects of PB, DEET, and permethrin on the brain and behavior. Early studies reported that high doses of mixtures of these chemicals produced significantly greater neurotoxicity than each compound individually. More recently, studies have assessed effects of combinations of these exposures using dosing levels and patterns comparable to those experienced by veterans in the Gulf War. These studies have identified multiple effects of single chemicals using low-dose, repeated exposures, effects not identified in earlier studies using higher dose exposures. Significant effects from mixtures of two or more exposures have also been identified, effects that did not occur with individual exposures. These include significant neurobehavioral changes, and regional alterations in the blood brain barrier and brain AChE activity, which varied with different chemical combinations. A limited number of neurochemical, autonomic, and behavioral effects have also been identified in relation to combined exposures to PB and sarin.

Overall, these studies consistently indicate that combinations of Gulf War-related neurotoxicants can produce effects that differ from those of individual exposures. Important questions remain, however, concerning the contribution of these effects to Gulf War illness. Existing studies provide little information on the degree to which interactive effects persist for an extended period of time after exposure. There is also little information on central effects of OP pesticides or the organochlorine lindane, in combination with other Gulf War neurotoxicants. In addition, Gulf War epidemiologic studies have not systematically evaluated combinations of self-reported and/or modeled exposures in theater in relation to Gulf War illness and other health outcomes.

## Research on the Health of Gulf War Veterans in Relation to Cholinergic and Related Neurotoxicants

DG was a Staff Sergeant with the 1165th Military Police Company. He recalled being awakened at 3:30 a.m. The Battalion NBC NCO was announcing that they were under chemical attack. An M-256 kit registered a positive reading for a chemical agent. They went to MOPP level 4 for four hours. Afterward, all of them had runny noses. When asked if people were sick from the attack, DG responded that most people were already sick from the pyridostigmine bromide pills. He said that they had been taking them for two or three days before the attack and that 'a lot of people got sick and three or four had to be medevaced out.'

DG currently suffers from headaches, fatigue, joint and muscle pain, an inability to concentrate, recurring rashes, irritability, night sweats, insomnia, diarrhea, gastrointestinal problems, dizziness, blackouts, excessive photosensitivity, sore gums, swollen lymph nodes, and a spot on his brain.

--1994 Senate Committee report on Gulf War veteran<sup>1688</sup>

A substantial proportion of U.S. military personnel who served in the Gulf War, including most ground troops, were exposed to one or more of the neurotoxicants described in this section, in different doses and combinations. Toxicological research in animal models indicates that compounds of this type can have persistent effects on the brain, and on behavioral, autonomic, and neuroendocrine parameters, effects that are generally compatible with types of biological alterations observed in Gulf War veterans. Studies in human populations have identified elevated rates of persistent symptomatic illness and subtle neurological alterations in relation to subsymptomatic exposure to pesticides and in relation to symptomatic, but sublethal, exposure to sarin. These research findings are extremely useful but, as previously described, do not precisely reflect characteristics of Gulf War exposures and Gulf War illness. Studies in the general population and in animals provide an indication that exposures of this type *could* have contributed to Gulf War illness. But given the complexity of the Gulf War exposure scenario and the unusual nature of Gulf War illness, it is important to evaluate studies of Gulf War veterans to determine what available evidence most clearly indicates *did* cause Gulf War illness.

Research findings on the effects of neurotoxicant exposures on the health of Gulf War veterans differ from those of all other exposures evaluated by Gulf War research studies. Epidemiologic studies have consistently identified two Gulf War-related exposures—PB and pesticides—to be significantly associated with Gulf War illness, after adjusting for effects of other exposures in theater. Clinical studies have also identified objective measures that distinguish Gulf War veterans exposed to PB, pesticides, and nerve agents, from veterans who were not exposed. Neurotoxicant-related effects have been identified on neuroimaging scans, neurobehavioral assessments, and neuroendocrine measures. Pyridostigmine and pesticides are also the only Gulf War-related exposures that previous government reviews and reports have suggested may be associated with Gulf War illness.<sup>504,1632</sup> Overall, the many different types and sources of evidence evaluated by the Committee—information on exposure patterns, toxicological and human population research, and studies of Gulf War veterans—most strongly and consistently implicate PB and pesticides as causal factors in Gulf War illness.

Results from Gulf War epidemiologic studies that evaluated independent associations of PB, pesticides, and variables related to chemical agents with symptomatic illness in Gulf War veterans are summarized in Table 8. Studies listed are those that controlled for confounding effects of multiple exposures in theater since, as described, failure to account for these effects can introduce serious error into study findings. The overall consistency of findings related to PB and pesticides is particularly noteworthy given the diversity of methods used to assess both exposures and symptomatic illness in different Gulf War veteran populations. Results related to the association of symptomatic illness with chemical agents, as shown, are mixed. Detailed findings from all assessments of associations of symptomatic illness in Gulf War

veterans with PB, pesticides, and variables related to chemical agents are provided in Appendix A. Results from these studies are summarized below.

**The health of Gulf War veterans in relation to pyridostigmine bromide (PB).** Studies of Gulf War veterans have assessed veterans' use of PB during deployment in different ways. Most simply posed a yes/no question, asking veterans whether they took the small white pills, variously described as "anti nerve gas pills" or "NAPPs" in the U.S. and "NAPs" in the U.K. Some asked veterans to report how many pills they took, or how many days they took the pills. Several studies also asked veterans if they had experienced side effects from PB pills when they took them during the war.

SH, assigned to the 145<sup>th</sup> Transportation Company, also reported getting very sick from the nerve agent pre-treatment pills. He reported severe nausea and diarrhea that did not abate until he stopped taking the pills after two days. He recalled thinking that 'if I'm going to feel like this I might as well be dead.'

-- 1994 Senate Committee report on Army Gulf War veteran<sup>1688</sup>

Acute side effects from PB during the Gulf War. Surveys of military personnel during the Gulf War indicated they experienced higher-than-expected rates of side effects from taking PB. Medical officers for the XVIII Corps reported that about half of the soldiers in their units had side effects.<sup>781</sup> Gastrointestinal effects were most common, but headaches were more problematic than had been expected. A small survey of Army personnel, mostly aviators, conducted just before their return from theater indicated that 37 percent of those who took PB had "problems" with it.<sup>207</sup> Few details are provided from these surveys, but both suggest higher rates of side effects from taking PB during the Gulf War than is typically reported for healthy individuals evaluated in research studies.<sup>271,272,1323</sup> An even higher proportion of Israeli soldiers (75%) who took PB during the Gulf War were reported to have side effects.<sup>1396</sup> The types of symptoms reported by these soldiers were also reported to differ from those most commonly seen in clinical settings, with Gulf War military personnel reporting higher rates of central nervous system complaints (headaches, cognitive difficulties) than typically affect healthy subjects in clinical studies.<sup>460</sup>

Gulf War veterans in the U.S. and the U.K. who reported they had acute side effects from PB during the war have also been shown to have significantly higher rates of symptomatic illness, six to 10 years after the war.<sup>241,564</sup> These findings are of particular interest, because both studies found an association of PB side effects with Gulf War illness, after controlling for effects of other exposures during the war. A third study, of Ohio reservists who served in the Gulf War, reported a significant correlation between adverse reactions to "medications" during the war and poorer overall health status since the war.<sup>1373</sup>

Association of PB with multisymptom illness in Gulf War veterans. Like most other exposures evaluated in Gulf War epidemiologic studies, PB use was reported to be significantly associated with Gulf War-related multisymptom illness in nearly all studies, when results were not adjusted for effects of other exposures during the war, as detailed in Appendix A-9. But unlike most other exposures, the use of PB in theater was also consistently associated with Gulf War illness in studies that conducted more credible analyses, adjusting for possible confounding effects of other exposures. As shown in Table 8, PB use and/or PB side effects were significantly associated with Gulf War-related symptomatic illness in all six of the six studies that evaluated this association, while controlling for effects of other exposures.

Dose-response effects, that is, a graded association between the amount of PB taken and greater risk of illness or more severe illness, have also been identified by multiple studies. Two U.S. studies have reported that taking less than 22 PB pills during the war was associated with a modestly increased risk for Gulf War illness, but that 22 or more PB pills was associated with a significantly increased risk for Gulf War illness, after controlling for effects of other exposures.<sup>1466,1804</sup> This is the equivalent of taking PB, at

**Table 8. Associations of Pyridostigmine Bromide, Pesticides, and Chemical Agents with Multisymptom Illness in Gulf War Veterans**

Study	Gulf War Veterans Studied	Symptomatic Illness Evaluated	Association of Neurotoxicant Exposure with Symptomatic Illness (adjusted for effects of other exposures)			Additional Information
			PB	Pesticides, Repellants	Chemical Agents	
Haley <sup>564</sup> 1997	249 GWV Navy Seabees	Haley syndromes	+ <sup>1</sup>	+	+	PB side effects “dose response” effect.; DEET dose response effect
Ishoy <sup>695</sup> Suadicani <sup>1507</sup> 1999	686 Danish GWV	Gastrointestinal and/or neuropsych symptoms		+	ns	
Nisenbaum <sup>1124</sup> 2000	1,002 Air Force GWV	Chronic multisymptom illness <sup>464</sup>	+	+	+	
Cherry <sup>241</sup> 2001	7,971 U.K. GWV	Overall symptom severity	+ <sup>2</sup>	+		PB dose response effect Pesticide dose response effect
Spencer <sup>1466</sup> 2001	1,119 GWV from Washington, Oregon	Gulf War unexplained illness (study defined)	+	ns		PB dose response effect; DEET was only pesticide evaluated in model
Gray <sup>527</sup> 2002	3,831 GWV Navy Seabees	Gulf War illness (study defined)	+	+	+	
Wolfe <sup>1804</sup> 2002	945 U.S. Army GWV	Chronic multisymptom illness <sup>464</sup>	+		ns	PB dose response effect no association with “pesticide odor”

Abbreviations: PB = pyridostigmine bromide, GWV = Gulf War veterans

Notes: blank cell = association not assessed in multivariable model, + = statistically significant association, ns = association not statistically significant, 1 = association with PB side effects only, 2 = association with PB use and PB side effects

recommended doses, for more than seven days. Other studies have reported that veterans who took PB during the war are at greater risk for more *severe* multisymptom illness,<sup>1124</sup> and that veterans who took PB for longer periods of time have more severe symptomatic illness than those who took PB for shorter periods.<sup>241</sup> Dose response effects for PB in relation to chronic ill health and multisymptom illness have also been reported by three studies that did not control for confounding effects of other exposures.<sup>788,789,938,1371-1373</sup> Overall, the highly consistent association of PB with multisymptom illness in epidemiologic studies analyzed to minimize effects of confounding, as well as identified dose response effects of PB, provide compelling evidence that supports PB as a causal factor for Gulf War multisymptom illness.

**Association of PB with other health outcomes in Gulf War veterans.** In addition to PB’s association with Gulf War multisymptom illness, a number of studies have identified significant associations between PB use and measured clinical outcomes in Gulf War veterans. Veterans who used PB during the war have been reported to have significant decrements on neurobehavioral measures, compared to veterans who did not use PB.<sup>1512</sup> Studies have also identified significant neuroendocrine alterations in relation to veteran-reported PB use. Specifically, veterans who took PB during the war exhibited significantly greater cortisol suppression with dexamethasone (DEX) challenge, and significantly reduced 24-hour levels of adrenocorticotrophic hormone (ACTH), compared to veterans who did not take PB. Neither measure was associated with PTSD or with combat stress during the war.<sup>502,503</sup> Additional studies have indicated that PB use was not associated with handgrip strength,<sup>738</sup> but may be associated with more subtle alterations in peripheral nerve function.<sup>241,1186</sup>

The Committee has reviewed results from two additional federally funded projects that have not yet been published, but also suggest an association between PB and clinical measures. One study, conducted by Midwest Research Institute, found that use of PB is associated with a dramatic, 40-fold increased risk for Gulf War illness among veterans with butyrylcholinesterase (BChE) genotypes associated with very low BChE activity.<sup>1353</sup> Preliminary findings from a second study, conducted by researchers at Boston University, indicate that use of high levels of PB during the war, in combination with higher-level pesticide exposure, is associated with significantly greater risk both for symptomatic illness and for measured neurobehavioral decrements.<sup>836</sup>

**The health of Gulf War veterans in relation to pesticides.** As previously described, a large number of pesticides and insect repellants were used by military personnel during the Gulf War, including personal pesticides used by the general military population, and area-use pesticides sprayed by pesticide applicators. Unfortunately, most Gulf War epidemiologic studies evaluated veteran-reported pesticide use only in very general terms, for example, by simply asking veterans if they had been exposed to “pesticides” during the war. A very limited number of studies asked how much pesticide was used, the number of days pesticides were used, or the specific types of pesticides to which veterans were exposed. One study indicated that the use of DEET and permethrin were highly correlated, and that the majority of personnel used either both repellants or neither.<sup>1466</sup>

Association of pesticides with multisymptom illness in Gulf War veterans. As detailed in Appendix A-7, nearly all Gulf War epidemiologic studies identified significant associations between pesticide exposure and symptomatic illness, in analyses that did not control for effects of confounding by other exposures in theater. Several associations identified by these analyses were quite pronounced, however, including a finding that British veterans who reported personal pesticide use had a 12 times greater risk of multiple chemical sensitivity than veterans who reported no use of personal pesticides.<sup>1264</sup>

Studies also consistently found that pesticide exposure was significantly associated with Gulf War symptomatic illness, after controlling for effects of other exposures in theater. As shown in Table 8, pesticide exposure was identified as a significant risk factor for Gulf War illness in five of the six studies that adjusted for effects of other exposures. The single study in which this association was not significant had evaluated only effects of DEET in multivariable modeling, although initial analyses indicated that use of insecticide spray was more strongly associated with Gulf War illness than DEET.<sup>1466</sup> Overall, the general consistency of results demonstrating an association of pesticides with Gulf War illness is especially noteworthy, given the variability in how pesticide use was assessed by different studies.

Only two epidemiologic studies evaluated dose-response effects in relation to pesticide use during the Gulf War. Both identified significant correlations between greater pesticide use and greater illness risk or severity. The University of Texas Southwestern study of Navy Seabees found that using larger amounts of government-issued DEET repellant, but not OFF or Skin-so-Soft, was significantly correlated with greater illness risk, adjusting for effects of other exposures. In addition, the large University of Manchester study of British Gulf War veterans reported a significant correlation between severity of symptomatic illness and the number of days that veterans reported using insect repellants or handling pesticides.<sup>241</sup>

Association of pesticides with other health outcomes in Gulf War veterans. Several studies have reported that pesticide use during the Gulf War is associated with measured clinical outcomes. This includes one published finding that veterans who reported using pesticides during the war had significantly poorer performance on neurobehavioral tasks, compared to veterans who did not.<sup>1782</sup> Use of pesticides in theater was also reported, in one study, to be significantly associated with lower 24-hour ACTH levels.<sup>503</sup> Preliminary results from an additional federal research project, which are not yet published, suggest that both symptomatic illness and reduced neurobehavioral performance are

significantly more pronounced among individuals with the highest levels of both pesticide exposure and PB use during the war.<sup>836</sup>

**The health of Gulf War veterans in relation to chemical agents.** A large number of studies have evaluated associations between variables related to possible nerve agent exposure and the health of Gulf War veterans. Results of these studies are much less consistent and interpretable than findings related to PB and pesticides. Difficulties in determining who was exposed to low level nerve agents during deployment introduce major ambiguities into this research. Although information related to all self reported exposures during the war is subject to inaccuracies, self-reported exposure to low-levels of nerve agents is particularly problematic. Veterans might not have known if they had been exposed to subsymptomatic levels of sarin in any case, but repeated chemical alarms and alerts, disregarding and turning off alarms, and information and misinformation conveyed through the ranks further undermined their ability to know whether or not they had been exposed. Studies indicate that chemical agent exposures are among the least reliably-reported exposures in Gulf War research.<sup>1165</sup> Modeled exposures related to the Khamisiyah demolitions are also subject to question, as previously detailed, and additional questions remain concerning chemical agent exposures in other locations.

Did Gulf War veterans have symptoms of chemical agent exposure in theater? It has generally been believed that few if any Gulf War veterans exhibited symptoms of exposure to chemical weapons during the war,<sup>1232</sup> but there is little systematically-collected data that addresses this question. The 2000 RAND report on possible health effects of chemical agents in the Gulf War pointed out that nonspecific symptoms of low-level exposure to nerve agents might have gone unnoticed or been attributed to other causes.<sup>74</sup> Department of Defense Case Narrative reports often indicate that few, if any, individuals interviewed in relation to suspected chemical events had symptoms of exposure at the time of the incident.<sup>1617,1628,1630</sup> Other suspected chemical incidents came to light specifically because of reports that individuals had experienced symptoms suggesting exposure.<sup>1558,1589,1614,1627,1688</sup> A recent survey of 335 U.S. Gulf War veterans indicated that 25 percent of veterans who said they had been exposed to chemical agents during the war based their belief on symptoms they had experienced at the time of the suspected incident.<sup>168</sup>

The only study of Gulf War veterans who were in the immediate vicinity of the Khamisiyah demolitions found that some did have symptoms of nerve agent exposure at the time. Investigators from VA's Portland Environmental Hazards Research Center surveyed nearly 3,000 Gulf War veterans who had been in different areas during the first two weeks after the cease fire, when the major Khamisiyah demolitions had taken place. Veterans were asked about symptoms they experienced during that period, as well as symptoms they had at the time of the survey, nine years after the war.<sup>990</sup> Overall, symptoms reported by veterans who were within a 50 km. radius of Khamisiyah during early March of 1991 were similar to those of veterans in other areas of theater. However, veterans who had directly participated in the Khamisiyah demolitions, or had witnessed the demolitions, reported significantly higher rates of a number of symptoms during that period, primarily symptoms suggestive of nerve agent exposure—headaches, nausea, vision problems, cramping, runny nose, and muscle twitching.<sup>990</sup> Results suggest that some veterans in close proximity to the Khamisiyah demolitions may have had cholinergic symptoms at the time of exposure.

Association of chemical agents with multisymptom illness in Gulf War veterans. In epidemiologic evaluations of health effects potentially resulting from chemical agents during the Gulf War, exposure has been assessed using a variety of self report measures, or using modeled estimates related to the Khamisiyah demolitions. Results of these studies are detailed in Appendix A-2. As has been described in relation to other Gulf war exposures, nearly every variable potentially indicative of chemical agent exposure—such as receiving notification from DOD about the Khamisiyah releases, wearing a gas mask, hearing chemical alarms, belief that chemical and biological weapons were used—has been shown to be significantly associated with symptomatic illness in analyses that made no adjustments for effects of other

exposures. Although subject to confounding, results from several of these studies are worth noting. The large U.S. National Study of Gulf War veterans indicated that veteran-reported exposure to “nerve gas” was associated with a 15-fold increased risk of the unique “Gulf War illness” symptom complex identified by that study.<sup>752</sup> In addition, the Portland study reported that individuals within 50 km. of the Khamisiyah demolitions, overall, had symptom profiles similar to those of veterans in other areas of theater.<sup>989</sup> In contrast, veterans who had assisted with or observed the demolitions had significantly higher symptom rates, nine years after the war, than other veterans who had been within 50 km. of the demolitions.

Results from epidemiologic studies that controlled for effects of other exposures in theater are less consistent and less clear. As shown in Table 8, of the five studies that evaluated associations between symptomatic illness and chemical agent variables, three identified significant associations, after adjusting for effects of other exposures. Each of these studies relied on different self-reported indicators of chemical agent exposure; none used exposure estimates from the Khamisiyah models. Individual results from the studies listed in the table also raise questions concerning the degree to which they do or do not support an association between Gulf War illness and chemical exposures. For example, of the two studies that found no association between chemical agents and symptomatic illness, one evaluated Danish veterans, who served only in peacekeeping missions and might not have been exposed to chemical agents at any time.<sup>695,1507</sup> Studies that identified positive associations also raise questions. The positive finding from the large Air Force study, for example, reflects an association between chronic multisymptom illness and veterans’ perceptions that “chemical or biological weapons were being used,” but not specifically with whether a veteran had reason to believe that he or she had personally been exposed to chemical weapons.<sup>1124</sup>

Overall, an association between Gulf War illness and exposure to chemical warfare agents in theater is not clearly supported nor clearly refuted by results of Gulf War epidemiologic studies. This is due to the inconsistency of study findings, overall, and to ambiguities in variables used to evaluate chemical agent exposures.

Association of chemical agents with other health outcomes in Gulf War veterans. In addition to the many studies of Gulf War-related multisymptom illness, studies have assessed other health outcomes in relation to chemical agent exposures during the Gulf War. In contrast to studies evaluating Gulf War illness, most other health outcomes have been assessed in relation to modeled chemical agent exposures associated with the Khamisiyah demolitions.

Department of Veterans Affairs investigators in Washington, D.C. used the 2000 Khamisiyah models to assess mortality rates in Gulf War veterans relative to nerve agent exposure. In 2005, they reported that modeled exposure to nerve agents was associated with a significantly increased rate of death due to brain cancer.<sup>190</sup> The rate of brain cancer mortality among veterans downwind from the Khamisiyah demolitions was about twice as high, overall, as the rate in veterans who had been located elsewhere. This reflected 25 brain cancer deaths prior to the year 2001 among the 100,487 Gulf War veterans identified as potentially exposed to nerve agents. A dose response effect was also identified, indicating that exposure for two or more days was associated with a greater than three-fold increased risk of death due to brain cancer. No other mortality effects, related to either disease or motor vehicle accidents, have been reported in relation to nerve agent exposure at Khamisiyah.<sup>190,470</sup>

Studies have also reported measurable difference in neurobehavioral performance and brain structure in relation to low-level nerve agent exposures following the Khamisiyah demolitions. Investigators from VA’s Boston Environmental Hazards Center assessed neurocognitive performance in veterans in the Fort Devens cohort between 1994 and 1996, and initially found that veterans who reported being exposed to chemical or biological warfare agents had significant decrements on a number of specific cognitive tasks.<sup>910</sup> Years later, testing results were reevaluated to assess measured outcomes in relation to DOD-

modeled exposures to sarin and cyclosarin following demolitions at Khamisiyah. Since testing had occurred before the Khamisiyah exposures had been made public, the available data allowed assessment of cognitive performance that was effectively blinded to exposure status. In tests conducted four to five years after exposure, modeled levels of nerve agent exposure were significantly associated with reduced performance on neurobehavioral tasks related to visuospatial and psychomotor abilities, in a dose response manner.<sup>1237</sup>

Twenty-six individuals in the Fort Devens cohort also received magnetic resonance imaging (MRI) scans of the brain between 1999 and 2001. Volumetric measures were evaluated in relation to DOD modeled exposure levels to sarin and cyclosarin in connection with Khamisiyah. No differences were identified by simple comparisons between “exposed” and “unexposed” individuals, that is, comparisons between all veterans identified as being potentially exposed at any level, and those who were not in areas affected by Khamisiyah. In contrast, dose-response analyses identified significant associations between levels of nerve agent exposure and structural differences in several brain areas. Specifically, veterans with the highest level of nerve agent exposures had significantly reduced white matter volume, and enlarged right and left ventricular volumes, controlling for both age and PTSD symptomatology.<sup>599</sup> These effects suggest subtle, persistent alterations in brain structure associated with low level exposure to nerve agents during the Gulf War. Identified differences related to the degree of exposure estimated by the Khamisiyah models, but were obscured in comparisons between all unexposed individuals and all those identified as exposed at any level.

Additional studies have reported on rates of medical diagnoses, healthcare utilization, and hospitalization in relation to the Khamisiyah demolitions. A 2002 survey indicated that Gulf War veterans located within 50 km. of the Khamisiyah demolitions reported similar rates of medical diagnoses and hospitalizations as veterans in other locations of theater.<sup>989</sup> In a later survey, U.S. Gulf War veterans who had been notified that they may have been exposed to nerve agents in relation to Khamisiyah reported generally similar rates of symptoms, medical conditions, and healthcare visits as veterans located elsewhere. Exposed veterans reported significantly higher rates of recurrent headaches, but significantly lower rates of diagnosed cancer and neuralgia.<sup>1165</sup> Findings suggest that veterans identified by the Khamisiyah plume models, overall, are generally similar to other Gulf War veterans in relation to most self-reported diagnoses and symptoms. They also indicate that veterans’ belief that they may have been exposed to nerve agents was not associated with a tendency to “over report” health problems or increased healthcare utilization.<sup>1165</sup>

Studies conducted by the U.S. Naval Health Research Center evaluated hospitalizations in military hospitals in relation to nerve agent exposures, estimated using both the 1997 and 2000 Khamisiyah models. Overall, military hospitalizations from 1991 through 1995 were generally similar in “exposed” and “not exposed” active duty personnel veterans identified by the 1997 plume models.<sup>529</sup> Later analyses compared military hospitalizations between 1991 and 2000 in relation to exposures estimated using the 2000 plume models.<sup>1433</sup> All-cause hospitalization rates were similar in exposed and unexposed veterans. Of the 15 disease-specific categories evaluated, hospitalization for diseases of the circulatory system was slightly (RR=1.07) but significantly elevated in exposed personnel. Within that category, a significantly greater proportion of Khamisiyah-exposed veterans had been hospitalized for cardiac dysrhythmias (RR=1.22), but no other specific conditions.<sup>1433</sup> No information was provided on hospitalizations relative to different nerve agent exposure levels estimated by the 2000 Khamisiyah models.

In general, studies that have used modeled estimates of nerve agent exposures in the Gulf War have provided more interpretable information than epidemiologic studies that relied on veterans’ reports of chemical alerts or their beliefs concerning chemical exposures. When all veterans identified as “exposed” in relation to Khamisiyah are considered as a single group, only two significant differences have been identified using “hard” endpoints—a significant increase in brain cancer mortality, and an excess of hospitalization for cardiac dysrhythmia. Overall, self-reported symptoms, self-reported medical diagnoses,

and healthcare utilization are similar among veterans identified as “exposed” and “not exposed” using the Khamisiyah models.

Differences related to possible nerve agent exposure were more consistently identified when *levels* of exposure estimated by the Khamisiyah models were considered, rather than combining all potentially “exposed” veterans into a single group. Identified health outcomes associated with greater and/or more sustained nerve agent exposure include higher rates of brain cancer mortality, differences in brain structure volume, and decrements in performance on neurobehavioral tasks. It is important to emphasize that these studies did not specifically identify excess rates of Gulf War multisymptom illness in relation to the Khamisiyah exposures, and none provided results that were adjusted for effects of other exposures during deployment. Epidemiologic studies that identified increased rates of symptomatic illness in relation to Khamisiyah also did not consider effects of other exposures.<sup>142,990,1476</sup> Therefore, despite important findings related to neurological effects of modeled nerve agent exposures, there is still no clear information that indicates whether Gulf War multisymptom illness is associated with nerve agent exposures related to the Khamisiyah weapons demolitions.

Although the accuracy of the Khamisiyah models has been questioned, it is unlikely that the exposure effects observed in studies of Gulf War veterans were anomalies introduced by shortcomings in the models. All identified effects related to modeled levels of nerve agent exposures resulting from Khamisiyah were related to brain pathology, and all occurred in a dose-response pattern. Inaccuracies in the Khamisiyah models are unlikely to differ with respect to the health outcomes assessed. Such “nondifferential” exposure misclassifications due to model inaccuracies would therefore be expected to *diminish* the apparent associations between nerve agents and the neurological outcomes reported. This raises the possibility that the actual effects of exposures in the Khamisiyah area could be more pronounced than those suggested by reported study results.

Results of these studies underscore the importance of evaluating effects of dosage and duration in assessing effects of Gulf War exposures, where possible, and evaluating health outcomes in identifiable subgroups of Gulf War veterans. Comparisons between all veterans identified as potentially “exposed” to nerve agents in relation to Khamisiyah obscured effects identifiable when different exposure levels were considered. Similarly, studies indicate that higher-dose or more sustained exposures to PB and pesticides were more strongly associated with Gulf War illness than lower-dose or brief exposures. In a broader sense, these studies provide an important example of the potential for overly generalized comparisons, for example, between all deployed Gulf War veterans and nondeployed veterans, to obscure findings related to specific veteran subgroups.

**Summary. Research on health effects of cholinergic and related neurotoxicant exposures in Gulf War veterans.** A large proportion of Gulf War veterans were exposed to different combinations of cholinergic and related neurotoxicants during deployment, compounds that include PB pills, pesticides, and low levels of nerve agents. Research in human populations and in animal models has shown that low level exposure to cholinesterase inhibitors can be associated with persistent symptomatic illness and with brain and autonomic alterations that parallel the types of problems affecting Gulf War veterans. Of the many diverse types of exposures evaluated by epidemiologic studies of Gulf War veterans, only two—PB and pesticides—are consistently identified as significant risk factors for Gulf War illness. Gulf War studies have also reported significant dose-response effects for both PB and pesticides in relation to Gulf War illness. In addition, clinical studies of Gulf War veterans have identified persistent alterations in neurobehavioral and hypothalamic-pituitary-adrenal measures related to PB and pesticide exposure during the Gulf War.

Findings related to the effects of low-level nerve agent exposures in the Gulf War have been less clear and consistent. Epidemiologic studies that have evaluated nerve agent exposure in relation to Gulf War illness have yielded mixed results. Modeled nerve agent exposures resulting from the Khamisiyah

weapons demolitions have, however, been associated with increased rates of brain cancer mortality, and with significant differences in brain structure and cognitive function in Gulf War veterans, all in dose-response patterns.

Taken together, consistent evidence from studies of Gulf War veterans, along with supporting evidence from research in other human populations and in animals, provide strong support for both PB and pesticides as causal factors in Gulf War illness. Questions about the extent of exposure to chemical agents in the Gulf War, and mixed findings from epidemiologic studies do not allow clear conclusions concerning nerve agents as risk factors for Gulf War illness. However, indications that low level nerve agent exposures have had adverse neurological effects in Gulf War veterans and additional evidence from research in humans and animals exposed to sarin, indicate that low-level nerve agent exposure cannot be ruled out as a contributing factor in Gulf War illness, for the subset of veterans who were exposed.

## Recommendations

During the 1990-1991 Gulf War, military personnel were widely exposed to a variety of neurotoxic compounds that included pyridostigmine bromide pills, different types and dosages of pesticides and insect repellants, and low-level exposure to nerve agents. The chemical action of many of these compounds is similar, involving dysregulation of the neurotransmitter acetylcholine. Animal studies have also found that these neurotoxicants, in combination with one another, can have effects that differ from those of individual exposures.

Epidemiologic studies that have assessed independent effects of multiple exposures during the Gulf War have consistently identified only two as significant risk factors for Gulf War illness—pyridostigmine bromide and pesticides. Evidence relating low-level nerve agent exposure to Gulf War illness has been inconsistent, but studies have identified adverse neurological effects in Gulf War veterans potentially exposed to low levels of nerve agents as a result of the Khamisiyah weapons demolitions.

The Committee gives high priority to studies that further characterize specific effects of Gulf War-related neurotoxicant exposures, and recommends the following research:

- Studies that evaluate and characterize delayed and persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposures to pyridostigmine bromide, pesticides, insect repellants, and low-level sarin
- Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This might include studies that utilize technologies capable of detecting toxins or secondary metabolites retained for many years following exposure, studies that identify persistent or “downstream” changes in biochemical processes in relation to past neurotoxic exposures, and studies that identify delayed or persistent changes in the central nervous system and autonomic function associated with exposure to Gulf War-related neurotoxicants.

## Infectious Diseases in Gulf War Veterans

The Gulf War theater was home to insects and other pests that carried diseases that posed a potential health threat to American troops. In earlier times, high rates of infectious diseases such as sandfly fever and malaria had affected large numbers of military personnel stationed in the Middle East. A variety of organisms, some endemic to the region, can produce persistent conditions with symptoms that can, in some cases, resemble the symptoms of Gulf War illness—fatigue, cognitive difficulties, persistent diarrhea, muscle and joint pain, and unusual skin rashes. In addition to naturally acquired infections, there has also been concern that Gulf War veterans might have been exposed to biological warfare agents in theater. Information available before and since the Gulf War indicated that Iraq had developed biological weapons, and had readied them for use prior to the war.

Throughout Operations Desert Shield and Desert Storm, protective measures were fielded to minimize problems resulting from infectious diseases in theater. Vaccines were given to prevent some diseases and ample amounts of repellants and pesticides were supplied to ward off biting insects. Surveillance efforts and an advanced diagnostic laboratory were established to identify and contain infectious disease problems that emerged during deployment. As a result of these measures, some infections that had posed serious problems in earlier military deployments had little impact on Gulf War personnel. Other familiar infectious diseases were problematic in theater, primarily short-lived diarrheal and respiratory conditions. However, two comparatively novel infections—viscerotropic leishmaniasis and *mycoplasma fermentans*—have emerged as issues of concern in relation to Gulf War service. It is important to determine whether these or other infectious conditions may have contributed to the chronic health problems affecting Gulf War veterans.

### Infectious Disease in the Gulf War

As military operations geared up for the massive deployment of troops to Southwest Asia in 1990, there was concern among military medical officials about the potential health threat posed by infectious diseases endemic to the region. Historically, infectious diseases had caused widespread problems among troops deployed to the region.<sup>596,666,1249</sup> Medical officials were aware of the potential for diverse types of vector-borne infections such as sandfly fever and leishmaniasis.<sup>475,664</sup> Diarrheal diseases due to viral agents, shigella, *E. coli*, and other agents were also thought to pose a threat,<sup>475</sup> a concern born out in the early months of troop deployment.

Several published reports have documented rates of infectious diseases detected in Gulf War personnel during the war. It is one of the few areas for which surveillance data were collected during deployment. A surveillance system was established in theater to monitor injury and disease rates, including infectious diseases, in the nearly 40,000 Marine Corps personnel stationed in northeastern Saudi Arabia. Data were collected from most Marine and Seabee unit aid stations and analyzed on an ongoing basis throughout the deployment period.<sup>1607</sup> In the early months of Operation Desert Shield, the U.S. Navy established a state-of-the-art laboratory facility, the Navy Forward Laboratory, headquartered in Al Jubayl, Saudi Arabia. The work of this laboratory was to identify infections in clinical samples and to assist in detection of biological warfare agents.<sup>661,1607</sup> In addition, health surveys were administered to nearly 900 Marines in three front-line units prior to deployment and immediately after their return to the U.S. five months later. Blood samples were also collected pre- and post-deployment to identify rates of seroconversion resulting from a variety of pathogens in theater.<sup>1280</sup>

Previous summary reports from the RAND Corporation and the Institute of Medicine have evaluated, in some detail, the likelihood that Gulf War veterans developed chronic health problems as a result of infectious diseases acquired in theater. These reports focused most specifically on infectious organisms

endemic to the region and/or those that have the potential to cause chronic illness.<sup>608,687</sup> These included Q fever, hepatitis, malaria, brucellosis, West Nile virus, malaria, shigellosis, and leishmaniasis, among others. Both reports generally concluded that there is little persuasive evidence indicating that a large number of Gulf War veterans have suffered long-term adverse effects due to infectious diseases. The IOM report did identify a number of chronic conditions for which scientific evidence supports an association with infectious agents. However, the conditions identified have not been associated with Gulf War service. The RAND report called for further characterization of mycoplasma infection in Gulf War veterans and did not rule out the possibility that an as yet undetected chronic infection may underlie the illness of some symptomatic veterans.

**Gastrointestinal infections in theater.** The most common infectious conditions affecting troops during deployment were diarrheal diseases. In the early months of Operation Desert Shield, when large numbers of troops were just arriving in theater, multiple diarrheal disease outbreaks were reported. These early outbreaks appeared to be largely related to consumption of fresh produce purchased from countries in the region, since the incidence of diarrheal diseases fell dramatically when those foods were banned.<sup>664</sup> Surveys conducted during this period indicated that nearly 60 percent of ground troops had experienced at least one episode of diarrhea. Twenty percent reported that one or more diarrheal episodes had been severe enough to interfere with their work and had required them to seek medical attention.<sup>662,665</sup> In addition, nearly half of over 700 surveyed shipboard personnel reported having at least one diarrheal episode during Operation Desert Shield.<sup>1167</sup> Laboratory tests from all branches indicated that the major causes of diarrheal diseases in theater were enterotoxigenic *E. coli* and *shigella sonnei*.<sup>662</sup>

Although the rate of diarrheal diseases dropped after local produce was removed from troops' diets, gastrointestinal infections resulting from a variety of pathogens continued to affect personnel throughout the deployment period.<sup>662</sup> Late in 1990, gastroenteritis outbreaks due to Norwalk virus infection were identified in units throughout theater.<sup>665</sup> Spread of these infections was thought to relate to crowded living quarters during some phases of deployment and with rugged living and sanitary accommodations in units deployed in the desert. However, parasitic diseases were reported to be uncommon, with only nine cases of *giardia lamblia* identified among 422 Marines tested, and no cases of amebiasis or other intestinal parasitic infections.<sup>960</sup>

**Respiratory infections during deployment.** Acute upper respiratory infections were also commonly reported during the war. Results of an in-theater survey of over 2,500 ground troops stationed in northeastern Saudi Arabia between November 1990 and January 1991 indicated that over forty percent had experienced respiratory symptoms.<sup>1279</sup> Smokers and those with a history of respiratory disease were at highest risk for developing upper respiratory conditions. Respiratory conditions were also more common among troops housed in air-conditioned buildings than those living in tents. Surveillance of Marine Corps troops indicated that respiratory conditions continued to affect troops throughout the deployment period, particularly during periods of initial deployment and at other times when troops were most crowded together.<sup>664</sup>

A self limited respiratory condition associated with persistent cough was commonly reported by troops early in their deployment. This condition was given various names, including the "Kuwaiti cough" and the "Kuwaiti crud." It continues to be reported among personnel serving in the region today, and is thought to be a reaction to high levels of particulates associated with the fine, blowing sand in the region.<sup>1349</sup>

One of the earliest mentions of an unusual Gulf War-related illness described an upper respiratory condition that affected troops who occupied long-abandoned housing units near the village of Al Eskan, Saudi Arabia.<sup>832</sup> The condition, termed Al Eskan disease, was initially described as a pneumonitis that resulted from exposure to the fine sand, in combination with infectious agents, pigeon droppings, and other possible contaminants. Most of the initial cases were described as self-limited, resolving with

antibiotic treatment. This condition is considered further in relation to particulates, discussed later in the report.

**Sandfly fever.** Sandfly fever was a particular concern for military medical planners for personnel deploying to the region. This disease is caused by an arbovirus transmitted by sand flies, and had been a serious problem for military troops in the region during World War II.<sup>596,1149,1249</sup> Acute symptoms of sandfly fever can include headache, fever, malaise, nausea, pain in limbs and back, and leucopenia.<sup>687</sup> Acute infection can be followed by persistent symptoms of fatigue, weakness, and depression.<sup>395,475,687</sup> About 80 percent of a group of captured Iraqi soldiers tested for sandfly fever were found to be positive.<sup>1592,1593</sup> But no cases of sandfly fever were identified among U.S. personnel during the 1990-1991 Gulf War deployment.<sup>664</sup> In addition, serological testing of the nearly 900 Marines in front-line units after their return home did not identify a single positive case.<sup>1280</sup>

**Leishmaniasis.** Leishmaniae are intracellular trypanosome protozoa transmitted by the bite of the same sand flies that carry sandfly fever. There are different presentations of leishmaniasis that result from infection by different leishmania species. Cutaneous leishmaniasis is very common in the region, typically the result of infection by *L. tropica* or *L. major*. Only twenty cases of cutaneous leishmaniasis were identified among U.S. troops who served in the Gulf War, however, all resulting from *L. major* infection.<sup>666,838,953,1142</sup>

Systemic infection by leishmania, visceral leishmaniasis, is usually the result of infection by *L. infantum* or *L. donovani*. Symptoms of this condition, referred to locally as *kala-azar*, typically include fever, diarrhea, weakness, and hepatosplenomegaly.<sup>1142</sup> No cases of *kala-azar* were identified in U.S. troops during the Gulf War.<sup>953</sup> However, diagnosis of leishmaniasis is difficult since there are no validated blood tests for this infection. Definitive diagnosis requires that the parasite be cultured from lymph node or bone marrow biopsies, an invasive process that involves highly specialized laboratory techniques.<sup>1142</sup>

A form of visceral leishmaniasis that had not previously been recognized in the region was identified in 12 Gulf War veterans after their return from theater, as will be described in detail below. This condition, referred to as viscerotropic leishmaniasis, was associated with infection by *L. tropica*. The total number of Gulf War veterans affected by this atypical leishmaniasis is not known. Some infectious disease specialists have speculated that it is unlikely that there were large numbers of undetected cases<sup>666</sup> because sandfly fever, an infection transmitted by the same vector as leishmaniasis, was not identified in Gulf War personnel during the war. In addition, reports from entomological surveys of the Gulf War theater indicated that relatively few sand flies were in open desert areas where many troops were located.<sup>275</sup>

**Other infections in theater.** Another infectious disease of potential concern was brucellosis, which is endemic to the region<sup>30,346</sup> and transmitted primarily through contact with infected animals or ingestion of contaminated dairy products or meat. Chronic brucellosis has been described in the medical literature for over sixty years,<sup>414</sup> and is characterized by persistent and/or delayed onset of symptoms that resemble those of Gulf War illness—fatigue, cognitive difficulties, muscle and joint pain, and respiratory symptoms. Several reports have indicated that no cases of brucellosis were reported during deployment, but the extent to which veterans were tested for this infection in theater is not clear from available reports.<sup>660,1278</sup>

There were seven reported cases of malaria in Desert Storm troops,<sup>664,666</sup> three cases of Q fever identified in theater<sup>664</sup> and one case of Q fever identified in a Gulf War veteran shortly after his return.<sup>432</sup> Seventy-five Gulf War personnel were hospitalized for chicken pox during deployment.<sup>1431</sup> Only a few cases of viral hepatitis were identified by clinicians in theater,<sup>664</sup> and 16 cases were identified among specimens submitted to the Armed Forces Institute of Pathology.<sup>1460</sup> Just one case of West Nile virus infection was detected in theater,<sup>664,1278</sup> although an analysis of samples taken from 865 Marines found that 30 had

positive antibody titers to this virus, in both pre- and post- deployment sera.<sup>1280</sup> One death due to an infectious disease, meningococcal meningitis, was reported during the Gulf War.<sup>1813</sup>

All told, the impact of infectious diseases during the Gulf War was much less extensive than had been expected based on previous U.S. and U.K. deployments to the region.<sup>664</sup> Various preventive measures taken by the military can be credited for this success, including vaccinations for infections endemic to the region, extensive spraying and personal use of pesticides, repellants and other protective measures, rapid identification and response to identified infectious agents, and broad efforts to provide clean water and food to troops in theater.<sup>666</sup>

**Infectious diseases in current military operations.** Infectious diseases have been more problematic for troops serving in the region for Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).<sup>67,687</sup> Respiratory and diarrheal conditions during deployment were reported by about 70 percent of surveyed OIF personnel.<sup>1344,1345</sup> Over 60 percent reported diarrheal episodes severe enough to seek medical treatment.<sup>1345</sup>

Cutaneous leishmaniasis has also been more frequently identified in OIF personnel. As of 2005, over 1000 cases had been verified, most due to *L. major*.<sup>399,687,954</sup> A survey of troops reporting diagnosed conditions suggests that the actual number of cutaneous leishmaniasis cases may be more than twice that number.<sup>1344</sup> Five cases of visceral leishmaniasis have also been verified.<sup>67</sup> Additional concerns have been raised in relation to *acinetobacter* infections in veterans injured in theater, principally in association with wound contamination.<sup>67,1833</sup>

Early in Operation Iraqi Freedom, 19 cases of a serious idiopathic eosinophilic pneumonia were reported. Affected patients required intubation and mechanical ventilation, and two individuals died from the disease.<sup>222,802,1405,1833</sup> No causative infectious agent has ever been determined. In addition, about 2.5 percent of personnel who have served in OIF and OEF have been reported to have acquired tuberculosis (TB) infections during deployment, although no active disease cases have been identified.<sup>687,802</sup> Over fifty cases of malaria had also been diagnosed among personnel serving in Afghanistan, as of 2005.<sup>67,802</sup>

## Chronic Symptoms and Syndromes Associated with Infectious Disease

Most familiar infectious diseases produce an identifiable acute illness that is self-limited, and resolves in a matter of days or weeks. Some infections, however, can be associated with subclinical disease that is not readily apparent or clearly identified.<sup>430,953</sup> In addition, some infectious conditions may not resolve in the usual time span, instead leading to a post-infectious chronic illness associated with persistent symptoms, or a chronic infection with symptoms that come and go as the infection vacillates between latent and active states.<sup>209,796,875,1144,1777</sup> Other organisms produce illness that does not become evident for months, or even years, after the initial infection.<sup>83,475,725</sup> A number of organisms found in the Middle East can produce subclinical and/or persistent infections of these types, including leishmaniasis, Q fever, and brucellosis.<sup>44,430,432,475,725,955,1563</sup>

Symptoms associated with chronic infection or post-infectious conditions can be similar to those of Gulf War illness—fatigue, muscle and joint pain, impaired cognition, gastrointestinal problems, and skin rashes. Such problems have been well described in studies of symptoms and syndromes that develop after diverse types of infections, including respiratory infection, central nervous system infection, and gastrointestinal infection.<sup>150,201,209,348,796,1144,1718,1776</sup> Postinfectious symptoms of fatigue, pain, malaise, and diarrhea are associated with increased production of central and peripheral proinflammatory cytokines in both animals and humans.<sup>784,953,1777</sup>

## Evaluation of Infectious Diseases in Gulf War Veterans Since the War

Despite the potential for infection in theater by a variety of unfamiliar organisms and the many epidemiologic studies of Gulf War veterans, surprisingly few studies have evaluated infectious diseases among Gulf War veterans since their return from the war. With the exception of one study of Air Force veterans conducted by the U.S. Centers for Disease Control and Prevention (CDC),<sup>464</sup> most attention to infectious disease in Gulf War veterans has focused on two very different types of organisms associated with intracellular infection: leishmania protozoa and mycoplasma, a single celled bacteria-like organism.

**Leishmania infection in Gulf War veterans.** As previously described, 12 cases of viscerotropic leishmaniasis due to *L. tropica* infection were verified in Gulf War veterans after their return to the U.S. Cases were identified by infectious disease specialists at Walter Reed using rigorous methods.<sup>955,956</sup> None of the affected individuals had symptoms of cutaneous leishmaniasis, the more common manifestation of *L. tropica* infection. Affected veterans presented with diverse, nonspecific symptoms including fatigue, abdominal pain, cough, headache, swollen lymph nodes, and hepatosplenomegaly. Some had fever, some did not; one patient was completely asymptomatic.<sup>953,955,956</sup> Estimated incubation times for the earliest identified infections ranged from 1 to 14 months, but one case was not verified until two years after deployment.<sup>956</sup> About half of the cases were evaluated for leishmania infection because of veterans' presenting symptoms, others were identified when serologic surveys were conducted in their units. Five of the initial eight cases described in a published study occurred in just two units.<sup>955</sup>

The number of undetected cases of viscerotropic leishmaniasis in Gulf War veterans is unknown, as is the potential for persistent undetected infection to have contributed to Gulf War illness. As summarized in Table 1, only limited assessment of leishmania infection has been carried out since veterans returned from theater. No systematic studies, using well-validated testing methods, have assessed the prevalence of leishmania infection in Gulf War veterans. This is likely due, in part, to the lack of well-validated screening blood tests for this infection. Identification and verification of *L. tropica* infection requires bone marrow aspirates or lymph node biopsies and rigorous laboratory methods.<sup>220,954,1142</sup> The 12 identified cases were characterized as a result of referral to infectious disease specialists at Walter Reed Army Medical Center and active screening of their units. Systematic evaluation of a larger sample of defined groups of Gulf War veterans is required to determine the rate at which Gulf War veterans, or particular subgroups, are affected by *L. tropica* or other leishmania infections.

**Table 1. Post-War Assessment of Infection in Gulf War Veterans: Leishmaniasis**

<b>Study</b>	<b>Method</b>	<b>Key Findings</b>
DeFraites <sup>327</sup>	Serology	2 of 78 symptomatic GWV had elevated titers to <i>L. tropica</i>
Magill <sup>955</sup>	Culture	12 cases of viscerotropic leishmaniasis due to <i>L. tropica</i> infection
Kreutzer <sup>338,954</sup>	unknown	20 cases of cutaneous leishmaniasis identified in GWV
Bourdette <sup>159</sup>	ELISA assay under development	9% of 200 GWV tested positive for <i>L. tropica</i> : 10% of GWI cases vs. 4% of controls (p = 0.15)
Fukuda <sup>464</sup>	Serology	5% of 158 GWV tested positive for <i>L. tropica</i> or <i>L. donovani</i> , no difference by CMI case status
Koch <sup>824</sup>	Serology	None of 24 GWV with chronic gastrointestinal symptoms tested positive for leishmaniasis (species not identified)

Abbreviations: GWV = Gulf War veterans, CMI = chronic multisymptom illness

The most informative research of this type comes from an unpublished study conducted by VA's Portland Environmental Hazards Research Center. The study assessed the prevalence of *L. tropica* infection in a random sample of 200 Gulf War veterans, using an assay that was being developed and tested in a collaborative effort between DOD and a private company. The Portland study was funded in 1994 by the Department of Veterans Affairs. Results were reported at the 1998 federal Gulf War research conference<sup>159</sup> and also shared in detail with the Committee.<sup>1478</sup> The enzyme-linked immunoassay (ELISA) test used to detect evidence of *L. tropica* infection had previously been shown to detect reactivity to this organism in Gulf War veterans with culture-verified viscerotropic leishmaniasis, and in patients with cutaneous leishmaniasis.<sup>345</sup>

Results of the Portland study indicated that, overall, nine percent of 200 Gulf War veterans tested positive for *L. tropica*, with values more than three standard deviations above the mean found in healthy, nonveteran controls. Among the 167 veterans identified as either Gulf War illness cases or controls using the Oregon case definition, the infection rate was somewhat higher for cases. Ten percent of Gulf War illness cases tested positive, compared to four percent of Gulf War veteran controls (exact p value = 0.15).<sup>1478</sup> This trend for a possible association of illness with infection was intriguing, but not statistically significant in this small sample. No follow up studies were conducted, and no additional efforts to validate the ELISA assay used in the study have been reported. Like the 12 Gulf War veterans determined to have viscerotropic leishmaniasis using more rigorous methods,<sup>955</sup> no Gulf War veterans in the Portland study exhibited signs of cutaneous leishmaniasis.

The Committee looks forward to reviewing results from an ongoing VA study that will assess the prevalence of occult leishmania infection in Gulf War veterans using an assay being developed by investigators at the Omaha VAMC.

**Mycoplasma infection in Gulf War veterans.** Mycoplasma are small bacteria-like organisms that lack a cell wall but are capable of independent self-replication. Various mycoplasma species are known to produce human diseases affecting different organ systems.<sup>107,1730</sup> Beginning in the middle 1990s, Dr. Garth Nicolson and colleagues reported that a sizable proportion of symptomatic Gulf War veterans were infected by a particular mycoplasma species, *mycoplasma fermentans (incognitus)*.<sup>1118</sup> This organism had first been described in the late 1980s by Dr. S.C. Lo, who identified it in patients infected with HIV.<sup>920,922,924</sup> Subsequent studies, however, called into question the uniqueness of the *incognitus* strain, indicating that it was not distinct from other *M. fermentans*.<sup>1339,1351</sup>

Questions have been raised about whether *M. fermentans* is pathogenic in humans,<sup>107,381</sup> although serious illness has been described in persons with well-characterized infections.<sup>118,921,925</sup> One study has reported that a large proportion of adults (44%) have *M. fermentans* in their saliva,<sup>244</sup> suggesting this organism may be a common constituent of human saliva. *M. fermentans* is less commonly found in the blood of healthy individuals, however, with studies generally detecting it in 5-10 percent of non-diseased controls and adults in the general population.<sup>381,525,772,835,1114,1116,1123</sup>

Dr. Nicolson reported that *M. fermentans* infection in Gulf War veterans could not be reliably detected using conventional serological methods, since the infection was intracellular and not, over the long term, associated with an identifiable antibody response.<sup>1117</sup> He identified the infection in Gulf War illness patients using specialized DNA detection methods developed in his laboratory.<sup>1118</sup> A high proportion of symptomatic family members of ill Gulf War veterans were also reported to test positive for *M. fermentans*.<sup>1113,1117,1118</sup> In case series reports, Dr. Nicolson indicated that treating mycoplasma-infected veterans with multiple extended courses of antibiotics successfully improved or eliminated their symptoms.<sup>1118,1119</sup> Speculation concerning possible sources of this infection included naturally acquired infection, exposure to bioweapons in theater, and vaccine contamination.<sup>589,608,1112,1113,1115</sup>

**Table 2. Post-War Assessment of Infection in Gulf War Veterans: Mycoplasma**

<b>Study</b>	<b>Assay</b>	<b>Key Findings</b>
Nicolson 1996 <sup>1118</sup>	Nucleoprotein gene tracking	14 (47%) of 30 symptomatic GWV tested positive for mycoplasma; 0 of 21 healthy controls tested positive for mycoplasma
1998 <sup>1111</sup>	Nucleoprotein gene tracking	76 (46%) of 170 GWV with GWI tested positive for mycoplasma; 2 (5%) of 41 healthy controls tested positive
2002 <sup>1116</sup>	Forensic PCR	8 of 8 GWV with ALS tested positive for mycoplasma, 7 for <i>M. fermentans</i> ; 22/28 civilian ALS patients tested positive for mycoplasma, 3 for <i>M. fermentans</i>
2003 <sup>1114</sup>	Forensic PCR	45 (41%) of 110 GWV with GWI tested positive for mycoplasma, 37 for <i>M. fermentans</i> ; 6 (9%) of 70 healthy controls tested positive for mycoplasma, 2 for <i>M. fermentans</i>
Donta <sup>263,355</sup> 2004	PCR	546 (39%) of 1,387 GWV with GWI screened for VA antibiotic clinical trial tested positive for at least one of three mycoplasma species
Vojdani <sup>1732</sup> 1999	Multiplex PCR	33 (55%) of 60 GWV with GWI tested positive for mycoplasma, 20 for <i>M. fermentans</i> ; 24 (15%) of 160 healthy controls tested positive for mycoplasma, 13 for <i>M. fermentans</i>
Gray <sup>525</sup> 1999	Serologic testing	7(11%) of 64 GWV were mycoplasma positive prior to deployment and 11 (19%) developed new mycoplasma infection after deployment; 3 (9%) of 32 nondeployed era veterans were mycoplasma positive prior to the war and 4 (14%) developed new mycoplasma infection after the war. No sign. association between mycoplasma infection and development of symptoms.
Lo <sup>923</sup> 2000	Serologic testing	34 (5%) of 718 GWV referred to Phase II of the CCEP had antibodies to <i>M.fermentans</i> prior to deployment, 8 (1%) seroconverted after deployment; 116 (5%) of 2233 GWV who were not in CCEP had antibodies to <i>M. fermentans</i> prior to deployment, 26 (1%) seroconverted after deployment.

Abbreviations: PCR = polymerase chain reaction, CCEP = DOD Comprehensive Clinical Evaluation Program, GWV = Gulf War veterans, GWI = Gulf War illness, ALS = amyotrophic lateral sclerosis, sign. = statistically significant

These reports stirred considerable interest and controversy, and several studies have now been conducted to determine rates of mycoplasma infection in Gulf War veterans. (Table 2) Dr. Lo indicated that evidence of *M. fermentans* infection should be detectable in most individuals using serological methods. His large study found no difference in *M. fermentans* seropositivity or wartime seroconversion rates in ill Gulf War veterans examined in DOD's Gulf War registry program compared to veterans not evaluated in the program.<sup>923</sup> Similarly, a large study of Navy Seabees reported no difference in rates of detectable antibodies to mycoplasma between Gulf War and nondeployed era veterans, and no association of mycoplasma antibodies with symptoms.<sup>525</sup>

In contrast, three research groups have identified evidence of mycoplasma infection in a substantial number of ill Gulf War veterans using specialized DNA detection methods. Dr. Nicolson and colleagues, in several studies, have reported DNA evidence of mycoplasma infection in 40 to 45 percent of symptomatic Gulf War veterans, but less than 10 percent of healthy controls.<sup>1111,1116-1118</sup> Similarly, a study evaluating samples submitted to a clinical laboratory indicated that 55 percent of symptomatic Gulf War veterans tested positive for mycoplasma, compared to 15 percent of healthy controls.<sup>1732</sup> In addition, 39 percent of symptomatic Gulf War veterans screened for participation in VA's large antibiotic clinical trial tested positive for mycoplasma infection using polymerase chain reaction (PCR) methods.<sup>263,355</sup>

The general consistency of studies that have detected mycoplasma DNA in Gulf War veterans appears compelling. But inconsistencies between PCR results from several laboratories that tested for mycoplasma infection for VA's antibiotic trial raises some doubt about whether the methods used to

**Table 3. Post-War Assessment of Infection in Air Force Gulf War Veterans: CDC Study**

<b>Method</b>	<b>Organism Tested: Key Findings</b>
Serologic testing for antibodies in 158 Gulf War veterans	Anthrax protective antigen: 9% positive, no difference by CMI case status
	Botulinum toxin: 6% positive, no difference by CMI case status
	<i>Coxiella burnetii</i> : 4% positive, no difference by CMI case status
	Dengue virus: 10% positive, no difference by CMI case status
	<i>E. chaffeensis</i> : 3% positive, no difference by CMI case status
	<i>Leishmania</i> : 5% positive, no difference by CMI case status
	Sandfly fever virus: CMI cases 9% positive, controls 2% positive
	<i>Toxoplasma gondii</i> : 19% positive, no difference by CMI case status
	Yellow fever virus: 83% positive (due to vaccine), no difference by CMI case status
	No veterans tested positive for <i>Shistosoma</i> species or <i>S. stercoralis</i> , or for West Nile, Sindbis, Toscana, Karimbad, or Ishafan viruses
Stool specimen cultures in 158 Gulf War veterans	<i>Blastocystis hominis</i> : 8% positive, no difference by CMI case status
	Enteroviruses: 9% positive, no difference by CMI case status
	<i>Giardia lamblia</i> : 1% positive, no difference by CMI case status
	No veterans tested positive for <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i> , pathogenic <i>E. coli</i> , <i>Microsporidia</i> , <i>Cryptosporidium parvum</i> , <i>Cyclospora cayetanensis</i> , <i>Isopora belli</i> , or <i>Entamoeba histolytica</i> .

Source: Fukuda;<sup>464</sup> CMI = chronic multisymptom illness

detect mycoplasma infection—prior to and throughout the trial—were reliable, as discussed in the Committee’s 2004 report.<sup>353,403</sup> As a result, it is not possible to say with certainty whether mycoplasma infection is associated with Gulf War illness. Uncertainties stem from questions about the reliability of the DNA methods used, the lack of replication of DNA findings reported from undefined samples, and conflicting information provided by serological testing.

Still, it is important that three different research teams, using somewhat different methods, have found that 39-50 percent of symptomatic Gulf War veterans show evidence of mycoplasma DNA in their blood, particularly studies that found rates in symptomatic Gulf War veterans to significantly exceed those of healthy controls.<sup>263,1111,1732</sup> Mycoplasma infection is one of a limited number of objectively-measured parameters reported to distinguish symptomatic Gulf War veterans from healthy controls. It is therefore important to learn, more definitively, whether it is a factor in even a subset of Gulf War illness cases.

If *M. fermentans* infection rates were shown more definitively to be elevated in ill Gulf War veterans, important questions would still remain, however.<sup>353,1730</sup> It would be important to determine if identifiable illness or deployment subgroups have higher or lower rates of mycoplasma infection. It would also be necessary to clarify whether mycoplasma is a causal factor in Gulf War illness or an opportunistic infection, perhaps associated with general debilitation. Studies using PCR methods similar to those used in Gulf War studies have reported elevated rates of mycoplasma infection in civilian patients with CFS, fibromyalgia, ALS, and rheumatoid arthritis.<sup>552,1095,1114,1116,1123,1731</sup> Investigators have suggested that mycoplasma infection may underlie some of the symptoms common to these conditions,<sup>1732</sup> perhaps acting as a cofactor that may stimulate increased production of proinflammatory cytokines.<sup>1081,1730</sup> Reports have documented recovery from symptoms of persistent fatigue and debilitation in civilian patients with elevated levels of *M. fermentans* who were successfully treated with antibiotics.<sup>118,921</sup>

It is important to determine more conclusively if mycoplasma infections occur at excess rates in Gulf War veterans, if they are associated with Gulf War illness, and to further characterize the nature of any identified association. Unanswered questions about detection methods requires that more conclusive studies be conducted to determine if testing results in blinded samples obtained from symptomatic and healthy veterans can be independently confirmed by more than one laboratory. Available evidence does not provide a clear indication of whether mycoplasma infection does or does not have a role in Gulf War illness. If such an association is confirmed, it will be important to ascertain if mycoplasma infection represents an initiating, perpetuating, or opportunistic infection in relation to veterans' symptoms, and if its detection provides a useful objective marker that identifies a subset of ill veterans.

**CDC evaluation of infection in Air Force veterans.** The most extensive assessment of diverse types of infection following Gulf War service comes from a study conducted by the U.S. Centers for Disease Control and Prevention (CDC).<sup>464</sup> Results are summarized in Table 3. The study evaluated serum and stool samples in 158 Gulf War veterans from a single Air Force National Guard unit: 99 who met criteria for chronic multisymptom illness (CMI) and 59 controls. Although laboratory testing of Gulf War personnel in theater and immediately after their return had identified no cases of sand fly fever, six percent of veterans in the CDC study tested positive. Veterans with CMI had a five-fold higher rate of seropositivity than controls, but this excess was not statistically significant in this small sample. Other identified infections generally occurred at low rates and affected similar proportions of veterans with CMI and controls.<sup>464</sup>

**Table 4. Post-War Assessment of Infection in Gulf War Veterans: Herpes Viruses**

<i>Study</i>	<i>Method</i>	<i>Key Findings</i>
Carver <sup>214</sup> 1994	Serology in 37 Gulf War veterans with CFS	EBV viral capsid IgG and nuclear antigen antibodies: 100% positive EBV early antigen and nuclear antigen antibodies: 68% positive EBV viral capsid IgM: 5% positive
Milner <sup>1050</sup> 1994	Serology in 85 symptomatic Gulf War veterans	49% positive for recent or reactivated EBV 39% positive for recent or reactivated CMV
Wallace <sup>1746</sup> 1999	PCR of PBMCs of 46 GW veterans with CFS, 32 healthy GW veterans	HHV6 DNA detected in 0 sick, and 0 healthy GW veteran HHV7 DNA detected in 48% of sick and 44% of healthy GW veterans EBV DNA detected in 1 sick, 0 healthy GW veterans No CMV DNA detected in sick or healthy veterans
Vojdani <sup>1734</sup> 2004	Serology in 100 GW veterans with GWI, 100 healthy controls	Veterans with GWI had significantly elevated IgM titers for EBV viral capsid antigen and IgG titers for CMV, HSV1, HSV2, HHV6 and VZV.

Abbreviations: EBV = Epstein-Barr virus, CMV = cytomegalovirus, HHV = human herpes virus, HSV = herpes simplex virus, VZV = varicella zoster virus, PCR = polymerase chain reaction, PBMC = peripheral blood mononuclear cells  
CFS = chronic fatigue syndrome, GWI = Gulf War illness

**Herpes virus infection in Gulf War veterans.** Herpes viruses are known to produce chronic infection that can lie dormant or become reactivated under a variety of conditions. In the large U.S. Gulf War clinical study, veterans who reported having mononucleosis, Epstein-Barr virus (EBV) infection, prior to the war had nearly three times the rate of chronic multisymptom illness as veterans who had not had mononucleosis.<sup>142</sup> Several herpes viruses have been associated with persistent symptoms and syndromes similar to those affecting Gulf War veterans.<sup>7,186,828,887</sup> One year after their return from theater, 73 percent of 37 Indiana reservists who met criteria for chronic fatigue syndrome (CFS) showed evidence of either active EBV infection or reactivation of a previous EBV infection.<sup>214</sup> Investigators speculated that

this activation may have resulted from deployment-related factors such as reduced sleep, prolonged exposure to sun and high temperatures, or psychosocial factors.

Findings from studies that have evaluated rates of herpes virus infections in Gulf War veterans are summarized in Table 4 and, as shown, have been variable. A 1994 clinical series reported by a VA investigator indicated that, among 85 symptomatic Gulf War veterans, 49 percent showed evidence of recent or reactivated EBV infection and 39 percent had evidence of cytomegalovirus (CMV) infection. A later study from New Jersey investigators evaluated antibody titers for human herpes virus six (HHV6) and EBV in 46 Gulf War veterans with CFS, and tested sick veterans and controls for PCR evidence of infection by multiple herpes viruses. No serological or PCR differences were found between veterans with CFS and healthy controls.<sup>1746</sup> In contrast, a study that compared clinical laboratory samples from 100 symptomatic Gulf War veterans and 50 healthy controls found that Gulf War veterans had significantly higher antibody titers to multiple herpes virus antigens, including EBV viral capsid antigen, CMV, HHV6, herpes simplex types 1 and 2, and varicella zoster virus.<sup>1734</sup>

Very little additional information is available concerning infectious diseases in Gulf War veterans. Clinical evaluation of a sample of over 350 Gulf War veterans from the Pacific Northwest identified none with HIV, hepatitis B, hepatitis C, or syphilis, and only one with an elevated Lyme disease titer.<sup>160</sup> Gulf War registry programs have provided limited information, since registry protocols did not require veterans to be screened for specific infectious diseases. The most frequently identified infections in both registries were fungal infections of the feet, nails, and groin area.<sup>1651</sup> In addition, a 1992 Army epidemiologic investigation of unexplained symptoms in an Indiana Army Reserve unit included a limited number of tests for infectious diseases. Serologic testing was conducted on six symptomatic soldiers for brucellosis and two for *Borrelia burgdorferi*, but none tested positive. Stool samples were analyzed for seven soldiers with diarrhea: none were positive for enteric pathogens, but two were positive for *Blastocystis hominis*.<sup>327</sup>

### Antibiotic Treatment of Gulf War Illness

A 48-year old U.S. Marine Corps officer, attached to the Central Command staff, was deployed in Saudi Arabia at ODS Central Command Headquarters. He examined SCUD (SS-1) missile impact sites. Within 10 months after his return to the United States he presented with chronic fatigue, skin rashes, diarrhea, headaches, aching joints, muscle pain, fevers, sleep problems, nausea, vision problems, memory loss, and dental problems. .... After two cycles of doxycycline, he completely recovered.

- Case report, antibiotic treatment of Gulf War veteran<sup>1118</sup>

In theory, insights concerning a possible link between infectious disease and Gulf War illness could be provided by results obtained when ill veterans are treated with antibiotics. As detailed in the first section of this report, two case series and two clinical trials have assessed the effectiveness of prolonged and/or high-dose antibiotic therapy for the chronic symptoms of Gulf War illness. The two case series reports from Dr. Nicolson and colleagues both indicated that repeated courses of antibiotics provided substantial improvement for symptomatic Gulf War veterans.<sup>1118,1119</sup> In response to these reports, VA conducted a large multi-center randomized trial of a 12 month course of doxycycline treatment for Gulf War illness in veterans who tested positive for mycoplasma infection.<sup>355</sup> Study results indicated that doxycycline therapy provided, at most, short term benefit, but no sustained improvement in veterans' functional status or symptoms. However, as described in the Committee's 2004 report, a number of methodological issues raised questions about the degree to which the study reliably addressed questions concerning detection and treatment of mycoplasma infection in symptomatic veterans.<sup>1268</sup>

A second federally-funded trial of antibiotic therapy was conducted by the Louisiana Medical Foundation, directed by Dr. Edward Hyman.<sup>670</sup> Results of this randomized, placebo-controlled trial of an

unconventional, high dose antibiotic regimen were never published. As presented to the Committee by Dr. Hyman's collaborators, however, the treatment appeared to provide marked improvement for veterans with Gulf War illness.<sup>332</sup> But questions surrounding the theory underlying the treatment,<sup>672,1455</sup> as well as the lack of peer review and publication of study results also leave major uncertainties about the utility of this protocol for Gulf War illness. So, although reports suggesting that antibiotic treatments provide benefit for ill Gulf War veterans are intriguing, they have not thus far provided clear insights regarding a potential role for infections in the pathophysiology of Gulf War illness.

## Biological Warfare Agents in the Gulf War

Questions have been raised about whether Gulf War veterans might have been exposed to biological weapons during deployment, and if such exposures could account, at least in part, for veterans' persistent symptoms.<sup>1559,1688</sup> Government and research reports that have reviewed the issue have generally considered this to be unlikely, based on information available from DOD, the Central Intelligence Agency (CIA), The United Nations Special Commission (UNSCOM), and other sources.<sup>666,1227,1616,1690,1749</sup> The Committee has identified little information—scientific or anecdotal—that suggests any association between biological weapons exposure and Gulf War illness. But evidence that directly addresses this issue is limited, due in part to limits in biological detection capabilities in theater and the postwar loss of military logs that recorded suspected biological events during the war.<sup>1602</sup>

No cases of acute or persistent disease due to identified biological warfare agents in the Gulf War have been reported. Therefore, the central outstanding question is whether exposure to still-unidentified biowarfare agents in theater could account for any cases of Gulf War illness. Determining if this is a reasonable possibility requires two types of information. The first relates to whether Iraq possessed one or more bioweapons that could potentially cause chronic symptoms similar to those of Gulf War illness. The second concerns the likelihood that Gulf War veterans were exposed to such agents.

**Iraqi biological weapons.** Iraq denied having biological weapons after the Gulf War, and actively concealed evidence related to its biological weapons program.<sup>693</sup> Iraqi officials were forced to acknowledge these weapons in 1995, when information came to light from U.N. inspections and the defection of Husayn Kamil, who had overseen Iraq's biological weapons program.<sup>693</sup> It has now been documented that Iraq had an active biological weapons program prior to and during the Gulf War. The program involved multiple types of pathogens—bacterial, viral, and fungal, as well as toxins—that were in various stages of research, production, and weaponization.<sup>693,1301,1494,1839</sup>

Prior to the Gulf War, bombs and missiles used for chemical weapons were adapted as delivery systems for biological weapons, and pesticide sprayers were adapted for dispersion of biological agents and installed on aircraft and land vehicles. These delivery systems have been described as inefficient and inaccurate, but capable of causing harm.<sup>693,1839</sup> Information obtained after the war from United Nations inspectors and Iraqi informants indicates that Iraq had loaded anthrax, botulinum toxin, and aflatoxin into missiles and bombs in preparing for the Gulf War<sup>1697,1749</sup> and that Saddam Hussein had authorized the use of biological weapons in relation to certain circumstances and targets.<sup>693,1616</sup> Central Intelligence Agency reports indicate that during the war, warheads containing anthrax were deployed to four locations in Iraq.<sup>693,1749</sup>

As described in relation to chemical weapons, biological weapon exposures might conceivably have occurred as a result of Iraq's offensive use of biological agents or inadvertently as a result of Coalition troops' handling or destruction of Iraq's biological weapons. Government investigations have consistently concluded, however, that it is unlikely that biological agents were released during the war, either as a result of Iraq's offensive use or due to Coalition bombing of biological weapons sites.<sup>1589,1616,1749</sup>

Anthrax causes an acute and serious upper respiratory condition that is often fatal; it is unlikely that an anthrax exposure event of any size would go undetected. Further, anthrax infection is not known to be associated with a persistent constellation of symptoms similar to those of Gulf War illness. Botulinum toxin is a neurotoxin, one of the deadliest poisons known. Exposures in theater, even at very low levels, would likely have caused noticeable casualties. Botulinum toxin is also not known to cause a persistent multisymptom condition in those who survive acute disease following exposure.

Iraq's development of aflatoxin as a bioweapon was not known until after the war and has puzzled observers.<sup>693,1494,1616,1839</sup> Although long-term exposure can cause cancer and adverse effects on liver and kidney function, aflatoxin has little identified utility for killing or disabling an enemy during war. The Iraq Survey Group speculated that Iraq may have overstated its development of aflatoxin to conceal production of other agents. It also indicated that Iraq had tested aflatoxin in combination with incapacitating chemical agents—CS (tear gas) and CN (chloroacetophenone)—as well as mustard. No evidence was identified, however, that combined biological/chemical weapons were produced or fielded.<sup>693</sup>

Two additional biological agents that were potentially available to Iraq are known to cause chronic problems that have similarities to Gulf War illness. T-2 mycotoxin, a type of trichothecene mycotoxin, was developed by the Soviets after World War II.<sup>1616</sup> Reports have suggested it may have been used by communist forces in Laos, Cambodia, and Afghanistan during the 1970s and possibly by Iraq, in combination with mustard gas, in the Iraq/Iran War in the 1980s.<sup>605,736,1301,1561</sup> Acute symptoms include skin redness and blistering, eye irritation, respiratory problems, vomiting and diarrhea, fatigue, and muscle pain. Long term sequelae include immune suppression, cognitive problems and diarrhea.<sup>298</sup> The RAND report on chemical and biological weapons concluded that acute exposures would not likely have gone undetected, however, due to the extreme sensitivity of skin and eyes to this substance.<sup>74</sup>

*Brucella* species are also known to have been developed as biological weapons by the Soviet Union.<sup>881</sup> Iraq was known to possess cultures of at least two species, and to have conducted research specifically on *B. abortus*.<sup>693</sup> *Brucella* can cause a subclinical infection or a delayed symptom complex that resembles Gulf War illness. Symptoms may include fever, headache, weakness, fatigue, joint pain, gastrointestinal symptoms, altered mood and cognition, and respiratory problems.<sup>574</sup> However, there has been no reported evidence, obtained prior to or after the war, indicating that Iraq mass-produced or weaponized brucella.

**Detection of biological agents in theater.** A number of measures were taken to detect and identify biological agents during the Gulf War. These focused primarily on anthrax and botulinum toxin, the two agents believed by military planners to have been weaponized by Iraq. Vaccines for both agents were provided to U.S. troops, as supplies allowed. In theater, biological teams were stationed in 12 locations, equipped with air sampling and biological detection equipment.<sup>1616</sup> Monitoring units collected airborne particulates and tested samples for the presence of anthrax and botulinum toxin. Identification of other agents required samples to be submitted to laboratories in theater or the states. Field samples were also collected from dead animals, water, and soil. Of 943 air samples taken in the field, 14 were initially identified as being positive for anthrax and three for botulinum toxin. All were later determined to be false positives after more definitive testing at military laboratories in Saudi Arabia.<sup>1616</sup> Other samples testing positive for chemical or biological agents in theater were sent to Fort Detrick for more definitive testing. Although specific results of these tests were not made available to OSAGWI investigators, DOD has reported that the samples “yielded no red flags identifying or confirming biological warfare agents.”<sup>1616</sup>

The Coalition's ability to detect biological agents in theater was limited, however. Air sampling was done primarily during night time hours in the 12 selected areas, and only anthrax and botulinum toxin could be detected in the field.<sup>1616</sup> Even for those agents, detection capabilities have been described as rudimentary.<sup>1227,1670,1688,1690</sup> For example, monitoring equipment could not reliably detect aerosols

containing anthrax or botulinum toxin, the form that would be expected in relation to an exploding missile used in a biological attack.<sup>1839</sup> The OSAGWI investigation concluded that it was not possible to categorically rule out any use of biological weapons in theater. However, data and information from multiple sources had not provided any confirmed evidence that biological agents had been released nor that any troops had been exposed.<sup>1616</sup>

It is not certain that Iraqi disclosures and subsequent investigations have provided a complete picture of Iraq's biological program. In addition, U.S. capabilities for detecting biological agents in theater were limited. But available results from air monitoring, environmental samples, and clinical testing provide no indication that Gulf War veterans were exposed to, nor that they became ill as a result of, biological weapons during deployment. It also appears unlikely that undocumented exposure to biological agents that may have been present in theater would have resulted in the types of chronic symptoms associated with Gulf War illness. So, although it is not possible to rule out the possibility of discrete incidents involving exposure to unknown agents, there is currently no basis for suggesting a link between biological weapons and Gulf War illness.

**Summary. Infectious diseases in Gulf War Veterans.** Acute respiratory and diarrheal diseases affected a sizable proportion of military personnel during the Gulf War. However, Gulf War personnel were minimally affected by diseases endemic to the region that had historically been problematic for troops deployed to the Middle East. No evidence has indicated that Gulf War veterans were exposed to biological weapons during the war, or that Gulf War illness is the result of such exposures. Some pathogens to which veterans may have been exposed in theater can produce chronic conditions similar to Gulf War illness. But relatively few studies have systematically evaluated Gulf War veterans for evidence of active or latent infection by those organisms. Primary interest has focused on two intracellular infections: an atypical systemic leishmaniasis caused by *L. tropica* and infection by *mycoplasma fermentans*.

Viscerotropic leishmaniasis has been confirmed in 12 Gulf War veterans, but the total number of cases is not known. This infection is difficult to identify and its prevalence in Gulf War veterans or association with Gulf War illness has not been systematically evaluated. Several studies have identified evidence of mycoplasma DNA in about 40 percent of symptomatic Gulf War veterans, a rate significantly higher than that found in healthy controls. But uncertainties about test reliability and conflicting results from other studies have called these findings into question. Therefore, questions remain concerning rates of infection by both leishmania and mycoplasma and their potential association with Gulf War illness.

## Recommendations

Because of unanswered questions related to possible associations between Gulf War illness and persistent infections in Gulf War veterans, the Committee recommends the following research:

- Using the most reliable assay methods available, determine the rate of leishmania infection, particularly *L. tropica* infection, in veterans with Gulf War illness and healthy controls
- Using the most reliable DNA and serological assay methods available, determine the rate of mycoplasma infection, particularly *M. fermentans*, in veterans with Gulf War illness and healthy controls

## Other Exposures in Theater

### Sand, Tent Heaters, Solvents, Jet Fuel, CARC, and Contaminated Food and Water

In the 17 years since Desert Storm, many possible causes or contributors to Gulf War illness have been suggested. In addition to the Gulf War-related exposures previously described, the Committee reviewed available information on the health of Gulf War veterans in relation to sand and particulates, petrochemical exposures other than oil well fires (tent heaters, solvents, jet fuel), chemical agent resistant coating (CARC paint), and contaminated food and water. Each of these exposures have the potential to cause adverse health effects, some chronic, and may have relevance to Gulf War veterans' multisymptom illness. They are considered in aggregate here in considerably less detail than exposures previously discussed for a number of reasons. For some, there was little systematically-collected information concerning their relationship with chronic symptoms or multisymptom illness in Gulf War veterans. In addition, some of the exposures considered here, despite their potential for causing adverse effects, are unlikely to have contributed to Gulf War illness for most ill veterans based on what is known about the pattern and extent of veterans' exposures during deployment. This would include exposures with known toxic effects that were encountered by a very limited number of Gulf War veterans, and exposures widely encountered during deployment, but in patterns similar to those associated with other deployments or military service at home.

The general approach used in evaluating each of these exposures, although described in less detail, was the same as that used for other Gulf War exposures. The Committee reviewed available information about the extent and patterns of the exposure in theater, what is known generally from human and animal studies about toxic effects of the exposure, and information from studies of Gulf War veterans concerning associations between the exposure and symptom complexes, multisymptom illness, and other health outcomes.

### Sand and Particulate Exposures in the Gulf War

Images of the dense, black smoke generated by burning oil well fires in Kuwait are quite familiar, but veterans also returned home with dramatic stories of blinding sandstorms in the desert that could last for many hours, sometimes days. On some days, sandstorms were extreme enough to drastically reduce visibility and require personnel to don protective goggles and/or tie cloths over their noses and mouths to continue their duties.<sup>1349,1625</sup> Levels of airborne particulates in Kuwait are among the highest in the world,<sup>1578</sup> and rates of asthma and other respiratory conditions in the local population are substantially higher than in the U.S.<sup>1621</sup> Newly arriving troops often developed what is commonly called the "Kuwaiti crud," a limited-duration cough or flu-like condition resulting from breathing in high levels of particulates.<sup>903,1349</sup> Airborne particulates were especially a problem during the spring and summer months, due to the intensity of the shamal winds blowing in the region.<sup>1625</sup>

Military personnel in the Gulf War were exposed to particulates from multiple sources, including the high, naturally occurring background levels in the region, particulates in the smoke generated from burning oil well fires, particulates in tents when tent heaters were in use, and additional particulates associated with engine exhaust and industrial pollution in the region. Air quality monitoring conducted by the Army at locations throughout Kuwait and Saudi Arabia beginning in May 1991 indicated that levels of particulates smaller than 10 microns were many time higher than those considered safe by U.S. air quality standards.<sup>1587,1625</sup> The Department of Defense estimated that troops in the region would have been exposed to elevated levels of particulates for an average of 153 days.<sup>1625</sup> Air monitoring indicated

that, during the months that oil fires were burning, 75 percent of measured particulates were due to sand.<sup>1587</sup>

Health effects of particulates vary with the concentration and duration of exposure, and with the physical and chemical properties of particles—their size, shape, and chemical composition. A number of health concerns relate particularly to smaller size particulates. Those between 2.5 and 10 microns in diameter can be inhaled into and accumulate in the lungs; those between 0.1 and 2.5 microns can lodge more deeply into the alveoli; and those smaller than 0.1 microns (also known as ultrafine particulates) can cross the pulmonary epithelium and enter the general circulation. The sand in the Kuwait region is extremely fine—almost powder-like—and has often been described as being more like dust than the types of sand more familiar to Americans. It also has a relatively low silica content. A 2000 report commissioned by DOD concluded that exposure to airborne particulates in the region was not expected to produce long term silica-related health effects.<sup>1536</sup>

Exposure to high levels of particulates have most commonly been associated with acute and chronic respiratory and cardiovascular effects, including exacerbation of preexisting conditions.<sup>1045,1201,1220</sup> Temporary spikes in urban levels of airborne particulates result in increases in emergency room visits and mortality for individuals who are most vulnerable.<sup>109,626,856</sup>

Recent animal studies also indicate that inhaled ultrafine particulates are associated with systemic immune and inflammatory effects.<sup>492,1703</sup> After entering the circulation from the lungs, ultrafine particulates access a variety of tissues, including the liver and the brain.<sup>1107,1135,1136</sup> Airborne ultrafine particulates may also enter the brain directly through the nose via olfactory neuronal pathways, where they can accumulate and, according to several recent studies, produce neuroinflammatory effects.<sup>147,206,397,1135,1719</sup> This is particularly of interest in light of research presented to the Committee indicating that DU entry into the brain through the nose was enhanced in the presence of nasal inflammation,<sup>896</sup> presumably a common condition in Kuwait as a result of the high levels of airborne particulates.

In 1992, the first published report of an unexplained illness in Gulf War veterans described a condition that affected troops housed in abandoned apartment buildings in Al Eskan village, Saudi Arabia, which had not been inhabited for the previous decade.<sup>832</sup> The report indicated that about two-thirds of the soldiers became ill with respiratory and gastrointestinal symptoms within 72 hours of arriving in quarters. Although most recovered with antibiotic treatment, some relapsed and were subsequently unresponsive to treatment. Investigators hypothesized that the condition had resulted from troops' exposure to the mix of fine dust and pigeon droppings that covered their living area, triggering immunopathologic reactions and a unique pneumonitis dubbed "Al Eskan disease." Their analysis of the sand in the area identified it as a very fine dust (0.1 – 0.25 microns) from which bacteria and fungi were isolated. Investigators hypothesized that this dust may have acted as a carrier, enhancing delivery of pathogens and/or chemical exposures during deployment and exacerbating their effects.<sup>831,833</sup> No data were provided, however, specifically demonstrating this carrier effect nor identifying health effects related to the combined particulate/toxin exposure. More recently, scientists at the Naval Medical Research Center have undertaken detailed investigations of the characteristics and composition of the sand in the Kuwait region, and its potential to cause adverse health effects.<sup>942</sup> It is hoped these data will provide additional insights regarding the "dirty dust" hypothesis put forward in the wake of the Gulf War.

As described, sand and particulate exposure were ubiquitous throughout the Gulf War theater. Consequently, very limited useful information can be obtained from epidemiologic assessment of associations between particulates and multisymptom conditions. About half of Navy Seabees and Australian veterans who served in the Gulf War reported they experienced sandstorms during deployment,<sup>524,790</sup> and a similar proportion of Air Guard troops reported they spent considerable time sandbagging or digging in sand while in theater.<sup>1124</sup> As shown in Appendix A-10, these variables were

associated with elevated rates of chronic symptoms and multisymptom illness in unadjusted analyses but, after adjustment for multiple exposures, sandstorms remained a significant risk factor for Gulf War illness only for Navy Seabees.<sup>527</sup> The location-related pattern of Gulf War illness observed in several studies<sup>692,1236,1476</sup> is inconsistent with the widespread presence of blowing sand and high levels of particulates throughout the region. In addition, if blowing sand and particulates were a primary cause for Gulf War illness, high rates of unexplained multisymptom conditions would be expected among personnel serving in the current Iraq War, which has thus far not been the case.<sup>631</sup>

In summary, Gulf War veterans were exposed to extremely high levels of airborne particulates from multiple sources during deployment. Most particulates, including fine and ultrafine particles, were due to the high levels of fine, blowing sand in the region. Animal studies have recently found that inhaled ultrafine particulates may have immune and inflammatory effects that were previously unrecognized, both systemically and in the brain. Many questions remain, however, concerning what implications these findings may have with respect to chronic brain and behavioral effects. Specific to the Gulf War experience, little is known about the potential for synergistic effects between inhaled particulates and other inhaled toxicants during the war. Given the many unanswered questions related to possible neuroinflammatory and synergistic effects of inhaled ultrafine particulates, it is unknown whether they may have contributed to chronic ill health in veterans in combination with other Gulf War exposures. However, given the widespread of exposure to sand and particulates in the Gulf War and in the current Iraq War, the Committee concludes they are unlikely to be a primary cause of Gulf War illness for most affected veterans.

### **Exposure to Combustion Products from Tent Heaters in the Gulf War**

Troops in the Gulf War theater experienced diverse living conditions during deployment. Some personnel, for varying periods of time, might have slept under the stars or under their tanks in the desert, been housed in tent cities erected for U.S. troops, camped in abandoned—sometimes waste infested—housing areas in Southern Iraq, or housed in relatively comfortable accommodations in apartment buildings or hotels. For those in tents during the colder months, November 1990 through April 1991, tent heaters were used to keep warm. Different fuels were burned in these heaters—jet fuel, diesel fuel, and kerosene—and reports indicate that heaters were typically unvented, allowing potentially harmful exhaust to accumulate inside tents. Current policy directs that only Army-approved, vented tent heaters are to be used in areas where people sleep and specify kerosene as the preferred fuel.<sup>1580</sup>

Fuel burned in heaters emits a complex mixture of gaseous compounds and particulates, similar to those described in relation to oil well fires—carbon monoxide (CO), carbon dioxide (CO<sub>2</sub>), nitrous oxides (NO<sub>x</sub>), sulfur oxides (SO<sub>x</sub>), volatile organic compounds, polycyclic aromatic hydrocarbons, and particulates of varying composition and size. Actual exposure levels experienced by troops inside tents would have varied with the type of heater used, the fuel burned, and the duration of time the heater was used. In cold weather, typical exposures might have occurred for a continuous 8 hours each day, for weeks to months. Two studies from Lovelace Respiratory Research Institute characterized emissions associated with three types of unvented heaters and three types of fuels used in the Gulf War, in simulation experiments conducted using vinyl-backed Army tents.<sup>238,1838</sup> Results indicated that when tent doors were closed, CO, NO<sub>x</sub> and SO<sub>x</sub> exceeded established air quality standards.<sup>1838</sup> Particulates, mostly in the ultrafine range (0.2 – 0.3 microns), were also in excess of established standards and contained high levels of sulfur, ammonium, and carbon.<sup>238</sup>

Adverse health effects potentially resulting from prolonged inhalation of fuel combustion products were previously described in relation to oil fires and particulates. Briefly, high levels of inhaled particulates can have adverse respiratory effects and ultrafine particulates may also be associated with neurological effects.<sup>147,1136</sup> Carbon monoxide impairs oxygen delivery to organs and tissues and can lead to

neurological and cardiovascular effects, even death at extremely high levels. Other combustion-related pollutants such as NO<sub>x</sub> and SO<sub>x</sub> are also associated with respiratory effects. The Institute of Medicine's report on *Fuels, Combustion Products, and Propellants* found that evidence supports an association between fuel combustion products and lung cancer,<sup>684</sup> but no excess of lung or other respiratory cancers have been reported in Gulf War veterans. Four individuals are reported to have been hospitalized for carbon monoxide poisoning during the Gulf War.<sup>1813</sup>

Epidemiologic studies indicate that a large proportion of Gulf War veterans used tent heaters during deployment. Fifty to seventy percent of U.S. Army veterans<sup>1239,1708,1804</sup> but only 21 percent of Navy Seabees reported using tent heaters.<sup>524</sup> Several studies have evaluated rates of symptom complexes and multisymptom illness among veterans who reported using tent heaters during the war, as summarized in Appendix A-5. In analyses that did not adjust for effects of other exposures in theater, use of tent heaters was associated with higher rates of multisymptom conditions in three studies, with odds ratios ranging from 1.9 for multisymptom illness to 2.8 for multiple chemical sensitivity.<sup>1264,1466,1698</sup> Three studies assessed this association, in two veteran populations, after adjusting for additional exposures in theater. Studies of the Fort Devens Army cohort found that the use of tent heaters was significantly associated with both cardiovascular and pulmonary symptoms,<sup>1239</sup> and also with a modest excess of multisymptom illness (OR = 1.4).<sup>1804</sup> There was no association between use of tent heaters and Gulf War illness in the Navy Seabees study.<sup>527</sup>

Taken together, this information indicates that a substantial proportion of personnel who served in the Gulf War were potentially exposed to excess levels of particulates and air contaminants for varying periods of time as a result of using unvented tent heaters. This exposure was more prevalent in Army than Navy personnel and any effects resulting from tent heaters might be more pronounced in Army veterans. It is unknown whether exposure to particulates and other contaminants produced by tent heaters may have interacted synergistically with other exposures in theater, including other sources of particulates and airborne pollutants in theater. The very limited amount of information available from epidemiologic studies does not provide a clear indication of whether tent heaters may have contributed to Gulf War illness for some individuals, but indicates that if there is an association, it is likely to be modest.

## Organic Solvents in the Gulf War

The term "solvents" refers to a broad range of compounds of different types that have the capacity to dissolve or dilute other chemicals. Organic solvents are widely used in the military and throughout society. There are no government reports documenting the specific types of solvents used or the degree of solvent exposures that occurred during the Gulf War. In the Institute of Medicine's *Gulf War and Health, Volume 2: Insecticides and Solvents*, the IOM panel reports that it gathered information from veterans and the Department of Defense to generate a list of 53 individual solvents likely used during the Gulf War.<sup>682</sup> The list includes a diverse array of compounds used in painting, vehicle maintenance, equipment repair, and cleaning and degreasing. There is little information concerning whether or how the solvents used by military personnel during the Gulf War might have differed from solvents used in other deployments or stateside, with the exception of jet fuels and CARC paint, which are discussed separately. In epidemiologic studies and registries, at least half of Gulf War veterans have consistently reported some exposure to "solvents," as a general category, during deployment.<sup>751,788,839,1698</sup>

Toxic effects of individual solvents vary with the specific type of compound, exposure route, and dosage. Solvent exposures often involve mixtures of multiple compounds, the combined effects of which are not well understood. The central nervous system is a primary target of solvents, although some solvents are known to have hematological effects or are associated with liver disease, renal toxicity, reproductive effects, and cancers.<sup>89</sup> Excess solvent exposure has long been associated with reports of toxic encephalopathy, and specifically with a neurasthenic-type syndrome that resembles Gulf War

illness.<sup>61,532,578,913,1110</sup> Symptoms typically include chronic headache, memory impairment, balance problems, fatigue, and mood changes. Subtle indications of neuropathology may also be identified with neurocognitive testing and brain imaging studies.<sup>33,595,1781</sup> The existence of a unique syndrome (e.g. “painters’ syndrome”) associated with chronic solvent exposure remains somewhat controversial, however.<sup>31,940,1554,1555</sup> Encephalopathy associated with solvent exposure is typically described in workers exposed to relatively high levels of solvents for many years, as opposed to the briefer-duration exposures associated with Gulf War service.<sup>1781</sup> In its review of the occupational literature on solvent exposure, the IOM concluded there was sufficient evidence to indicate that solvents are associated with leukemia and suggestive evidence of an association between solvents and chronic neurobehavioral effects.<sup>682</sup>

Solvent exposure during the war, as a risk factor for chronic symptomatic illness, has been evaluated in four Gulf War veteran populations. As shown in Appendix A-11, each study identified significant associations between solvents and chronic symptom complexes in analyses that did not adjust for effects of other exposures in theater.<sup>692,788,1264,1698</sup> Solvents were not associated with chronic symptomatic illness, however, in the one study that did control for effects of other exposures.<sup>695</sup> Additional information relevant to solvent exposures is provided by a population-based study of Gulf War veterans from the Pacific Northwest. The study reported that veterans whose work in theater involved degreasing machinery or repair of vehicles, generators, or batteries, had a 2-3 fold higher rate of multisymptom illness than those with other occupations.<sup>1466</sup> While interesting, these results are from crude analyses that did not consider effects of other work activities or exposures, so it is not possible to determine whether they are indicative of a true association.

In summary, chronic exposure to high levels of solvents has been associated, in occupational studies, with a chronic encephalopathy that resembles Gulf War illness. It is likely that a large proportion of Gulf War veterans were exposed to solvents of various types and at varying concentrations and durations during deployment. There is little information, however, indicating that solvent exposure patterns in the Kuwaiti Theater of Operations were either unique or excessive. The Committee identified no studies that identified solvent exposure as an independent risk factor for chronic symptoms in Gulf War veterans. The Committee also did not identify any reported incidents related to unusual or excess solvent exposure, with the exception of fuels and CARC painting operations, and no testimony or anecdotal reports from veterans describing the development of symptoms in relation to solvent exposure. Therefore, the Committee concludes that solvent exposures during the Gulf War are not likely to have caused Gulf War illness.

## **Jet Fuel in Relation to Gulf War Illness**

Veterans in all areas of the Gulf War theater were commonly exposed to fuels of different types during deployment. Government estimates indicate that nearly two billion gallons of fuel were used by the U.S. military between August 1990 and May 1991 in the Gulf War.<sup>1506</sup> About 75 percent of that was jet fuel, used to power not only jets but vehicles on the ground—tanks and trucks. Jet fuel, along with kerosene, was also burned in tent heaters, cook stoves, and generators, used to incinerate trash and human waste, and burned to generate smoke as a method of obscuring troops and equipment. Uncombusted fuels were also commonly sprayed or dumped on the ground to suppress dust and blowing sand, and used as solvents in cleaning weapons and equipment. Twenty-four percent of the fuel used in theater was diesel, used for many of the same purposes as jet fuel. Only one percent of the fuel used was regular gasoline.<sup>1506</sup> The majority of the fuel used by the U.S. during the war was obtained from local sources, primarily Saudi Arabia.

The chemical and physical properties of uncombusted fuels differ from those of burning fuels and exhaust. The present discussion focuses on health effects potentially associated with exposure to uncombusted fuels; effects of combusted fuels are addressed in sections of the report related to oil well

fires and tent heaters. During the Gulf War, the highest-level exposures to uncombusted fuels would have occurred among personnel whose work related to the supply and storage of fuels, those who fueled and worked with aircraft, those who fueled, maintained, or drove ground vehicles, and those exposed to fuels that were sprayed or dumped onto the ground to suppress the blowing desert sand. In national studies, about 80 percent of both U.S. and U.K. Gulf War veterans report being exposed to fumes from diesel or petrochemicals during deployment, and 57-67 percent report dermal exposure to fuels.<sup>751,1698</sup>

He described one brigade dumping 30,000 gallons of diesel fuel on the roads daily, and said U.S. service members living in tents near the roads—and particularly truck drivers carrying out the spraying—complained of nausea from breathing the resulting fumes. As a result, the preventive medicine person to whom they reported obtained respirators for the drivers' use.

-- Report on testimony of Gulf War Army Sanitary Engineer, 1996<sup>1227</sup>

Petroleum-derived fuels are complex mixtures of organic compounds—hundreds of aliphatic and aromatic hydrocarbons, other toxic solvents (e.g. benzenes, toluenes, xylenes) and various performance-enhancing additives.<sup>1287</sup> The most widely-used fuel in the Gulf War was jet fuel and several types were in use in theater. JP-4, a kerosene/gasoline mix, was used but was being phased out in 1991. JP-5, primarily kerosene, was the Navy's primary jet fuel. JP-8, a military version of the commercial jet A-1 fuel with additional additives, was designated the primary fuel for use in Army and Air Force aircraft and ground vehicles. These generalizations did not always hold in the actual circumstances of war when, for example, Air Force units were located on bases where only JP-4 was available, or Army vehicles used diesel fuel due to operational problems. Different types of fuels have different toxicity profiles that relate to the source and type of petroleum used, variability in refinery processes, and specific compounds and additives contained in the fuel. JP-8 was designated as the primary military fuel of choice to replace JP-4 because it is less volatile, reducing the risk of explosions and fires, and contains lower levels of the toxic chemicals n-hexane and benzene.<sup>1506,1579</sup> However, JP-8 carries greater potential for dermal toxicity than JP-4. In 2003, the National Research Council, citing uncertainties related to adverse effects of exposure to JP-8, recommended that the military no longer use JP-8 for desert sand control or for obscuring troops and equipment.<sup>1103</sup>

As with other classes of hazardous exposures, toxic effects of fuels depend on the specific type of fuel, the physical state of the fuel, the dosage, and the route of exposure. Fuel exposure can occur through inhalation of vapors and aerosols, through dermal absorption, and through ingestion. Despite their widespread use, uncertainties remain concerning toxicological effects of jet fuels, particularly chronic effects. The U.S. Air Force has sponsored a number of research initiatives in the past decade to address questions relating to biological and behavioral health effects of jet fuels, particularly JP-8.<sup>792,1287</sup> Health effects described in association with jet fuel exposure include pulmonary effects, dermal effects, neurobehavioral effects, and immune effects. People acutely exposed to high levels of JP-8 report symptoms that include nausea, dizziness, fatigue, memory impairment, headache, respiratory distress, and skin irritation, but are not reported to have excess healthcare visits or diagnosed medical conditions.<sup>792,1221,1287</sup>

Studies evaluating effects of jet fuel exposure on the central nervous system are of particular interest in relation to the chronic symptoms affecting Gulf War veterans. Human studies conducted more than twenty years ago indicated that chronic exposure to jet fuel was associated with a multisymptom syndrome (dizziness, headache, nausea, fatigue, memory difficulties, respiratory problems) accompanied by shortened attention span, reduced auditory evoked cortical potentials, electroencephalogram abnormalities, and psychiatric symptoms.<sup>817-819,1504</sup> More recently, several studies have demonstrated subtle central nervous system (CNS) effects in relation to lower-dose jet fuel exposure.<sup>1287,1290</sup> For example, exposure to JP-8 among workers at an Air National Guard base, some of whom had no direct

contact with fuels, was associated with significant neurocognitive impairment on the day of exposure.<sup>1557</sup> Deficits were observed on measures of information processing and executive function and were most pronounced in relation to more complex tasks. In a large study of Air Force personnel, workers with higher level exposure to jet fuel continued to exhibit deficits in cognitive capacity (digit span, symbol digit tests), and simple motor skills (tapping tests) 14-72 hours after exposure.<sup>792</sup> Other studies have demonstrated balance abnormalities<sup>1430</sup> and alterations in blink response in workers exposed to jet fuel.<sup>1002</sup> Although these studies have provided important insights regarding short-term effects of exposure to jet fuels, they did not determine whether jet fuel can produce longer-term CNS effects in humans.

In animal studies, inhalation of jet fuel has been shown to modulate behavior and CNS neurotransmitters as long as 85 days after exposure, resulting in reduced dopamine levels and increased levels of serotonin metabolites HVA and 5-HIAA.<sup>1131,1317</sup> Animal studies have also indicated that repeat inhalation of jet fuel produces impaired learning of complex tasks, but not simple tasks, that persists for up to 180 days post exposure.<sup>1289</sup> In addition, inhalation of jet fuel vapors has been associated with genomic alterations related to neurotransmitter signaling pathways.<sup>904</sup> Also of possible relevance to chronic symptoms affecting Gulf War veterans, animal studies have demonstrated diverse effects of jet fuel on immunity<sup>367,582-585,782,1691</sup> and on pulmonary function.<sup>363,1298,1492,1796</sup>

In discussions with the Committee, Dr. Glenn Ritchie, a neurotoxicologist with expertise in neurological and behavioral effects of jet fuel, suggested that jet fuel exposure, when combined with other Gulf War-related exposures, might have unexpected consequences that are relevant to Gulf War illness.<sup>1288</sup> This could include, for example, adverse effects from inhalation of “sand aerosols” formed by the mix of fuel vapors with fine airborne particulates in the region, or unanticipated effects of other exposure combinations. Few studies have evaluated interactions between jet fuel and other Gulf War-related exposures, however. One study identified limited immune alterations (suppressed plaque-forming cells, decreased delayed hypersensitivity) in mice exposed to a mixture of jet fuel, PB, and DEET.<sup>1187</sup> In addition, jet fuel has been shown to enhance the absorption of permethrin in a porcine skin model,<sup>1295</sup> and to inhibit metabolism of DEET and carbamate pesticide in a liver cell culture model.<sup>391,611</sup>

The Institute of Medicine’s Gulf War and Health report on *Fuels, Combustion Products, and Propellants* reviewed hundreds of studies related to the human health effects of fuels. The report concluded that there was insufficient evidence to determine whether there is an association between exposure to uncombusted fuels and any of the health outcomes evaluated.<sup>684</sup> This conclusion relied on results of human studies, but the studies considered did not include the human studies of neurological effects referred to above.

Studies of Gulf War veterans have provided information on the relationship of veteran-reported exposures to fuels in theater and rates of chronic symptoms and multisymptom conditions, as shown in Appendix A-5. Five studies specifically evaluated the association of skin contact/direct contact with fuels with chronic symptom complexes in Gulf War veterans.<sup>695,1264,1466,1507,1698</sup> All reported significant associations in analyses that did not consider effects of other exposures in theater, with one suggesting a dose-response effect.<sup>1466</sup> Two studies found that fuel contact was not associated with chronic symptoms, when effects of other exposures in theater were considered.<sup>695,1507</sup> In addition, four studies specifically assessed whether veterans who were exposed to fuel sprayed on the ground had higher rates of multisymptom conditions. Three found no association between fuel sprayed on the ground and chronic symptoms in analyses that controlled for effects of other exposures,<sup>527,695,1507</sup> and one reported no association between this exposure and defined syndromes in unadjusted analyses.<sup>564</sup>

In summary, fuel exposures during the Gulf War were widespread. Most Gulf War veterans were likely exposed to some level of uncombusted petroleum fuels during deployment, predominantly jet fuel, and subgroups experienced higher-level exposures related to their work activities. There is no information indicating that fuel exposures associated with Gulf War service differed markedly from those of other military deployments or service in the U.S., with one exception. That exception is the use of fuels to

control blowing sand, which may have resulted in high levels of inhalation and dermal exposure for some individuals, and lower level, repeat inhalation exposures for others. Multiple studies in humans have suggested that inhalation exposure to uncombusted fuel is associated with acute neurobehavioral effects. In studies that assessed chronic symptoms or multisymptom conditions in relation to uncombusted fuel exposure in the Gulf War, however, no significant associations were identified. In addition, the Committee identified no incident reports or anecdotal reports from veterans indicating that they developed acute or chronic illnesses that they attributed to exposure to fuels. As a result, the Committee concludes that, although uncombusted petroleum-based fuels may have the potential to cause health effects similar to the chronic health problems affecting Gulf War veterans, it is unlikely that they are a primary cause of Gulf War illness for the majority of affected veterans.

### **CARC Paint: Exposure to Chemical Agent Resistant Coating in the Gulf War**

In addition to the hundreds of thousands of troops mobilized to the Middle East during Operation Desert Shield, thousands of military vehicles were brought into theater for the war effort. Prior to their arrival, most military vehicles were painted in the familiar green “woodland” camouflage, necessitating a massive effort to repaint them a tan color more appropriate for desert warfare.<sup>1619</sup> Large painting operations were set up in theater to paint incoming vehicles prior to the initiation of Operation Desert Storm. After the ceasefire in February 1991, similar operations repainted many vehicles with woodland camouflage colors before they were shipped back to the United States.

Because of prewar concerns regarding Iraq’s arsenal of chemical weapons, many of the newly arriving vehicles were painted with a special compound, chemical agent resistant coating, or CARC paint. CARC paint is a heavy polyurethane coating that, when applied to tanks and other vehicles, provides protection from chemical warfare agent penetration, facilitates decontamination from chemical agents, and extends the service life of the vehicle. CARC contains multiple potentially hazardous compounds, including toluene, benzene, crystalline silica, and ketones. The compound in CARC considered most hazardous is hexamethylene diisocyanate (HDI), which hardens the paint. In addition, large amounts of potentially hazardous solvents (paint thinners, cleaners, etc.) were used in painting operations. Exposure to aerosolized CARC paint, at sufficiently high levels, causes respiratory problems, dizziness, fatigue, headache, skin rashes, nausea and vomiting, and chemical hypersensitivity.<sup>326,1577,1619</sup> CARC is not considered particularly hazardous after it dries, however, unless it is aerosolized by sanding or chipping, or heated to high temperatures.

Military occupational safety guidelines require personnel applying CARC paint to use respirators, wear protective gear that covers all exposed parts of the body including head and hands, and work in properly ventilated areas.<sup>1585,1619</sup> DOD reports indicate that CARC paint was used almost exclusively for Army vehicles during the Gulf War. Inadequate CARC paint supplies required the Marine Corps to paint their vehicles with other types of tan paint that did not contain isocyanates. The Air Force and Navy routinely use other types of paint for their vehicles and aircraft.<sup>1619</sup>

The most concentrated and sustained exposures to CARC paint occurred among personnel who worked in painting operations established for mass painting of vehicles. In September of 1990, the first painting operation involving CARC paint was set up at the Port of Ad Dammam, Saudi Arabia, where painting was initially done by experienced civilian contractors who had proper protective equipment. Two additional major CARC spray painting operations were established by the Army at Ad Dammam and Al Jubayl.<sup>1619</sup> These sites were operated by a Florida Army National Guard unit, the 325<sup>th</sup> Maintenance Company, which had not been trained in CARC painting operations. The 325<sup>th</sup> began painting vehicles in December, 1990. Members of the unit worked around the clock in tents erected to spray paint vehicles. Reports indicate that they lacked both proper personal protective gear and the required air circulation equipment. According to a December 1990 memo from a safety officer with the Army Central

Command, personnel began reporting health problems—dizziness, rashes, vomiting, and nausea—within a very short time.<sup>1584</sup> Onsite investigations were conducted at Ad Dammam and Al Jubayl between December 1990 and June 1991. Painting operations were temporarily shut down at times, due to safety concerns.<sup>1573,1619</sup> Eventually, protective gear and respiratory equipment were provided to members of the unit but, in some situations, not until many months after painting operations began.<sup>1619</sup>

A report from DOD's Special Assistant for Gulf War Illnesses indicates that other, smaller CARC painting operations were established throughout theater, but that these operated for shorter periods of time and generally applied CARC using brushes and rollers, rather than by aerosol spray painting.<sup>1619</sup> In addition, CARC was used on a smaller scale by individual units in painting and touching up vehicles. The DOD report also indicates that their office had received word, in 2000, of medical problems reported by civilian painting contractors that they attribute to their use of CARC paint during the Gulf War.<sup>1619</sup>

I served nine months in the Persian Gulf in the 325<sup>th</sup> Maintenance Combat Support Unit, a Florida Army National Guard Company. I have chemically induced asthma, experience allergic reaction to various substances from cigarette smoke to household cleaners. I have shortness of breath, muscle aches and cramps, reappearing sores, cognitive dysfunction, numbness in my face and hands, and extreme fatigue. Fourteen months after returning from the Gulf I was forced to take a medical disability from a job of 11 years and I'm not able to do the physical labor nor the mental work I did before my Gulf War service.

- 1996 testimony, Gulf War veteran<sup>1229</sup>

Members of the 325<sup>th</sup> Maintenance Company continued to report health problems, some of them severe, after their return from theater. Despite concerns raised by military authorities and Congressional offices, no systematic evaluation of the health of members of this unit was ever conducted. In addition, the Committee identified no other reports systematically documenting short or long-term health effects of personnel who used CARC paint during the war. To find out more about possible long-term health effects related to CARC exposure, Committee staff obtained information from memos and reports describing the health of members of the 325<sup>th</sup> Maintenance Company during and after the war, from DOD's report on the use of CARC paint during the war, from testimony presented to Congress and the Presidential Advisory Committee, from a Congressional office that assisted veterans in the 325<sup>th</sup>, from physicians who evaluated and assisted ill veterans in the unit, and from the regional VA office that processed disability claims for veterans in the unit.

In the years since the war, media reports have continued to describe chronic health problems among members of the 325<sup>th</sup> Maintenance Company.<sup>279,1772</sup> In 1993, Dr. William Johnson testified to Congress that personnel he had examined from the 325<sup>th</sup> had a number of symptoms commonly seen in Gulf War veterans—headache, dizziness, fatigue, and neurocognitive problems—as well as asthma-like symptoms.<sup>719</sup> An occupational medicine physician who had evaluated about 20 veterans in the unit reported to DOD that the paint fumes from the Al Jubayl operations had permeated the entire camp, affecting eating, sleeping, and administrative areas. He indicated that the air was so permeated with solvent vapor that lights had to be replaced with a type that resisted explosions.<sup>1611</sup> Dr. Bruce Pettyjohn was medical officer for the 325<sup>th</sup>, and examined many of those in the unit both before and after they deployed to the Gulf War. He reported that, in addition to the respiratory problems he observed, most of the ill veterans he examined after the war had memory problems, skin rashes, muscle pain, and gastrointestinal problems. He told Committee staff that many of the veterans had been seriously ill, but it had not been possible for him to determine whether their ailments had stemmed from the CARC paint exposures, other Gulf War-related exposures, or a combination.

Because of the large number of personnel from the 325<sup>th</sup> who were reporting health problems, claims representatives from the Department of Veterans Affairs (VA) met with members of the unit at their annual training in Fort Stewart, Georgia, after the unit returned from Saudi Arabia. As of 2000, a DOD

report indicated that of the approximately 200 members of the 325<sup>th</sup> that had participated in painting operations, 163 had been evaluated in DOD or VA Gulf War registries. Findings from registry examinations of these individuals were never compiled and summarized, according to the DOD report, due to medical privacy issues.<sup>1619</sup> Officials with the VA Regional Office in St. Petersburg, Florida, recalled that close to 200 disability claims had been filed in connection with CARC exposures by members of the 325<sup>th</sup> but that disposition of those claims had not specifically been tracked. No numbers regarding final claim adjudication were available. News articles and Congressional staffers described stories of individual veterans who had difficulties getting their medical problems service connected.<sup>279,1772</sup>

Few epidemiologic studies of Gulf War veterans queried veterans about their use of and exposure to CARC paint during the war. In the U.S. national study of Gulf War veterans, just over 20 percent of veterans reported being exposed to CARC paint. A higher proportion of those enrolled in the CCEP and VA Gulf War Registries—35 to 48 percent—reported CARC exposure.<sup>751,839</sup> As shown in Appendix A-1, CARC exposure was identified as a significant risk factor for multisymptom illness in two of the three studies that addressed this question,<sup>564,752,1466</sup> but neither determined if CARC was an independent risk factor, controlling for effects of other exposures. Unadjusted analysis of data from the U.S. national study indicated that veterans who reported CARC exposure had a 5-fold greater risk than unexposed veterans for the unique neurological symptom complex identified by that study.<sup>752</sup>

In summary, it appears that some exposure to CARC paint, before or after it dried, was fairly common among troops serving in the Gulf War and that a limited number of personnel involved in intensive painting operations were exposed to excessive levels of fresh CARC paint. The greatest concern in relation to long-term effects of CARC is for personnel who had the highest-level exposure to this toxic substance, particularly those for whom protective measures were inadequate. Available information indicates that some individuals in the Florida Army National Guard's 325<sup>th</sup> Maintenance Company suffered acute and chronic health effects consistent with known effects of CARC paint. Without a systematic evaluation, however, it is not possible to determine the extent of health problems affecting members of this unit, or if those problems are uniquely the result of CARC exposure or may be related to other exposures in theater.

The committee concludes that, overall, the limited extent of exposure to fresh CARC paint during the Gulf War is not consistent with the high prevalence of Gulf War illness, or its pattern of occurrence. It is therefore unlikely that CARC paint caused or contributed to Gulf War illness for the majority of ill veterans. However, CARC paint may have had adverse health effects in the limited number of personnel with more intensive and sustained exposure.

## **Contaminated Food and Water in the Gulf War**

Rapid deployment of American military personnel to the Middle East in the fall of 1991 presented many logistical challenges, including those related to providing living accommodations and safe food and water supplies for hundreds of thousands of arriving troops. In the early months of the troop buildup, canned and frozen food and prepackaged meals were shipped from the U.S. and were supplemented with fresh produce and dairy products obtained from countries in the region.<sup>662</sup> Throughout the deployment period, potable water was obtained from reverse-osmosis purification units run by the U.S. military, from local commercial bottled water suppliers, and from local municipal systems that supplied chlorinated water.<sup>662</sup>

Despite extensive efforts by the military to provide safe food and water to the troops, widespread outbreaks of diarrheal disease occurred in the early months of Operation Desert Shield. In September 1991 this posed a serious threat, when over 50 percent of troops surveyed in theater reported diarrheal episodes and 20 percent reported they had been temporarily unable to perform their duties due to diarrhea.<sup>662</sup> The primary pathogens identified were *e. coli* and *shigella* species, and the primary source of

contamination in those months was believed to be the produce supplied by regional countries, since rates of diarrheal diseases dropped after these items were banned in late September.<sup>664</sup> Diarrheal diseases continued to occur, at reduced rates, throughout the deployment period. Additional outbreaks were reported to occur most commonly in relation to interpersonal transmission of enteropathogens in field units and when food was supplied or prepared by foreign food handlers.<sup>664</sup>

In addition, there were difficulties obtaining sufficient supplies of potable water and some units had to rely on water supplied by host nations, delivered in tanker trucks.<sup>1618</sup> Policy at the time allowed for the use of petroleum transport tankers to carry drinking water, once the tanks had been superchlorinated and thoroughly flushed.<sup>1618</sup> Although water supplies were regularly monitored by U.S. personnel, testing results were typically not available for 18-24 hours.<sup>1618</sup> The Department of Defense's report on water use during the Gulf War also indicates that there were occasions when non-potable water was used for drinking and food preparation.<sup>1618</sup> In addition, personnel located close to the spewing and burning oil wells experienced another source of food and water contamination resulting from the "oil rain." Troops in those areas described being completely soaked with oil and having their food and water taste like oil.<sup>1688</sup>

Exposure to contaminated food and water during deployment appears to have been fairly widespread. Twenty-one percent of veterans in the CCEP reported eating contaminated food and 20 percent indicated they had bathed in contaminated water during deployment.<sup>839</sup> In addition, 30 percent of veterans in the U.S. National Study of Gulf War era veterans indicated they had eaten food contaminated with oil or smoke.<sup>751</sup> Overall, 75 percent of Gulf War veterans said they ate food and 34 percent drank water that had not been supplied by the military.<sup>751,988</sup>

Some enteric pathogens have the potential to cause chronic illness,<sup>268,970</sup> but reports from field medical units indicate that most diarrheal episodes and outbreaks of gastroenteritis during deployment were brief and resolved within days.<sup>662</sup> Still, persistent digestive disturbances, including chronic diarrhea, are frequently reported problems among ill Gulf War veterans.<sup>370,393,695,751,824,1451,1565</sup>

Several epidemiologic studies have evaluated rates of chronic symptoms and multisymptom illness in relation to veterans' reports of exposure to contaminated food and water in theater (Appendix A-3). In unadjusted analyses, eating food contaminated with petroleum or oil was associated with an elevated risk for multisymptom illness in two studies.<sup>564,752</sup> This was a particularly strong risk factor in the U.S. national study, in which veterans who reported eating food contaminated with oil had a 10-fold higher rate of the unique neurological symptom complex defined in that study.<sup>752</sup> These data come from unadjusted analyses, however, and it is not possible to determine whether this excess risk resulted from ingestion of the oil-contaminated food or if eating oil-contaminated food may reflect, more generally, risk resulting from being in close proximity to the spewing oil wells. In addition, two studies, after adjusting for effects of multiple exposures, reported that bathing in or drinking contaminated water was a significant risk factor for chronic symptomatic illness.<sup>527,1507</sup> Among Danish veterans, this association was with water contaminated with oil or fumes, so may have reflected proximity to the oil well fires.

In summary, exposure to contaminated food and water appears to have been fairly common during Gulf War deployment, and acute diarrheal diseases commonly occurred among Gulf War personnel. Relatively little clear information is available concerning their association with chronic symptomatic illness in Gulf War veterans, however. It is also not known if exposure to contaminated food and water was more or less common during the Gulf War than in other military deployments to the region. Overall, it appears unlikely that food and water contamination were major causes of Gulf War illness for most ill veterans.

## Other Potential Hazards Encountered by Military Personnel in the Gulf War

A variety of additional exposures have been suggested as possible contributors to the development of chronic symptoms affecting Gulf War veterans. These include sources of electromagnetic radiation in theater, industrial pollution, exposure to the decontaminating agent DS<sub>2</sub>, and exposure to hydraulic fluids, among others. Almost no information is available concerning the extent of exposure to these substances, or their likely health effects. The Committee therefore has no basis on which to draw conclusions regarding any health effects potentially attributable to these exposures, although most were likely to have been encountered by a limited number of Gulf War veterans. They are mentioned here, in brief, for the sake of completeness and to indicate the Committee's awareness of veterans' concerns regarding these exposures.

**Sources of electromagnetic radiation.** Veterans have expressed concern about possible adverse effects of electromagnetic radiation for individuals who may have had particularly high exposure during the war. Several sources have been described. These include radio and microwaves in locations at which high-level communications towers and equipment were located. Veterans have also indicated that new weapons systems that utilized energy beams, while not in wide use, were being tested during the 1991 Gulf War.<sup>1269</sup>

There has been extensive research exploring possible adverse effects of exposure to electromagnetic radiation, of various types, in other settings. While individual studies have reported that exposure to radio waves, microwaves, and other types of electromagnetic radiation may be associated with increased risk of cancers and other health outcomes, findings have been equivocal, and no clear consensus has emerged concerning long-term effects of higher-level exposures.<sup>401,498</sup> Studies have not specifically assessed adverse effects of short term, concentrated exposure to radiation frequencies emitted by microwave communications equipment comparable to those that may have been encountered by military personnel during the Gulf War.

Between 20 and 30 percent of U.S. veterans reported being exposed to "microwaves" in the U.S. National Survey and federal registry programs,<sup>751,1505,1651</sup> but the sources of those exposures were not queried or identified. In unadjusted analyses, exposure to "ionizing or non-ionizing radiation" was associated with higher rates of cognitive and fibromyalgia symptoms in Iowa veterans, but not in Canadian veterans.<sup>511,692</sup> No government documents or veteran reports were identified that provide additional information concerning individuals potentially exposed to electromagnetic radiation during the Gulf War in connection with the testing or use of energy weapons.

**Sources of industrial pollution.** During the Gulf War, U.S. troops were frequently stationed in industrial areas where operating chemical plants and refineries were located. Government reports have routinely identified industrial pollution as a source of airborne particulates and other contaminants during the Gulf War.<sup>1625</sup> Almost no information is available, however, about the specific types of pollution in those areas or the extent of exposures to contaminants associated with local industry.

There are incident reports describing chemical exposures of unknown type and origin, however, the best known of which is the "purple T-shirt event." On March 19, 1991, Navy Seabees camped in an industrial sector of Al Jubayl, in northern Saudi Arabia, described being enveloped in a cloud of noxious fumes that contained a purple colored dust. They experienced symptoms that included burning in their eyes, noses, and throats, nosebleeds, and choking. At the same time, their brown T-shirts turned purple, as did portions of their combat boots. Some of the soldiers sought medical attention, and their symptoms are reported to have resolved in a short time. Despite a later environmental hazard investigation, and chemical testing of some of the affected shirts, no specific chemical or source of the fumes was identified. Military investigators have generally concluded that the unknown chemical likely came from an unidentified incident at one of the industrial plants located near the camp.<sup>1627</sup>

**Chemical decontaminating agent.** Decontamination Solution 2, or DS<sub>2</sub>, is a solution used by the military to decontaminate vehicles following exposure to chemical warfare agents. This solution contains ethylene glycolmonomethyl ether (2ME), a type of solvent widely used in industry that has been associated with adverse reproductive and hematological effects.<sup>1615,1690</sup> Although it is known that DS<sub>2</sub> was used during the Gulf War,<sup>675</sup> no documentation is available concerning the extent of its use. The Committee identified only one report of an incident involving the use of DS<sub>2</sub> during the Gulf War, in which a group of soldiers were said to have developed rashes after exposure.<sup>1690</sup>

**Airplane hydraulic fluid.** In recent years, studies have suggested that inhalation exposure to fumes produced by hydraulic fluids used in aircraft may have adverse neurological effects. Airline crew members flying certain aircraft have reported nonspecific symptoms such as headache, cognitive impairment, and fatigue that some have attributed to fumes from hydraulic fluid and engine oil leaks.<sup>287,1794</sup> Several types of hydraulic fluid were used in military aircraft during the Gulf War, some of which contained tricresyl phosphates (TCPs),<sup>978</sup> organophosphate esters that have been associated with neurotoxic effects.<sup>1067,1570</sup> However, no information is available on the extent of exposure to these substances during the Gulf War, or on adverse effects potentially attributable to them. One U.S. Gulf War study, in unadjusted analyses, found that veterans whose work activities during the war included cleaning “hydraulic leaks” had an elevated rate of Gulf War illness.<sup>1466</sup>

**Summary. Other exposures in theater.** The Committee reviewed information on a variety of Gulf War exposures that have the potential to cause adverse effects but for which there is relatively little information concerning individual exposures and/or associations with Gulf War illness. This includes sand/particulates in theater, tent heaters, solvents, jet fuel, CARC paint, and contaminated food and water. Several of these exposures are unlikely to have been primary causes of Gulf War illness for the majority of ill veterans based on what is known about their distribution during deployment. Gulf War illness affects between 25 and 30 percent of those who served in the 1990-1991 Gulf War, and occurs in a nonrandom distribution pattern—that is, its prevalence differs by branch of service and by location in theater. Primary causes of Gulf War illness, therefore, would have to have been widespread enough to affect a substantial number of individuals, but not equally distributed in all sectors of theater. This suggests that exposures such as solvents, fuels, and particulates, encountered throughout theater by most units, are unlikely candidates as primary causal factors in Gulf War illness. It also suggests that freshly sprayed CARC paint, encountered by relatively few veterans in very limited areas, is also an unlikely cause of Gulf War illness for most veterans. These observations are generally supported by epidemiologic studies that have assessed rates of multisymptom illness in relation to these exposures.

Descriptive reports during and after the war, however, indicates that some military personnel involved in intensive CARC painting operations, particularly those who had inadequate training and protective equipment, have suffered chronic health problems since the war. In different individuals these problems have resembled Gulf War illness, adverse consequences of CARC exposure, or both. Systematically-collected information is needed to understand the degree to which these individuals have been affected by persistent adverse effects of CARC or other Gulf War-related exposures.

Less commonly-encountered exposures such as these raise questions about the potential for various substances to have contributed to Gulf War illness in some as-yet-unknown way, as part of a “cocktail” effect resulting from combinations of exposures. As described here in relation to particulates, scientists are just beginning to identify neurotoxic effects of substances not previously associated with diagnosed neurological diseases. Little is currently known about how some of these exposures, particularly when combined with other neurotoxic substances, might contribute to adverse effects that are currently unknown.

## Recommendations

A number of exposures in theater are unlikely to have been primary causes of Gulf War illness in the majority of ill veterans, but may have contributed to illness risk in identifiable subsets of Gulf War veterans. To better understand the potential contributions of two of these exposures, CARC paint and unvented tent heaters, the Committee recommends the following:

- Conduct an epidemiologic investigation to determine if personnel who served with the Army National Guard's 325<sup>th</sup> Maintenance Company in the Gulf War suffer excess health problems in comparison to nondeployed personnel, to describe the nature of any excess problems, and to evaluate the degree to which problems are associated with veterans' exposure to CARC during deployment, alone or in combination with other Gulf War exposures.
- In existing and future epidemiologic studies of Gulf War veterans, analyze data collected relating to exposure to unvented tent heaters during the Gulf War using analytic methods that control for the effects of other exposures in theater, to determine whether tent heaters contributed to the risk of Gulf War illness, particularly among Army veterans in theater during winter months.

## Synthesis: What the Weight of Evidence Tells Us About the Causes of Gulf War Illness

The 1990-1991 Gulf War was unique in many respects. Although the combat period was brief, military personnel encountered a variable mix of chemical, biological, psychological, and physical exposures during deployment. For many years, complexities related both to what occurred in theater and the multisymptom illness resulting from the war have given rise to widespread uncertainty and debate. Different deployment-related factors have been put forward by individuals from different sectors—government officials, veterans, clinicians, scientists, and members of the public—as *the* cause or most important cause of Gulf War illness. As viewed through different lenses, detailed and sometimes persuasive cases have been made that different exposures—stress, oil well fires, depleted uranium, vaccines, nerve agents—appeared, at least in theory, to be the most likely cause of Gulf War illness.

Seventeen years after the war, the extensive body of scientific research on the health of Gulf War veterans and the large number of government investigations related to exposures in theater permit a more in-depth, evidence-based evaluation. Earlier observers have suggested that it might not be possible to determine the cause of Gulf War illness so many years after the war. Based on its broad review of available information, however, the Committee found that evidence of different types from different sectors points consistently to a limited number of factors as the most prominent and likely causes of Gulf War illness.

The Committee believes it is extremely important to understand why Gulf War veterans became ill. Veterans and their healthcare providers need this information to inform appropriate treatment strategies. Scientists need this information to design research studies that most accurately characterize pathological processes, tests, and treatments for Gulf War illness. Government officials need this information to improve programs that care for ill Gulf War veterans and to prevent similar problems in the future. Seventeen years after the Gulf War, answers to the question of what caused Gulf War illness are long overdue.

Scientific determination of disease causality is neither routine nor straightforward. There is no general agreement, from a scientific perspective, on how best to characterize or determine disease causation, especially when considering links between chronic disease and environmental factors.<sup>1321</sup> Unlike infectious disease, there are no accepted criteria, like Koch's postulates, used to judge if an exposure/disease causal relationship exists. Understanding such relationships in human populations is often complicated by factors such as the potential for multiple "causes" to contribute to disease, uncertainties related to exposure levels, latency of observable clinical effects, and variability in individual susceptibility to hazardous exposures. Multiple factors must be considered and weighed in making scientific judgments about disease causation, based on a variety of indicators that have been suggested as important.<sup>609,1321,1516</sup> These typically include the overall consistency of epidemiologic findings relating an exposure to a disease, the biological plausibility of the association, the presence of a dose/response effect, and whether the exposure/illness link is consistent with other knowledge in the field.

The Committee considered factors such as these in reviewing the broad spectrum of evidence related to each of the putative risk factors for Gulf War illness. For each exposure topic, the Committee systematically considered three general types of information: (1) what was known about the extent and patterns of the exposure in theater, (2) what was known, overall, about adverse effects of the exposure from human and animal studies, and (3) what studies of Gulf War veterans have determined about associations between the exposure and Gulf War illness. Available information in all three categories was reviewed in a similar way for the different wartime experiences and exposures of interest. For example, evidence related to psychological stressors as a possible cause of Gulf War illness was considered in the same way as evidence related to exposures such as depleted uranium and oil well fires. The types and strength of evidence in each area were then compared, to allow the Committee to determine where

evidence of an association was strongest, where there appeared to be no association, and where there was insufficient information to support firm conclusions.

### **General Patterns of Exposure in the Gulf War**

Gulf War illness, that is, the complex of chronic symptoms consistently found at excess rates in Gulf War veterans, affects between 25 and 32 percent of veterans who served in the 1990-1991 Gulf War. Its primary cause or causes would therefore be expected to have been commonly encountered by Gulf War personnel during deployment. General insights about the causes of Gulf War illness might also be provided by comparing what is known about the extent and patterns of exposures during the 1990-1991 Gulf War with the distribution of Gulf War illness in different veteran subgroups. Gulf War illness has been shown to affect ground troops, particularly Army personnel, at significantly higher rates than other personnel in theater, and to be most prominent among troops who served in forward areas. In addition, a similar pattern of widespread multisymptom illness, unexplained by identifiable medical or psychiatric diagnoses, has not been reported in veterans who served in Bosnia in the 1990s or in personnel returning from current conflicts in the Middle East. This suggests that insights into the cause or causes of Gulf War illness might also be provided by comparing the circumstances and exposures of the 1990-1991 Gulf War with those of more recent deployments.

Overall, it would generally be expected that the most prominent etiologic factors for Gulf War illness should be widespread enough to have affected a large number of troops during the 1990-1991 Gulf War, and most frequently experienced by ground troops, particularly those serving in forward areas. And, based on currently available evidence, the most prominent causes of Gulf War illness should also have been widespread in the 1990-1991 Gulf War, but not in current Middle East deployments. Information of this type, summarizing key aspects of what is known about general patterns of Gulf War exposures, is provided in Table 1.

General information on exposure patterns in the 1990-1991 Gulf War indicates that a number of exposures were widespread during Gulf War deployment, and most prominent among ground troops who were in forward locations at some time during the war. These include psychological stressors, oil well fire smoke, depleted uranium (DU), use of pyridostigmine bromide (PB) pills, and pesticide use. Two of these, psychological stressors and DU, have also been prominent among personnel serving in Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF), although reports have not identified a widespread Gulf War illness-type problem in veterans of those conflicts. Major vaccine exposures of interest do not generally distinguish the Gulf War from current conflicts, since all personnel serving in recent deployments were to have received the six-shot anthrax vaccine series, and multiple other vaccines for deployment. Anthrax vaccine was administered to a lower proportion of 1990-1991 Gulf War troops, and preferentially given to those in fixed locations in support areas during the war.

Overall, there is sufficient information on exposure patterns in theater to indicate that two exposures of interest are generally compatible with what is known about the distribution of Gulf War illness in Gulf War veterans. Exposure to oil well fire smoke and the use of PB pills were both widely experienced, most prominently in forward areas of theater and by ground troops. Neither have affected troops in current Middle East conflicts to a significant extent, although isolated exposures might have occurred.

The general patterns summarized in Table 1 also suggest that four other exposures of interest are not “good fits” with the patterns in which Gulf War illness affects veterans. These include the fine, blowing sand in the region, exhaust from tent heaters, fuel exposures, and freshly-applied chemical agent resistant coating (CARC) paint. Exposures to sand and military fuels were ubiquitous throughout the Gulf War

**Table 1. General Patterns of Exposures in the 1990-1991 Gulf War and Current Middle East Deployments**

	<i>Was Gulf War exposure widespread, and most prominent among ground troops in forward areas?</i>	<i>Was exposure more prominent in the 1990-1991 Gulf War than in current Middle East deployments?</i>
<b><i>Veterans' Experiences and Exposures in Theater</i></b>		
Pyridostigmine bromide	Yes	Yes
Pesticides	Yes	
Psychological stressors	Yes	No
Chemical weapons		Yes
Oil well fires	Yes	Yes
Number of vaccines	No	No
Anthrax vaccine	No	No
Tent heater exhaust	No	
Sand/particulates	No	No
Depleted uranium	Yes	No
Solvents	No	No
Fuel exposures	No	No
CARC paint	No	

Abbreviation: CARC = freshly applied chemical agent resistant coating

Note: Blank cells indicate that available information is insufficient to characterize pattern of interest.

theater, and would be generally similar in the current Iraq War. The most intensive exposures to freshly-applied CARC paint in the 1990-1991 Gulf War occurred in limited areas, at vehicle spray painting operations located in Saudi Arabia.

There is insufficient evidence on patterns of exposure to clearly indicate whether two Gulf War exposures of concern—chemical agents and pesticides—are supported by this type of general analysis. Although DOD models indicate that about 100,000 troops were potentially exposed to low levels of nerve agents in relation to munitions demolitions at Khamisiyah, Iraq, in 1991, the full extent and locations of low-level chemical weapons exposures during the 1991 Gulf War is unclear. *Concern* about chemical weapons exposures was very prominent early in the current Iraq War, but there have been no indications that a substantial number of troops were exposed to chemical agents in current Middle East deployments. There is also no detailed information available as yet on patterns of pesticide use in current deployments. Several pesticide products of concern during the 1990-1991 Gulf War are no longer used by the military, however, and there are multiple indications that, overall, pesticides have been used at lower levels in current deployments, in keeping with current military pest control policies.

It is important to emphasize that this type of general assessment can provide only preliminary indications of which exposure patterns are consistent with exposures likely to have been most prominently associated with Gulf War illness. Firm conclusions cannot be based on this type of general assessment for a number

of reasons, including the well-recognized limitations of ecological inferences of this type.<sup>811</sup> However, this information can help to narrow the broad field of exposures in question, particularly by identifying exposures that are unlikely to have been primary causes of Gulf War illness. Such insights can add to an overall assessment of evidence, when considered with the more detailed types of information provided by research on biological effects of exposures in humans and animals, as well as epidemiologic and clinical studies of Gulf War veterans.

## **General Information on Health Effects of Exposures**

As detailed in earlier sections of the report, a large number of diverse types of research studies have provided information on health and biological effects of many of the exposures associated with Gulf War service. These include studies of human populations exposed to psychological stressors and chemical hazards. It also includes multiple types of laboratory studies that have evaluated biological effects of these exposures in animals. The Committee reviewed research of these types to determine what insights they provide concerning likely causes of Gulf War illness.

**Evidence from animal studies evaluating biological effects of exposures.** There is no clear animal model for Gulf war illness, in part because there are not objective measures to determine if animals experience many of the symptoms associated with Gulf War illness. As described in previous sections, however, a large number of studies have evaluated effects of Gulf War-related exposures in animals, and have identified effects that are compatible with Gulf War illness-type symptoms. These include adverse effects on brain structure and neurobiological measures, as well as effects on memory and behavior. Most such studies have evaluated effects in animals over relatively brief time periods. For example, animal studies have demonstrated that stressors can produce short-term changes in behavior and hypothalamic-pituitary-adrenal (HPA) axis measures. Little information is available, however, about the potential for time-limited stressors to produce adverse effects that persist for an extended period in adult animals.

Animal studies have demonstrated persistent neurological effects of exposure to pyridostigmine bromide, fuels, solvents, and receipt of multiple vaccines that include neurobehavioral effects and changes in brain waves, neurotransmitters, and sleep patterns. Low-level sarin exposures have also been found to have persistent effects on the brain and behavior, including EEG effects and alterations in cholinergic receptors in brain areas associated with learning and memory, as well as long-term effects on HPA parameters and autonomic function. In addition, research in animal models indicates that different classes of pesticides used during the Gulf War can have long-term effects on the brain, including effects on learning and behavior. Repeat, low level exposures to organophosphate pesticides have been shown to have persistent effects that differ from effects of single exposures, even at higher dosage levels.

Animal studies have also demonstrated that soluble forms of DU, when ingested or injected, and DU pellets implanted under the skin can have effects on the brain and behavior. Little information is available, however, concerning persistent central effects of short-term DU exposure, in forms and dosages most commonly encountered by Gulf War veterans. There is also little information from animal studies to indicate whether time-limited exposure to stressors, smoke from oil well fires, anthrax vaccine, sand, tent heaters, or CARC paint produce persistent effects that are compatible with symptoms associated with Gulf War illness.

Research in animal models has also identified significant neurological effects resulting from different combinations of neurotoxicant exposures associated with the Gulf War—organophosphate pesticides, permethrin, DEET, PB, and low-level sarin—and from combinations of these exposures with stress. Diverse findings have been reported in relation to chemical absorption, metabolism, and biological effects of mixtures of these neurotoxicants, effects that differ from those of single exposures.

**Evidence from studies evaluating effects of occupational and environmental exposures in human populations.** An extensive number of research studies have described human health effects of many of the types of exposures encountered by military personnel in the Gulf War. Relatively few, however, have evaluated rates of persistent symptoms and symptom complexes in relation to these exposures. As catalogued in some detail in the Institute of Medicine's *Gulf War and Health* series of reports, research on humans occupationally exposed to diverse types of chemical exposures such as petroleum exhaust or uranium dust have primarily evaluated rates of cancers and limited other diagnosed conditions. Therefore, general research on the effects of Gulf War-related exposures in human populations provides only limited insights concerning possible links between exposures and persistent symptomatic illness.

The Committee identified human population studies that evaluated chronic symptoms and symptom complexes in relation to only three types of chemical exposures associated with Gulf War service: pesticides, nerve agents, and organic solvents. Community studies have identified significant associations between low level exposure to agricultural pesticides and increased rates of symptoms similar to those of Gulf War illness—chronic cognitive problems, headaches, gastrointestinal problems, sleep disturbances, and mood alterations. Persistent symptoms similar to those of Gulf War illness have also been described in occupational studies of British sheep farmers regularly exposed to organophosphate sheep dip, and in other pesticide-exposed workers. In both community and occupational settings, chronic symptoms of this type have been reported in individuals with no history of pesticide poisoning, generally in relation to low-level exposures over a prolonged period. Long-term follow up of individuals exposed to sarin in terrorist attacks in Japan in the 1990s also indicates that some individuals developed persistent symptoms, balance irregularities, neurocognitive decrements, and alterations in brain structure that parallel those observed in Gulf War veterans. Individuals evaluated in these studies, however, had higher-level sarin exposures than those generally believed to be associated with Gulf War service.

In addition, chronic neurocognitive and mood symptoms have been described in workers occupationally exposed to organic solvents. Acute neurological, respiratory, and skin symptoms have also been reported in relation to fuel exposures, but studies have not reported on chronic symptomatic outcomes. No studies were identified that provide information on persistent symptoms or symptom complexes in relation to other types of Gulf War exposures. That is, human studies have not provided information on chronic symptomatic illness, unrelated to diagnosed conditions, that persists for many years after time-limited exposure to psychological stressors, petroleum smoke, uranium dust, vaccines, PB, sand and particulates, exhaust from tent heaters, or CARC paint.

In summary, studies in animal models have demonstrated delayed or persistent neurological effects following short-term exposure to a number of compounds associated with Gulf War service—PB, low-level sarin, pesticides, fuels and solvents, and multiple vaccines—effects that could plausibly relate to symptoms of Gulf War illness. Animal studies also indicate that some combinations of neurotoxicant exposures, at levels comparable to those experienced by Gulf War veterans, can produce neurological effects that differ from those of individual exposures. Research in human populations indicates that low-level exposure to pesticides, sublethal exposure to sarin, and exposure to organic solvents can be associated with chronic symptoms and symptom complexes similar to those of Gulf War illness. These chronic symptom complexes develop, in some cases, after exposure to neurotoxicants at levels that do not cause acute symptoms.

Overall, research in animal models has provided information essential for understanding the biological effects of Gulf War exposures. Recent studies that have identified persistent effects of low level exposures have been especially useful in this regard. General research on health effects of exposures in human populations has also been important in identifying exposed populations in whom elevated rates of persistent symptoms similar to those of Gulf War illness have been reported. Although both types of research provide valuable insights related to the cause or causes of Gulf War illness, application of these

findings to the Gulf War experience is limited in some respects. It is important, therefore, that general research findings related to biological and health effects of Gulf War exposures be considered in the context of what is known about the extent and patterns of exposures during the Gulf War, as well as associations between Gulf War exposures and Gulf War illness identified in studies of Gulf War veterans.

## **Evidence from Studies of Gulf War Veterans**

Although informative, research in animal models and general findings from studies of human populations cannot precisely characterize the impact of Gulf War exposures on military personnel who served in the 1990-1991 Gulf War. Associations between Gulf War illness and the diverse psychological, biological, and chemical exposures experienced during Gulf War deployment, at different levels and in different combinations, can only be directly evaluated in Gulf War veterans themselves. In light of the complex exposure scenario of the Gulf War, understanding the cause or causes of Gulf War illness requires careful consideration of findings from research on Gulf War veterans. The Committee reviewed, in detail, results from the large number of studies that have evaluated associations between chronic symptomatic illness in Gulf War veterans and experiences and exposures during the Gulf War. These include epidemiologic studies that have assessed risk factors for multisymptom illness in Gulf War veterans, as well as clinical studies that have evaluated measurable health outcomes in relation to Gulf War exposures.

**Major findings from Gulf War epidemiologic studies.** As detailed in previous sections of the report, epidemiologic studies have evaluated many possible risk factors for Gulf War illness. These have included hundreds of evaluations of persistent symptoms and multisymptom illness, variously defined, in relation to numerous exposures assessed by diverse variables. Exposure-illness associations have been assessed in many different populations of Gulf War veterans, with some veteran groups evaluated by multiple studies. Appendix A provides detailed findings from these studies, listed by type of exposure. For example, identified associations between symptomatic illness and variables related to chemical agents (e.g., being put on chemical alert, DOD-modeled proximity to the Khamisiyah demolitions) are listed together in a single table, Appendix A-2.

In reviewing epidemiologic findings related to risk factors for Gulf War illness, the Committee sought to determine the overall strength of evidence related to each exposure of interest. This required an assessment of whether Gulf War epidemiologic studies consistently indicated that an exposure was or was not significantly associated with symptomatic illness in Gulf War veterans, and whether there was evidence of a dose/response relationship. Table 2 summarizes findings from all epidemiologic studies that evaluated associations between Gulf War exposures and multisymptom illness in Gulf War veterans. As shown, the table identifies both the number of different Gulf War veteran populations in which each type of exposure was assessed, and the number of populations in which each exposure was significantly associated with symptomatic illness. Detailed results for all exposure variables are provided in Appendix A. For purposes of the summary in Table 2, findings related to each type of exposure in a given veteran population were counted only once. For example, some studies evaluated many different psychological stressors as risk factors for symptomatic illness in a given population of Gulf War veterans. Table 2 reports the number of different Gulf War veteran populations in which at least one psychological stressor was significantly associated with symptomatic illness.

Consistency of associations between exposures in theater and Gulf War illness. Epidemiologic studies have evaluated an extensive number of risk factors for Gulf War illness in numerous Gulf War veteran populations. As previously described, epidemiologic studies that reported only results of preliminary analyses—that is, analyses that did not adjust for confounding effects of multiple exposures—were not useful in identifying risk factors for Gulf War illness. As shown in Table 2, preliminary analyses of this type identified nearly all Gulf War exposures as significant risk factors for Gulf War illness in all Gulf War veteran populations. Illogical findings of this type are an expected result

of confounding in epidemiologic research, that is, the result of confusing the effects of multiple exposures with one another. For example, most Gulf War personnel who served in combat also took PB pills and used personal pesticides. In assessing exposure-illness associations, effects of serving in combat would be “mixed in” with, or confounded by, the effects of PB and pesticides, unless effects of each exposure are assessed independently, while controlling for the effects of other exposures.

Given the large number of exposures in theater and the high degree of correlation among exposures, epidemiologic studies that did not control for the confounding effects of multiple wartime exposures invariably produced results that were not helpful, and even misleading, for determining the causes of Gulf War illness. As detailed in Appendix A, the magnitude of associations identified by these preliminary analyses also provided little basis for distinguishing between effects of Gulf War exposures. These measures, typically odds ratios (OR) or risk ratios (RR), reflect the degree of increased illness risk associated with a given exposure. Individual OR and RR values for different exposures varied in different studies, but median values across studies were generally similar. For the majority of Gulf War exposures, median values indicated a three-to-four times greater risk for exposed, compared to unexposed personnel, in unadjusted analyses. Anthrax vaccine was consistently the weakest of identified risk factors in these analyses. That is, Gulf War illness risk for veterans who reported receiving the anthrax vaccine was usually less than twice that of veterans who did not recall receiving the vaccine, in unadjusted analyses.

In contrast, Gulf War epidemiologic studies that controlled for confounding effects of multiple wartime exposures provided clear distinctions between the many Gulf War exposures of interest. Across all studies that adjusted for effects of multiple exposures, only two exposures—the use of pyridostigmine bromide (PB) pills and the use of pesticides—were consistently identified as significant risk factors for Gulf War illness. As shown in Table 2, use of PB was significantly associated with multisymptom illness in six of six Gulf War veteran populations, and pesticide use was significantly associated with multisymptom illness in five of six veteran populations, in studies that controlled for effects of other wartime exposures.

Epidemiologic studies that controlled for effects of multiple exposures also identified factors that were *not* significantly associated with Gulf War illness. The largest number of risk factor variables assessed in Gulf War epidemiologic studies related to diverse psychological stressors during deployment. These included experiences that may have been extremely traumatic, (e.g. seeing soldiers maimed or killed), experiences associated with prolonged and intense stress (e.g., being in combat), and other types of psychological stressors not directly related to combat (e.g., change in marital status).

Results of adjusted analyses consistently indicated that psychological stressors during deployment were *not* significantly associated with Gulf War illness. Psychological stressor variables were assessed in seven different Gulf War veteran populations, using analyses that controlled for effects of other wartime exposures. As shown in Table 2, no stress-related variables were identified as significant risk factors for multisymptom illness in six of the seven Gulf War populations, after controlling for effects of deployment exposures. In addition, two of three studies that evaluated effects of sand exposures, and two studies that evaluated fuel exposures found they were *not* significant risk factors for Gulf War illness, after adjusting for effects of other exposures.

Epidemiologic findings related to exposure to smoke from oil well fires and possible exposure to chemical agents were not consistent, as indicated in Table 2. Oil fire smoke was identified as a significant risk factor for Gulf War illness by two of four studies that controlled for effects of other deployment exposures. In three of five populations, variables potentially indicative of exposure to chemical agents (e.g. hearing chemical alarms, exposure to nerve gas), were found to be significant risk factors for Gulf War illness, after adjusting for effects of other exposures. For several other deployment

**Table 2. Gulf War Illness in Relation to Experiences and Exposures During the 1990-1991 Gulf War:  
Summary of Evidence from Studies of Gulf War Veterans**

	Epidemiologic Studies of Gulf War Veterans: Association of Deployment Exposures With Multisymptom Illness				Clinical Evaluations of Gulf War Veterans: Association of Deployment Exposures with Measured Clinical Outcomes	
	<i>Preliminary Analyses* (no controls for other exposures)</i>	<i>Adjusted Analyses* (controlling for effects of other exposures)</i>				
	GWV populations in which association was assessed <sup>a</sup>	GWV populations in which association was assessed <sup>a</sup>	GWV populations in which association was sign. <sup>b</sup>	Dose-response effect identified?		
<b>Pyridostigmine bromide</b>	10	9	6	6	Yes	associated with sign. neurocognitive and HPA differences in Gulf War veterans
<b>Pesticides</b>	10	10	6	5	Yes	associated with sign. neurocognitive and HPA differences in Gulf War veterans
<b>Psychological stressors</b>	14	13	7	1		
<b>Chemical weapons</b>	16	13	5	3		associated with sign. neuroimaging and neurocognitive differences in Gulf War veterans
<b>Oil well fires</b>	9	8	4	2	Yes	
<b>Number of vaccines</b>	2	2	1	1	Yes	
<b>Anthrax vaccine</b>	5	5	2	1		
<b>Tent heater exhaust</b>	5	4	2	1		
<b>Sand/particulates</b>	3	3	3	1		
<b>Depleted uranium</b>	5	3	1	0		
<b>Solvents</b>	4	4	1	0		
<b>Fuel exposures</b>	5	4	2	0		
<b>CARC paint</b>	3	2	0	0		

Abbreviations: GWV = Gulf War veterans, sign. = statistically significant, HPA = hypothalamic-pituitary-adrenal axis, CARC = chemical agent resistant coating  
Notes: \*Detailed results for all exposure variables are provided in Appendix A; Preliminary analyses refer to methods that did not adjust for effects of other exposures during deployment.  
<sup>a</sup> Indicates total number of Gulf War veteran populations in which an association of multisymptom illness with the exposure of interest was evaluated  
<sup>b</sup> Indicates number of Gulf War veteran populations in which one or more variables reflecting the exposure of interest was sign. associated with multisymptom illness

exposures, there was insufficient information from Gulf War epidemiologic studies to assess their contributions as independent risk factors for Gulf War illness. These included DU, vaccines, exhaust from tent heaters, and CARC paint.

**Evidence of dose-response effects in relation to Gulf War illness.** A parameter commonly used to evaluate the likelihood of a causal relationship between an exposure and a health outcome is whether there is evidence of a dose-response pattern of association. This refers to a graded relationship between increasing levels of exposure and greater degrees of illness risk or severity. As indicated in Table 2, Gulf War epidemiologic studies have reported dose-response associations between multisymptom illness and several deployment exposures. Dose-response effects have been identified in relation to PB use, pesticide use, oil well fires, and the number of vaccines received, both by Gulf War studies that controlled for effects of confounding by other exposures, and by studies that did not.

A dose-response pattern of association between PB and Gulf War multisymptom illness has been identified by multiple studies, both in relation to the number of days PB was used, and the total number of pills taken during deployment.<sup>241,788,789,938,1466,1804</sup> Dose-response effects associated with pesticide use have also been identified, both in relation to the number of days that pesticides were used<sup>241</sup> and the amount of DEET used.<sup>564</sup> In addition, several studies provided indications that veterans who were closest to the Kuwaiti oil well fires, or were exposed to oil fire smoke for longer periods of time, have higher rates of symptomatic illness than veterans with less exposure.<sup>241,564,752,1466,1687</sup> A dose-response effect is also reflected in the observed association between Gulf War illness and the number of vaccines received for deployment.<sup>241,641,788,789,1698</sup>

**Association of Gulf War exposures with clinical findings in Gulf War veterans.** In addition to epidemiologic research on risk factors for multisymptom illness in Gulf War veterans, a variety of studies have assessed measurable clinical outcomes in Gulf War veterans in relation to Gulf War exposures. As summarized in Table 2, these studies have identified significant findings in Gulf War veterans on brain scans, neurocognitive testing, and measures of hypothalamic-pituitary-adrenal axis (HPA) function, which differ in relation to exposures during the Gulf War. Objectively-measured differences have been identified in association with veterans' reported use of PB and pesticides, as well as modeled estimates of exposure to nerve agents.

A recent collaborative study by investigators from the Army, the Boston VA, and Boston University School of Public Health, identified structural differences in the brains of Gulf War veterans in association with possible nerve agent exposure. Reduced white matter volume, identified using magnetic resonance imaging (MRI) scans, was significantly correlated, in a dose-response manner, with DOD-modeled estimates of nerve agent exposures resulting from the Khamisiyah weapons demolitions in March of 1991.<sup>599,1780</sup> In an earlier study, this research team also identified neurocognitive decrements in Gulf War veterans, which also differed in a dose-response manner with modeled levels of nerve agent exposure.<sup>1237</sup>

Boston investigators had previously identified measurable differences on tests of memory and attention among symptomatic Gulf War veterans, which were significantly associated with veterans' reported use of PB during the war.<sup>1512</sup> They have recently reported results from a DOD-funded project that evaluated neurocognitive function in a sample of Gulf War veterans who worked with pesticides during deployment.<sup>836</sup> Findings indicated that veterans with the highest level exposures to both pesticides and PB exhibited significantly increased rates of multisymptom illness, as well as significantly greater memory and motor function decrements, compared to veterans with low or no exposures. In addition, investigators from the Bronx VA have identified significant differences between Gulf War and nondeployed era veterans on multiple measures of hypothalamic-pituitary-adrenal (HPA) function. HPA differences were significantly associated with veterans' symptoms and with their reported use of PB and pesticides during deployment, but were not associated with psychological stressors or other Gulf War exposures.<sup>501-503</sup>

## Overview of the Evidence Linking Gulf War Illness with Experiences and Exposures During Gulf War Deployment

An extensive amount of information is available that contributes to understanding what caused Gulf War illness. Individually, single studies or types of information might suggest the possibility that an exposure *could* have caused Gulf War illness. But it is important to consider evidence of all types and studies from all sources to determine what the evidence most clearly indicates *did* cause Gulf War illness. Studies of Gulf War veterans consistently implicate only two wartime exposures as significant risk factors for Gulf War illness: use of pyridostigmine bromide pills as a nerve agent protective measure, and use of pesticides during deployment. This is consistent with what is known about the extent and patterns of these exposures in theater, and with general information from other human and animal studies. Studies of Gulf War veterans have also consistently indicated that psychological stressors during deployment are *not* significant risk factors for Gulf War illness. For several other deployment exposures an association with Gulf War illness cannot be ruled out, due to inconsistencies or limitations of available information.

**Psychological stress.** Studies of Gulf War veterans consistently indicate that serving in combat and other psychological stressors during the war are not significantly associated with Gulf War illness, after adjusting for effects of other wartime exposures. Time-limited biological effects of psychological stressors have long been described in human studies, and more extreme psychological stressors and trauma can lead to chronic psychiatric disorders such as PTSD. Combat and extreme psychological stressors were less widespread and less sustained in the Gulf War than in other wars, including current Middle East deployments, and PTSD rates are lower in Gulf War veterans than in veterans of other wars. Population-based studies generally indicate that between three and six percent of Gulf War veterans are diagnosed with PTSD and that the large majority of veterans with Gulf War illness have no psychiatric disorders. Serving in combat and other wartime stressors are associated with higher rates of PTSD in Gulf War veterans, but not with higher rates of Gulf War illness.

**Kuwaiti oil well fires.** Widespread exposure to smoke from the Kuwaiti oil well fires was unique to military service in the 1991 Gulf War, and most prominently affected ground troops in forward locations. Epidemiologic findings relating oil well fire smoke exposure to Gulf War illness have been mixed, although a dose-response effect has been identified by several studies. There is little information from human or animal research to indicate whether intense exposure to petroleum smoke or vapors can lead to persistent multisymptom illness. Although studies of Gulf War veterans do not provide consistent evidence that exposure to oil fire smoke is a risk factor for Gulf War illness for most veterans, questions remain about effects for personnel located in close proximity to the burning wells for an extended period. Limited findings from epidemiologic studies indicate that higher-level exposures to smoke from the Kuwaiti oil well fires may be associated with increased rates of asthma in Gulf War veterans, and that an association with Gulf War illness cannot be ruled out.

**Depleted uranium (DU).** Low-level exposure to spent DU munitions and dust is thought to have been widespread during the Gulf War and was most prominent among ground troops in forward locations. Recent animal studies have demonstrated acute effects of soluble forms of DU on the brain and behavior, but persistent effects of short term, low-dose exposures like those encountered by the majority of Gulf War veterans have only minimally been assessed. There is little information from Gulf War or other human studies concerning chronic symptomatic illness in relation to DU or uranium exposure. Exposure to DU in post-Gulf War deployments, including current conflicts in the Middle East, has not been associated with widespread multisymptom illness. This suggests that exposure to DU munitions is not likely a primary cause of Gulf War illness. Questions remain about long-term health effects of higher-dose exposures to DU, however, particularly in relation to other health outcomes.

**Vaccines.** Receipt of multiple vaccines over a brief time period is a common feature of overseas military deployments. About 150,000 Gulf War veterans are believed to have received one or two

anthrax shots, most commonly troops who were in fixed support locations during the war. Although recent studies have demonstrated that the anthrax vaccine is highly reactogenic, there is no clear evidence from Gulf War studies that links the anthrax vaccine to Gulf War illness. Taken together, limited findings from Gulf War epidemiologic studies, the preferred administration to troops in support locations, and the lack of widespread multisymptom illness resulting from current deployments, combine to indicate that the anthrax vaccine is not a likely cause of Gulf War illness for most ill veterans. However, limited evidence from both animal research and Gulf War epidemiologic studies indicates that an association between Gulf War illness and receipt of a large number of vaccines cannot be ruled out.

**Pyridostigmine bromide (PB).** Widespread use of PB as a protective measure in the event of nerve gas exposure was unique to the 1990-1991 Gulf War. Pyridostigmine bromide is one of only two exposures consistently identified by Gulf War epidemiologic studies to be significantly associated with Gulf War illness. About half of Gulf War personnel are believed to have taken PB tablets during deployment, with greatest use among ground troops and those in forward locations. Several studies have identified dose-response effects, indicating that veterans who took PB for longer periods of time have higher illness rates than veterans who took less PB. In addition, clinical studies have identified significant associations between PB use during the Gulf War and neurocognitive and neuroendocrine alterations identified many years after the war. Taken together, these diverse types and sources of evidence provide a consistent and persuasive case that use of PB during the Gulf War is causally associated with Gulf War illness.

**Pesticides.** The widespread use of multiple types of pesticides and insect repellants in the Gulf War theater is credited with keeping rates of pest-borne diseases low. Pesticide use, assessed in different ways, is one of only two exposures consistently identified by Gulf War epidemiologic studies to be significantly associated with Gulf War illness. Multisymptom illness profiles similar to Gulf War illness have been associated with low-level pesticide exposures in other human populations. In addition, Gulf War studies have identified dose-response effects, indicating that greater pesticide use is more strongly associated with Gulf War illness than more limited use. Pesticide use during the Gulf War has also been associated with neurocognitive deficits and neuroendocrine alterations in Gulf War veterans in clinical studies conducted many years after the war. Taken together, all available sources of evidence combine to support a consistent and compelling case that pesticide use during the Gulf War is causally associated with Gulf War illness.

**Nerve agents.** There have been no reports that U.S. forces encountered large-scale, high-dose exposures to chemical weapons during the Gulf War, but concerns have emerged related to possible long-term effects of low-dose nerve agent exposures during the war. Recent animal studies have identified brain, autonomic, behavioral, neuroendocrine, and immune effects of low-level sarin exposure that were previously unknown. Studies of individuals exposed to symptomatic but sublethal doses of sarin in Japanese terrorist incidents in the 1990s have identified central nervous system effects that have persisted for many years. The extent of low-level exposure to nerve agents during the Gulf War is unclear, however. Monitoring equipment used by U.S. forces had little capacity to detect nerve agents at levels that did not cause immediate symptoms. The Department of Defense estimates that about 100,000 U.S. troops may have been exposed to low levels of nerve agents following weapons demolitions at Khamisiyah, Iraq, but serious questions have been raised about the models used to determine who was exposed, and at what levels. It is also unclear whether additional low-level exposures may have occurred in other locations. Veterans' self-reported experiences concerning low-level nerve agent exposure in the Gulf War are particularly uncertain, and findings from epidemiologic studies linking chemical agents with Gulf War illness are inconsistent. Studies of Gulf War veterans have identified increased rates of brain cancer and measurable differences in brain structure and function that relate, in a dose response manner, to modeled nerve agent exposure levels resulting from the Khamisiyah demolitions. Findings from Gulf War clinical studies, and from other human and animal research, suggest that an association between Gulf

War illness and low-level nerve agent exposure cannot be ruled out, for whatever subgroup of veterans were exposed.

**Infectious disease.** A substantial proportion of Gulf War military personnel contracted acute gastrointestinal and respiratory infections during deployment, but there is little information concerning patterns of infection in theater and no evidence of widespread chronic illness resulting from those infections. Atypical leishmania infections were identified in a limited number of veterans who served in the 1990-1991 Gulf War, and a much larger number of leishmaniasis cases have been reported in personnel serving in the current Iraq War. Several studies have identified DNA indicators of mycoplasma infection in about 40 percent of symptomatic Gulf War veterans, but questions about testing methods have not been adequately addressed. Taken together, there is little clear evidence implicating infectious diseases as prominent causes of Gulf War illness. Questions remain, however, concerning the possibility that some individuals with Gulf War illness have undetected chronic leishmania and mycoplasma infections.

**Other exposures in theater.** A number of other potentially hazardous exposures in theater have been suggested as causing or contributing to Gulf War illness. These include fine sand and airborne particulates, exhaust from tent heaters, other fuel exposures, solvents, and freshly-applied CARC (chemical agent resistant coating) paint. For most, there is limited evidence of the types considered for other exposures. Available information, however, suggests that these exposures are not likely to have caused Gulf War illness for most affected veterans. Epidemiologic studies have provided little clear information linking any of these exposures to Gulf War illness and most were not most prevalent among ground troops who were forward deployed. Some, like sand, solvents, and fuel exposures, have also been widely encountered by personnel in current Middle East deployments. General information from human and animal studies indicates that fuel and solvent exposures can have neurological effects compatible with symptoms of Gulf War illness but neither has been associated with Gulf War illness in studies of Gulf War veterans.

**Combinations of exposures.** Compared to the diverse types of evidence available related to effects of individual exposures, research on effects of combinations of Gulf War-related exposures is limited. Gulf War studies consistently indicate that exposures in theater were highly correlated, that is, that personnel most often experienced individual exposures in connection with multiple other exposures. This includes significant correlations between use of different types of pesticides and between use of PB and pesticides. Animal studies have identified significant effects of exposure to combinations of PB, pesticides and insect repellants, sarin, and stress, at dosage levels comparable to those experienced by veterans during the Gulf War. Diverse findings have been reported in relation to chemical absorption, metabolism, and biological effects of mixtures of neurotoxicants, which differ from those of individual exposures. There is little information from human studies, however, including the many epidemiologic studies of Gulf War veterans, concerning combined effects of Gulf War exposures.

A persuasive theoretical case can be made that exposure to mixtures of neurotoxic compounds in theater are likely contributors to Gulf War illness. Such a case would draw on the consistency of evidence from all sources indicating that both PB and pesticides are significantly associated with Gulf War illness, the high correlation between troops' use of PB and pesticides during deployment, and synergistic effects between these exposures demonstrated by animal studies. Many of the pesticides used in the Gulf War, as well as PB and nerve agents, exert toxic effects on the brain and nervous system by altering levels of acetylcholine, an important nerve signaling chemical. Although such a case is compelling, little evidence is available from studies of Gulf War veterans to indicate whether or not Gulf War illness is associated with combinations of these exposures. This important possibility can and should be fully evaluated in Gulf War studies. Pending such assessments, it is not possible to definitively determine the extent to which mixtures of cholinergic and other neurotoxicant exposures during deployment contributed to Gulf War illness. Based on evidence from toxicological research in animals and what is known about patterns

of exposures during the Gulf War, an association between Gulf War illness and combined effects of neurotoxicant exposures cannot be ruled out.

There is almost no research to indicate if other wartime exposures interact synergistically with these neurotoxic compounds or with one another. That is, the biological effects of different mixtures of PB, multiple pesticides, low-level nerve agents, oil and dense smoke from burning wells, depleted uranium dust, fuel vapors, exhaust from tent heaters, CARC paint, airborne particulates, infectious agents, and receipt of multiple vaccines, experienced concurrently or over a brief time period, are unknown. Many have suggested that unknown and difficult-to-characterize effects may have been precipitated by an “exposure cocktail” or “toxic soup” effect during Gulf War deployment. While such a theory is intriguing, there is currently little evidence to indicate whether or not such effects actually occurred, and the extent to which they may have contributed to Gulf War illness.

### **Summary: What the Weight of Evidence Tells Us About the Causes of Gulf War Illness**

Seventeen years after the Gulf War, answers to the question of what caused Gulf War illness remain vitally important. An extensive amount of available information now permits an evidence-based assessment of the relationship of Gulf War illness to the many experiences and exposures encountered by military personnel during the Gulf War. The strongest and most consistent evidence indicates that use of pyridostigmine bromide (PB) pills and pesticides are significantly associated with increased rates of Gulf War illness. The consistency of epidemiologic evidence linking these exposures to Gulf War illness, identified dose-response effects, findings from Gulf War clinical studies, additional research supporting biological plausibility, and the compatibility of these findings with known patterns of exposure during deployment, combine to provide a persuasive case that use of PB pills and pesticides during the 1990-1991 Gulf War are causally associated with Gulf War illness. Gulf War studies also consistently indicate that psychological stressors during deployment are *not* significantly associated with Gulf War illness.

Evidence related to other deployment-related exposures is not as abundant or consistent as evidence related to PB, pesticides, and psychological stressors. For several wartime exposures, there is some evidence supporting a possible association with Gulf War illness, but that evidence is inconsistent or limited in important ways. Clinical studies of Gulf War veterans, studies of other populations exposed to sarin, and findings from animal studies all suggest that low-level nerve agent exposure can produce persistent neurological effects that may be compatible with symptoms of Gulf War illness. Therefore, an association between Gulf War illness and low-level nerve agents cannot be ruled out for those veterans who were exposed. However, inconsistencies in epidemiologic studies and unreliable exposure information preclude a clear evaluation of the extent to which such exposures occurred and may have contributed to Gulf War illness. Limited evidence from several sources also suggests that an association with Gulf War illness cannot be ruled out in relation to combined effects of neurotoxicant exposures, receipt of multiple vaccines, and exposure to the Kuwaiti oil fires, particularly for personnel in close proximity to the burning wells for an extended period.

There is little reliable information from Gulf War studies concerning an association of depleted uranium or anthrax vaccine to Gulf War illness. The prominence of both exposures in more recent deployments, in the absence of widespread unexplained illness, suggests that they are unlikely to have been major causes of Gulf War illness for the majority of ill veterans. Fine, blowing sand, solvents, and fuel exposures were also widely encountered in both the 1990-1991 Gulf War and in the current Iraq War. Limited evidence from Gulf War studies does not support an association between these exposures and Gulf War illness. All of the exposures described can be hazardous in some circumstances, however, and some veterans may have experienced adverse effects on a more limited basis.



### 3 | The Nature of Gulf War Illness

As described throughout this report, Gulf War illness refers to the complex of chronic symptoms that affect veterans of the 1991 Gulf War at excess rates. The Committee was charged with assessing the degree to which federally-funded Gulf War research programs have been effective in answering questions related to the nature, causes, and treatments of Gulf War-related conditions. Previous sections of the report have reviewed evidence related to the causes of Gulf War illness, and the limited amount of information available on its treatment. This section provides information related to the nature of Gulf War illness, that is, scientific research on biological and clinical characteristics of Gulf War illness, and the relationship of Gulf War illness to symptom-defined medical conditions in the general population. It also provides the Committee's recommendations for additional research to improve understanding of pathophysiological mechanisms associated with Gulf War illness.

Although veterans' symptoms are the most obvious and consistent indicators of Gulf War illness, dozens of research studies conducted by multiple investigators have identified objective biological parameters that significantly distinguish veterans with Gulf War illness from healthy controls. Identified differences relate to structure and function of the brain, function of the autonomic nervous system, neuroendocrine and immune alterations, and variability in enzymes that protect the body from neurotoxic chemicals. Most of these biological differences have been identified by research methods and protocols not routinely used in healthcare settings. They span a wide variety of findings that provide diverse indicators of biological differences associated with Gulf War illness but have not, as yet, provided measures that can be used as diagnostic tests. While scientific progress has been made in understanding the nature of Gulf War illness, important work remains in identifying the specific pathophysiological processes that underlie veterans' symptoms.

Understanding the biological nature of Gulf War illness and the specific physiological processes that contribute to veterans' symptoms is of great importance. Veterans have long sought answers to questions about the nature of Gulf War illness, as have their healthcare providers. Government policymakers also need this information to improve healthcare and benefits programs that serve Gulf War veterans. But identifying the specific biological mechanisms that contribute to Gulf War illness is most essential in order to identify processes that can be targeted for treatment and improved diagnostic testing.

The Committee reviewed the broad spectrum of studies that have evaluated biological and clinical parameters in Gulf War veterans, focusing most specifically on Gulf War-related multisymptom illness. That information is summarized in the pages that follow, with the Committee's recommendations for research needed to better understand the physiological nature of Gulf War illness. Preliminary information is also provided in connection with the current emphasis of the Committee's work, exploring biological processes not yet studied in Gulf War veterans that may contribute to a better understanding of Gulf War illness. Additional information is provided from the Committee's review of research on multisymptom conditions in the general population, conditions that include chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. These conditions are often compared to Gulf War illness, and have frequently been studied in Gulf War veterans. As will be described, studies indicate that Gulf War illness has both similarities and differences with multisymptom conditions found in the general population. Research related to these conditions can potentially provide useful insights concerning the biological mechanisms associated with Gulf War illness, and contribute to identifying beneficial treatments.

## Biological and Clinical Characteristics of Gulf War Illness

In its 2004 report, the Committee provided findings and recommendations on the major areas of research reviewed to that time. This included the Committee's finding that a growing body of evidence indicated that Gulf War Illness had an important neurological component. Since that time, the Committee has reviewed more recent studies of neurological findings in Gulf War veterans, as well as a wide range of studies evaluating other biological and clinical parameters.

The majority of studies of Gulf War veterans have historically provided broad assessments of population patterns of symptoms, hospitalization, and mortality, or have focused on psychiatric assessments in smaller, clinical samples. Studies that provided clinical evaluations of Gulf War veterans usually found that physical examinations and standard clinical testing methods identified a limited number of medical diagnoses, but few objective abnormalities in symptomatic veterans who did not have diagnosed conditions.<sup>160,393,464,879,1651</sup> This sometimes led investigators to conclude that there are no unusual or abnormal medical problems in Gulf War veterans. The absence of consistent diagnostic indicators from routine clinical testing methods suggested to some that Gulf War illness was not a medical problem with identifiable biological abnormalities. An alternate interpretation was that the biological abnormalities that underlie veterans' symptomatic illness were unfamiliar, and could not be detected by clinical tests routinely used to diagnose more familiar conditions.

Results from a diverse spectrum of research studies that are now available support the second perspective, that is, that veterans are medically ill, but that the physiological abnormalities that contribute to their illness are not captured by tests routinely used in clinical practice. This view has long been supported, in a broad sense, by the large number of population studies documenting consistent symptom profiles affecting substantial numbers of Gulf War veterans from different units and regions. This pattern of medically unexplained symptoms distinguished Gulf War veterans from contemporary veterans who did not serve in the Gulf War, and from veterans who have since served in hostile engagements in Bosnia and Iraq. Moreover, veterans' illnesses have not been linked to combat or deployment stress, but are consistently associated with neurotoxic exposures in the 1990-1991 Gulf War. The view of Gulf War illness as an organic illness is further supported by more recent studies that have identified diverse biological alterations in symptomatic veterans. Overall, available evidence consistently indicates that veterans with Gulf War illness are medically ill, but that clinicians have lacked the diagnostic tools needed to determine the nature of veterans' symptomatic illness.

For the first 10 years after Desert Storm, before most research described in the present report was available, the view of Gulf War illness as a stress-related psychological problem was more common. Limited research was conducted during those years to assess unfamiliar biological abnormalities in symptomatic veterans, that is, abnormalities not detected by routine clinical examination and testing. When the Committee issued its last major report, nearly all scientific findings that provided objective evidence of biological alterations in veterans with Gulf War illness came from studies of neurological parameters in symptomatic veterans. In the last several years, a growing number of studies have provided more detailed evaluations of biological parameters in relation to Gulf War illness, using research methods not previously used in Gulf War veterans and, in some cases, methods that have only recently been developed.

As will be described in the following pages, multiple studies have now reported diverse biological findings that distinguish symptomatic Gulf War veterans from control groups. These differences relate to a variety of biological systems, and include findings related to brain structure and function identified by neuroimaging scans and neurocognitive studies, alterations in autonomic function, findings associated with the immune system and hypothalamic-pituitary-adrenal axis, as well as novel findings related to the body's ability to protect itself from neurotoxic exposures. Recent studies that have relied on more routine

clinical testing methods, however, have continued to identify only limited differences between symptomatic Gulf War veterans and comparison groups.

In reviewing existing research on biological characteristics of Gulf War illness, the Committee has identified several methodological issues that appear to have played a role in whether studies identified clear distinctions, or raised additional questions as a result of inconclusive or conflicting results. Overall, the most informative studies have compared symptomatic Gulf War veterans to healthy controls, rather than combining all deployed Gulf War veterans into a single group—symptomatic and healthy veterans together—and comparing them to referent groups. Different Gulf War illness case definitions also appear to affect the clarity of study findings, with fewer distinctions identified by studies that use less specific case definitions of “ill” versus “well” veterans. Studies that distinguish Gulf War illness subgroups of importance appear to be particularly informative, for example, subgroups of veterans with different clinical characteristics, symptom profiles, and/or exposure histories.

Important progress has been provided by the growing body of research studies that have identified diverse, objectively measured biological alterations in veterans with Gulf War illness. These studies have provided insights into the biological systems and processes affected by Gulf War illness. Significant work remains, however, in characterizing the precise pathophysiological processes that underlie veterans’ symptoms. It is important to determine if differences identified by individual studies are replicable in other veterans affected by Gulf War illness or are most relevant to identifiable Gulf War illness subgroups. A clearer understanding is needed of how identified biological abnormalities contribute to veterans’ persistent symptoms, and how findings in different areas interrelate with one another. Most importantly, additional research is needed to determine how biological findings in veterans with Gulf War illness can be most usefully applied to identifying diagnostic tests and beneficial treatments.

## Brain and Central Nervous System Alterations in Gulf War Veterans

I had never had headaches before the war, but now I was having them frequently and they were getting worse. My dizziness was getting worse but wasn't bad enough yet to make me nauseous or to make me fall. By the summer of 1992, I was having violent and explosive vertigo attacks, and it was becoming more difficult to focus on anything. My concentration was so poor that I would forget how to reach my projected destination ...

--Army Colonel, Gulf War veteran<sup>716</sup>

As described in detail in the Committee's previous report, a growing body of evidence available in 2004 indicated that an important component of Gulf War illness is neurological in character. From the earliest years that veterans first returned from the Gulf War with symptoms of persistent headache, problems with memory and concentration, and balance and mood disturbances, clinicians have suspected that veterans' symptoms could be associated with central nervous system abnormalities. Clinical examinations, however, typically provided few indications of identifiable neurological disorders in Gulf War veterans. Today, multiple lines of research have supported early clinical and research indications that service in the Gulf War, for many veterans, has had persistent adverse effects on the central nervous system, as summarized in Table 1.

**Table 1. Summary of Research Findings Indicative of Persistent Central Nervous System Effects Associated with Gulf War Service**

<i>Area of Research</i>	<i>Major Findings in Gulf War Veterans</i>
Symptom evaluations in large population-based studies	All epidemiologic studies have identified prominent neurological symptom complexes affecting Gulf War veterans at significantly excess rates. Characteristic symptoms include persistent headache, memory and concentration difficulties, dizziness, mood, and visual disturbances.
Diagnosed neurological diseases	ALS affects Gulf War veterans at twice the rate of nondeployed veterans; Gulf War veterans downwind from 1991 Khamisiyah demolitions have died from brain cancer at twice the rate of other veterans in theater.
Neuroimaging research	Studies utilizing MRI, MRS, and SPECT scans have identified abnormalities in basal ganglia, brain stem, hippocampus, white matter volume, and cerebral blood perfusion that distinguish symptomatic from healthy veterans. MRI studies have identified reduced white matter volume in relation to the Khamisiyah demolitions.
Neuropsychological research	Multiple differences in neurocognitive function sign. distinguish symptomatic Gulf War veterans from healthy controls, after controlling for effects of psychological status. Neurocognitive abnormalities have also been identified in relation to neurotoxic exposures in theater.

Abbreviations: ALS = amyotrophic lateral sclerosis, MRI = Magnetic Resonance Imaging, MRS = Magnetic Resonance Spectroscopy, SPECT = Single Photon Emission Computed Tomography, sign. = statistically significant

All population-based studies have consistently identified symptom complexes suggestive of central nervous system abnormalities at significantly elevated rates in Gulf War veterans. Identified rates of two diagnosed diseases also suggest that Gulf War service led to neurological sequelae. Amyotrophic lateral sclerosis (ALS), a rare and fatal neurodegenerative condition, has been shown to affect Gulf War veterans at twice the rate of nondeployed era veterans.<sup>557,633,634,636</sup> The mortality rate from brain cancer has also been reported to be twice as high for veterans downwind from munitions demolitions at Khamisiyah, Iraq, in March of 1991, compared to veterans in other areas of theater.<sup>105,192</sup> Elevated rates of ALS and brain

cancer suggest the need for additional research to determine rates of other neurological disorders in Gulf War veterans, research that has not yet been conducted. These diagnoses have been identified in a relatively small number of Gulf War veterans, however, compared to the widespread problem of Gulf War illness.

This section of the report provides information on research that has evaluated central nervous system parameters in Gulf War veterans, with a particular focus on veterans with Gulf War illness. Several research teams have identified objective indicators of central nervous system alterations in Gulf War veterans using sophisticated brain scans and neurocognitive testing methods. Objectively measured differences identified in these studies are not diagnostic of familiar neurological diseases, but have been significantly associated both with veterans' symptoms and with chemical exposures during the war. Additional findings related to other aspects of neurological function, including autonomic regulation, peripheral neuromuscular and sensory findings, and neuroendocrine alterations, are each considered in separate sections.

Observers have sometimes commented, in reviews and editorials, that studies have not identified evidence of neurological abnormalities in Gulf War veterans.<sup>101,686,1310</sup> These comments have referred, most generally, to the lack of neurological findings identified on standard clinical evaluation, or the infrequency of peripheral neuromuscular and sensory abnormalities in Gulf War veterans. The Committee's review of findings from standard clinical examinations and peripheral nerve studies also found that these types of evaluations provide little indication of abnormalities in Gulf War veterans. It is important to distinguish the lack of findings in these areas, however, from the many significant findings identified in relation to other aspects of neurological function in symptomatic Gulf War veterans, including identified alterations in brain structure and function, and autonomic nervous system dysregulation.

## Neuroimaging Findings in Gulf War Veterans

Computed tomography (CT) scans and conventional MRI help rule out naturally occurring disorders; they rarely show lesions specific for neurotoxic disease.

-- *Experimental and Clinical Neurotoxicology*, 2000<sup>1359</sup>

Gulf War veterans have been evaluated with different types of neuroimaging scans, in research studies and clinical practice, to determine if Gulf War illness is associated with discernable abnormalities in brain structure or function. Several studies of this type were described in the Committee's 2004 report, and additional research has been reported in recent years, as summarized in Tables 2 and 3. The earliest clinical reports evaluated symptomatic Gulf War veterans using electroencephalograms (EEG), as well as standard computerized tomography (CT) and magnetic resonance imaging (MRI) scans of the head. As has often been the case with more routine clinical testing methods, few abnormalities were identified in these studies, and no significant differences between Gulf War illness cases and controls.<sup>46,563,878,893,1109</sup>

Early evaluations of Gulf War veterans at the University of Texas Southwestern (UTSW) also had not identified differences between symptomatic and healthy veterans on MRI or SPECT (single photon emission computed tomography) scans.<sup>563</sup> In a later study, UTSW investigators assessed the same veterans using long echo proton (<sup>1</sup>H) magnetic resonance spectroscopy (MRS).<sup>568</sup> Results indicated that veterans with the three Haley syndromes had significantly reduced N-acetyl-aspartate to creatine (NAA/Cr) ratios compared to healthy controls, reflecting reduced functioning brain cell mass in the brainstem and bilaterally in the basal ganglia. The specific regions affected differed for each of the three Haley Syndromes, as detailed in Table 2. Investigators also reported that reduced brain cell mass was associated with central dopamine activity in symptomatic veterans. Specifically, reduced neuronal mass

**Table 2. Published EEG and Brain Imaging Findings in Symptomatic Gulf War Veterans**

<b>Study</b>	<b>Group Studied</b>	<b>Method(s)</b>	<b>Key Findings</b>
Newmark <sup>1109</sup> 1995	65 active duty GWV evaluated in the CCEP	EEG	No EEG abnormalities identified
Haley <sup>563</sup> 1997	23 GWV with Haley Syndromes, 10 well GWV, 10 nondeployed controls	MRI, SPECT	No MRI differences between cases and controls. Similar proportion of cases and controls had foci of T2 signal intensity in subcortical white matter (26-30%). No SPECT abnormalities identified.
Amato <sup>46</sup> 1997	20 GWV referred for neurological evaluation	EEG, CT	No abnormalities on EEG, CT scans of the head.
Haley <sup>568</sup> 2000	22 Navy Reserve GWV with Haley syndromes, 2 <sup>nd</sup> sample of 6 GWV with Haley Syndrome 2, 18 veteran controls (9 GWV, 9 nondeployed)	Proton MRS	NAA/creatine ratio sign. lower in symptomatic GWV than controls: Syndrome 1 in basal ganglia, Syndrome 3 in brainstem, and Syndrome 2 in basal ganglia (14%) and brainstem (26%). Choline/creatine ratio sign. lower in basal ganglia of Syndrome 1 GWV than in controls. Syndrome 2 findings replicated in 2 <sup>nd</sup> GWV sample.
Meyerhoff <sup>1027</sup> 2001	11 GWV with CMI, 11 nonveteran controls	Proton MRS	NAA/creatine ratio sign. lower in right basal ganglia of ill GW veterans compared to controls. No differences in choline/creatine ratio.
Lee <sup>878</sup> 2005	33 symptomatic GWV evaluated in the UK GVMAP	EEG, CT or MRI	Results reported as “no evidence of any neurological disorder” specific measures not provided.
Menon <sup>1022</sup> 2004	10 symptomatic GWV, 5 nonsymptomatic GWV, Vietnam veteran controls	Proton MRS	NAA/creatine ratio in hippocampus was sign. lower in symptomatic GWV than in GWV and Vietnam controls, and in younger GWV than older GWV. No difference in choline/creatine ratios.
Levine <sup>893</sup> 2006	27 symptomatic GWV, 15 GWV with PTSD, 11 symptomatic nondeployed GWV, 4 nonsymptomatic GWV	EEG	GWV had no abnormalities on EEG
Spence <sup>1462</sup> 2006	21 GWV with Haley syndromes, 17 veteran controls (9 GWV, 8 nondeployed)	SPECT	Using a modified method to control for global signal effect, Syndrome 2 GWV had sign. lower average intracerebral blood flow and regional emission in areas of insula and frontal cortex. Effects were not observed using standard global scaling measure.

Abbreviations: GWV = Gulf War veterans, CCEP = DOD's Comprehensive Clinical Evaluation Program, EEG = electroencephalogram, MRI = Magnetic Resonance Imaging, MRS = Magnetic Resonance Spectroscopy, CT = Computerized Tomography, GVMAP = Gulf Veterans' Medical Assessment Program (U.K. registry for GWV), NAA = N-acetyl aspartate, SPECT = Single Photon Emission Computed Tomography, CMI = chronic multisymptom illness,<sup>464</sup> sign. = statistically significant

in the left, but not the right, basal ganglia was significantly correlated with increased central dopamine activity, estimated using the ratio of plasma homovanillic acid (HVA) to 3-methoxy-4-hydroxy-phenylglycol (MHPG).<sup>562</sup>

The UTSW MRS findings were soon replicated, in part, in a pilot study conducted by investigators at the San Francisco VAMC, in which 11 Gulf War veterans with chronic multisymptom illness (CMI) were found to have a significantly reduced NAA/Cr ratio in the right basal ganglia, compared to healthy

**Table 3. Preliminary Findings from Additional Neuroimaging Research on Symptomatic Gulf War Veterans**

<b>Study</b>	<b>Group Studied</b>	<b>Method(s)</b>	<b>Key Findings</b>
Weiner <sup>1758</sup> 2005	52 GWV with CMI, 83 GWV with inconsistent symptoms, 90 healthy GWV controls (GWV include 25 with Haley Syndrome 2)	Proton MRS	No sign. differences between groups in NAA/creatine ratios or NAA/choline ratios in basal ganglia or brainstem. Choline/creatine ratio in right basal ganglia sign. lower in Syndrome 2 GWV than healthy controls.
Haley <sup>558</sup> 2006	21 GWV with Haley syndromes, 17 veterans controls (9 GWV, 8 nondeployed)	CBF response to cholinergic challenge, using SPECT	Sign. differences in global CBF response to physostigmine infusion in Syndrome 2 GWV compared to controls and Syndromes 1 and 3; multiple regional differences identified between Syndrome 2 and controls.

Abbreviations: GWV = Gulf War veterans, CMI = chronic multisymptom illness,<sup>464</sup> CBF = cerebral blood flow, MRI = Magnetic Resonance Imaging, NAA = N-acetyl aspartate, SPECT = Single Photon Emission Computed Tomography, sign. = statistically significant

controls.<sup>1027</sup> More recently, researchers at the VAMC in Jackson, Mississippi, identified significantly lower NAA/Cr ratios in the left and right hippocampus of symptomatic Gulf War veterans compared to both healthy Gulf War veterans and Vietnam-era controls.<sup>1022</sup> And in 2006, UTSW researchers reported that veterans with Haley Syndrome 2 had significantly reduced cerebral blood flow, both globally and regionally in the frontal cortex and insula, compared to healthy controls. These findings were obtained with SPECT scans using a newly developed analytic method to control for global signal effect.<sup>1462</sup>

As previously mentioned, an additional Gulf War neuroimaging study of interest comes from the Boston VA Environmental Hazards Research Center, which did not specifically evaluate differences between symptomatic and healthy veterans. The Boston study used MRI scans to assess the volume of brain structures in 26 Gulf War veterans in relation to DOD-modeled exposure levels to sarin and cyclosarin after the Khamisiyah weapons demolitions in March of 1991.<sup>599</sup> Results indicated that Gulf War veterans had significantly reduced white matter volume, and enlarged right and left ventricles that varied, in a dose response manner, with increasing sarin and cyclosarin exposure. These results parallel findings of regional reductions in white matter volume in sarin-exposed survivors of the Japanese subway attack in 1995.<sup>1816</sup>

One additional MRI study of Gulf War veterans comes from National Institutes of Health investigators, but did not evaluate either multisymptom illness or exposures in theater. Rather, it compared brain volume measures in 37 Gulf War veterans with and without PTSD to those of nondeployed reservists and healthy civilians. Gulf War veterans, overall, as well as nondeployed reservists, had significantly smaller hippocampal volumes than healthy nonveteran controls. There were no significant differences between Gulf War veterans with and without PTSD.<sup>1739</sup>

Overall, accumulated findings from published studies have indicated that Gulf War illness is not associated with abnormalities on EEG, CT, or standard MRI evaluations. In contrast, proton MRS studies from three research teams have identified Gulf War illness-related alterations in three brain areas: brainstem, basal ganglia, and hippocampus. Additional studies have identified significantly reduced cerebral blood flow in the most severely ill Gulf War veterans, using specialized SPECT scan analyses, and reduced white matter volume in relation to modeled levels of nerve agent exposure. Most published imaging findings come from relatively small studies that assessed different types of abnormalities in different areas. Therefore, additional research is needed to determine if these findings can be replicated and/or further extended in larger samples.

The Committee also reviewed preliminary results from three additional federally-funded Gulf War neuroimaging projects. Although final results have not yet been published, early findings from two of the studies have been presented at Committee meetings and research conferences, and are summarized in Table 3. As shown, preliminary results from the San Francisco VAMC MRS project<sup>1758</sup> do not appear to support earlier findings from that group's pilot project<sup>1027</sup> and the initial UTSW MRS study.<sup>568</sup> Symptomatic veterans in this study have not been found to have reduced NAA/Cr ratios in basal ganglia or the brainstem.<sup>1758</sup> The Committee will review additional information from this study and final results when they are available, in order to gain a clearer understanding of the study's findings and apparent discrepancies with earlier projects.

Preliminary findings from an additional SPECT study of Gulf War veterans conducted by UTSW suggest additional cerebral blood flow abnormalities in Gulf War veterans with Haley Syndrome 2. Specifically, results indicate that symptomatic veterans differ from healthy controls in the magnitude and direction of cerebral blood flow response to cholinergic challenge, globally and in several identified brain regions.<sup>558</sup> In addition, early results from an additional MRI study of Gulf War veterans have been reported by researchers from Boston VA and Boston University.<sup>1224,1780</sup> Preliminary findings indicate that highly symptomatic Gulf War veterans have significantly reduced total white matter volume, compared to veterans with few or no symptoms.

Overall, a variety of neuroimaging studies have provided multiple indications of differences in brain structure and function that distinguish symptomatic Gulf War veterans from healthy controls. Few Gulf War illness-related brain abnormalities or case/control differences have been identified on tests routinely used in clinical practice—EEGs, CT scans, and visual evaluation of MRI. More specialized brain imaging studies, however, have consistently provided significant findings. Of the seven identified projects that have compared symptomatic Gulf War veterans with healthy controls using proton MRS, specialized SPECT analyses, and volume assessment of brain structures using MRI, six have identified significant Gulf War illness-related differences with healthy controls. This includes findings from four published studies and preliminary findings from two additional projects that have not yet been published. No case/control differences have been identified in preliminary findings from one unpublished study. An additional study has identified brain structure alterations in Gulf War veterans whose symptom profiles were not considered, finding an overall reduction in white matter volume in relation to modeled nerve agent exposures during the Gulf War.

The neuroimaging findings described have been an important step forward in documenting central nervous system alterations in relation to Gulf War illness and, to a limited extent, Gulf War exposures. Significant findings from the structural MRI and SPECT studies depended on technical methods developed in recent years, and therefore could not have been identified when the earliest Gulf War studies were conducted. Thus far, however, the variable methods used to evaluate different types of parameters in different brain regions have, in effect, produced multiple one-of-a-kind findings. In most cases, there have not been attempts to reproduce these results or integrate them with other findings in Gulf War veterans. The Committee appreciates and encourages the ongoing efforts of different research teams to carefully reexamine existing findings and to evaluate measures of brain structure and function in relation to additional health, functional, and exposure parameters in order to provide a fuller understanding of the nature of brain abnormalities in Gulf War veterans.

## Neurocognitive Findings in Gulf War veterans

When I first came back from the war, I had a lot of problems remembering things. One day I drove my kids to school and dropped them off, but then instead of driving home I just wandered around for a couple of hours because I couldn't remember where I was going.

-- SSgt PB, Gulf War veteran<sup>716</sup>

Prominent symptoms suggestive of neurological abnormalities in returning veterans—headache, memory and concentration problems, balance abnormalities, mood alterations—prompted early use of neuropsychological assessments in Gulf War veterans.<sup>78,499,624,1778,1779</sup> Neuropsychological studies provide objective measures of brain function, and constitute the largest body of research on central nervous system function in Gulf War veterans. Neuropsychological testing assesses different cognitive domains, which reflect function in areas of the brain that support different types of cognitive tasks. Executive system tasks, for example, reflect frontal lobe functioning. A wide variety of specialized tests are used clinically and in research studies to assess cognitive domains that include attention, executive system functioning, motor skills, visuospatial functioning, memory, mood, and performance effort. Neuropsychological testing has been used for many years to quantify neurocognitive deficits related to chemical exposures.<sup>47</sup> Evaluations can be used to assess damage in individuals who exhibit clinically obvious effects of chemical poisoning and also to identify more subtle dysfunction in exposed individuals without clinically obvious disease.<sup>48,939</sup> For example, neuropsychological studies indicate that agricultural workers chronically exposed to organophosphate pesticides exhibit identifiable decrements in processing speed and mood.<sup>1320,1483</sup>

There are two general categories of neuropsychological tests: (1) tests that characterize cognitive measures that are relatively stable over time, used to estimate baseline abilities that predate the illness condition being assessed, and (2) tests that have high specificity for detecting functions differentially affected by particular diseases or neurotoxicants. Performance on neurocognitive tests can be affected by a number of factors, which should be assessed and controlled for in well-conducted studies. These include age, education, gender, medical conditions, and psychiatric conditions like PTSD and depression. Motivational measures should also be assessed to ascertain if the examinee is exerting adequate effort to ensure the test battery is a valid assessment of their cognitive functioning.

The impact of psychological parameters—as contributors, as cofactors, and as outcomes, are extremely important considerations in neuropsychological testing, and can be complex. Changes in affect and emotional functioning, for example, depression or abnormal mood swings, can be symptoms of brain injury, and so are important to measure when assessing central nervous system function.<sup>1359,1779,1781</sup> On the other hand, posttraumatic stress disorder (PTSD) and other psychiatric conditions can directly affect neurocognitive function and test measures. It is important, therefore, to adjust measured neuropsychological outcomes for the effects of psychiatric conditions like PTSD or depression. But this can be problematic if psychological factors, such as depression, are “overcontrolled,” reducing or eliminating the effect of the brain injury being evaluated.<sup>1709,1779</sup>

The large number of projects that have evaluated neuropsychological parameters in Gulf War veterans have used diverse tests to assess different aspects of brain function in studies of varying design, size, and quality. One important distinction in this group of studies relates to whether neurocognitive function was assessed in relation to Gulf War deployment overall (e.g., comparing outcomes in deployed and nondeployed veterans), in relation to Gulf War illness (comparing symptomatic to healthy veterans), or in relation to exposures during deployment (comparing Gulf War veterans who had a particular exposure in theater to unexposed veterans). The first type of studies, those that assessed neuropsychological outcomes in relation to Gulf War deployment, do not provide insights specific to Gulf War illness, since they combine neuropsychological measures obtained in symptomatic veterans with those of healthy veterans. Those studies are summarized in Table 4.

**Table 4. Neurocognitive Evaluation of Gulf War-Deployed Veterans Overall, Not Differentiated by Veterans' Health Status**

<b>Study</b>	<b>Sample</b>	<b>Key Findings</b>
Goldstein <sup>499</sup> 1996	21 GWV, 38 nonveterans	GWV had sign. lower overall test performance, as measured by global impairment index based on 14 tests. No sign. differences on individual tests. Adjustment for psychological covariates reduced or eliminated group differences.
Axelrod <sup>78</sup> 1997	44 male GWV from Army Guard unit	Compared to normative values, GWV had sign. deficits on measures of motor speed and executive functioning.
Sillanpaa <sup>1409</sup> 1997	49 GWV from a single Army reserve military police unit	Neuropsych test performance sign. corr. with emotional dysfunction.
White <sup>1782</sup> 2001	193 GWV, 47 Germany deployed veterans	GWV scored sign. worse on tests of attention and executive functioning and mood states. Only mood functioning scores differed sign. after controlling for multiple comparisons and psychological diagnoses.
Lindem/Heeren <sup>910</sup> 2003		In GWV, sign. corr. between PTSD severity and poorer performance on tests of intellectual ability, sustained attention, motor speed and coordination, verbal learning, and mood. PTSD-related effects differed in veterans who did/did not report exposure to chemical agents.
Lindem/Proctor <sup>911</sup> 2003		Sign. more neuropsych symptoms reported by GWV than Germany deployed veterans. GWV neuropsych symptoms not sign. associated with performance deficits but were correlated with mood measures.
Lindem/White <sup>912</sup> 2003		In subset of 58 GWV and 19 Germany-deployed veterans tested for motivation and effort, most had perfect or near-perfect scores; similar subset of GWV and Germany deployed scored suboptimally.
David <sup>315</sup> 2002	207 British GWV, 78 nondeployed era veterans	GWV had sign. worse performance on tests of verbal and intellectual performance, motor speed, and dexterity. Differences were reduced or eliminated with adjustments for depression, multiple comparisons.
Gray <sup>527</sup> 2002	3,831 GWV Seabees, 4,933 Seabees deployed elsewhere, 3,104 nondeployed Seabees	GWV had sign. higher (worse) scores than other two groups on Cognitive Failures Questionnaire.
Vasterling <sup>1708</sup> 2003	72 GWV, 33 nondeployed veterans	No sign. difference on neuropsych measures.
Proctor <sup>1240</sup> 2003	143 Danish GWV, 72 nondeployed veterans	No sign. differences on neuropsych tests. GWV reported sign. more mood disturbances than nondeployed veterans.
Vythilingham <sup>1739</sup> 2005	14 GWV with PTSD, 23 GWV without PTSD, 22 nondeployed veterans, 29 healthy civilians	No neuropsych differences associated with PTSD or Gulf War deployment. GWV with and without PTSD and nondeployed reservists had sign. worse scores than healthy civilians on measures of visual and verbal memory.
Barrash <sup>102</sup> 2007	301 GWV, 99 era veterans deployed elsewhere	Only 1% of GWV and 4% of era veterans had neuropsych test results judged to be noncredible by independent reviews.

Abbreviations: GWV = Gulf War veterans, neuropsych = neuropsychological, PTSD = posttraumatic stress disorder, sign. = statistically significant, corr. = correlated

As shown in Table 4, studies that assessed neuropsychological function in relation to Gulf War deployment overall, but not specifically in veterans with chronic symptomatic illness, typically identified limited, or no, differences with reference groups. Deployment-related differences most often were found on tests of mood and emotional functioning, while identified differences in other neurocognitive domains were often diminished or eliminated when adjusted for effects of psychiatric conditions or emotional functioning.<sup>315,499,910,911,1782</sup> In reviewing these studies, the Institute of Medicine suggested that several may have overcorrected for depression and multiple comparisons, potentially masking subtle cognitive deficits in several domains.<sup>686</sup> Studies indicated that veterans' subjective cognitive symptoms were often not associated with objectively-measured performance deficits, and were more closely correlated with reduced mood scores.<sup>78,911</sup> Several studies reported that Gulf War veterans' level of motivation and effort during cognitive testing was similar to that of nondeployed era veterans, and that noncredible neuropsychological examination due to insufficient effort or malingering was not a significant problem in studies of Gulf War veterans.<sup>102,912,1782</sup>

**Neurocognitive findings in Gulf War veterans with multisymptom illness.** Studies that evaluated neurocognitive measures in symptomatic Gulf War veterans provide information more specifically relevant to Gulf War illness. Results of these studies are summarized in Table 5. As shown, neuropsychological evaluations consistently identified significant differences in neurocognitive function between symptomatic Gulf War veterans and healthy controls. These included differences in tests of attention and executive system functioning, memory, visuospatial skills, psychomotor skills, and mood and emotional functioning. Identified differences, while generally not large, were consistently significant and remained significant after adjustments for emotional functioning and psychiatric disorders. Findings, in some cases, indicated that symptomatic veterans display a slowing of response speed that affects their mental flexibility across multiple cognitive domains. This was most apparent on tests that were timed and computerized, on which small differences in reaction times could be detected.<sup>49,864</sup>

A potentially important distinction was first identified in a 1999 study of symptomatic Gulf War veterans from the Pacific Northwest,<sup>49</sup> confirmed in an expanded sample,<sup>1497</sup> and generally supported by other studies.<sup>1782</sup> The Pacific Northwest study identified a subgroup of symptomatic veterans who had significantly reduced neurocognitive performance on a variety of tests. These “slow cases” were similar to other symptomatic veterans on measures of psychological distress but exhibited a unique profile of objective deficits in memory, attention, and response speed. Investigators suggested that this subgroup should be the focus of additional study,<sup>49,1497</sup> supporting the broader point that subgroups of importance can be obscured when all symptomatic veterans are considered as a single group.<sup>1709</sup>

Neuropsychological evaluation of symptomatic veterans again indicated that many who report cognitive difficulties do not have objectively measurable neurocognitive deficits and that performance motivation is not generally a problem in Gulf War studies.<sup>78,135,315,1497,1512,1708</sup> And, although psychiatric and emotional parameters are often associated with reduced cognitive function in symptomatic Gulf War veterans, psychological factors do not account for or explain the neurocognitive deficits identified in symptomatic Gulf War veterans.<sup>686,1709,1779</sup>

**Neurocognitive function in relation to exposures in theater.** In discussing results of their studies of Gulf War veterans, some investigators have commented that identified neurocognitive deficits resemble those associated with neurotoxic exposures.<sup>49,78,864</sup> Several Gulf War studies have specifically evaluated veterans' neurocognitive function in relation to exposures they encountered during deployment, and are summarized in Table 6. Most evaluated neuropsychological outcomes in relation to neurotoxic exposures—nerve agents, pesticides, and pyridostigmine bromide (PB)—without specific reference to multisymptom illness. The majority of these studies have been conducted by researchers from VA's Boston Environmental Hazards Research Center and Boston University. A 2001 study from Dr. Roberta White and colleagues reported that, among veterans in the Fort Devens cohort, self reported pesticide use

**Table 5. Neurocognitive Evaluation of Symptomatic Gulf War Veterans**

<b>Study</b>	<b>Sample</b>	<b>Key Findings</b>
Axelrod <sup>78</sup> 1997	17 GWV with neurocog symptoms, 27 GWV with no neurocog symptoms	Veterans with cognitive symptoms exhibited sign. lower scores on tests of motor speed and executive functioning, and exhibited more psychological distress.
Haley <sup>563</sup> 1997	23 GWV with Haley Syndromes, 10 GWV and 10 nondeployed veteran controls	Symptomatic GWV, overall, scored sign. worse than controls on measures of generalized brain function and on specific measure of executive system functioning. Most sign. deficits were in veterans with Syndrome 2.
Hom <sup>624</sup> 1997	26 GWV with Haley Syndromes, 10 GWV and 10 nondeployed veteran controls	Symptomatic GWV had sign. lower scores on summary measures of intellectual and cognitive function and performed sign. worse on tests of abstract reasoning and problem solving, flexibility of thought, verbal and perceptual motor skills, tactile and visual perception, psychological and emotional functioning.
Anger <sup>49</sup> 1999	66 GWV with unexplained symptoms from WA and OR, 35 GWV controls	Symptomatic GWV, overall, had sign. poorer performance on memory test. "Slow case" subgroup of symptomatic GWV had sign. poorer performance on tests of memory, attention, and response speed.
Binder <sup>135</sup> 1999	100 GWV with unexplained symptoms	Subjective cognitive complaints sign. corr. with measures of response latency and affective distress, but modestly corr. with other neuropsych measures.
Storzbach <sup>1496</sup> 2000	241 GWV with unexplained symptoms, 113 GWV controls	Symptomatic GWV had sign. poorer performance on tests of memory, attention, and response time, and sign. greater psychological distress.
Storzbach <sup>1497</sup> 2001	239 symptomatic GWV, 112 GWV controls	In expanded sample, subgroup of "slow cases" were again identified who performed sign. worse on tasks of memory, attention, and response time. Other symptomatic GWV had very limited neuropsych differences from controls.
Binder <sup>136</sup> 2001	32 GWV with CFS, 62 GWV controls	GWV with CFS performed sign. worse on measures of reaction time and forced choice after controlling for effects of premorbid cognitive differences.
Bunegin <sup>193</sup> 2001	8 symptomatic GWV, 8 GWV controls	Symptomatic GWV had sign. poorer performance on tasks of memory and executive function on a computerized battery.
Lange <sup>864</sup> 2001	48 symptomatic GWV, 39 GWV controls	Symptomatic GWV had sign. poorer performance on measures of attention, concentration, information processing, and abstraction and conceptualization. Sign. differences remained after controlling for concurrent psychopathology.
David <sup>315</sup> 2002	65 GWV with CMI, 33 GWV with no symptoms	GWV with CMI performed sign. worse on multiple measures than healthy controls. Sign. poorer performance on vocabulary and digit-symbol tests after adjusting for depression, no sign. differences after Bonferroni correction.
Gray <sup>527</sup> 2002	845 GWV Seabees who met study criteria for GWI, 2986 who did not.	GWV with any of 4 multisymptom illnesses or more than 12 symptoms were sign. more likely to score $\geq 42$ on Cognitive Failures questionnaire than GWV without GWI (odds ratios between 3.3 and 12.7).
Sullivan <sup>1512</sup> 2003	207 treatment seeking GWV (120 referred for neuropsych evaluation), 53 treatment seeking nondeployed veterans	GWV performed sign. worse on measures of attention, visuospatial skills, memory, and mood. Differences remained sign. after controlling for effects of PTSD.

Abbreviations: GWV = Gulf War veterans, corr=correlated, neurocog = neurocognitive, neuropsych = neuropsychological, WA = Washington state, OR = Oregon, CFS = chronic fatigue syndrome, sign. = statistically significant

**Table 6. Neurocognitive Evaluation of Gulf War Veterans in Relation to Exposures in Theater**

<b>Study</b>	<b>Sample</b>	<b>Key Findings</b>
Sillanpaa <sup>1409</sup> 1997	49 GWV from a single Army reserve military police unit	Neuropsych test performance not sign. associated with exposure score derived from multiple exposures combined.
White <sup>1782</sup> Lindem <sup>910</sup> 2001	193 Army GWV in Fort Devens cohort	Self-reported pesticide exposure associated with sign. worse scores on all POMS subscales; self-reported exposure to chemical weapons associated with sign. worse scores on measures of memory, attention/executive functioning, and mood.
Proctor <sup>1237</sup> 2006	140 Army GWV with modeled estimates of nerve agent exposure	Modeled nerve agent exposure sign. associated, in dose-dependant pattern, with poorer performance on tests of fine psychomotor dexterity and visuospatial skills. Nerve agent exposure was not sign. associated with mood state.
Vasterling <sup>1708</sup> 2003	26 GWV with higher exposure levels, compared to 46 GWV with lower level exposures	Neuropsych test performance not sign. associated with higher level exposures (all exposures combined into one measure).
Sullivan <sup>1512</sup> 2003	207 GWV seeking treatment	GWV who reported using PB performed sign. worse than GWV who did not use PB on measures of executive system functioning.

Abbreviations: GWV = Gulf War veterans, POMS = Profile of Mood States, DU = depleted uranium, PB = pyridostigmine bromide, sign. = statistically significant

was significantly associated with measures of reduced mood functioning, and veterans who reported exposure to chemical warfare agents had significantly greater deficits on tests of memory, attention, and mood.<sup>1782</sup> Dr. Kim Sullivan and colleagues later reported that Gulf War veterans who used PB during deployment scored significantly worse on measures of executive system function than veterans who did not use PB, after controlling for effects of PTSD.<sup>1512</sup>

In 2006, Dr. Susan Proctor and colleagues identified significant neurocognitive deficits in veterans potentially exposed to sarin and cyclosarin following weapons demolitions near Khamisiyah, Iraq, in March of 1991. In detailed analyses, slowed performance on psychomotor and visuospatial tasks was significantly associated with modeled nerve agent exposure levels in a dose-response pattern, that is, greater deficits were correlated with greater exposure levels. This study is noteworthy for a number of reasons. In contrast to previous studies, exposure data were provided by DOD models that estimated levels of sarin and cyclosarin exposure for troops in specific locations, rather than relying on veterans' self-reported exposures. In addition, the neuropsychological testing had been done prior to veterans being notified about the Khamisiyah demolitions, providing test results for which both veterans and investigators were blind to veterans' exposure status.<sup>1237</sup> Study results parallel those from neurocognitive studies of Japanese citizens exposed to sarin in the 1995 subway terrorist incident, in whom persistent neurocognitive deficits were documented several years after exposure.<sup>1054,1128,1827,1828</sup>

Boston researchers are currently completing a project that involves neuropsychological testing of a large cohort of Gulf War military pest control personnel. Results of preliminary analyses are available in a DOD project report.<sup>836</sup> Early findings suggest that Gulf War veterans who had the highest-level exposure to both pesticides and PB during deployment have significantly worse performance in several psychomotor domains than veterans with low exposures. This study is particularly noteworthy because it evaluated a group of veterans who were highly knowledgeable concerning types and methods of pesticide use during the Gulf War, and is evaluating combined effects of PB and pesticides in relation both to neurocognitive measures and to multisymptom illness. The Committee looks forward to reviewing final results from this study as they become available.

As previously described, VA investigators have conducted periodic examinations of a small cohort of Gulf War veterans with high-level exposure to depleted uranium (DU) resulting from friendly fire incidents. The project did not specifically evaluate DU exposure, or compare outcomes in veterans exposed vs. not exposed to DU. Investigators did report, however, that in several of the longitudinal clinical evaluations, veterans with the highest levels of circulating uranium exhibited poorer accuracy on automated neurocognitive tests than veterans with lower-level circulating uranium.<sup>994,997,998</sup> Differences were statistically significant only in the 1997 evaluation, and investigators indicated that identified differences were driven by a subset of individuals who had suffered severe medical and psychiatric complications from their injuries. Therefore, there is no clear indication of whether or not circulating levels of DU are associated with identifiable neurocognitive deficits.

Two additional studies have assessed neurocognitive function in relation to a generalized “total exposure burden” measure that combined self-reports of multiple different deployment exposures such as oil fire smoke, combat, poor sanitation, and vehicle exhaust.<sup>1409,1708</sup> Measured neurocognitive deficits were not associated with exposure levels measured in this way. This supports other indications that identified associations between neurocognitive deficits and self-reported exposure to PB, chemical weapons, and pesticides are exposure-specific, that is, not attributable to greater endorsement of exposures, overall, by symptomatic veterans.

In summary, neuropsychological studies in Gulf War veterans consistently indicate that symptomatic veterans are affected by persistent, but subtle, "subclinical" central nervous system damage. Symptomatic veterans exhibit decrements in attention and executive system functioning, memory, visuospatial skills, psychomotor functioning, and mood. In some instances, study results reflected slowed response latencies across several cognitive domains. Measured deficits are generally modest and are not identified in all Gulf War veterans with cognitive symptoms. Characterizing Gulf War illness-related cognitive effects requires careful testing and analytic methods, involving comparisons between symptomatic Gulf War veterans and healthy controls, with appropriate adjustments for psychiatric and other confounders.

Neuropsychological research involving broad comparisons of deployed Gulf War veterans, overall, with nondeployed veterans, has provided limited information relevant to Gulf War illness. In contrast, comparisons between symptomatic and healthy Gulf War veterans consistently identify subtle neurocognitive decrements not explained by PTSD or other psychological conditions. A number of studies have indicated that research on identifiable veteran subgroups—those with more pronounced cognitive impairment and those with differing exposure histories, is likely to be most informative. This includes findings from several studies that neurocognitive decrements in Gulf War veterans are associated with exposure to pesticides, PB, and nerve agents during Gulf War deployment.

### **Assessment of Audiovestibular Function and Postural Stability**

Veterans with Gulf War illness consistently report multiple symptoms suggestive of central nervous system alterations. Dizziness and balance difficulties are common, and figure prominently in two Gulf War illness case definitions.<sup>565,752</sup> Two research teams have conducted investigations to determine if these problems relate to measurable organic irregularities associated with balance. University of Texas Southwestern investigators identified a variety of audiovestibular abnormalities in symptomatic veterans.<sup>563,1304</sup> These included greater interocular asymmetry in saccadic velocity and rotation-induced nystagmus, particularly among veterans meeting criteria for Haley Syndrome 2, the group in whom dizzy spells were most frequent.

Symptomatic Gulf War veterans were also evaluated on measures of sensory organization and postural sway by investigators at the East Orange, New Jersey, VA. Preliminary results were presented to the Committee by Dr. Thomas Findley<sup>438</sup> and additional details presented at the 2004 conference of the

American Academy of Physical Medicine and Rehabilitation.<sup>27</sup> Significant abnormalities related to postural stability and sensory organization were identified in symptomatic veterans: over 50 percent scored more than 2 standard deviations below normal on quantitative balance testing, compared to 10 percent of healthy controls. Only methodological papers related to this study have been published in the peer reviewed literature, however.<sup>233,234</sup>

## **Autonomic Nervous System Alterations in Gulf War Veterans**

The autonomic nervous system (ANS) is the part of the nervous system that regulates involuntary, or “automatic” physiological activities. The body’s ability to maintain normal organ function and respond to changing biological conditions depends on ANS regulation of processes such as circulation, breathing, digestion, and temperature control. Autonomic neurons connect the brain and spinal cord with all major organs and glands of the body via its three major components, the sympathetic, parasympathetic, and enteric nervous systems. Signaling utilizes the neurotransmitters acetylcholine and norepinephrine, as well as a variety of other chemical messengers. Autonomic pathology can be associated with diverse symptoms such as dizziness, weakness, digestive abnormalities, and sexual dysfunction, and can also be an important feature of conditions such as diabetes and Parkinson’s disease.<sup>457,537,935,1368</sup> Different aspects of autonomic function can be evaluated in different ways; no single test is all inclusive.<sup>936</sup> Autonomic tests frequently assess ANS regulation of cardiovascular function, by determining effects of different types of physiological challenges on parameters related to heart rate and blood pressure.

A potential link between Gulf War illness and ANS dysregulation has been posited from several perspectives. These include concern about effects of cholinergic exposures during the war,<sup>740,1071</sup> the possible relationship of many Gulf War illness symptoms to ANS dysregulation, and observed ANS alterations in multisymptom conditions like chronic fatigue syndrome and fibromyalgia. One of the earliest reports of a possible autonomic problem in Gulf War veterans came from a study presented at a federal Gulf War research conference. Investigators from the Detroit VA identified an excess of gall bladder disease requiring surgery in Gulf War veterans and hypothesized the condition could be the result of bile stasis due to autonomic dysregulation.<sup>1049</sup> Since then, multiple research teams have evaluated autonomic function more directly in symptomatic veterans, using a variety of testing methods. Key findings from published studies are summarized in Table 4.

Additional information on autonomic testing of symptomatic Gulf War veterans has been provided by two federally-funded research projects. Preliminary results from a project conducted by Midwest Research Institute were presented to the Committee by Dr. Antonio Sastre.<sup>1352</sup> Findings from this and additional Gulf War autonomic research conducted at Georgetown University are publicly available in Department of Defense project reports, but have not been published in research journals.<sup>251,1353</sup> Findings are included in the summary discussion here because the projects were, in some respects, more comprehensive than other Gulf War ANS studies and provide context for the published studies listed in Table 4. Key findings from the two additional federal Gulf War ANS projects are summarized in Table 5.

As shown in the tables, studies have identified a variety of ANS measures that significantly distinguish veterans with Gulf War illness from healthy controls, using different testing methods and evaluating different Gulf War illness populations. The diversity of study approaches used and groups evaluated make direct comparison of study results problematic, although a number of commonalities can be identified.

First, it appears, from all but one of the studies listed, that veterans with Gulf War illness differ significantly from healthy controls on multiple measures of autonomic function. Studies identified few or no differences in baseline cardiovascular parameters, but significant differences in response to

**Table 4. Published Studies of Autonomic Function in Symptomatic Gulf War Veterans**

<b>Study</b>	<b>Group Studied</b>	<b>Autonomic Tests</b>	<b>Key Findings</b>
Davis <sup>321</sup> 2000	14 GWV with CFS or ICF, 27 GWV and nonveteran controls	NMH during 3-stage tilt table testing (isoproterenol in stages 2 and 3)	Sign. more symptomatic GWV had NMH response to tilt in stage 1 and overall. Symptomatic GWV had sign. greater systolic BP, HR, and change in HR with stage 1 tilt.
Peckerman <sup>1184,1185</sup> 2000, 2003	51-55 GWV with CFS or ICF (16 with PTSD), 42-47 GWV controls	BP responses to speech and arithmetic stress tests, cold pressor test, BP change between supine and standing positions	Symptomatic GWV had sign. less BP response to cognitive stressors, responses correlated with symptom severity and functional impairment. BP differences were most pronounced in symptomatic GWV with PTSD. No differences on cold pressor test.
Sharief <sup>1397</sup> 2002	39 symptomatic GWV, 18 GWV controls	Valsalva ratio, standing ratio, sympathetic skin response	Findings reported as “no real differences” on any tests (statistical results not provided).
Fiedler <sup>433</sup> 2004	12 GWV with CFS, 19 GWV controls	BP and HRV response to diesel vapor exposure	Symptomatic GWV had sign. increased systolic BP and respiratory variability response to diesel vapors. They also had blunted reactivity to (less increase in BP, HRV) and recovery from behavioral tasks in the presence of diesel exposure, but not in the absence of exposure.
Stein <sup>1481</sup> 2004	11 GWV with CMI (6 male/5 female), 26 FM patients, 36 controls	24 hour electrocardiogram	GWV had sign. lower 24-hour short term high frequency HRV than controls. Males and females differed on multiple HRV measures over the 24 hour period. Overall, female GWV and FM patients had sign less. HRV than controls and male patients.
Haley <sup>569</sup> 2004	21 GWV with Haley syndromes, 17 veteran controls	24 hour electrocardiogram and BP, Valsalva ratio, tests of sympathetic function (silastic sweat imprint, sympathetic skin response)	Symptomatic veterans had sign. less nighttime increase in HRV high frequency power and less decrease in nighttime HR than healthy controls. No differences on measures of circadian BP, Valsalva ratio, sympathetic function tests.
Lucas <sup>937</sup> 2005	49 GWV with CMI, 44 GWV, 45 nondeployed veteran controls	BP, HR, respiratory rate, end-tidal CO <sub>2</sub> , symptoms, and NMH in relation to 2 stage tilt test (isoproterenol in stage 2)	Veterans with CMI had sign. more and faster onset of symptoms during tilt than controls. Symptomatic GWV had nonsign. higher rate of NMH, sign. higher respiratory rate, and sign. lower tidal CO <sub>2</sub> with stage 1 tilt.

Abbreviations: GWV = Gulf War veterans, CFS = chronic fatigue syndrome, ICF = idiopathic chronic fatigue, NMH = neurally mediated hypotension, PTSD = posttraumatic stress disorder, FM = fibromyalgia, CMI = chronic multisymptom illness,<sup>464</sup> BP = blood pressure, HR = heart rate, HRV heart rate variability, sign. = statistically significant

physiological challenges. Findings most often indicated a blunted, or reduced, autonomic response to those challenges.<sup>321,433,1185,1353</sup> In addition, both published studies that monitored electrocardiograms over a 24-hour period identified significantly diminished heart rate variability in the high frequency range in symptomatic Gulf War veterans—observed over a 24-hour period in one study, and during nighttime hours in the other.<sup>569,1481</sup> Second, results of these studies indicate that methodology is extremely important in understanding ANS function in Gulf War illness. All three studies that tested ANS function using the Valsalva maneuver, for example, found no difference between cases and controls, indicating

**Table 5. Additional Results from Federally-Funded Gulf War Autonomic Research**

<b>Study</b>	<b>Group Studied</b>	<b>Autonomic Tests</b>	<b>Key Findings</b>
Clauw <sup>251</sup> 2001	17 symptomatic GWV, 31 controls	24 hour electrocardiogram and effects of tilt testing on HR and HRV	No differences in baseline HR and BP. GWV had sign. greater diastolic BP increase response to tilt and sign. greater daytime low frequency HRV than controls that, unlike controls, dropped significantly during the night .
Sastre <sup>1353</sup> 2004	49 GWV with GWI (KS), 19 GWV and 23 nondeployed veteran controls	Continuous BP and electrocardiogram during deep breathing, sustained hand grip, Valsalva maneuver, arithmetic stress, emotional stressor, and tilt testing	Limited case/control BP and HR differences with breathing and emotional stressors, no differences with Valsalva, arithmetic or hand grip stress. Cases had sign. higher mean BP at baseline, numerous sign. case/control HRV differences during and after tilt. GWI cases had sign. less HR and HRV response to tilt in both spectral and time domains (lower total power, low frequency power, SDNN, and %NN).

Abbreviations: GWV = Gulf War veterans, GWI (KS) = Gulf War illness, defined using Kansas criteria,<sup>1476</sup> BP = blood pressure, HR = heart rate, HRV heart rate variability, NN = time interval between normal beats in electrocardiogram, SDNN = standard deviation of NN intervals, %NN = the proportion on NN intervals greater than 50 msec., sign. = statistically significant

that pathways involved in this test are not associated with Gulf War illness.<sup>569,1353,1397</sup> Alterations in sympathetic skin response and simple assessments of cardiovascular changes with standing also were not linked with Gulf War illness in several studies.<sup>569,1185,1397</sup> The only study that found no ANS differences between symptomatic Gulf War veterans and controls relied on three tests also shown by other studies not to be informative.<sup>1397</sup> In contrast, significant differences between cases and controls were demonstrated in all studies that assessed ANS function using tilt table testing and/or 24-hour electrocardiogram.<sup>251,321,569,937,1353,1481</sup> It is important to emphasize, therefore, that ANS research in Gulf War veterans requires the use of appropriate ANS testing methods, and that reliable conclusions about ANS function cannot be based on tests that are not informative in this population.<sup>686,1310,1397</sup>

In addition, the specific ANS differences associated with Gulf War illness varied from study to study. In general, it appears that more pronounced ANS differences were identified in studies that used more symptomatic, narrowly-defined Gulf War illness “case” subjects. Gulf War veterans who meet case criteria for chronic fatigue syndrome (CFS), for example, are required to be more highly symptomatic than cases defined according to the less restrictively defined chronic multisymptom illness (CMI).<sup>465</sup> In tilt table testing, Gulf War veterans with CFS had significantly higher rates of neurally mediated hypotension (NMH) than healthy controls.<sup>321</sup> Using a similar tilt testing protocol, however, veterans who met CMI criteria had only a nonsignificant excess of NMH, but did have a pronounced symptomatic responses to tilt.<sup>937</sup>

In addition to differences associated with case definition, studies with small sample sizes generally identified fewer significant ANS findings than larger studies. Studies have also indicated that ANS function may vary in different veteran subgroups. Single studies have reported that some ANS findings were more pronounced in symptomatic veterans who also had PTSD,<sup>1184</sup> and in female compared to male veterans.<sup>1481</sup> This suggests that sample size and selection can have important effects on the types of ANS findings obtained, and on whether Gulf War illness-related distinctions are identified at all. For example, the study that identified pronounced ANS distinctions between male and female Gulf War veterans, but less difference between Gulf War illness cases and controls, relied on a sample of just 11 Gulf War veterans.

Many of the research limitations described appear to have been addressed in the Midwest Research Institute project, which identified the most extensive ANS differences between Gulf War illness cases and healthy veteran controls.<sup>1353</sup> The project administered a multifaceted ANS battery to a relatively large, population-based sample of Gulf War-era veteran cases and controls, and identified Gulf War illness cases using a validated case definition. Some ANS tests identified no differences between cases and controls, while others identified multiple ANS differences that were internally consistent. The Committee is troubled that these results have not yet been published, however. Still, the consistent and extensive Gulf War illness-related ANS findings identified in this project support the importance of using more thorough testing protocols in suitably-sized and defined Gulf War illness case and control groups. The Committee urges these investigators to publish their findings at the earliest opportunity and looks forward to reviewing them further at that time.

Despite consistent indications that symptomatic Gulf War veterans differ significantly from healthy controls on ANS measures, the variability and limitations of current studies do not allow a clear characterization of Gulf War illness-related autonomic dysfunction. Individual findings appear to suggest alterations in central,<sup>1185</sup> parasympathetic,<sup>569,1481</sup> or sympathetic<sup>251,1481</sup> ANS processes, or a combination of these.<sup>1353</sup> Understanding the physiological implications of these findings is also complex. Neurophysiologists do not universally agree on how some ANS alterations are best interpreted, for example, whether HRV frequencies in different ranges clearly reflect sympathetic tone, parasympathetic tone, or aspects of both.<sup>385,1169,1527</sup> More comprehensive research is needed to better understand existing ANS findings and further characterize autonomic function in symptomatic Gulf War veterans.

## **Neuromuscular and Sensory Findings in Gulf War Veterans**

Symptoms reported by Gulf War veterans frequently include muscle pain and weakness and can also include numbness, and tingling sensations in the extremities. Such symptoms potentially indicate abnormalities in peripheral nerve function related to sensation and motor function. In addition to research on central nervous system and autonomic function in veterans with Gulf War illness, multiple studies have tested peripheral nerve parameters associated with sensory and neuromuscular function.

Theories concerning possible causes of muscle weakness and fatigue in Gulf War veterans have included suggestions that exposure to acetylcholinesterase inhibitors may have had persistent adverse effects on neuromuscular junctions. As previously described, peripheral neuropathy is a characteristic feature of the delayed neurotoxic condition associated with organophosphate poisoning.<sup>934</sup> One large survey of British Gulf War veterans queried veterans in detail about the presence and severity of numbness and tingling in each limb to identify patterns indicative of peripheral neuropathy. Ten percent of Gulf War veterans had symptoms suggestive of peripheral neuropathy, with highest rates among veterans who reported handling pesticides and experiencing side effects from pyridostigmine bromide pills during deployment.<sup>241</sup>

Several of the largest U.S. Gulf War studies that assessed peripheral nerve function compared measures obtained in all deployed Gulf War veterans with those of veterans who did not serve in the Gulf War. These studies, summarized in Table 6, combine clinical results from symptomatic and healthy Gulf War veterans and so do not provide information specifically related to Gulf War illness. In the large VA clinical study that compared Gulf War with nondeployed era veterans, Gulf War *deployment* was not associated with excess rates of peripheral neuropathy.<sup>319</sup> Similarly, two additional studies reported no significant differences in peripheral nerve or muscle strength measures between Gulf War veterans, as a group, and veterans who did not serve in the Gulf War.

**Table 6. Studies Assessing Sensory and Neuromuscular Function in Gulf War Veterans, Not Differentiated by Health Status**

<i>Study</i>	<i>Groups Studied</i>	<i>Parameter(s) evaluated</i>	<i>Key Findings</i>
Kaiser <sup>738</sup> 2000	527 GWV Seabees, 969 nondeployed GW-era Seabees	Handgrip strength	No differences in muscular strength between GWV and nondeployed veterans. No associations between muscular strength and use of PB or insecticides.
Joseph <sup>729</sup> 2004	56 GWV and 120 other veterans referred to a physical medicine/ rehabilitation clinic	Motor and sensory nerve conduction tests, needle EMG	GWV referrals had sign. fewer confirmed cases of radiculopathy, no sign. difference in confirmed cases of generalized peripheral neuropathy or mononeuropathy.
Davis <sup>319</sup> Eisen <sup>393</sup> 2004,2005	1,061 Gulf War and 1,128 nondeployed GW-era veterans	Neurological examination (reflex and manual muscle testing, sensory testing), nerve conduction studies	Deployed GWV had sign. more symptoms of limb numbness or tingling. No sign. difference in rates of diagnosed peripheral neuropathy based on abnormalities on exam or nerve conduction studies. Group results for specific tests not reported.

Abbreviations: GW = Gulf War, GWV = Gulf War veterans, PB = pyridostigmine bromide, EMG = electromyography, sign.= statistically significant

Most Gulf War studies in this area, however, have evaluated sensory and neuromuscular parameters specifically in symptomatic Gulf War veterans. Results of these studies are more relevant to Gulf War illness, and are summarized in Table 7. As shown, multiple studies used a variety of testing methods to objectively measure sensory and motor nerve function and muscle strength in symptomatic Gulf War veterans. Several studies focused specifically on Gulf War veterans who had pronounced symptoms of muscle weakness, numbness, and pain.

Despite the prominence of symptoms of this type in Gulf War veterans, very few studies have identified any objective indications of peripheral neuropathy or abnormal muscle function in symptomatic veterans. Standard neurological examinations revealed very few abnormalities and no significant differences between symptomatic and healthy veterans. This parallels the sparsity of neurological findings identified, overall, in Gulf War studies that have included physical examinations.<sup>464,788,878,893</sup> In addition, electrodiagnostic testing using electromyography (EMG) and nerve conduction tests identified few abnormalities or significant differences related to Gulf War illness.

Four studies identified measurable, but limited, peripheral nerve findings in symptomatic Gulf War veterans.<sup>160,563,704,1186</sup> Three indicated that symptomatic veterans have significantly higher (less sensitive) sensory thresholds than well veterans. These included two early studies—one from the U.K. and one from the University of Texas Southwestern—which reported that symptomatic Gulf War veterans had elevated cold sensory thresholds.<sup>563,704</sup> A third study from the East Orange, New Jersey, VA reported that symptomatic veterans had elevated thresholds for detecting light touch.<sup>1186</sup> The New Jersey study also found that higher tactile thresholds in both symptomatic and healthy Gulf War veterans were strongly associated with use of pyridostigmine bromide during the war.

Findings of small sensory fiber abnormalities in Gulf War veterans can only be considered preliminary, however. The two studies that reported cold threshold abnormalities relied on very small, nonrepresentative samples—14 symptomatic British veterans from a veterans' organization<sup>704</sup> and five symptomatic U.S. Navy Seabees from a single reserve unit.<sup>563</sup> The New Jersey study that identified elevated tactile thresholds utilized a larger and more diverse sample of symptomatic Gulf War

**Table 7. Studies Assessing Sensory and Neuromuscular Function in Symptomatic Gulf War Veterans**

<b>Study</b>	<b>Groups Studied</b>	<b>Parameter(s) evaluated</b>	<b>Key Findings</b>
Jamal <sup>704</sup> 1996	14 symptomatic GWV, 13 civilian controls	Heat, cold, and vibratory sensory testing; motor and sensory nerve conduction, needle EMG	Symptomatic GWV had sign. higher cold threshold, greater sural nerve latency, and reduced median nerve sensory action potential compared to controls. No case/control differences on other measures.
Amato <sup>46</sup> 1997	20 GWV referred for neuromuscular evaluation with severe muscle weakness or pain (no controls)	Serum CK, muscle strength tests, nerve conduction studies, repetitive nerve stimulation, quantitative and single-fiber EMG, muscle biopsies	All GWV had normal muscle strength and tone, no evidence of polyneuropathy. 6 GWV had mildly elevated CK, 2 had abnormal nerve conduction. EMGs were normal except for 1 GWV with single-fiber jitter. 5 GWV had nonspecific abnormalities on muscle biopsy.
Haley <sup>563</sup> 1997	23 male GWV with Haley syndromes, 10 GWV controls, 10 nonveteran controls	Somatosensory evoked potentials in all subjects. In 5 cases: nerve conduction studies, quantitative and single fiber EMG, sensory testing (heat, cold, vibration)	Syndrome 2 cases had prolonged mean LP-P37 latency, syndrome 3 cases had prolonged PF-LP latency. No case/control differences in evoked potential abnormalities. All 5 cases tested had cold threshold abnormalities, 3 had abnormal vibratory threshold. Normal nerve conduction, EMGs.
Peckerman <sup>1186</sup> 1999	29 male GWV with CFS, 31 GWV controls	Tactile, thermal, and vibratory sensory testing	Symptomatic GWV had sign. higher tactile thresholds than controls. No case/control differences in thermal and vibratory tests. In all GWV, elevated tactile thresholds were sign. associated with using PB and burning human waste in theater.
Bourdette <sup>160</sup> 2001	244 GWV with GWUI, 107 GWV controls	Handgrip strength in fatigued cases, nerve conduction studies and EMG in 13 veterans with neurological exam abnormalities	Sign. more GWUI cases had reflex abnormalities. Cases with unexplained fatigue had sign. less handgrip strength than controls. 15 of 23 GWUI cases with peripheral neurological symptoms had abnormal findings on neuro exam (distal sensory impairment, abnormal reflexes). None had nerve conduction abnormalities, 1 of 13 had EMG abnormality.
Rivera-Zayas <sup>1293</sup> 2001	12 GWV with 2 or more symptoms of peripheral neuropathy (no controls)	Reflex and manual muscle tests, motor and sensory nerve conduction studies, needle EMG	No reflex or muscle abnormalities on physical exam. 2 GWV had nerve conduction abnormalities consistent with carpal tunnel syndrome, all other test results normal.
Sharief <sup>1397</sup> 2002	49 male GWV with $\geq 4$ neuromuscular symptoms, 26 male GWV controls (< 2 neuromuscular symptoms)	Neurological exams, motor and sensory nerve conduction studies, thermal and vibratory sensory tests, needle and concentric single fiber EMG	No abnormalities on reflex or manual muscle testing. No differences between ill GWV and controls on sensory or motor nerve conduction or on sensory thresholds. All EMG results within normal range, no differences between ill and well GWV.
Rose <sup>1311</sup> 2004	49 male GWV with $\geq 4$ neuromuscular symptoms, 26 male GWV controls (< 2 neuromuscular symptoms)	Myometric measures of muscle strength and static and dynamic fatigue in 8 muscle groups, handgrip fatigue, muscle biopsies, glycolytic activity	No sign. differences in quantitative measures of muscle strength and fatigue. Measured muscle fatigue levels generally were not correlated with veteran-perceived fatigue. No case/control differences in muscle biopsies, fiber type ratios, or muscle atrophy. Symptomatic GWV required sign. more effort on exercise test, and had sign. higher plasma lactate levels.
Blanchard <sup>142</sup> 2006	327 GWV with CMI, 708 GWV controls	Neurological exam, sensory and nerve conduction studies	No association between CMI and peripheral neuropathy in GWV or era veterans.

Abbreviations: GWV = Gulf War veterans, CMI = chronic multisymptom illness,<sup>464</sup> CFS = chronic fatigue syndrome, GWUI = Gulf War unexplained illness (defined by study), EMG = electromyography, CK = creatine kinase, LP = lumbar potential, P37 = cerebral cortical potential, PF = popliteal fossa potential, PB = pyridostigmine bromide, sign. = statistically significant

veterans.<sup>1186</sup> Just one other study tested temperature thresholds—the King’s College study of British veterans—and found no significant differences in symptomatic Gulf War veterans.<sup>1397</sup>

Studies of symptomatic Gulf War veterans have also identified very few abnormalities related to muscle function, and none indicative of diagnosable muscle pathology. The most comprehensive muscle function study found that symptomatic British Gulf War veterans required significantly more effort to perform a subanaerobic exercise test than healthy veterans, and produced significantly higher plasma lactate levels with exercise.<sup>1311</sup> Investigators suggested that this indicated mitochondrial inefficiency in symptomatic Gulf War veterans. Lactate levels were not as high as those associated with traditional mitochondrial disease, however, and few mitochondrial and muscle fiber abnormalities were identified in muscle biopsies.

Overall, the majority of research studies that have assessed peripheral sensory and neuromuscular function in Gulf War veterans have not identified objective indicators of pathology. Standard clinical examination, EMG, and nerve conduction tests consistently provide no indication that symptomatic veterans are affected by generalized polyneuropathies or abnormal neuromuscular transmission. It is important to note, however, that the one type of abnormality identified in several studies related to altered sensory thresholds. These findings suggest that some symptomatic Gulf War veterans may have subtle small sensory fiber neuropathies, abnormalities that would not be detected by methods (nerve conduction studies, EMGs, neurological examinations) used in most of the studies listed in Tables 6 and 7. It is possible that such abnormalities are more prominent in more highly symptomatic veterans, like the cases evaluated in the Texas and New Jersey studies, or among veterans with specific exposures in theater, as suggested by the New Jersey study.<sup>1186</sup>

Even if these more subtle sensory findings are confirmed by larger studies, consistent findings that Gulf War veterans are not affected by generalized polyneuropathies or abnormal neuromuscular transmission suggest that veterans’ neuromuscular symptoms are not attributable to overt muscle damage or peripheral nerve pathology. Alternate explanations include the possible contribution of lower-level mitochondrial insufficiency, suggested by one study, and alterations in central nervous system processing of peripheral sensorimotor input.

## Neuroendocrine Alterations in Gulf War Veterans

Elevated rates of diagnosable endocrine disorders such as diabetes and thyroid disease have not been associated with Gulf War service.<sup>46,142,393,464,751,1476</sup> Endocrine measures not routinely evaluated in standard medical workups have only minimally been assessed, however. As previously described, evaluations of the cohort of Gulf War veterans with high-level exposure to depleted uranium identified first elevated, then reduced serum levels of prolactin in this group.<sup>992,997</sup> One MR spectroscopy study of symptomatic Gulf War veterans also reported a significant correlation between reduced neuronal function in the left basal ganglia and elevated central dopamine activity.<sup>562</sup>

Function of the hypothalamic-pituitary adrenal (HPA) axis is known to be altered in several conditions that have affected Gulf War veterans since the war, including posttraumatic stress disorder (PTSD) and chronic fatigue syndrome (CFS).<sup>333</sup> In other populations, PTSD is associated with reduced baseline levels of serum cortisol, elevated levels of corticotrophin releasing factor (CRF), increased levels of glucocorticoid receptors and an enhanced cortisol and ACTH suppression response to low-dose dexamethasone (DEX) challenge.<sup>1822-1824</sup> One small study assessed eight active duty Gulf War veterans within 18 months of their return from theater. Findings indicated that, as expected, posttraumatic symptoms were correlated with lower salivary cortisol levels. All Gulf War veterans who took the DEX, however, had a dramatically enhanced cortisol suppression response, independent of the effects of combat or posttraumatic symptoms.<sup>785,786</sup>

In several recently-reported studies, investigators at the Bronx VA assessed HPA parameters in Gulf War veterans in more detail. Gulf War veterans with and without PTSD were compared to nondeployed controls. No differences in baseline levels of cortisol, ACTH, or glucocorticoid receptors were identified between the three groups. However, Gulf War veterans responded to low dose DEX with significantly greater suppression of both ACTH<sup>501</sup> and cortisol<sup>502</sup> than nondeployed veterans. Identified differences were associated with Gulf War deployment, overall, but were unrelated to combat exposure or whether veterans had PTSD. In Gulf War veterans, the degree of ACTH suppression was significantly related, instead, to veterans' symptoms, most prominently musculoskeletal symptoms. Cortisol suppression was also significantly related to musculoskeletal symptoms in Gulf War veterans and significantly more pronounced in veterans who reported using pyridostigmine bromide in theater.<sup>502</sup>

Twenty-four hour ACTH levels were also found to be significantly reduced among Gulf War veterans who did *not* have PTSD.<sup>503</sup> Lowered ACTH values were associated with veterans' reported use of pesticides and pyridostigmine bromide during deployment, especially in veterans who had experienced acute symptoms at the time of exposure. The ratio of cortisol to ACTH was also significantly elevated in Gulf War veterans, and significantly associated with veterans' cognitive and mood symptoms. None of the 24-hour HPA measures were associated with combat stress, with other self-reported exposures during deployment, or with PTSD.

This group of studies provides a first detailed look at HPA function in Gulf War veterans. Results indicate that Gulf War service, and symptoms in Gulf War veterans, are associated with significant alterations in HPA function, many years after the war. Identified changes are independent of combat stress, but significantly correlated with veterans' use of pesticides and/or pyridostigmine bromide during deployment. It is important to note that identified HPA abnormalities in Gulf War veterans constitute a unique profile, which is biologically distinct from the HPA profile associated with PTSD.<sup>500</sup> Additional research on HPA function in symptomatic Gulf War veterans is needed, however, and the Committee looks forward to reviewing findings from ongoing research at the Bronx VAMC, as well as related research at the St. Louis and East Orange, New Jersey VAMCs.

### **Vulnerability to Neurotoxicants: Variation in Genotype and Activity of Protective Enzymes**

A question often asked about Gulf War illness is why some Gulf War military personnel developed chronic symptoms during and after deployment, while others who served along side them remained well. There is more than one possible reason for this. Genetic and other differences between individuals can dictate different reactions to a given exposure. Additionally, different individuals encountered varying doses and combinations of exposures in theater, over different durations. Identifying specific factors responsible for these differences would provide important insights into the biological nature of Gulf War illness, as well as its causes. It could also help prevent similar problems in future deployments.

A large body of research, from different sectors, has demonstrated that some individuals are more vulnerable to adverse effects of certain chemicals than others.<sup>469,884,928,983,1533</sup> Such differences relate to variability in biological processes associated with binding, metabolizing, and clearing these chemicals from the body. The enzyme paraoxonase (PON1), for example, circulates in the blood and hydrolyzes organophosphate compounds, converting them to relatively harmless chemicals that are excreted from the body. There is more than one form of this enzyme, and inherited variations determine what form and how much the body produces. Individuals who produce different types and amounts of PON1 differ, sometimes dramatically, in their ability to neutralize organophosphate compounds.<sup>281,317,877</sup>

Other enzyme systems are also involved in neutralizing neurotoxic chemicals, including some that are not as well characterized as PON1.<sup>468,602,1130,1440</sup> In several studies, both Gulf War illness and service in the

Gulf War theater have been linked to variation in PON1 measures. Preliminary information is also available concerning a possible link between Gulf War illness and another enzyme, butyrylcholinesterase, which also plays an important role in protecting the body from some types of chemical exposures associated with the Gulf War.

**Paraoxonase (PON1) variability and Gulf War illness.** Differences in PON1 genotype, concentration, and activity levels all contribute to individual variability in the degree to which organophosphate chemicals are neutralized by the body. PON1 genetic variants produce different isozyme forms that hydrolyze specific organophosphate chemicals at different rates. The isoform containing the amino acid glutamine (Q) at gene locus 192 hydrolyzes diazinon, sarin, and soman at a high rate, but paraoxon more slowly. The isoform with arginine (R) at position 192 hydrolyzes paraoxon at a high rate, and hydrolyzes chlorpyrifos more efficiently than the Q form.<sup>262,317,468</sup> Other PON1 polymorphisms, including the L/M (leucine/methionine) substitution at position 55, are also associated with variations that affect organophosphate detoxification.<sup>176,281,1150</sup> PON1 enzyme activity can also vary substantially among people with the same genotype, and has been shown to be affected by factors such as diet, medical conditions, smoking, medications, and some environmental chemicals.<sup>282,325,1457</sup>

In laboratory studies, information on PON1 activity is only meaningful in the context of the specific substrate in which enzyme activity is measured. Similarly, in chemically-exposed human populations, whether a given PON1 genotype provides better protection or increased vulnerability depends on the chemical exposure in question.

Recent studies have identified significant links between PON1 variability and conditions that are relevant to Gulf War illness. As previously described, a chronic symptomatic illness similar to Gulf War illness affects some British sheep farmers who regularly use a chemical sheep dip containing organophosphate pesticides. A large study has reported that sheep farmers with this illness were significantly more likely to have at least one R allele at PON1 site 192 than healthy farmers, who were more commonly QQ homozygotes. Compared to healthy sheep farmers, symptomatic farmers exhibited poorer PON1 hydrolysis of diazinon, an organophosphate chemical used in sheep dip.<sup>242,1223</sup>

Studies of both Polish and North American populations have linked PON genetic polymorphisms to non-familial amyotrophic lateral sclerosis (ALS). In the Polish study, significantly more ALS patients than controls had the R allele at PON1 position 192, and a second polymorphism in the PON2 gene, which codes for a similar enzyme widely distributed in the body.<sup>1426</sup> The North American study identified PON gene cluster variants that significantly distinguished sporadic ALS cases from healthy controls and identified both protective and detrimental ALS haplotypes.<sup>1338</sup> Additional research, from multiple studies, links Parkinson's disease to increased frequency of the L allele at PON1 position 55.<sup>1840</sup> Multiple chemical sensitivity has also been associated with higher rates of PON1 heterozygosity at positions 55 and 192.<sup>1005</sup> For all these conditions, investigators concluded that the disease-PON1 connection indicates that interaction between an environmental exposure and genetic vulnerability leads to increased risk for developing the disease.

Results from published studies that have evaluated PON1 measures in Gulf War veterans are summarized in Table 8. These studies addressed different questions in different ways, in case and control populations that differed markedly from one another. Additional information on the PON1-Gulf War illness relationship is available from two federally-funded projects whose results have not been published. Findings were presented to the Committee for discussion at public meetings and/or are available in agency research reports. Results from these projects can only be considered preliminary pending peer review and publication, but provide additional insights and context for the published research findings.

Five of the six Gulf War projects identified significant PON1 differences related to Gulf War illness or, more generally, with Gulf War service. Specific findings from these studies have varied, however, reflecting different types of data obtained to address different questions. As a result, existing studies do not provide a complete understanding of the Gulf War illness-PON1 relationship. The Committee examined the study questions, measures, and outcomes evaluated by each study to identify commonalities and differences, and to determine what issues remain.

The earliest study, from the University of Texas Southwestern (UTSW) evaluated PON1 measures in 25 ill veterans from a single Navy reserve unit, compared to 20 veteran controls. Investigators reported differences between cases and controls associated both with PON1 genotype and enzyme activity.<sup>561</sup> Overall, PON1 activity using phenyl acetate as a substrate (also referred to as arylesterase activity) was *lower* in cases than controls—significantly lower for the type Q isozyme, which provides the most efficient hydrolysis of sarin. A follow up study, in fact, indicated that serum hydrolysis of sarin was highly correlated with PON1 type Q isozyme activity in the veterans studied, reflecting a reduced capacity for neutralizing sarin in this group.<sup>853</sup> In contrast, PON1 activity using paraoxon as a substrate was nonsignificantly *higher* in cases than controls. Significantly more cases than controls had the R allele at position 192, the polymorphism that provides less efficient hydrolysis of sarin. The study found no genetic differences at locus 55 and did not evaluate differences between deployed and nondeployed veterans.

In a second, larger study, investigators from the University of Manchester reported that 152 British Gulf War veterans who self-identified as having Gulf War illness had significantly reduced PON1 enzyme activity, compared to controls, using paraoxon as a substrate. PON1 activity appeared to be unrelated to disease severity; it was reduced in veterans with both low- and high-level symptomatology. No genetic differences between groups were identified, either at position 152 or position 55, and enzyme activity was not measured using phenyl acetate as a substrate.<sup>947</sup> Investigators suggested their results indicated that veterans with reduced PON1 enzyme activity, due either to environmental or unidentified genetic factors, had developed Gulf War illness at higher rates. The control group in this study had not served in the Gulf War, however, so it was not possible to determine whether PON1 activity differences related to Gulf War illness specifically or, more generally, to Gulf War deployment.

A second British study compared PON1 measures in a subgroup of the most disabled Gulf War veterans from a large population sample (“ill” Gulf War veterans) to those in three other groups: (1) other Gulf War veterans in the sample (“well” Gulf War veterans), (2) “ill” nondeployed Gulf War-era veterans, and (3) “ill” Bosnia veterans.<sup>645</sup> PON1 genotype at position 192 did not differ between ill and well Gulf War veterans, but significantly fewer ill Gulf War veterans were LM heterozygotes at position 55. Ill and well Gulf War veterans had similar mean PON1 activity using paraoxon as a substrate. As a group, however, Gulf War veterans had significantly lower PON1 activity than ill nondeployed and Bosnia veterans. Investigators commented that service in the Gulf War theater, or specific exposures during deployment, appeared to produce reduced PON1 activity that persisted many years after veterans returned from theater. As in the earlier British study, it is difficult to disentangle “illness” effects in this study, since the “well” Gulf War control group reported symptom levels similar to those of the “ill” Bosnia and nondeployed Gulf War-era groups, and no “well” Bosnia or era veterans were evaluated.

The only report that identified no PON1 differences in relation to Gulf War service was a collaborative project from the University of Iowa, the West Haven VA, and Hebrew University of Jerusalem.<sup>266</sup> The study analyzed enzyme activity in blood samples retained from an earlier clinical study that addressed other, unrelated questions. Results indicated that PON1 activity did not differ between veterans who met case criteria for chronic multisymptom illness (CMI)<sup>464</sup> and controls. Key information was not provided,

**Table 8. Evaluation of PON1 Genotype and Enzyme Activity in Gulf War Veterans**

<b>Study</b>	<b>Group Studied</b>	<b>Parameter/Assay</b>	<b>Key Findings</b>
Haley <sup>561</sup> 1999	25 Navy Seabees with Haley Syndromes, 10 well GWV controls, 10 nondeployed era controls	PON1 genotype (positions 192 and 55), Enzyme activity in paraoxon, phenyl acetate (arylesterase), calculated Q,R-specific arylesterase activity	GWV with Haley syndromes sign. more likely to have PON1 R allele than controls. No sign. differences in L,M alleles. Mean PON1 activity nonsign. higher in cases, mean arylesterase activity nonsign lower in cases; type Q arylesterase activity sign. lower in cases; low Q arylesterase activity also sign. associated with having more severe side effects from PB during deployment.
Mackness <sup>947</sup> 2000	152 GWV with self-reported GWI, 152 nonveteran controls	PON1 genotype (positions 192 and 55), serum PON1 concentration, enzyme activity in paraoxon and diazoxon	GWV with GWI had sign. lower PON1 concentration and activity in paraoxon than controls (activity < 50% of controls), overall and within genotype. No differences in Q,R gene frequencies or L,M frequencies in cases vs. controls. No differences in PON1 activity in diazoxon.
Hotopf <sup>645</sup> 2003	115 "ill" GWV, 95 "well" GWV controls, 137 ill nondeployed GW era and Bosnia veterans	PON1 genotype (positions 192 and 55), enzyme activity in paraoxon	Sign. lower proportion of ill than well GWV had LM genotype (position 55). Overall, Gulf-deployed had sign. lower PON1 activity than non-PGW veterans. No sign. PON1 activity difference between ill and well GWV.
Concato <sup>266</sup> 2007	140 male GWV with CMI, 125 male GWV controls, 80 nondeployed era veterans (29 with CMI)	PON1 activity (substrate not specified)	No sign. difference in adjusted mean difference of PON1 activity between cases and controls, or in deployed vs. nondeployed veterans.

Abbreviations: PON1 = paraoxonase, GWV = Gulf War veteran, GWI = Gulf War illness, CMI = chronic multisymptom illness,<sup>464</sup> PB = pyridostigmine bromide, sign. = statistically significant

however, concerning substrate and assay methods, test results, and health characteristics of the sample. It was therefore not possible to clearly interpret these results or compare them with other studies. It is not known, for example, how many study subjects were healthy Gulf War controls or healthy nondeployed veterans, since subjects identified as both CMI "cases" and "controls" also had conditions evaluated in the original clinical study—depression, cognitive dysfunction, and fibromyalgia.

The two additional federal projects that have evaluated PON1 measures in Gulf War veterans provide information relevant to results of published articles. Investigators from the East Orange, New Jersey VA, reported to the Committee preliminary results of analyses of PON1 activity in blood samples collected for the large VA Gulf War clinical study of over 1,000 deployed Gulf War and 1,000 nondeployed era veterans. Results indicated that Gulf War veterans with chronic multisymptom illness (CMI)<sup>464</sup> had *elevated* PON1 activity using paraoxon as a substrate, with the increase most pronounced in veterans who also had PTSD.<sup>1160,1161</sup>

Preliminary results from the Midwest Research Institute project, described previously in relation to autonomic testing, also indicated that PON1 activity using paraoxon as a substrate was significantly *higher* in 40 Gulf War illness cases than in 18 healthy Gulf War controls.<sup>1353</sup> The 18 Gulf War controls, however, had *lower* PON1 activity (p=0.09) than the 15 healthy nondeployed controls evaluated for the study. Both associations were masked when the two control groups were combined, giving the appearance that PON1 activity did not differ between cases and controls. These preliminary findings suggest the possibility that PON1 activity differences may be associated both with Gulf War illness and, more generally, with Gulf War service, but in opposite directions. Such differences can be obscured unless appropriate subgroups are evaluated.

Overall, differences between studies related not only to which PON1 measures were assessed, but also to how “symptomatic” and “healthy” veterans were identified, if comparisons were made to healthy controls, and whether controls had also served in the Gulf War. Several commonalities exist between study findings, but the importance of specific differences are difficult to interpret without more comprehensive evaluation of larger samples of well characterized Gulf War illness cases, healthy Gulf War controls, and healthy nondeployed controls.

Four of the six existing Gulf War PON1 projects identified altered PON1 enzyme activity in symptomatic veterans compared to controls, three using paraoxon as the substrate.<sup>561,947,1161,1353</sup> The remaining study, from UTSW, identified reduced arylesterase activity of PON1 type Q isozyme, a measure not assessed by other studies. It is not clear whether different results from individual studies relate to chance findings, or to actual differences that reflect PON1 factors associated with subgroups of Gulf War veterans with different illness or exposure histories, as suggested by the New Jersey and UTSW studies. It may also be important that only projects that compared ill Gulf War veterans to healthy Gulf War veterans found ill veterans to have *elevated* PON1 activity using paraoxon as the substrate.<sup>561,1161,1353</sup> All studies that identified *reduced* PON1 hydrolysis of paraoxon in Gulf War veterans compared them to individuals who had not served in the Gulf War.<sup>645,947,1353</sup>

A key issue not addressed by Gulf War PON1 studies relates to the important fact that the effects of variability in PON1 hydrolyzing activity are substrate specific. While one PON1 genotype might render an individual more vulnerable to specific types of pesticides, another would be more problematic if an individual had been exposed to nerve agents. As a result, differences in health effects that might have occurred in relation to different PON1 genotypes during the Gulf War would only be apparent among subgroups of individuals with specific chemical exposures. No adverse effects or PON1-related differences would be apparent in individuals who were not exposed to chemicals affected by their genotype. Therefore, PON1 studies that do not assess Gulf War illness case status as a function of both PON1 parameters and exposure history could easily mask differences related to PON1 subgroups of importance. Unfortunately, Gulf War studies have not yet evaluated case/control outcomes in relation to both exposures and PON1 measures.

If considered in the context of differences in methods, research questions, and study populations, results from Gulf War PON1 studies are not so much contradictory as they are parallel findings that remain to be reconciled. There is a general type of consistency from these studies indicating that variations in PON1 activity are linked to Gulf War service. But important questions have only been partially addressed. More comprehensive research and analyses are needed to provide the answers needed to better characterize the relationship of PON1 variability with Gulf War illness and/or Gulf War service.

Observed PON1 variability in relation to Gulf War service provides additional support for other types of evidence that implicate neurotoxic exposures in the etiology of Gulf War illness. Major research issues that remain to be addressed in relation to PON1 and the health of Gulf War veterans include: (1) whether Gulf War service, in general, produced alterations in PON1 activity in Gulf War military personnel, and if specific exposures in theater can account for those changes, (2) whether persistent alterations in PON1 activity put Gulf War veterans at increased risk for adverse effects of chemical exposures encountered after their return from theater, and (3) further characterization of specific PON1 parameters and PON1/exposure interactions associated with Gulf War illness. The Committee looks forward to reviewing final results from the preliminary findings described, as well as results from recently-funded Gulf War PON1 studies undertaken by UTSW and the Naval Health Research Center.<sup>1205</sup>

**Butyrylcholinesterase (BChE) and Gulf War illness.** As previously described, the best understood mechanism through which organophosphate and carbamate compounds exert their toxic effects involves inhibition of the enzyme acetylcholinesterase (AChE). Another enzyme, butyrylcholinesterase (BChE), circulates in the blood and brain and binds irreversibly to AChE-inhibiting

chemicals, acting as a “scavenger” that protects AChE from inhibition by these compounds. Because of its efficiency in binding AChE-inhibitors, BChE is now being evaluated as a protective pretreatment against nerve agents on the battlefield.<sup>1357,1389</sup> Recent animal studies have shown that circulating BChE spares AChE inhibition both in peripheral blood and in the brain following sarin inhalation<sup>1389</sup> and may directly control excess levels of brain acetylcholine when AChE levels are reduced.<sup>380,590</sup>

A number of BChE genetic variants have been identified, with different affinities for AChE-inhibiting chemicals. Individuals with certain BChE genotypes, for example, have long been known to be at risk for adverse effects from the use of succinylcholine as a muscle relaxant in surgery.<sup>926</sup> Individuals with slower-acting BChE are thought to be at potentially greater risk for adverse effects from AChE-inhibiting pesticides and nerve agents.<sup>928</sup>

Three published studies have evaluated BChE measures in Gulf War veterans. The UTSW enzyme study assessed BChE phenotype and enzyme activity in 25 Gulf War veterans with the three Haley syndromes, compared to 20 veteran controls.<sup>561</sup> Mean BChE activity levels did not differ between cases and controls, although Gulf War illness cases were almost three times as likely to have BChE activity levels in the lowest activity quartile, and veterans with the AU phenotype had a nearly four-fold increased risk for having Haley Syndrome 2. Neither association was statistically significant in this relatively small group, however. The larger British study found that Gulf War veterans who self-identified as having Gulf War illness had significantly *higher* BChE enzyme activity than nonveteran controls.<sup>947</sup> And the Iowa/West Haven/Hebrew University collaborative study reported that mean BChE activity did not differ between Gulf War multisymptom illness cases and controls, although it is not clear what specific measures and comparisons were made.<sup>266</sup>

Additional information on BChE-Gulf War illness associations is provided by reports from two additional federally-funded projects that are publicly available, but not yet published in research journals. A DOD report on a study of 221 Gulf War veterans conducted by the University of Nebraska indicated that mean BChE activity levels were similar in veterans who indicated they had Gulf War illness and controls. A significant association was found between BChE genotype and Gulf War illness, however. All but one (91%) of the 11 Gulf War veterans with the rare atypical (A) or fluoride (F) BChE alleles had Gulf War illness symptoms.<sup>927</sup> Given the small number of A and F variants in this study, however, investigators cautioned that this finding required further testing.

A second DOD-funded project, conducted by Midwest Research Institute, further evaluated the association of BChE with Gulf War illness in 304 Gulf War veterans. Results were presented at a public Committee meeting, and are also provided in a DOD project report.<sup>1352,1353</sup> Mean BChE activity, again, did not differ between Gulf War illness cases and controls. Neither were individual BChE genotypes or specific alleles associated with Gulf War illness. As a group, veterans with the most common BChE genotypes (U/U and U/K) were identified as “nonvariants,” and veterans with other, rarer, genotypes were identified as BChE “variants.” As expected, the BChE variant group had significantly lower BChE activity than nonvariants. Subgroup analyses revealed that associations between Gulf War illness and several wartime exposures differed dramatically in BChE variants compared to nonvariants. Most prominently, nonvariants who reported using pyridostigmine bromide (PB) were 2.7 times as likely to have Gulf War illness as those who did not use PB. However, BChE genetic variants who used PB had a 40-fold increased risk of Gulf War illness, compared to variants who did not use PB. Although these results can only be considered preliminary pending peer review, they suggest the importance of assessing enzyme-exposure interactions in relation to Gulf War illness, as was previously described for PON1 research.

Overall, studies of BChE measures in relation to Gulf War illness have produced varied results. Like PON1 studies, BChE projects are generally not directly comparable, owing to important differences in study questions, populations, and methods. The most consistent finding, from four of the five Gulf War

BChE projects, was that mean BChE activity does not differ between Gulf War illness cases and controls. More complex associations were suggested by three of the projects, however. The Nebraska study suggested a possible link between BChE genotype and Gulf War illness, limited to the subgroup of veterans with relatively rare genetic BChE alleles. The UTSW and Midwest Research Institute studies suggest that Gulf War illness may be associated with BChE in subgroups of Gulf War veterans with particularly low BChE activity. The Midwest Research Institute study also suggests that this association is only apparent in the context of exposures in theater. That is, BChE genotype is a risk factor for Gulf War illness only among veterans who experienced specific war-related exposures, most prominently PB.

A similar gene-exposure-illness interaction was previously suggested by the reported case of an Israeli soldier who suffered severe symptoms after taking PB during the Gulf War.<sup>929</sup> This soldier was determined to be a rare AA homozygote for BChE, with dramatically reduced ability to bind carbamate compounds. Although generally healthy before the use of PB, the soldier had previously experienced succinylcholine-induced difficulties following surgery.

**Acetylcholinesterase (AChE) and Gulf War illness.** A number of chemical exposures in the Gulf War theater acutely reduce serum and brain levels of acetylcholinesterase (AChE), but only one study has assessed AChE measures in relation to Gulf War illness. Research in other populations has shown that individuals chronically exposed to low-level pesticides or stress express increased levels of the AChE read-through variant, AChE-R.<sup>1024,1418,1448</sup> Based on these reports and early indications of possible treatment implications<sup>424,1446,1447</sup> the Committee suggested that VA assess levels of AChE-R in veterans with Gulf War illness. VA Office of Research and Development subsequently authorized a study to determine whether AChE enzyme activity, more generally, was associated with anxiety and mood disorders in Gulf War veterans previously evaluated in the Iowa clinical study. Investigators later attempted to accommodate the Committee's original suggestion by adding an evaluation of AChE-R in relation to Gulf War illness to the study, but this was not accomplished because of insufficient serum. Instead the study focused on AChE enzyme activity in relation to Gulf War deployment, as well as anxiety disorders and multisymptom illness in Gulf War veterans.<sup>266</sup>

Study results indicated that Gulf War deployment, overall, was not associated with significant differences in AChE activity. Mean value of AChE activity for veterans with chronic multisymptom illness (CMI) was nonsignificantly higher than in veterans who did not have CMI. For all veterans combined (sick and healthy), AChE activity was not significantly associated with any self-reported exposures during deployment. Veterans who reported exposure to chemical warfare agents, however, had an adjusted mean activity level that was 126 points lower than those not exposed, a difference that approached significance ( $p=0.09$ ).<sup>266</sup> As previously described, results of this study are difficult to interpret. Both Gulf War illness cases and controls had originally been recruited for a study of depression, fibromyalgia and cognitive dysfunction, and study subjects, overall, had elevated rates of anxiety disorders. Further, the study did not evaluate associations between AChE and Gulf War illness in veterans with different exposure histories, particularly AChE-inhibiting chemicals. The Committee therefore concludes that the question of whether AChE variability is associated with Gulf War illness has not been adequately addressed, and so remains open.

**Summary. Vulnerability to neurotoxicants: variation in genotype and activity of protective enzymes.** Explanations for why some Gulf War veterans developed Gulf War illness while others remained well may relate to different exposure profiles between individuals in theater, and to biological differences in veterans' vulnerability to those exposures. The enzyme paraoxonase (PON1) has an important role in neutralizing effects of organophosphate exposures, and PON1 genetic differences have been implicated in the risk for developing conditions relevant to Gulf War service, including ALS. Six projects have evaluated diverse PON1 measures in Gulf War veterans; five identified significant differences in PON1 enzyme activity related to Gulf War illness and/or Gulf War deployment. Available results, however, have provided a somewhat piecemeal look at the potentially complex relationships

between PON1 measures and the health of Gulf War veterans. More precise understanding of PON1 variability in relation to Gulf War illness requires more comprehensive comparisons of PON1 measures in suitable Gulf War illness cases and healthy Gulf War and nondeployed controls. It also requires a detailed evaluation of PON1-exposure interactions in relation to Gulf War illness and, more broadly, to Gulf War deployment.

Gulf War illness may also be linked to biological variability related to other enzymes that protect from, and are affected by, neurotoxic exposures. The question of whether acetylcholinesterase (AChE) variability is associated with Gulf War illness remains open, due to limited research in this area. Three Gulf War studies have provided preliminary indications of a possible link between BChE variability and Gulf War illness. Several studies have reported that *mean* BChE enzyme activity is not related to Gulf War illness, but provided preliminary indications that an identifiable link involves the subgroup of Gulf War veterans with very low BChE activity. Precise understanding of BChE variability in relation to Gulf War illness requires more thorough evaluation of interactions between BChE genetic factors, enzyme activity, and specific exposures.

Overall, identified differences in PON1 measures, and preliminary indications related to BChE, suggest that variability in circulating enzymes that confer protection from AChE-inhibiting chemicals rendered some Gulf War veterans more susceptible to prolonged, adverse effects of neurotoxic exposures. Although details of gene-enzyme-exposure interactions remain to be fully elucidated, current findings provide support for consistent evidence from other sectors that implicates neurotoxic exposures as causal factors in Gulf War illness.

## Immune Parameters in Gulf War Veterans

The immune system, the body's multifaceted defense system, involves the production and coordination of diverse cells and messenger chemicals in multiple tissues and organs. This system provides the body's response to potential threats, on a continuing basis, and restores equilibrium in the wake of the defensive response. Healthy immune function depends on multiple regulatory mechanisms that involve actions and counteractions not only of immune cells, but of diverse neurological and endocrine processes.<sup>23,1485</sup> Abnormalities in the intricate workings of the immune system, or its complex interactions with other biological systems, can result in diverse types of pathology.

In 2001, the Research Working Group of the federal Military and Veterans Health Coordinating Board reported on immune function in Gulf War veterans by indicating that studies had not identified excess rates of serious infectious or autoimmune diseases in Gulf War veterans,<sup>1273</sup> based largely on hospitalization rates identified in military hospitals. Studies of this type do not provide satisfactory insights into the question of immune abnormalities, however, since infectious diseases and autoimmune diseases are not adequately tracked by hospitalization rates, and most ill Gulf War veterans were no longer in service at the time of this assessment. In addition, the report did not consider other types of immune alterations potentially associated with Gulf War illness.

Multiple studies have now assessed immune parameters in Gulf War veterans, as summarized in Tables 7 and 8. As shown, different immune parameters have been evaluated using varied methods in different groups of veterans. In a general sense, results have been mixed, with some studies showing immune alterations in symptomatic veterans, and others finding no abnormalities. But as with other areas of Gulf War research, a simple tabulation of whether Gulf War immune studies have yielded positive or negative results is not sufficiently informative. It is important to assess which types of immune parameters have been found to differ in relation to veterans' symptoms, and which have not.

**Table 7. Immune Evaluation of Gulf War Veterans, Not Differentiated by Veterans' Health Status**

<b>Study</b>	<b>Groups Evaluated</b>	<b>Immune Findings</b>
Bregenholt <sup>167</sup> 2001	686 Danish GWV, 231 nonveteran controls	No sign. differences in NK activity or levels of most cytokines, with possible exception of CD2+ production of IL-2. Results unclear, due to effects of freezing/thawing on samples.
Eisen <sup>393</sup> 2005	1061 GWV, 1128 nondeployed era veterans	No sign. differences in mean levels of total leukocytes, leukocyte counts, ESR.

Abbreviations: GWV = Gulf War veterans, NK = natural killer cells, ESR = erythrocyte sedimentation rate, sign. = statistically significant

Two studies, including the large national VA clinical study, have broadly compared immune measures in veterans who deployed to the Gulf War with those of a nondeployed reference group,<sup>167,393</sup> as shown in Table 7. Results reported in these studies combine data from symptomatic and healthy Gulf War veterans, so are of limited use in understanding possible immune aspects of Gulf War illness. In both studies, no immune findings were associated with Gulf War service, when deployed veterans were evaluated as a single group.

**The Rook hypothesis: Th1-Th2 immunity in Gulf War veterans.** In 1997, Drs. Graham Rook and Alimuddin Zumla, of University College in London, hypothesized that the symptoms of Gulf War illness could be the result of a systemic shift towards a Th-2 immune profile.<sup>1306</sup> The human immune response includes two functionally distinct classes of CD4, or T-helper (Th) cells. Th-1 cells are associated with cell-mediated immunity and phagocyte-dependent inflammation, and production of the cytokines IL-2 and IFN- $\gamma$ . Th-2 cells are associated with humoral immunity and allergy, and production of IL-4,5,6,9, and 13.<sup>329,1305</sup> The suggested association of Gulf War illness with a Th1-Th2 shift constituted a plausible and testable hypothesis, often referred to as the Rook hypothesis. According to the original hypothesis, this shift could have been precipitated by the many vaccines received by service members, perhaps in conjunction with deployment-related stressors and exposures.<sup>1306</sup>

The Rook hypothesis received early support from two large epidemiologic studies of British Gulf War veterans, which found that veterans who had received a greater number of vaccines had modestly elevated rates of multisymptom illness, compared to veterans who received fewer vaccines.<sup>241,1698</sup> Several studies subsequently assessed the Rook hypothesis more directly, by evaluating levels of different classes of T lymphocytes and cytokines in veterans with Gulf War illness.

In 1999, Dr. Quanwu Zhang and colleagues from the East Orange, NJ, VA reported that compared to healthy veteran controls, Gulf War veterans with chronic fatigue syndrome had significantly more total lymphocytes, and significantly higher levels of mRNA for IFN- $\gamma$ , TNF- $\alpha$ , IL-2 and IL-10.<sup>1835</sup> IL-10 was once thought to be produced by Th-2 cells, but is now known to come from multiple cell types, and to have a role in limiting excess inflammation.<sup>1065,1556</sup> Results of this study indicated that Gulf War illness was associated with immune alterations, but did not support a shift towards Th-2 immune reactivity. Findings instead suggested a possible increase in Th-1-type immunity.

A 2002 study from investigators at the Birmingham VA evaluated *in vitro* levels of cytokines produced by blood cells both at rest, and after PHA stimulation.<sup>422</sup> Supernatant levels of IL-4, associated with Th2-type activation, did not differ between sick and healthy veterans. Nor did levels of IL-6, IL-10, or TNF- $\alpha$ . The study did not assess levels of IL-2, but IFN- $\gamma$  levels produced by cells at rest were significantly *lower* in symptomatic veterans, while stimulated levels of IFN- $\gamma$  were nonsignificantly *higher*. Results therefore did not support the notion of Th-2 immune activation, while insights regarding Th-1 activation were limited.

**Table 8. Studies Comparing Immune Measures in Symptomatic Gulf War Veterans and Controls**

<b>Study</b>	<b>Groups Evaluated</b>	<b>Immune Findings</b>
Haley <sup>563</sup> 1997	23 GWV with Haley Syndromes, 10 GWV, 10 nondeployed controls	ESR, ANA, and IG levels similar in symptomatic GWV and controls.
Zhang <sup>1835</sup> 1999 Brimacombe <sup>172</sup> 2002	43 GWV with CFS, 34 GWV controls	Peripheral blood lymphocytes of symptomatic GWV included sign. more total T cells and MHC II+ T cells, higher % CD3 cells, lower % NK cells, sign. higher levels of mRNA for IFN- $\gamma$ , TNF- $\alpha$ , IL-2 and IL-10. In modeling, apparent association of factor grouping of Th-2 cytokines with CFS was related to slowed cognitive reaction time in ill veterans.
Asa <sup>69</sup> 2000	38 symptomatic GWV, 12 GWV controls	36/38 (95%) of symptomatic veterans had IgG antibodies to squalene, compared to 0/12 GWV controls.
Everson <sup>422,423</sup> 2000, 2002	52 symptomatic GWV, 31 healthy GWV controls	No differences on <i>in vitro</i> measures of acquired immunity, including mean levels of mitogen-stimulated T cell proliferation, mixed leukocyte reactivity, IG production. Antibody response to anthrax vaccine was sign. greater in healthy GWV. NK cell activity nonsign. lower in symptomatic GWV. Unstimulated IFN- $\gamma$ sign. lower in symptomatic GWV; stimulated IFN- $\gamma$ nonsign. higher.
Skowera <sup>1421</sup> 2002	130 symptomatic British GWV, 90 healthy GWV controls	No difference in levels of ANAs generally, no evidence of ANAs against nuclear envelope antigens in either symptomatic or healthy GWV.
Skowera <sup>1420</sup> 2004	40 symptomatic British GWV, 80 healthy GWV	Symptomatic veterans had sign. elevated levels of unstimulated IL-2+ cells, IFN- $\gamma$ cells. Sign. elevated IL-10 producing cells following polyclonal stimulation.
Vojdani <sup>1734</sup> 2004	100 symptomatic GWV, 50 healthy GWV, 50 healthy nonveteran controls	Higher proportion of symptomatic GWV had elevated T cells, elevated B cells, elevated CD4:CD8 ratio, decreased NK activity, reduced response to PHA and PWM, increased immune complexes, increased antibodies to myelin basic protein and muscle.
Allen <sup>39</sup> 2006	17 symptomatic GWV, 11 healthy GWV controls with vaccine records	12-15 years after being vaccinated in the Gulf War, GWV exhibit immune responses to anthrax and plague vaccines. Cytokine responses to vaccines were similar in symptomatic and well GWV.
Hokama <sup>617</sup> 2007	8 GWV, 328 nonveteran CFS patients, 52 controls	All 8 GWV, 91% of CFS patients, and 8% of controls had elevated antibody titers for CTX, a neurotoxic lipid associated with ciguatera poisoning.

Abbreviations: GWV = Gulf War veterans, ESR = erythrocyte sedimentation rate, ANA = antinuclear autoantibody, IG = immune globulin, NK = natural killer cells, PHA = phytohemagglutinin, PWM = pokeweed mitogen, CFS = chronic fatigue syndrome, sign. = statistically significant

Dr. Anna Skowera and colleagues at King's College in London took a different approach by directly assessing levels of different classes of Th cells in relation to Gulf War illness. They identified evidence of persistent cellular immune activation in symptomatic veterans, finding significantly elevated levels of IL-2 and IFN- $\gamma$ -producing cells, in the absence of stimulation.<sup>1420</sup> Short term *in vitro* polyclonal stimulation resulted in significantly greater memory cell production of IL-10 in ill veterans, compared to healthy controls. This study provides the most direct assessment of the posited Th1-Th2 shift, since cell counts were specifically measured, rather than inferred from cytokine levels. Cytokine levels in serum or supernatant may not accurately reflect levels of different CD4 cytokine-producing cells, since cultured macrophages and NK cells can also produce IFN- $\gamma$ , IL-4, and IL-10.<sup>1065</sup> Investigators concluded that, nine years after the Gulf War, symptomatic veterans showed evidence of an ongoing, low-grade Th-1-type immune activation.

The King's College team has also suggested that assessing global T cell cytokine production may not reflect Gulf War-related changes, given the complex mix of vaccines, infections, and other antigens that veterans have likely encountered since deployment. Taking an alternate approach, they looked

specifically at T cell responses to vaccines, including two that provided novel exposures at the time of the war: anthrax and plague vaccine antigens. Results indicated that 12-15 years after the Gulf War, vaccinated veterans continued to have T cell memory responses to anthrax and plague antigens. Cytokine responses to anthrax and tetanus-diphtheria vaccines were balanced, with neither TH1 nor TH2 response dominating, while plague and pertussis vaccine responses were Th-1 dominant. Importantly, there were no vaccine response differences between symptomatic and well veterans.<sup>39</sup>

Although these studies provide support for an association between Gulf War illness and immune alterations, a shift towards a Th-2 immune profile has not been supported. The posited link between Gulf War illness and receipt of multiple vaccines has not been ruled out, however, in light of modest associations identified in several epidemiologic studies.<sup>241,789,1698</sup> Animal experiments have identified CNS-related changes, but not peripheral immune effects, following receipt of multiple vaccines, or vaccines combined with other Gulf War exposures.<sup>535,632,1486,1752,1789</sup>

It is of interest that, using entirely different methods and study populations, researchers from the New Jersey VA and King's College both identified evidence of elevated production of IL-2 and IFN- $\gamma$  (Th-1-related cytokines) and increased levels of the regulatory cytokine, IL-10, in symptomatic Gulf War veterans.<sup>1420,1835</sup> These studies provide independent support for an ongoing, low level cellular immune activation in veterans with Gulf War illness.

**General evaluation of immune competence in symptomatic veterans.** As summarized in Table 8, individual studies have assessed a variety of immune parameters in relation to Gulf War illness. The focus of the Birmingham VA immune study was to assess the functional integrity of the acquired immune response in symptomatic veterans, using multiple *in vitro* measures.<sup>422</sup> Immune challenges to blood cells of symptomatic and healthy veterans revealed no differences in reactions of antigen presenting cells, primary and secondary responses to a variety of antigens, or T cell-dependent B cell response to pokeweed mitogen. Investigators concluded that their results provided no indication that symptomatic veterans were immunodeficient, that is, that veterans with Gulf War illness had impaired ability to respond to infection. This is compatible with results from population studies, which have provided little indication that veterans with Gulf War illness have excess rates of commonly diagnosed infectious diseases.<sup>393,464,1698</sup>

In contrast, a number of immune alterations were identified by a study that compared clinical blood testing results in symptomatic Gulf War veterans, nondeployed veterans, and community controls. Dr. Aristo Vojdani and colleagues at Immunosciences Lab<sup>1734</sup> reported that Gulf War illness was significantly associated with values either above or below the normal reference range for percentages of CD3 T cells (30% of ill veterans above normal, 9% below) and CD19 B cells (49% above normal, 4% below), as well as the CD4:CD8 ratio (33% above normal, 4% below). Significantly more ill veterans also had below-normal responses to mitogens, and exhibited depressed NK cell activity. For several tests, these differences were not apparent when average values of the patient and control groups were compared. Differences related, instead, to the distribution of results, with an excess number of symptomatic veterans having abnormally high or abnormally low test results. Investigators concluded that significant subsets of veterans with Gulf War illness exhibit immune alterations.

Although different studies have assessed different immune cell parameters in differently-defined groups of ill veterans, several commonalities can be identified. Symptomatic veterans were reported to have elevated percentages of CD3 cells in both the New Jersey VA study and the Immunosciences study. Mitogen responses appeared similar in cases and controls in both the Birmingham and Immunosciences studies, when group means were compared. However, the Immunosciences study identified a significant subgroup of veterans with below-normal mitogen responsivity, a difference that was obscured when only group means were considered.

**NK cell function.** As shown in Table 8, three studies have evaluated NK cell number or function in relation to Gulf War illness. The New Jersey VA study reported a significantly lower mean percent of NK cells in symptomatic veterans than controls,<sup>1835</sup> while the Immunosciences study reported significantly reduced NK cell activity in symptomatic veterans.<sup>1734</sup> The Birmingham study, in preliminary results, reported that NK cell activity was lower in symptomatic than healthy veterans, but this difference was not statistically significant.<sup>423</sup> Dr. Nancy Klimas at the Miami VA also reported to the Committee that preliminary results from her ongoing immune study indicated that veterans with Gulf War illness have significantly reduced NK cell numbers and activity levels.<sup>813</sup>

**Abnormal antibody production and autoimmunity in relation to Gulf War illness.** Some observers have suggested that the symptoms of Gulf War illness may result from persistent production of antibodies or autoantibodies generated in response to wartime exposures.<sup>69,1077</sup> There is limited research information on the question of autoimmunity in Gulf War veterans, however. Hospitalization studies have not identified excess rates of diagnosed autoimmune diseases in Gulf War veterans.<sup>1432</sup> Reliable prevalence information cannot be provided by hospitalization studies, however, but require more comprehensive population-based research. Results provided by clinical assessments of symptomatic Gulf War veterans have provided little support for an association between Gulf War illness and nonspecific indicators of autoimmunity, such as erythrocyte sedimentation rates (ESR) and antinuclear autoantibodies (ANA).<sup>160,464,563</sup>

As previously described, Dr. Pamela Asa and colleagues at Tulane University reported that 36 of 38 symptomatic Gulf War veterans tested positive for IgG antibodies to squalene, compared to none of 12 healthy Gulf War veterans tested.<sup>69</sup> A minority of symptomatic veterans in this study also had test abnormalities suggestive of autoimmunity, and several met criteria for Sjogren's syndrome and systemic lupus erythematosus. Although the use of a squalene-containing adjuvant in anthrax vaccine has not been supported by analyses of vaccine lots used during the Gulf War, a possible link between Gulf War illness and squalene antibodies has not been directly assessed by other investigators. No conclusions concerning the prevalence of autoimmunity or other immune abnormalities in Gulf War veterans can be drawn from the Asa/Tulane study, in light of the relatively small, nonrepresentative sample evaluated.

Three additional studies have evaluated indicators of autoimmunity in relation to Gulf War illness. Symptomatic Gulf War veterans were reported to have ANA and ESR values similar to those of healthy controls in the King's College study of U.K. veterans,<sup>1421</sup> in Navy Seabees,<sup>563</sup> and in the Immunosciences evaluation of clinical samples.<sup>1734</sup> The Immunosciences study, however, reported that symptomatic veterans were significantly more likely to have antibodies to striated and smooth muscle, and to myelin basic protein (MBP).<sup>1734</sup> Elevated levels of MBP antibodies may have relevance to concerns raised by veterans' groups about a possible excess of multiple sclerosis among Gulf War veterans,<sup>1694,1721</sup> but no studies have investigated this issue. Additional studies are required to determine whether these abnormalities are detectable in other groups of symptomatic Gulf War veterans.

**Assessment of allergy in Gulf War veterans.** Although sinus congestion and dermatitis are commonly reported in surveys of Gulf War veterans,<sup>464,751,789,1476,1698</sup> little information is available concerning the prevalence of diagnosed allergies in this group. Ten percent of Kansas Gulf veterans reported being diagnosed by a physician with allergies, similar to the rate reported by nondeployed era veterans.<sup>1476</sup> Diagnosed hay fever has also been reported at similar rates by Gulf War and nondeployed veterans.<sup>464,789,1698</sup>

In the first reported study of immune function among ill Gulf War veterans, investigators from an allergy and immunology clinic tested a sequential series of 20 symptomatic veterans evaluated in a Gulf War referral center at the West Los Angeles VA.<sup>810</sup> As a group, these symptomatic Gulf War veterans had higher-than-average levels of IgE, and nearly two-thirds had positive allergy tests. No evidence of immune deficiencies were identified in any of the symptomatic veterans. Although a high proportion of

symptomatic Gulf War veterans were classified as atopic in this clinical series, it is not possible to draw conclusions about the prevalence of allergies in symptomatic veterans overall, and no additional studies of this issue have been reported.

**Summary. Immune parameters in Gulf War veterans.** Although questions have been raised for many years about immune function in ill Gulf War veterans, limited research has been conducted in this area. No population studies have provided comprehensive information on rates of infectious or autoimmune diseases in Gulf War veterans. The largest clinical study of U.S. Gulf War veterans provided no information on immune characteristics of veterans with Gulf War illness. Other clinical studies have provided only limited information regarding indicators of autoimmunity and allergy in relation to Gulf War illness.

A well-known hypothesis, suggesting that veterans' multisymptom illness is related to a systemic shift favoring Th-2-type immunity, has not been supported by studies comparing Th-1 and Th-2 measures in symptomatic and healthy veterans. Clinical findings from several studies have provided no indication that veterans with Gulf War illness are immune deficient, that is, that they have an impaired ability to respond to infection. However, a number of immune parameters have been associated with Gulf War illness. These generally occur as research findings that differ between groups of sick and healthy veterans, as opposed to clinical test results that are diagnostic of familiar disease conditions in individual veterans. Although parameters evaluated by different studies have been highly variable, some areas of consistency have emerged.

Results from two studies, using different methods in different groups of symptomatic veterans, indicate that Gulf War illness is associated with a low-level, persistent immune activation, reflected in elevated levels of the cytokines IL-2, IFN- $\gamma$  and IL-10. In addition, several studies have reported that NK cell numbers and/or cytotoxic activity are significantly reduced in veterans with Gulf War illness. A fuller understanding of immune function in ill Gulf War veterans is needed, particularly in veteran subgroups with different clinical characteristics and exposure histories. It is also important to determine the extent to which identified immune perturbations may be associated with altered neurological and endocrine processes that are associated with immune regulation.

### **Additional Clinical and Research Findings Associated with Gulf War Illness**

As described throughout this section, a variety of studies have identified biological measures that distinguish veterans with Gulf War illness from healthy controls. The areas of research already described have included multiple studies focused on different biological characteristics of symptomatic veterans. Most positive findings were obtained using research protocols that compared groups of symptomatic Gulf War veterans to healthy controls. Few of the identified Gulf War illness-related differences or abnormalities—whether related to the central nervous system, autonomic function, neurotoxicant-neutralizing enzymes, endocrine parameters, or immune perturbations—were identified with diagnostic tests routinely used in clinical practice.

There is comparatively little information on other types of biological processes or objective measures in relation to Gulf War illness. The limited information available comes primarily from two sources: (1) reports describing clinical findings from specialty evaluations such as rheumatologic or gastrointestinal workups, and (2) results from single studies that have evaluated particular issues, such as pain sensitivity or the burning seminal fluid problem reported by veterans and their spouses.

**Table 9. Clinical Findings in Symptomatic Gulf War Veterans: Rheumatologic and Pain Evaluations**

<b>Report/Study</b>	<b>Key Findings</b>
Rheumatologic evaluation of a subgroup of 20 GWV with muscle weakness or pain <sup>46</sup>	No autoimmune or connective tissue disorders identified.
Evaluation of 139 GWV referred for rheumatology consult by CCEP <sup>517</sup>	Most diagnosed conditions similar to those of other veteran populations (e.g. 25% patellofemoral syndrome, 18% mechanical low back pain). Higher than usual rate of FM (17%). 21 veterans positive for RF, 2 diagnosed with RA; 14 had abnormal ANA, 1 diagnosed with SLE.
Musculoskeletal symptoms evaluated in 145 symptomatic GWV referred to a rheumatology clinic <sup>412</sup>	Most patients had widespread pain. FM diagnosed in 34%, variety of other diagnoses in fewer GWV. Overall, 4 were positive for RF, 3 had elevated ANA. Veterans' functional status substantially impaired, with all mean SF36 scores below national 25 <sup>th</sup> percentiles.
Evaluation of 60 male GWV referred to VA rheumatology clinic for myalgia <sup>1362</sup>	15% had elevated muscle enzymes (CPK or aldolase) with weakness, arthralgia, and rashes. Limited other test abnormalities.
Evaluation of 241 GWV with GWUI, including 92 with unexplained musculoskeletal symptoms <sup>160</sup>	21% of GWV with GWUI diagnosed with FM (16% male, 43% female). Higher rate of patellofemoral syndrome in GWV than controls, but similar rates of other diagnoses. No autoimmune or inflammatory conditions identified.
Pain tolerance assessment in 11 GWV, 25 FM patients, 24 controls <sup>1481</sup>	Pain ratings indicated sign. greater pain sensitivity in GWV than controls, and sign. greater pain sensitivity in female GWV than male FM patients.
Tender point evaluation of 327 GWV with CMI and 708 GWV without CMI <sup>142</sup>	GWV with CMI had sign. higher rate of FM (5.2%) than GWV without CMI (0.7%).
Synovial biopsy in 10 GWV with GWI and arthralgia <sup>342,1199</sup>	Despite significant joint pain, GWV biopsies were normal on histology findings, vascular density, and inflammatory cell populations.

Abbreviations: GWV = Gulf War veteran, CCEP = DOD Comprehensive Clinical Evaluation Program, FM = fibromyalgia, SF36 = Medical Short Form Survey, GWUI = Gulf War unexplained illness, RF = rheumatoid factor, RA = rheumatoid arthritis, ANA = antinuclear antibodies, SLE = systemic lupus erythematosus, CPK = creatine phosphokinase, sign. = statistically significant

**Clinical findings related to pain and musculoskeletal symptoms.** Widespread muscle and joint pain are among the most prevalent complaints of symptomatic Gulf War veterans.<sup>1489</sup> Objective findings from studies and clinical evaluations of Gulf War veterans with prominent pain symptoms are summarized in Table 9. As shown, the profile of clinical rheumatologic findings in Gulf War veterans has been unremarkable in most respects. The one exception is the observation of a higher-than-expected number of fibromyalgia cases in this primarily young, male population.<sup>46,142,160,517</sup> This parallels results from one study indicating that veterans with Gulf War illness have significantly greater sensitivity to peripheral pain stimuli than controls, on objective measures of hyperalgesia.<sup>1481</sup>

**Assessment of gastrointestinal symptoms and conditions.** Gastrointestinal (GI) difficulties are frequently reported by ill Gulf War veterans, with individual cases ranging from serious, ongoing problems with diarrhea to less severe, but persistent, abdominal pain or indigestion. Despite the prominence of these symptoms, few studies have investigated the biological underpinnings of veterans' gastrointestinal difficulties. As previously described, one early report identified an excess of gallbladder disease requiring surgery in Gulf War veterans compared to other veterans in the VA healthcare system.<sup>1049</sup> Clinical case series of symptomatic Gulf War veterans, summarized in Table 10, generally identified GI diagnoses and laboratory findings similar to those of other patients referred to gastroenterologists. Several reports indicated that veterans' GI symptoms resembled irritable bowel

**Table 10. Clinical Findings in Symptomatic Gulf War Veterans: Gastrointestinal Evaluations**

<i>Report/Study</i>	<i>Key Findings</i>
Upper and lower endoscopy and biopsies in 15 GWV from a group of 57 symptomatic GWV and 44 nondeployed veterans from a single Guard unit. <sup>1451</sup>	Most GWV had GI symptoms during deployment that continued to the time of the study. No specific or consistent GI pathology identified. Six of 15 biopsies showed evidence of mild chronic inflammation.
Visceral and cutaneous sensitivity in 12 GWV with chronic abdominal pain and diarrhea that began during the Gulf War, 12 civilian and veteran controls <sup>370</sup>	All GWV met criteria for irritable bowel syndrome. Visceral pain sensitivity (rectal distension) and cutaneous pain sensitivity (foot immersed in hot water) sign. greater in GWV than controls
Different GI endoscopic, laboratory, and histological evaluations in 24 male GWV on VA Registry referred to GI clinic for chronic GI symptoms <sup>824</sup>	8/17 GWV had hiatal hernia, 10/17 had antral erythema, 2/17 had ulcers, 5/18 had diverticulosis, 9/17 had gastritis (6 with <i>H. pylori</i> ), stool cultures normal, diverse other findings in individual GWV
327 GWV with CMI, 708 GWV without CMI <sup>142</sup>	16% of GWV with CMI diagnosed with dyspepsia, sign. more than GWV without CMI (6%)

Abbreviations: GWV = Gulf War veterans, GI = gastrointestinal, CMI = chronic multisymptom illness,<sup>464</sup> sign. = statistically significant

syndrome (IBS), a “multisymptom illness” found in the general population characterized by prominent GI symptoms, often with no objective diagnostic abnormalities. The prevalence of IBS in Gulf War veterans has not been assessed, but preliminary information from an ongoing VA study of IBS in Gulf War veterans was presented to the Committee by Dr. Ashok Tuteja.<sup>1565</sup> The project includes assessment and treatment of Gulf War veterans with IBS, and the Committee looks forward to reviewing study results when they become available.

**Respiratory function in Gulf War veterans.** Respiratory symptoms like wheezing, shortness of breath, and persistent cough are also commonly reported by ill Gulf War veterans. As previously described, studies have suggested that rates of asthma and chronic bronchitis may be elevated in U.S. Gulf War veterans exposed to pollutants from the Kuwaiti oil fires.<sup>285,866</sup> Several articles have reported results of pulmonary function testing in symptomatic Gulf War veterans. Two indicated that a subset of veterans referred for evaluation by respiratory specialists do exhibit evidence of reduced pulmonary function.<sup>313,1012</sup> The large VA clinical study later reported that Gulf War veterans with chronic multisymptom illness (CMI) have the same rate of identifiable obstructive lung disease as veterans without CMI.<sup>142</sup>

Several large population studies have compared respiratory function in Gulf War veterans overall—those with and without multisymptom illness—to nondeployed veterans. A large study of Navy Seabees conducted in 1994 and 1995 indicated that, overall, Gulf War and nondeployed era veterans had similar values on pulmonary function tests.<sup>524</sup> In the large VA clinical study, U.S. Gulf War and nondeployed era veterans had similar rates of respiratory symptoms, pulmonary function abnormalities, and diagnosed obstructive lung disease.<sup>393,755</sup> However, active duty military personnel potentially exposed to nerve agents after the 1991 Khamisiyah demolitions, based on DOD models, were reported to have a small, but significant, increased rate of hospitalization for respiratory diseases.<sup>529</sup> For Australian Gulf War veterans, exposure to oily smoke was associated with reduced pulmonary forced vital capacity (FVC) and with an increased risk of emphysema.<sup>790</sup> Findings such as these underscore the importance of evaluating respiratory and other health outcomes in Gulf War veterans in subgroups with specific exposure histories.

**Table 11. Clinical Findings in Symptomatic Gulf War Veterans: Evaluation of Respiratory/Lung Function**

<b>Report/Study</b>	<b>Key Findings</b>
Evaluation of 29 GWV referred to pulmonary clinic for assessment of dyspnea on exertion <sup>1012</sup>	15 of 29 GWV had abnormal resting pulmonary function measures. No common pattern of pulmonary abnormality identified on resting or exercise tests.
Pulmonary function tests in 37 GWV volunteers (32 with respiratory symptoms), 38 veteran and nonveteran controls <sup>313</sup>	Midvital capacity ratio was sign. higher in GWV than controls, and greater than 1.0 in 86% of GWV, indicating variable extrathoracic airflow obstruction. All GWVs evaluated by bronchoscopy and biopsy showed evidence of larynx and trachea inflammation; findings not attributable to smoking.
Pulmonary function at baseline and during low-level acetone inhalation in 8 symptomatic GWV and 8 well GWV <sup>193</sup>	Pulmonary function similar in symptomatic and healthy GWV at baseline and during acetone exposure.
Pulmonary function tests in 327 GWV with CMI and 708 GWV veteran controls <sup>142</sup>	GWV with CMI had similar rate of diagnosed obstructive lung disease as GWV without CMI.

Abbreviations: GWV = Gulf War veterans, CMI = chronic multisymptom illness,<sup>464</sup> sign. = statistically significant

**Women’s health issues in Gulf War veterans.** As described in the first section of the report, multiple studies have assessed pregnancy outcomes and fertility issues in Gulf War veterans. But little information is available on other types of health problems of concern for women veterans, and no studies have assessed female-specific complaints in women with Gulf War illness. A study of over 200 British women Gulf War veterans found that overall, in contrast to other populations, women and men Gulf War veterans report generally similar rates of symptoms.<sup>1699</sup> Compared to nondeployed female veterans, however, women who served in the Gulf War reported substantially higher rates of frequent yeast infections (OR=5.0) and bladder infections (OR = 9.8). A longitudinal study of Air Force women veterans of the Gulf War conducted by the University of Michigan found that, in addition to the Gulf War illness-type symptoms reported by other studies, women Gulf War veterans were significantly more likely to report lumps or cysts in their breasts and abnormal Pap smears than era veterans.<sup>1207,1208</sup> This contrasts with a report from DOD’s Armed Forces Institute of Pathology, which identified similar types and rates of cervical findings in Gulf War and nondeployed era veterans from Pap smears conducted on 6,715 active duty Air Force women in 1994.<sup>463</sup> It is important to emphasize, again, that these studies only looked at Gulf War veteran women overall, and did not provide information specific to women with Gulf War illness.

**Skin abnormalities in Gulf War veterans.** Skin problems that include anomalous rashes and growths, and other abnormalities, are commonly reported by symptomatic Gulf War veterans but have only minimally been evaluated in research studies. Skin conditions are among the most prevalent physician diagnoses reported in surveys of Gulf War veterans,<sup>751,789,1476,1698</sup> and an early case series report indicated that rashes were clinically verified in 39 percent of 166 symptomatic Gulf war veterans.<sup>1050</sup> In the large King’s College study, 48 percent of disabled U.K. Gulf War veterans had diagnosed skin conditions.<sup>607</sup> A group of miscellaneous benign skin problems—including lipomas, seborrheic warts, and vitiligo—were significantly more common in disabled Gulf War veterans than well veterans. Seborrheic dermatitis occurred in more Gulf War veterans (8%), overall, than non-Gulf veterans (2%). In the large U.S. clinical study, skin conditions were not evaluated in relation to multisymptom illness. Overall, 35 percent of deployed Gulf War veterans, were diagnosed with “Type 2” skin conditions, that is, various dermatologic findings more serious than freckles, moles, and scars.<sup>393</sup>

**Genetic findings in symptomatic Gulf War veterans.** In addition to research on genetic variability related to toxin-neutralizing enzymes, two studies have evaluated other genetic parameters in symptomatic Gulf War veterans. Investigators at the East Orange, New Jersey VA assessed allele frequencies and genotypes associated with muscle metabolism and physical endurance in 49 Gulf War veterans and 61 nonveterans with chronic fatigue syndrome (CFS).<sup>1725</sup> In Gulf War veterans, CFS was highly associated with insertion/deletion (I/D) polymorphisms in the gene that encodes for angiotensin-converting enzyme (ACE), an enzyme associated with muscle metabolism, electrolyte balance, and blood pressure. Frequency of the I allele was significantly reduced in ill veterans. Compared to II homozygotes, the DD genotype was associated with an eight-fold greater risk for CFS in Gulf War veterans, but was not related to CFS in nonveteran patients.

Researchers from Pennsylvania State University evaluated the frequencies of HLA A, B, DR, and DQ antigens in 32 symptomatic Gulf War veterans compared to a local reference population.<sup>1139</sup> One HLA class I antigen, A28, was significantly elevated in Gulf War veterans (22%) compared to the general population (7%). This antigen has been associated with a variety of clinical conditions, and possible implications for Gulf War illness are unclear. Investigators suggested the association may have been a chance finding and concluded that HLA variability is not strongly associated with Gulf War illness.

**Additional findings in symptomatic Gulf War veterans.** A number of additional studies have provided single looks at specific medical problems or laboratory parameters in Gulf War veterans. Findings from these studies are briefly summarized below.

Burning seminal fluid in Gulf War veterans. After the Gulf War, some returning male veterans and their female sexual partners reported a painful burning reaction to veterans' seminal fluid. The problem was particularly unique to Gulf War service, with mild-to-severe "burning semen" reported by seven percent of Gulf War veterans nationally, but mild problems only by one percent of nondeployed veterans.<sup>751</sup> Researchers from the University of Cincinnati collected questionnaire data from 211 Gulf War veterans with this problem and conducted detailed clinical evaluations of 20 Gulf War couples (male veterans and their female partners).<sup>131</sup> For about half the veterans, the problem had initially occurred with their first sexual contact after the war. Most had not sought medical attention for the problem and fewer than half the couples obtained relief using a condom. About 40 percent of women met criteria for seminal hypersensitivity syndrome, which is also found in the general population, but important differences were identified in Gulf War couples. In the general population, male partners typically do not react to their own seminal fluid and nearly all cases are relieved using condoms. For Gulf War couples in which women did not have IgE-mediated reactivity to veterans' semen, no explanation for the burning semen problem was identified.

Coagulation abnormalities in symptomatic Gulf War veterans. Based on earlier indications of coagulation abnormalities in chronic fatigue syndrome patients, a team of clinical investigators compared results from a battery of five coagulation assays done on 33 symptomatic veterans (27 Gulf War veterans, six era veterans) and 33 healthy nonveteran controls.<sup>577</sup> Two-thirds of symptomatic veterans tested positive on two or more of the assays, compared to none of the controls, a highly significant difference. Investigators concluded that veterans' symptoms were associated with reduced blood flow resulting from a hypercoagulable state, likely induced by exposures in theater, particularly in veterans with inherited thrombotic risk factors. The proposed association between hypercoagulation and Gulf War illness is being further investigated by a research team at the Minneapolis VA. Dr. Ronald Bach presented preliminary findings from the pilot project to the Committee, which identified significantly greater platelet tissue factor procoagulant activity in veterans with Gulf War illness than in veteran controls.<sup>81</sup> The Committee looks forward to reviewing final results from this project, which will evaluate additional markers of coagulation in larger samples.

**Identification of RNA sequences associated with Gulf War illness.** Chromosomal abnormalities have been reported in Gulf War veterans evaluated in relation to depleted uranium exposure, as previously described. An additional study evaluated genetic alterations in 24 symptomatic veterans by testing their sera for the presence of polyribonucleotides with enterovirus-related primers.<sup>1700</sup> Using reverse transcriptase PCR, researchers identified multiple nucleotide bands common to Gulf War veterans, mostly in the 300-750 base pair range with some longer than 2,000 base pairs. Few bands were identified in healthy nonveteran controls, and all were under 450 base pairs. DNA sequencing of two of the amplicons unique to Gulf War veterans identified polynucleotides that had not previously been characterized, but contained sequences with 100 percent homology to sequences in human chromosome 22q11. Alterations at 22q11 have been associated with other medical conditions, and investigators suggested it contains “hot spots” for genetic deletions and rearrangements. They concluded that their findings indicate that Gulf War illness may be associated with genetic alterations, induced by exposure to multiple hazardous substances during the war.

**Proteomic findings in Gulf War veterans and other multisymptom illness patients.** Investigators from Georgetown University evaluated proteins expressed in the cerebral spinal fluid (CSF) of study subjects with Gulf War illness, fibromyalgia (FM), and chronic fatigue syndrome (CFS) that differentiated them from healthy controls. Results from two study cohorts identified 10 proteins that were differentially expressed in the multisymptom illness patients, whose CSFs were pooled for these analyses.<sup>96</sup> The identified proteome included central nervous system, innate immune, and amyloidogenic proteins not expressed in the CSF of healthy controls. Investigators had earlier indicated, in a conference presentation, that a substantial number of proteins differentiated veterans with Gulf War illness from FM/CFS patients,<sup>215</sup> but these differences were not identified or further explored in the research publication.

**Report of reduced bone formation in Gulf War veterans.** A study of British veterans compared results of ileac crest bone biopsies from 17 symptomatic Gulf War veterans and healthy nonveteran controls.<sup>265</sup> Histology and cell function measures indicated that symptomatic veterans had significantly reduced bone formation at both the tissue and cellular levels, resulting in reduced areas of cancellous bone. Investigators were not able to ascertain the cause of this reduction, but noted that the findings were not associated with reduced physical activity in this group and that similar findings had been reported in symptomatic farmers chronically exposed to organophosphate sheep dip.<sup>264</sup> These results have since been questioned by Ministry of Defence researchers, owing to several limitations in this small, preliminary study.<sup>143</sup>

## **Future Directions in Identifying Physiological Mechanisms that Underlie Gulf War Illness**

Information described throughout this report reflects the primary focus of the Committee’s work thus far, reviewing all research studies, investigations, and reports that provide information pertaining to the health of Gulf War veterans. To address the goal of improving the health of Gulf War veterans, the highest priority research that remains will advance efforts to identify effective treatments and diagnostic tests for Gulf War illness. To accomplish these objectives, it is essential that the specific biological mechanisms that underlie veterans’ symptoms be more specifically characterized.

The current phase of the Committee’s work, therefore, involves an expanded focus on reviewing research related to pathophysiological processes that may underlie the symptoms of Gulf War illness. Research will be considered that may not currently be directed to Gulf War health issues, but can potentially contribute to improved understanding of the biology of Gulf War illness or identifiable subgroups. In undertaking this work, the committee has conducted preliminary discussions in several areas, and has considered one topic in more depth.

In attempting to understand the biological mechanisms that contribute to Gulf War illness, it is useful to consider physiological abnormalities that might explain some of the prominent “unknowns” related to this condition. These include questions about what types of biological processes could manifest as multiple diverse symptoms affecting different systems, what types of processes would elude detection by standard medical evaluation and clinical testing, and what mechanisms might contribute to the long-term nature of veterans’ symptoms. And, as the etiology of Gulf War illness has become better understood, it also includes questions about what biological processes with these characteristics could be induced by toxic exposures. The Committee has discussed diverse questions of this nature, and considered a variety of possible answers.

The biological mechanism considered in most depth involves the potential for proinflammatory processes in the central nervous system to precipitate and sustain the diverse symptoms associated with Gulf War illness. In addition, preliminary discussions have focused on the possible role of neuroplasticity in veterans’ chronic symptoms, neurological and neuroendocrine alterations associated with multisymptom conditions in the general population, and the potential for mitochondrial deficiencies to contribute to Gulf War illness. Information related to these topics is briefly summarized below. The Committee will continue to consider research in these and other areas, and will provide additional information on research that can potentially improve understanding, diagnosis, and treatment of Gulf War illness in future reports.

**Neuroplasticity in relation to Gulf War illness.** A fundamental question related to the biological processes that underlie veterans’ chronic symptomatic illness relates to whether they are the direct result of acute damage caused by a toxic insult in 1991, or the result of persistent alterations in brain processes that are “downstream” from an initial insult. It was long believed that the adult brain is relatively static, and that central nervous system tissues have little capacity for adaptive change in response to damage. In recent years, processes involved in brain regeneration have begun to be better understood. The adult human brain has substantial capacity for structural plasticity, that is, adaptation of brain cells and reorganization of neural pathways in response to damage.<sup>248</sup> These processes have an important role in recovery from brain injury, but can also lead to problems that result from cellular changes and circuitry alterations that are maladaptive. It has been suggested, for example, that some neurodegenerative diseases may be the long-term effect of aberrant brain cell responses to injury.<sup>59</sup>

Dr. Floyd Bloom, a member of the Committee and a prominent neuroscientist, provided a preliminary overview of processes involved in neuroplasticity for Committee discussion, and described how structural reorganization of brain cells can be visually mapped.<sup>151,1820</sup> Long-term damage from an acute central nervous system insult could potentially result from induction of neuroplastic processes, leading to sustained alterations in brain cells and pathways that are inefficient or pathological. For example, repeated inhibition of acetylcholine receptors in the locus ceruleus might result in alterations, locally and in other brain structure, that affect responses to subsequent exposures or other novel events. Knowing the primary areas of cholinergic neurons in the brain, it might be possible to determine which specific areas are dysregulated through animal research or human post mortem studies. Understanding the contribution of these processes to persistent symptoms in Gulf War veterans would potentially have diagnostic and treatment implications.

A variety of related concepts were considered in a 2000 conference on the role of neuroplasticity in chemical sensitivity.<sup>1450</sup> The conference, sponsored jointly by federal agencies and private organizations, included information on Gulf War illness and other multisymptom conditions. Scientists from diverse fields were convened to review relevant research and develop testable hypotheses, based on the premise that chemical injury involves a change in central nervous system function that results in persistent symptoms. Discussions included a chemical “kindling” model whereby chemical exposures precipitate permanent hypersensitive responses to electrical stimulation in brain cells,<sup>490</sup> and research indicating that persistent pain states can result from central sensitization that involves neuroplastic processes in the spinal cord that lead to hyperalgesia.<sup>1021,1790</sup>

**Central nervous system abnormalities associated with disordered sensory processing and autonomic/neuroendocrine dysregulation.** As will be described in the next section of the report, Gulf War illness has similarities to multisymptom conditions found in the general population, conditions like fibromyalgia (FM) and chronic fatigue syndrome (CFS). In addition to similarities in the symptom profiles of these conditions, a number of biological systems affected by FM and CFS also appear to be involved in Gulf War illness. This suggests some overlap in the pathophysiological processes that underlie these conditions.

Dr. Daniel Clauw is a member of the Committee and a leading expert on FM and related pain and multisymptom disorders. His research, and that of other FM researchers, indicates that FM is primarily a central nervous system (CNS) disorder that involves abnormal CNS processing of pain stimuli.<sup>253,254</sup> This has been demonstrated in different ways, including FM-associated elevations in cerebrospinal fluid levels of pronociceptive factors, and enhanced response to nonpainful stimuli in brain regions associated with pain processing, demonstrated on functional MRI.<sup>515</sup> Studies have also demonstrated autonomic dysregulation and neuroendocrine alterations in FM patients, including abnormalities in HPA axis parameters, and reduced circulating levels of norepinephrine and serotonin.<sup>975,1330</sup> Many of the biological abnormalities associated with FM have not been evaluated in Gulf War veterans, however. Research in these areas can potentially provide important insights into biological mechanisms that underlie veterans' symptoms. This is especially important in relation to biological processes amenable to treatment. Two medical FM treatments that address neuroendocrine irregularities have recently been approved by the U.S. Food and Drug Administration (FDA).<sup>398,1666</sup> Additional information comparing FM, CFS, and Gulf War illness is provided in the following section of the report, with related recommendations.

**Mitochondrial paradigm in relation to Gulf War illness.** Mitochondria are the “power plants” of the cell that produce adenosine triphosphate (ATP), the cell’s primary energy source. Mitochondrial function is essential for cell viability, and cells that utilize large amounts of energy, like brain and muscle cells, are particularly sensitive to effects of mitochondrial damage. Dr. Beatrice Golomb, a Committee member, and Dr. Douglas Wallace, a prominent expert in mitochondrial disease, presented information suggesting a link between Gulf War illness and multisystem effects arising from mitochondrial injury.<sup>505,1744</sup>

Drs. Golomb and Wallace described a general model in which toxic environmental exposures can cause damage by inducing increased cellular levels of reactive oxygen species (ROS). The ROS damage mitochondrial DNA, leading to mitochondrial dysfunction, cell damage and cell death. This generates additional release of ROS, triggering a self-perpetuating cycle. Clinical effects become apparent over time, as cell and tissue damage accrue. Prominent symptoms associated with mitochondrial disease can include fatigue, headache, muscle weakness, and cognitive problems, symptoms that parallel those affecting Gulf War veterans. In addition, recent research has indicated that acetylcholinesterase inhibitors, and other toxic chemicals, can exert adverse effects on brain and muscle tissues through pathways that involve oxidative stress and mitochondrial damage.<sup>775,1030,1400</sup>

Studies have linked mitochondrial DNA damage with age-related diseases that include cancer, diabetes, and neurodegenerative diseases.<sup>1742,1743</sup> But there is little information from studies of veterans with Gulf War illness to indicate whether mitochondrial abnormalities may play a role in veterans' symptoms. As previously described, muscle tests and biopsies have generally found little indication of muscle pathology in veterans with Gulf War illness, although one study identified an exercise-induced excess of circulating lactate suggestive of low-level mitochondrial insufficiency.<sup>1311</sup> Muscle symptoms in other multisymptom conditions are generally considered central in origin, although limited muscle abnormalities have been identified.<sup>1470,1832</sup> Identification of frank mitochondrial damage in symptomatic veterans could have important implications for diagnostic testing and treatment.

### **Multisymptom illness associated with central nervous system inflammatory processes.**

The Committee reviewed extensive materials and heard multiple interrelated presentations concerning the potential for chronic central nervous system inflammatory processes to contribute to Gulf War illness. Attention to this area stemmed from the Committee's interest in identifying pathophysiological processes that could explain the complex of concurrent symptoms affecting Gulf War veterans but would go undetected with routine clinical testing.

The Gulf War illness symptom complex prominently includes chronic widespread pain, cognitive difficulties, and unexplained fatigue, along with diverse other symptoms. Similar, usually time-limited symptom complexes, occur in relation to a number of other health conditions that include infection, sleep deprivation, and the therapeutic use of cytokines.<sup>310,378,549,784,876</sup> All these time-limited "multisymptom illness" conditions have one thing in common: they occur in conjunction with increased levels of proinflammatory cytokines. Cytokines are chemical messengers generated as part of the body's nonspecific, innate immune response to diverse threats that include infection, tissue injury, and toxic exposures. Proinflammatory cytokines have a variety of effects. In infectious disease, they precipitate a specific immune response that neutralizes the infection, but they also precipitate the pain/fatigue/impaired cognition complex of somatic symptoms. These symptoms are commonly believed to be adaptive, promoting recovery from sickness by imposing reduced physical and mental activity.<sup>784</sup>

This symptom complex parallels a group of "symptoms" studied in animal models that are referred to as "sickness behaviors"—reduced activity, impaired memory and learning, and heightened pain sensitivity—which are precipitated by infection and proinflammatory cytokines.<sup>309,330,784</sup> The association between proinflammatory cytokines and "sickness response" symptoms in animals and humans has been known for some time,<sup>311</sup> but in recent years has been the subject of a fast-growing body of research in diverse fields.<sup>37,82,309,694,715,1041,1524,1736,1784</sup> Studies have demonstrated that these symptoms are the result of cytokines acting in the brain, not the periphery, and can be precipitated by increases in brain cytokine levels that are either stimulated from the periphery, or generated by resident brain cells.<sup>95,784,794</sup>

Immune processes in the brain differ in important ways from those in the periphery and involve different cell populations.<sup>84</sup> Microglial cells are widely distributed in the brain and have a primary role in immune surveillance and the central immune response, including production of proinflammatory cytokines in response to injury—chemical, physical, or biological.<sup>1153,1502</sup>

The Committee reviewed diverse types of information related to central proinflammatory processes and discussed them with scientists whose research related these processes more specifically to Gulf War illness. Dr. James O'Callaghan, a Committee member and the director of the Molecular Neurotoxicology Laboratory at the U.S. Centers for Disease Control and Prevention, provided an introductory overview of toxin-induced inflammation and cytokine activation in the brain.<sup>1140</sup> He described the multiple overlapping feedback mechanisms whereby the brain, autonomic, immune, and endocrine systems interact with and regulate one another. Acute microglial activation is a protective response to toxins, brain injury, and infection. Persistent microglial activation, however, has been linked to a number of chronic disease states, including Parkinson's disease. Dr. O'Callaghan's own research has demonstrated the role of the proinflammatory cytokine TNF- $\alpha$  in the generation of cell damage and gliosis by the dopaminergic neurotoxicant MPTP.<sup>1473</sup>

Beyond the parallels between Gulf War illness and symptoms that develop with increased brain levels of proinflammatory cytokines, the potential relevance of these processes to Gulf War illness is suggested by several indicators. First, studies indicate that exposures encountered in the Gulf War can stimulate production of cytokines and related proinflammatory processes in the brain, and inhibit processes that down regulate inflammation. Inflammation is controlled by both autonomic and hypothalamic-pituitary-adrenal (HPA) axis function in the periphery, both of which appear to be dysregulated in Gulf War veterans. There are also indications that Gulf War illness is associated with a low-level immune

activation, evident in the peripheral circulation, although this has not yet been assessed in the central nervous system.<sup>1420,1835</sup>

Enhanced glial activation and central nervous system cytokine production have been demonstrated in animal models following exposure to high<sup>306</sup> and low-level<sup>601</sup> sarin, in response to combined exposure to PB, DEET, permethrin and stress, at levels comparable to those of Gulf War veterans,<sup>3</sup> and in response to inhalation of DU<sup>896</sup> and particulates.<sup>147,1719</sup> In addition, animal studies have demonstrated that low level sarin exposure results in a delayed reduction of M1 cholinergic receptors in the brain,<sup>601</sup> delayed effects on autonomic function,<sup>1070,1071</sup> and persistent reduction of corticosteroid.<sup>740,868,1445</sup>

Dr. Kevin Tracey presented research from his laboratory, which has characterized the mechanism by which the autonomic nervous system regulates cytokine production and inflammation in the periphery, termed the “cholinergic anti-inflammatory pathway.”<sup>1552</sup> It involves autonomic detection of inflammation, afferent vagal signaling to the brain, and efferent signaling that inhibits cytokine production.<sup>301</sup> This pathway is regulated by the brain, and depends on the activation of central muscarinic receptors, specifically M1 receptors.<sup>1178</sup> It is not known if similar processes are involved in regulating inflammatory processes in the brain.

Additional information was presented by Dr. Mariana Morris, who described her research demonstrating delayed autonomic and neuroendocrine effects of low-level sarin exposure<sup>1070,1071</sup> and Dr. Mohan Sopori, describing M1 receptor alterations, increased central cytokine production,<sup>601</sup> and persistent reductions in corticosteroid levels following low-level sarin exposure.<sup>740,868,1445</sup> Dr. Nancy Klimas summarized the broad spectrum of findings related to increased cytokine production in patients with CFS.<sup>812,814</sup>

Dr. Jau-Shyong Hong described his research demonstrating the potential for an acute proinflammatory stimulus to generate a persistent, self-perpetuating process of microglial activation and inflammation in the brain following toxic insult.<sup>146,625</sup> Dr. Hong also provided preliminary information related to several compounds that are being studied for their potential to inhibit aberrant microglial activation and inflammation in the brain, including drugs currently approved for use in other conditions. In addition, Dr. Tomas Guilarte provided an overview of the use of PET scans and other methods to detect PK11195 binding on peripheral benzodiazepine receptors in the brain, a sensitive marker for glial cell activation.<sup>540</sup> These methods are used in research studies to identify and localize evidence of central nervous system inflammation resulting from neurotoxicant exposures in animal models. They are also used to characterize central inflammatory processes associated with neurological diseases in humans, including ALS, multiple sclerosis, and Parkinson’s disease.<sup>94,204,481,843,1564</sup>

The research considered suggests the potential for Gulf War exposures to precipitate an inflammatory response in the brain, a response that may have become dysregulated due to effects of multiple repeat exposures and/or disruption of processes that down regulate the central inflammatory response. It also suggests the potential for persistent neuroinflammatory processes to develop, promoted by alterations in autonomic and neuroendocrine mechanisms that normally keep inflammatory processes in check, or by self-perpetuating mechanisms.<sup>146,494</sup> Lastly, it suggests that these processes can precipitate a multisymptom complex similar to that affecting Gulf War veterans.

The Committee considers the potential involvement of central proinflammatory processes in precipitating and sustaining veterans’ multisymptom illness to be a promising area for further research. The mechanisms of central nervous system injury and chronic illness suggested by this model also appear to be compatible with other mechanisms considered more briefly by the Committee. Central nervous system inflammatory processes may contribute to or result from neuroplastic changes following an initial insult to the brain or additional alterations that develop over time.<sup>204,309,510</sup> The mechanisms described imply an epiphenomenon involving interactive dysregulation of neuroendocrine parameters, autonomic function, and neuroinflammatory processes that, in combination, result in persistent symptoms that include

widespread pain, cognitive difficulties, fatigue, and additional problems. Central inflammatory processes also generate, and can be triggered by, increased levels of ROS and mitochondrial alterations in brain tissues.<sup>93</sup> Whether or not these processes are detectable in the peripheral circulation and tissues, their occurrence in the brain and spinal cord may plausibly explain veterans' symptoms.

Research in this area is especially warranted because of its possible clinical implications. If veterans with Gulf War illness are affected by dysregulated central inflammatory processes, imaging methods are available that can potentially identify these abnormalities in ill veterans, providing possible diagnostic applications. Most importantly, a number of therapeutic agents have been studied and are being further developed for their effectiveness in treating dysregulated central inflammatory processes.<sup>289,1047,1417</sup>

## Recommendations

The Committee places a high priority on identification of biological markers for Gulf War illness and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing significant associations between Gulf War illness and neurological, immune, endocrine, and enzyme parameters, the Committee recommends the following research:

- Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with Gulf War illness, including illness or exposure subgroups, from healthy Gulf War veterans
- Comprehensive evaluation of autonomic nervous system function in veterans with Gulf War illness, including illness and exposure subgroups
- Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures
- Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups
- Comprehensive evaluation of hypothalamic-pituitary-adrenal axis parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups
- Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by Gulf War illness
- Animal studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs
- Studies that utilize new technologies (proteomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, as well as illness and exposure subgroups

## Gulf War Illness in Relation to Multisymptom Conditions in the General Population

Research reports often point to general similarities between Gulf War illness and multisymptom conditions found in the general population—conditions such as chronic fatigue syndrome and fibromyalgia—that are defined primarily on the basis of patients’ symptoms. Such conditions share many features with Gulf War illness. They are characterized by multiple symptoms affecting multiple systems, are not well understood biologically, and are not typically distinguished by objective diagnostic tests. The symptoms of these conditions are also rather general, that is, they include problems such as fatigue, pain, and cognitive/mood difficulties that are commonly seen in healthcare settings, and are associated with a wide range of medical conditions. These general similarities were recognized by Congress when, in 1998, it directed that special regulations permitting Gulf War veterans to receive disability compensation for “undiagnosed illnesses” also apply to veterans diagnosed with chronic fatigue syndrome, fibromyalgia, and similar conditions defined primarily on the basis of symptoms.<sup>259</sup>

There are also strong parallels in the historical and social contexts surrounding Gulf War illness and other multisymptom conditions. All are chronic and debilitating to varying degrees, often persisting for many years, and present difficult challenges for patients seeking healthcare support and for clinicians seeking to provide useful treatments.<sup>369,919,1535,1783</sup> All of these conditions have been considered controversial, particularly so in the early years they were recognized, with much of the controversy focused on the degree to which the conditions represent distinct syndromes and are essentially organic or psychiatric in nature.

For its initial consideration of similarities between Gulf War illness and multisymptom conditions in the general population, the Committee focused on three defined syndromes—chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity syndrome (MCS). A number of other conditions also reasonably fall under the “multisymptom illness” rubric, conditions such as irritable bowel syndrome, myofascial pain syndrome, and temporomandibular joint dysfunction syndrome. Such syndromes may have similarities to some of the symptom domains affecting veterans, but are less obviously associated with the diversity of systems involved in Gulf War illness and have seldom been evaluated in Gulf War veterans.

In contrast, multiple studies have reported the prevalence of CFS, FM, and MCS in Gulf War veterans.<sup>1534</sup> Identification and diagnosis of CFS, FM, and MCS cases depends on definitions that have varied between investigators and over time.<sup>299,465,621,1262,1398,1408,1437,1801</sup> While each syndrome is associated with multiple symptom types, CFS, FM, and MCS case definitions differ markedly from one another, with each distinguished by a sentinel symptom or core characteristic. The sentinel symptom for CFS is persistent and debilitating fatigue, for FM it is chronic widespread pain, and for MCS it is the exacerbation of symptoms by low-level chemical exposures. However, the *syndromes* CFS, FM, and MCS are not synonymous with these sentinel symptoms and are much less prevalent. The symptom of fatigue, for example, is extremely common, affecting up to one fourth of the general population.<sup>1179,1234</sup> Chronic fatigue *syndrome*, on the other hand, is far less common. As currently defined, CFS affects less than one half of one percent of the general population.<sup>709,1277</sup>

Research studies consistently find significant overlap between defined multisymptom conditions in the general population. That is, patients who meet diagnostic criteria for one of these conditions frequently also meet criteria for others.<sup>2,187,710,1425,1775</sup> The extent to which some or all of these conditions represent different aspects of a unified “multisymptom” disease entity or are associated with common underlying physiological abnormalities has been the subject of considerable discussion by researchers.<sup>255,807,1766</sup> There is also ongoing discussion of the extent to which each syndrome, individually, should be considered a single condition or a heterogeneous mix of illnesses that manifest in similar symptoms but

are actually the result of various etiologic pathways and underlying pathologies.<sup>72,1257,1330,1735</sup> Investigators have observed that the most widely used case definition for CFS,<sup>465</sup> for example, is problematic in that it includes a heterogeneous group of symptomatic patients.<sup>707,708,793,1791</sup> Therefore, determining the extent to which Gulf War illness is essentially the “same type of thing” as CFS, FM, MCS, or perhaps all of them, is complicated by the lack of agreement about whether these conditions individually can rightly be considered single or unique disease entities.

## **Fatigue and Chronic Fatigue Syndrome in Gulf War Veterans**

Poorly understood fatiguing conditions accompanied by multiple symptoms such as chronic pain and cognitive impairment have been described in the medical literature for centuries.<sup>113,600,1498</sup> The clinical condition now identified as chronic fatigue syndrome (CFS) was first described in relation to an outbreak of unexplained fatiguing illness in Nevada in 1984.<sup>622</sup> CFS is now most often defined using criteria established by an expert panel convened by the U.S. Centers for Disease Control and Prevention in 1994.<sup>465</sup> According to these criteria, CFS is defined as the presence of debilitating fatigue for a minimum of six months in the absence of exclusionary medical and psychiatric conditions, and the persistence of at least four of eight chronic symptoms that include headache, muscle aches and pains, joint pain, problems with memory or concentration, unrefreshing sleep, and atypical fatigue following exertion.

Prevalence estimates for CFS, as currently defined, range from 235<sup>1277</sup> to 422<sup>709</sup> cases per 100,000, or 0.2 - 0.4 percent of the general population. A recently-proposed broader CFS case definition yields higher prevalence rates.<sup>1261</sup> CFS affects about three times as many women as men, with individuals age 40-60 most often affected.<sup>1277</sup> The severity of CFS symptoms typically waxes and wanes over time. Longitudinal studies report that between 10 and 60 percent of CFS patients may show symptom improvement on follow-up but fewer than 10 percent achieve full recovery or sustained remission.<sup>205,733,1126,1792</sup>

Although there has been considerable research on patients with CFS—over 3,000 studies are listed in the National Library of Medicine database—the nature and causes of this condition have remained elusive. Studies have pointed to possible viral etiologies<sup>7,186,493</sup> as well as abnormalities related to immune function,<sup>814,815,1098,1175,1419</sup> neurological function<sup>158,270,858,862,1375</sup> and endocrine parameters.<sup>256,334,712,1170</sup> However, results reported in each of these areas have been mixed, with questions about discrepancies between findings still largely unresolved.<sup>26</sup>

As shown in Table 1, the symptom of persistent fatigue is commonly reported by Gulf War veterans. A much smaller proportion meet CFS case definition criteria or report being diagnosed with CFS. By almost any definition, however, the rate of CFS in Gulf War veterans is substantially higher than CFS rates in nondeployed era veterans and the general population. In the subset of studies utilizing clinical evaluations, CFS prevalence estimates have ranged from 1.6 - 5.1 percent in Gulf War veterans,<sup>393,464,987</sup> much higher than the 0.2 - 0.4 percent CFS prevalence in the general population. Most significantly, recent findings from VA’s Phase III clinical study indicated that the rate of CFS in Gulf War veterans was over 40 times the rate in their nondeployed veterans peers.<sup>393</sup>

Taken together, these results demonstrate a dramatically elevated rate of CFS in Gulf War veterans, perhaps the highest rate of CFS yet documented in a large defined population. The VA study also reported, however, that veterans who met diagnostic criteria for CFS represented only a small subset—less than six percent—of Gulf War veterans affected by multisymptom illnesses.<sup>142</sup>

**Table 1. Prevalence of Fatigue and Chronic Fatigue Syndrome Among Gulf War Veterans and Nondeployed Era Veterans**

Study	Fatigue				Chronic Fatigue Syndrome			
	Fatigue Measure	Non deployed vets	Gulf War vets	OR	Chronic Fatigue Syndrome Measure	Non deployed vets	Gulf War vets	OR
Kelsall 2004 <sup>789</sup>	fatigue	56 %	66 %	1.6*	self-reported diagnosis	1.0 %	1.0 %	0.8
Eisen 2005 <sup>393</sup>					clinically diagnosed	0.1 %	1.6 %	40.6*
Fukuda 1998 <sup>464</sup>	fatigue > 6 months	13 %	41 %	4.7*†	clinically diagnosed		5.1 %	
Goss Gilroy 1998 <sup>511</sup>					presumed CFS based on symptoms	1.9 %	8.5 %	5.3*
Gray 1999 <sup>524</sup>	fatigue > 1 month	5 %	20 %	4.4*				
Gray 2002 <sup>527</sup>	fatigue > 1 year	1 %	39 %	3.7*	self-reported diagnosis	0.7 %	5.2 %	7.6*
Iowa 1997 <sup>350,692</sup>	feeling tired	19 %	38 %	2.6*†	presumed CFS based on symptoms	0.6 %	1.9 %	3.1*
Ishoy 1999 <sup>696</sup>	abnormal fatigue	11 %	26 %	3.0*†				
Kang 2000 <sup>751,753</sup>	fatigue	15 %	38 %	3.5*†	presumed CFS based on symptoms	1.2 %	5.6 %	4.8*
McCauley 2002 <sup>987</sup>					clinically diagnosed		2.2 %	
Proctor 2001 <sup>1238</sup>	chronic fatigue	9 %	29 %	4.4*†	presumed CFS based on symptoms	0	2.0 %	ns
Reid 2001 <sup>1264</sup>					presumed CFS based on fatigue score, SF36	1.8 %	2.1 %	1.2
Simmons 2004 <sup>1411</sup>	fatigue	1 %	11 %	9.1*	self-reported diagnosis	0.1 %	0.4 %	3.5*
Steele 2000 <sup>1476</sup>	fatigue > 1 year	12 %	36 %	4.1*	presumed CFS based on symptoms	0.7 %	7.1 %	8.2*
Unwin 1999 <sup>1698</sup>	fatigue	28 %	51 %	2.7*	self-reported diagnosis	0.8 %	3.3 %	4.2*

Abbreviations: CFS = chronic fatigue syndrome, OR = odds ratio, SF36 = Medical Outcome Study Short Form Survey

Notes: \* Odds ratio is significantly elevated in Gulf War veterans; †Value calculated from data provided in referenced article

### Chronic Pain and Fibromyalgia in Gulf War Veterans

Fibromyalgia, or fibromyalgia syndrome (FM) is a condition associated with chronic widespread pain that is typically accompanied by a variety of persistent symptoms such as fatigue, cognitive and mood disturbances, sleep abnormalities, headache, and gastrointestinal difficulties. Chronic widespread pain is a common problem, affecting between seven and 11 percent of the general population.<sup>296,1774,1799</sup>

Fibromyalgia, as defined by the American College of Rheumatology, is much less common. Defining

**Table 2. Prevalence of Pain and Fibromyalgia Among Gulf War Veterans and Nondeployed Era Veterans**

Study	Pain				Fibromyalgia			
	Pain Measure	Non deployed vets	Gulf War vets	OR	Fibromyalgia Measure	Non deployed vets	Gulf War vets	OR
Bourdette 2001 <sup>160</sup>					clinically diagnosed		2.5 %	
Eisen 2005 <sup>393</sup>					clinically diagnosed	1.2 %	2.0 %	2.3*
Fukuda 1998 <sup>464</sup>	muscle pain > 6 months	6 %	18 %	3.4*†				
Goss Gilroy 1998 <sup>511</sup>					presumed FM based on symptoms	9.6 %	16.2 %	1.8*
Gray 1999 <sup>524</sup>	unusual muscle pain > 1 month	2 %	7 %	3.8*				
Gray 2002 <sup>527</sup>	unusual muscle pain > 1 year	6 %	23 %	4.4*				
Iowa 1997 <sup>350,692</sup>	muscle aches, soreness or stiffness	17 %	31 %	2.2*†	presumed FM based on symptoms	11.1 %	20.9 %	2.1*
Kang 2000 <sup>751</sup>	muscle pain	17 %	33 %	2.4*†				
Kelsall 2004 <sup>789</sup>	general muscle aches or pains	56 %	66 %	1.3*	self-reported diagnosis	0	< 1 %	-
Simmons 2004 <sup>1411</sup>	skeletal/muscular symptoms	13 %	15 %	1.1*				
Smith 2000 <sup>1432</sup>					hospitalization for FM	0.04 %	0.04 %	1.2*
Steele 2000 <sup>1476</sup>	muscle pain > 1 year	6 %	21 %	4.6*	self-reported diagnosis	< 0.5%	2.0 %	3.7
Unwin 1999 <sup>1698</sup>	pain without swelling	14 %	32 %	2.2*				

Abbreviations: FM = fibromyalgia, OR = odds ratio

Notes: \*Odds ratio is significantly elevated in Gulf War veterans; †Value calculated from data provided in referenced article

criteria require that a patient have a history of chronic widespread pain persisting for at least three months, and experience pain in response to digital pressure applied to at least 11 of 18 specified locations on the body, or tender points.<sup>1801</sup> Fibromyalgia has been reported to affect two-to-three percent of the adult population,<sup>1340,1549,1774,1799</sup> with rates substantially higher in women than men. Studies have also consistently demonstrated a high degree of overlap between FM and CFS, with patients diagnosed with one condition frequently also meeting criteria for the other.<sup>2,187,710,1775</sup>

An extensive amount of research has been conducted in relation to fibromyalgia—about 4,000 studies are listed in the National Library of Medicine database. Although the precise pathophysiological mechanisms underlying FM are not entirely understood, research conducted since the 1990s has provided a number of important insights. Studies have suggested a genetic predisposition for FM, as indicated by the elevated

rate of FM among family members of FM patients.<sup>64,199,1191</sup> Fibromyalgia has been reported to develop in conjunction with a variety of conditions and apparent triggers, including physical trauma, infectious diseases, and emotional stress.<sup>1,200,201,348,531</sup> Affected patients have been shown to exhibit abnormalities of the hypothalamic-pituitary-adrenal axis<sup>24,294,534,544,1106</sup> as well as autonomic irregularities.<sup>974-976,1204</sup> The hallmark clinical finding associated with fibromyalgia is a significantly reduced threshold for pain, a phenomenon associated with abnormalities in pain processing mechanisms in the central nervous system.<sup>164,269,516,871,1210,1474</sup>

Epidemiologic studies have consistently found that chronic pain is one of the most frequently-reported symptoms affecting Gulf War veterans, as summarized in Table 2. Clinical studies have also found that a relatively high proportion of Gulf War veterans referred for rheumatology consults are diagnosed with fibromyalgia.<sup>412,517</sup> In two population-based studies involving clinical evaluation of Gulf War veterans, the prevalence of FM was estimated to be about two percent.<sup>160,393</sup> Although similar to the overall FM prevalence in the general population, this rate is higher than would be expected in a predominantly male population of comparable age, and about twice as high as the rate diagnosed in nondeployed Gulf War era veterans.<sup>393</sup> Additional results from VA's large clinical study of Gulf War veterans indicate that among Gulf War veterans with multisymptom illnesses, only a small fraction—about five percent—meet diagnostic criteria for fibromyalgia.<sup>142</sup>

### **Sensitivity to Chemicals and Multiple Chemical Sensitivity in Gulf War Veterans**

The condition referred to as multiple chemical sensitivity (MCS), like CFS and FM, is characterized by diverse types of symptoms in the absence of other explanatory conditions. The unique hallmark of MCS is that these symptoms are exacerbated by exposure to common chemicals (e.g. household cleaners, motor vehicle exhaust, perfumes, paint, pesticides, tobacco smoke) at levels that do not cause symptoms in healthy individuals. Several case definitions for MCS have been proposed and used in different studies,<sup>71,140,299,1006,1408</sup> although none has been widely adopted as a standard. About half of MCS patients report that their condition first developed after identifiable exposures to chemicals of various types, such as remodeling their home, occupational exposure to solvents, or exposure to agricultural pesticides.<sup>212,1044</sup> Regardless of the presence of an initiating event or specific type of exposure, MCS patients typically report symptoms in response to a variety of odors and classes of chemicals, often including sensitivity to specific foods.

Epidemiologic studies indicate that the *symptom* of being sensitive to common odors or chemicals is fairly common, affecting between 13 and 33 percent of the general population, with rates higher in women than men.<sup>211,837,1018</sup> Investigators have suggested that self-reported rates of chemical sensitivity may underestimate the actual extent of the problem, since some individuals may not be aware that symptoms they experience are triggered or perpetuated by chemical exposures.<sup>1042</sup>

No studies have yet determined the proportion of the general population who meet criteria for the more debilitating manifestation of chemical sensitivity, MCS or MCS syndrome, as defined by any of the proposed case definitions. These criteria generally require that cases be affected by symptoms in multiple organ systems that are made worse by low-level chemical exposures, and sometimes require that patients report some type of lifestyle accommodation to minimize such exposures. In general population surveys, three-to-six percent of respondents have reported being medically diagnosed with MCS or environmental illness.<sup>211,837</sup>

There has been considerably less scientific research on MCS than on FM and CFS, and little consensus with respect to its nature and underlying physiological mechanisms. Historically, persistent reactivity to

**Table 3. Prevalence of Sensitivity to Chemicals and Multiple Chemical Sensitivity Syndrome Among Gulf War Veterans and Nondeployed Era Veterans**

Study	Sensitivity to Chemicals or Odors				Multiple Chemical Sensitivity			
	Symptom Measure	Non deployed vets	Gulf War vets	OR	Multiple Chemical Sensitivity Measure	Non deployed vets	Gulf War vets	OR
Australian DVA 2003 <sup>75</sup>					self-reported MCS diagnosis	< 1 %	< 1 %	1.3
Black 2000 <sup>141</sup>	sensitive to chemicals	6 %	13 %	1.9*	presumed MCS based on symptoms	2.6 %	5.4 %	1.9*
Fukuda 1998 <sup>464</sup>	sensitive to chemicals > 6 months	2 %	5 %	2.6*†				
Goss Gilroy 1998 <sup>511</sup>					presumed MCS based on symptoms	0.5 %	2.7 %	4.0*
Gray 2002 <sup>527</sup>	chemical sensitivity > 1 year	0.7 %	4 %	5.9*	self-reported MCS diagnosis	0.4 %	1.6 %	4.5*
Kang 2000 <sup>751</sup>	sensitive to chemicals	8 %	15 %	2.0*†				
McCauley 2002 <sup>989</sup>					self-reported MCS diagnosis	1.2 %	1.2 %	1.0
Proctor 2001 <sup>1238</sup>	symptoms triggered by odors	2 %	14 %	7.6*†	presumed MCS based on symptoms	0	2.9 %	-
Reid 2001 <sup>1264,1265</sup>	symptom response to any of 11 chemicals	14 %	28 %	2.3*	presumed MCS based on symptoms	0.2 %	1.3 %	7.2*
Steele 2000 <sup>1476</sup>	symptom response to chemicals > 1 year	4 %	17 %	4.6*				
Unwin 1999 <sup>1698</sup>					self-reported MCS diagnosis	0.3 %	0.8 %	2.2

Abbreviations: MCS = multiple chemical sensitivity, DVA = Department of Veterans Affairs, OR = odds ratio

Notes: \*Odds ratio is significantly elevated in Gulf War veterans; †Value calculated from data provided in referenced article

low-level chemical exposures following an acute initiating exposure was described by Hans Selye in the 1930s.<sup>1385</sup> In the 1960s, Theron Randolph diagnosed a chemical maladaptation syndrome in patients whose diverse symptoms improved after living up to a week in a specially designed chemical-free environment.<sup>1253</sup> Inhaled exposure to the types of chemicals that trigger MCS symptoms have also been reported to induce or exacerbate diagnosable medical conditions. These include, most prominently, asthma, rhinosinusitis, and inflammation of the upper airway.<sup>175,1019</sup> Physicians who treat chemical injury have also reported that headache, depression, arthritis, and a persistent intestinal dysfunction syndrome can be precipitated by common chemical exposures.<sup>902,1252,1254</sup>

A limited number of studies have investigated possible biological mechanisms underlying MCS. These have included enhanced neural sensitivity resulting from a time-dependent kindling process elicited by chemical exposure,<sup>50,121,431,1449</sup> a generalized loss of tolerance to chemicals induced by toxic exposures,<sup>1043</sup> chronic neurogenic inflammation<sup>106,1015</sup> possibly in conjunction with chronic airway inflammation,<sup>358,1016,1017</sup> and behaviorally-conditioned responses to odors.<sup>152</sup> Japanese investigators have

reported that MCS patients have significantly elevated plasma levels of substance P and other neuroinflammatory mediators, levels that are further increased with exposure to volatile organic compounds.<sup>804</sup> Researchers have also suggested that MCS is associated with other immune and neuroendocrine abnormalities,<sup>604,808,891,1014</sup> although none of the proposed biological mechanisms for MCS have been extensively studied.

Several studies have evaluated chemical sensitivity and MCS in Gulf War veterans, as shown in Table 3. Among generally representative groups of Gulf War veterans, 13-17 percent endorse the symptom of being sensitive to chemicals or odors, with lower rates (4-5%) among Air Force and Navy veterans. Although the proportion of Gulf War veterans with this symptom appears, overall, to be similar to that in the general population, it may be higher than rates expected among males of similar age in the general population, and is significantly higher than rates found in nondeployed Gulf War era veterans. As is the case for the symptoms of fatigue and widespread pain, the symptom of chemical sensitivity is more commonly reported by veterans who are ill, or have enrolled in VA's Gulf War Registry.<sup>123,809,1044</sup> As summarized in Table 3, studies have indicated that a much smaller proportion of Gulf War veterans meet criteria for a MCS syndrome, variously defined, with rates ranging from 1.3 to 5.6 percent. Because there are no population-based prevalence estimates for defined MCS, it is not clear whether Gulf War veterans experience higher rates of MCS than the general population. However, studies using MCS-defining criteria have consistently found MCS to be significantly more common in Gulf War veterans than in nondeployed era veterans.

Clinical studies have evaluated additional characteristics of Gulf War veterans who report being chemically sensitive.<sup>122,140,1044</sup> For example, research from the University of Arizona and the Tucson VAMC found that veterans with Gulf War illness were more likely to report being chemically sensitive *before* the war than veterans who did not have Gulf War illness.<sup>123</sup> In addition, the subset of ill veterans with increased chemical sensitivity also reported the highest degree of chemical exposures during the war, particularly exposures to pesticides and insect repellants. Similarly, a U.K. study found a dramatically elevated MCS risk (ORs = 10.9 – 12.3) among U.K. veterans who reported using personal pesticides during the war, an association substantially higher than with other reported exposures.<sup>1264</sup> A team of investigators from the University of Medicine and Dentistry of New Jersey reported that Gulf War veterans who met criteria for both CFS and MCS had a significantly greater symptomatic response to experimental diesel vapor exposure than healthy controls.<sup>433</sup> This response was accompanied by increased autonomic arousal, as indicated by changes in blood pressure and respiratory measures, but not with measurable declines in cognitive performance.

## **Is Gulf War Illness the Same as Multisymptom Conditions Found in the General Population?**

**Direct comparisons between Gulf War veterans and nonveterans with multisymptom conditions.** Researchers have commonly alluded to similarities between ill Gulf War veterans and patients diagnosed with CFS, FM, and MCS. But few studies have directly compared illness characteristics of Gulf War veterans with those of civilian patients with other multisymptom diagnoses. The general impression that these conditions are similar is largely the result of their “multisymptom” nature. Only one published study has directly compared symptom frequencies and patterns reported by Gulf War veterans with those of civilians with the same defined multisymptom diagnosis. Investigators at Ninewells Hospital and Medical School in Scotland compared the symptoms of three groups who met CFS case-defining criteria: CFS cases in the general population, individuals with CFS who had served in the Gulf War, and individuals who developed CFS following occupational exposure to high levels of

**Table 4. Projects Evaluating Biological Measures in Both Ill Gulf War Veterans and Nonveteran Patients with Defined Multisymptom Conditions**

<i>Study</i>	<i>Groups Studied</i>	<i>Results similar in veterans and nonveterans?</i>	<i>Findings</i>
Khan <sup>800</sup> 2004	24 symptomatic Gulf veterans, 52 nonveterans with CFS, 40 healthy controls	no	Enhanced vascular sensitivity to acetylcholine in peripheral circulation among civilians with CFS, but not symptomatic Gulf War veterans
Peckerman <sup>1186</sup> 1999	29 Gulf veterans with CFS, 31 healthy Gulf veterans, 11 nonveterans with CFS, 29 healthy nonveterans	no	Gulf veterans with CFS had sign. higher tactile threshold than healthy veterans. CFS not associated with differences in tactile thresholds in nonveterans.
Skowera <sup>1419,1420</sup> 2004	40 ill Gulf veterans, 80 healthy Gulf veterans, 35 nonveterans with CFS, 28 healthy controls	no	Ill Gulf veterans, but not civilians with CFS, exhibit TH1-type immune activation, increased levels of IFN- $\gamma$ , IL-2, and IL-10 producing cells
Stein <sup>1481</sup> 2004	11 Gulf veterans with FM, 26 nonveterans with FM, 36 healthy controls	yes	Reduced 24-hour heart rate variability in symptomatic women Gulf War veterans and women with FM
Vojdani <sup>1732</sup> 1999	40 ill Gulf veterans, 100 nonveterans with CFS, 40 nonveterans with FM, 160 controls	yes	55% of ill Gulf veterans, 52% of CFS patients, 54% of FM patients, and 15% of controls tested positive for mycoplasma infection
Vladitiu <sup>1725</sup> 2004	49 Gulf veterans with CFS, 61 nonveterans with CFS, 75 healthy controls	no	Angiotensin-converting enzyme genotype was associated with CFS among Gulf War veterans but not with CFS in nonveterans
Zhang <sup>1835</sup> 1999	43 Gulf veterans with CFS, 68 nonveterans with CFS, 87 healthy controls	no	Gulf War veterans with CFS, but not civilians, had sign. elevated levels of IFN- $\gamma$ , TNF- $\alpha$ , IL-2, and IL-10

Abbreviations: CFS = chronic fatigue syndrome, FM = fibromyalgia, sign. = statistically significant

organophosphate insecticides. Severity of physical symptoms, overall, was significantly greater in Gulf War veterans with CFS than in the other two groups. Severity measures for fatigue, muscle and joint pain, and headaches were particularly prominent in Gulf veterans. Gulf War veterans with CFS were also more impaired on measures of general health and bodily pain than nonveteran CFS patients.<sup>793</sup> In contrast, investigators from the East Orange, New Jersey, VA, have reported that Gulf veterans diagnosed with CFS were considerably less disabled by their condition than nonveteran CFS patients.<sup>250,1219</sup>

A number of research teams have evaluated identical physiological parameters in both symptomatic Gulf War veterans and multisymptom illness patients from the general population. Results of these studies are summarized in Table 4. Of the seven studies, five found differences between Gulf War veterans and nonveteran patients with similarly-defined multisymptom conditions and two found similarities. These results suggest that there may be some parallels between physiological mechanisms underlying Gulf War illness and conditions such as CFS and FM, but there also appear to be differences. No definitive conclusions can be drawn from this small group of studies, however, since they address a limited number of research questions and have not been replicated in larger, more representative samples. It is interesting to note, however, that two groups have identified indicators of immune activation that distinguish ill Gulf War veterans, but not civilian CFS patients, from healthy controls.

### **Research findings in multisymptom conditions compared to those in Gulf War illness.**

The relationship of Gulf War illness to other multisymptom conditions can also be evaluated by a general comparison between research findings in Gulf War veterans and those associated with CFS, FM, and MCS. A large number of studies have investigated a variety of biological mechanisms potentially underlying CFS and FM, some of which have also been studied in Gulf War veterans. These include studies evaluating neurological, endocrine, immune, and infectious processes in multisymptom conditions. In addition, epidemiologic studies have provided a fairly consistent picture of multisymptom illnesses in the general population, one that differs from epidemiologic patterns associated with Gulf War illness.

**Neuroimaging findings.** Neuroimaging studies have identified a variety of differences between multisymptom illness patients and healthy controls.<sup>164,274,1315</sup> Imaging studies have provided useful insights concerning altered central pain processing in FM patients. Both SPECT and fMRI studies have identified consistent differences between FM patients and controls in cerebral blood flow responses to low-level pain stimuli.<sup>164,515,1079</sup> A recently-reported positron emission tomography (PET) study indicated that FM patients exhibit reduced binding of endogenous opioids in brain regions associated with pain processing, compared to healthy controls.<sup>587</sup>

Studies utilizing structural MRI have reported significantly reduced total volume of gray matter in CFS patients, compared to controls.<sup>322,1143</sup> Regional differences in grey matter volume have also been described in FM patients.<sup>1363</sup> An early report from an ongoing MRI study indicates that symptomatic Gulf War veterans may have significantly reduced white matter volume, compared to veteran controls.<sup>1780</sup> MRI studies have also found evidence of increased ventricular volume and the appearance of scattered punctuate lesions in the white matter of brains of CFS patients.<sup>186,270,863,1375</sup> Foci of increased signal intensity in white matter have also been described in Gulf War veterans, but these did not differ between Gulf War illness cases and controls.<sup>563</sup>

Proton magnetic resonance spectroscopy (<sup>1</sup>H MRS) studies have reported a significantly *elevated* ratio of choline to creatinine in the occipital cortex and basal ganglia of CFS patients compared to controls.<sup>235,1245</sup> This contrasts with the *reduced* choline to creatinine ratios identified by one study in the basal ganglia of subgroups of ill Gulf War veterans, relative to healthy controls.<sup>568</sup> In short, brain imaging studies have provided diverse types of information regarding multisymptom conditions. Studies conducted to date, however, have not permitted clear comparisons between brain abnormalities in patients with FM and CFS and those in veterans with Gulf War illness.

**Neurocognitive studies.** Patients with CFS, FM, MCS, and Gulf War illness commonly report difficulties with memory and concentration, sometimes referred to as “brain fog” or “fibrofog” by patients. Research studies evaluating neurocognitive function in CFS and FM patients have identified objective indicators of impaired information processing, memory, and attention in some patients, although measured deficits are often not as severe as patients’ subjective impressions of their cognitive difficulties.<sup>434,743,874</sup> Neurocognitive studies of veterans with Gulf War illness have reported similar, limited types of measurable cognitive impairment, as previously described.<sup>864,1497,1512</sup>

**Autonomic dysregulation.** Abnormalities in autonomic nervous system function have been described in studies of CFS and FM patients, with somewhat inconsistent findings,<sup>155,277,323,456,482,974-976,1204</sup> and in several studies of Gulf War veterans. For example, some studies have reported that FM and CFS patients have elevated rates of neurally mediated hypotension (NMH), an autonomic abnormality characterized by a drop in blood pressure after moving to an upright position.<sup>157,158,261,467,722,858,1367</sup> A significantly elevated rate of NMH has also been reported from one study of Gulf War veterans with CFS<sup>321</sup> but not in a study of Gulf War veterans with multisymptom illness.<sup>937</sup> Additional studies have demonstrated other ANS abnormalities in Gulf War illness patients, as previously described.<sup>569,1185,1353,1481</sup> The specific nature and

role of autonomic dysfunction has not been clearly elucidated in Gulf War veterans nor in nonveterans with multisymptom conditions.

**Endocrine measures.** Endocrine abnormalities associated with the hypothalamic-pituitary-adrenal (HPA) axis have been associated with both CFS and FM.<sup>24,294,333,1170,1210</sup> Reported alterations in HPA parameters have varied somewhat between studies, and differed between CFS and FM patients. Most consistently, CFS patients have been shown to have reduced baseline cortisol levels and accompanying indicators of central adrenal insufficiency, possibly involving modulation of central CRH and 5-HT feedback loops.<sup>256,334,712,1170</sup> There is less information on HPA parameters in FM patients, with conflicting findings on whether baseline cortisol is normal or low<sup>24,294</sup> and two studies indicating enhanced ACTH response to CRH.<sup>294,534</sup> HPA perturbations in both CFS and FM differ from those seen in primary depression,<sup>256,534</sup> which is associated with hyperactive HPA function and elevated cortisol levels.<sup>1171</sup> As previously described, investigators at the Bronx VA Medical Center reported that Gulf War veterans do not differ from nondeployed veterans on baseline measures of cortisol and ACTH, but that both are significantly reduced in response to dexamethasone challenge, responses that correlate with veterans' symptom levels and exposures in theater.<sup>501,502</sup>

**Sleep abnormalities.** Unrefreshing sleep and difficulties getting to sleep or staying sleep are among the most commonly-reported problems associated with multisymptom conditions, including Gulf War illness. Disturbed sleep and lack of sleep, even in healthy individuals, can result in increased levels of pain and fatigue and reduced levels of cognitive function.<sup>885,1059,1300,1319</sup> Identifiable sleep abnormalities have been described in multiple studies of FM and CFS patients.<sup>189,443,580,834,872,1058,1073,1437,1695</sup> Although sleep difficulties are commonly reported by ill Gulf War veterans, only two reports have described results of sleep studies in this population. Researchers from Brooke Army Medical Center reported that, of 192 Gulf War veterans evaluated in their CCEP program, 46 (24 %) were referred for formal sleep evaluation and 16 (8 %) were diagnosed with sleep apnea.<sup>1181</sup> Investigators considered this rate to be lower than that in CFS patients, and comparable to the rate in the general population. University of Texas Southwestern investigators reported that symptomatic Gulf War veterans did not differ from healthy control veterans in any measures evaluated in sleep studies.<sup>569</sup>

**Immune parameters.** Research studies have assessed diverse immune parameters in CFS patients, and, to a lesser degree in FM and MCS patients and in Gulf War veterans. As previously indicated, results of immunological studies in CFS and FM patients have been mixed.<sup>419,603,861,941,1707,1737</sup> Positive findings most consistently relate to indicators of low-level immune activation or limited deficits in immune response (reduced activity of NK cells and cytotoxic T cells) in CFS patients.<sup>186,208,814,958,1174,1200,1328,1329,1745</sup>

Elevated levels of some cytokines have been associated with symptoms of fatigue, cognitive impairment, muscle pain, respiratory distress, and altered sleep patterns and mood in other medical conditions.<sup>224,572,901,1424,1736</sup> and may also be associated with these symptoms in patients with multisymptom illnesses. A recent study identified elevated levels of white blood cells and cytokines in the cerebrospinal fluid of a subgroup of CFS patients, pointing to possible immune dysregulation within the central nervous systems of this group.<sup>1099</sup> Alterations in an antiviral pathway (2-5A synthetase/RNase L) have been reported in some CFS patients.<sup>1122,1511,1543</sup> Subgroups said to be affected include CFS patients with evidence of viral activation, and those who developed multisymptom illness following chemical exposures.<sup>1510,1733</sup>

Many of the immune parameters reported in CFS and FM patients have not been evaluated in Gulf War veterans. As previously described, however, several research teams have identified evidence of reduced NK cell function<sup>812,1734,1835</sup> and low level immune activation in symptomatic Gulf War veterans.<sup>1420,1835</sup> Taken together, these studies indicate that Gulf War illness, as well as CFS and perhaps FM, are associated with variable immune perturbations, although a signature immune abnormality has not been clearly established for any multisymptom condition. Studies suggest that reduced NK cell activity may

be common to both CFS and Gulf War illness. But two studies have reported that measures of cellular immunity differ between symptomatic Gulf War veterans and CFS patients.<sup>1420,1835</sup>

**Infectious agents in multisymptom illnesses.** Infectious agents have long been thought to play a role in either triggering or perpetuating the symptoms of some patients with CFS and FM. Elevated rates of fibromyalgia have been reported among patients infected with human immunodeficiency virus, hepatitis C, and Lyme borreliosis.<sup>198,201,348</sup> Prospective studies have also demonstrated that a subset of patients develop CFS following different types of acute viral infection.<sup>209,796,875,1718,1776,1777,1787</sup> Although findings have been mixed, some studies have identified elevated viral titers in CFS and FM patients who have been ill for prolonged periods—most prominently human herpes viruses and enteroviruses—suggesting a possible role for reactivation of latent viruses in multisymptom conditions.<sup>7,186,243,360,471,493,822,1100,1499,1797</sup>

An association between mycoplasma infection and chronic multisymptom illness has been suggested for both veteran and nonveteran populations.<sup>402,1118</sup> Standard serological evaluations have not detected evidence of mycoplasma infection in either Gulf War illness patients<sup>525,923</sup> or civilians with CFS.<sup>829</sup> However, studies using specialized polymerase chain reaction (PCR) methods have detected excess rates of mycoplasma infection in both symptomatic Gulf War veterans<sup>355,1732</sup> and in civilians with CFS and FM.<sup>1095,1114,1123,1731,1732</sup>

**Genetic parameters.** A number of studies have indicated that multisymptom illnesses—both in the general population and in Gulf War veterans—occur at higher rates among individuals with specific genetic vulnerabilities or predispositions. Fibromyalgia and CFS have been reported to aggregate in families<sup>64,199,1750</sup> with CFS occurring at particularly elevated rates in identical twins of CFS cases.<sup>188,1513</sup> Findings related to CFS and HLA genotype have been mixed,<sup>783,1429,1693</sup> but several specific genetic differences have been found to distinguish multisymptom illness patients from healthy controls. These include associations between CFS and polymorphisms of the corticosteroid-binding globulin gene<sup>1550</sup> and between FM and polymorphisms in both serotonin receptor genes<sup>154,452</sup> and a gene that encodes an enzyme that inactivates catecholamines.<sup>546</sup> Chronic fatigue syndrome, but not FM, has been associated with serotonin transporter gene variants.<sup>545,1094,1141</sup>

As previously described, one study has reported that Gulf War illness is associated with a variant in position 192 of the PON1 gene, which encodes for paraoxonase, an enzyme involved in neutralizing sarin and organophosphate pesticides.<sup>561</sup> Other studies have reported associations between PON1 enzyme activity and Gulf War illness or Gulf War service.<sup>645,947,1353</sup> Canadian researchers have reported that women with MCS are significantly more likely than controls to be heterozygous for the PON1 gene at positions 192 and 55.<sup>1005</sup> These results are consistent with views that both MCS and Gulf War illness are related, in some individuals, to biological vulnerability to particular types of environmental exposures.

**Multisymptom illness parameters not evaluated in Gulf War veterans.** A variety of biological parameters have been studied in civilian patients with FM and CFS, but have not yet been evaluated in ill Gulf War veterans. As previously described, recent progress in understanding FM has resulted from studies demonstrating that the chronic pain of FM likely results from abnormal pain processing in the central nervous system. Studies have reported that FM patients have abnormally high cerebrospinal fluid levels of substance P, a neuropeptide involved in pain signal transmission.<sup>1333,1702</sup> Additional findings indicate that FM patients have reduced levels of an enzyme, prolyl endopeptidase, that can break down substance P as well as other neuropeptides associated with central pain processing.<sup>952,1330</sup> Fibromyalgia patients have also been shown to have reduced levels of norepinephrine metabolites and, in some patients, reduced serotonin levels.<sup>1106,1332,1800,1831</sup> Two studies have reported that CFS patients have reduced levels of serotonergic receptors and transporters in the brain.<sup>258,1815</sup> Increased levels of substance P have been reported in MCS patients,<sup>804</sup> but not CFS patients.<sup>420</sup> None of the neuropeptides studied in relation to these conditions have yet been evaluated in ill Gulf War veterans.

In recent years, research teams in the U.S. and U.K. have used microarray technologies to compare gene expression in the blood cells of CFS patients and healthy controls. Such studies can potentially provide insights into the pathophysiology of CFS and lay the groundwork for developing biomarkers and treatments. Genes differentially expressed in CFS patients have included those associated with basic metabolic processes as well as immune and neuronal function.<sup>776,1482,1717,1769</sup> A massive project undertaken by the U.S. Centers for Disease Control and Prevention (CDC) integrated genomic information with epidemiologic and clinical data obtained from a large population-based study of CFS patients and controls.<sup>1716</sup> These data, analyzed by multiple groups from different disciplines, supported previous observations that patients meeting CFS criteria are heterogeneous. Specific differences in gene expression that distinguished CFS cases from healthy controls included genes related to function of the HPA axis, immune function, and a number of neurotransmitter systems. More recently, British investigators have identified seven CFS patient subgroups, based on different patterns of gene expression, groups that also differed in their clinical characteristics.<sup>795</sup> No information of this type is yet available in relation to Gulf War illness, although a genomic profile study is currently underway at the Miami VA and another is planned at UTSW.

**Epidemiologic comparisons between Gulf War illness and multisymptom conditions in the general population.** From an epidemiologic perspective, Gulf War illness is very different from multisymptom conditions like CFS and FM. Chronic fatigue syndrome and FM are generally not identified at high rates in large defined populations, but develop sporadically in different individuals and under different circumstances. In contrast, Gulf War illness developed within a relatively short time period in a well-defined group of individuals who were, in 1990, much healthier on average than people in the general population. After a shared experience, deployment to the Kuwaiti Theater of Operations, this group developed a much-higher-than-normal rate of unexplained symptoms and multisymptom illness. Gulf War illness, from this perspective, more closely resembles an illness associated with an epidemic or a common hazardous exposure than it does CFS or FM.

One of the most striking differences between Gulf War illness and other multisymptom conditions relates to the population groups who are most affected. In the general population, CFS, FM, and MCS affect women at much higher rates than men. CFS and MCS also disproportionately affect those age 40-60, compared to younger and older age groups. Gulf War illness occurs in a distinctly different pattern. About seven percent of U.S. troops who served in the Gulf War were women.<sup>1594</sup> On a proportional basis, however, women are affected by Gulf War illness at the same<sup>464,753,1699</sup> or only slightly higher rates<sup>142,160,1476,1804</sup> than men. Studies have also not found that veterans over age 40 have higher Gulf War illness rates. In fact, several studies have reported that *younger* veterans are more affected by Gulf War illness than older veterans.<sup>160,753,1476</sup>

As previously described, there has been considerable discussion about the extent to which symptom-defined conditions such as FM, CFS, and MCS themselves represent distinct disease entities. Studies have indicated a high degree of overlap between patients meeting criteria for these conditions, with 58 – 70 percent of FM patients meeting CFS criteria<sup>187,1775</sup> and 40 percent of CFS patients meeting criteria for MCS.<sup>710</sup> In general, Gulf War illness appears not to overlap with these conditions to the same extent,<sup>250</sup> although the degree of overlap depends on how Gulf War illness is defined. The largest clinical study of Gulf War veterans found that only 5-6 percent of Gulf War veterans with multisymptom illness met criteria for CFS or FM.<sup>142</sup> A smaller study from the Pacific Northwest found that, after clinical evaluation, 25 percent of veterans who met Oregon criteria for Gulf War illness also met criteria for FM, 18 percent met CFS criteria, and 19 percent reported symptoms of chemical sensitivity.<sup>160</sup>

**Treatments for multisymptom illnesses.** Identifying effective treatments for conditions whose pathophysiological mechanisms are not clearly understood has been an ongoing challenge both for Gulf War illness and for multisymptom conditions in the general population. Over the years, numerous studies have evaluated the effectiveness of many different types of therapeutic interventions for CFS and FM.

Most notably, a burgeoning number of clinical trials have evaluated new pharmacologic treatments for FM in recent years.<sup>8</sup> The majority of tested drugs act on one or more neurotransmitter systems. Drugs that inhibit uptake of both serotonin and norepinephrine have been shown to provide significant improvement in pain and other symptoms for FM patients, and global improvements in function. These include pregabalin,<sup>295,1011</sup> milnacipran,<sup>479,886,1724</sup> and duloxetine.<sup>65,66</sup> Symptomatic and functional improvements have also been reported from early studies of the serotonin reuptake inhibitor paroxetine,<sup>1176</sup> the selective serotonin-3 antagonist tropisetron,<sup>594,1382</sup> the dopamine agonist pramipexole,<sup>619</sup> and the synthetic cannabinoid nabilone.<sup>1422</sup> Pregabalin, marketed as Lyrica, became the first drug to receive FDA approval for the treatment of FM in 2007.<sup>1666</sup> In 2008 a second drug, duloxetine (trade name Cymbalta), was approved for FM treatment.<sup>398</sup>

Studies of graded exercise and cognitive behavioral therapy (CBT) have consistently demonstrated benefit for FM patients, yielding improvements in both functional status and symptoms.<sup>196,962,1318,1410</sup> Antidepressant medications have also been shown to benefit some FM patients, providing significant improvements in somatic symptoms, as well as mood and functional status.<sup>1154,1318,1545</sup> Researchers report that the most optimal FM treatment strategies combine pharmacologic with nonpharmacologic interventions.<sup>292,1256,1318</sup> A variety of complementary therapies have been suggested for their potential in benefiting FM patients, but relatively few have been studied.<sup>293</sup> Acupuncture treatment has been evaluated in multiple trials for its effectiveness in relieving FM symptoms, with mixed results.<sup>73,128,588,1413</sup> Suggestive evidence of benefit has also been reported from small studies of massage therapy<sup>166</sup> and several nutritional supplements.<sup>701,1023,1331,1526</sup>

A 2001 systematic review identified 350 CFS treatment studies, including 44 controlled treatment trials, in the published literature.<sup>1783</sup> This and similar projects have identified a number of treatment approaches that appear to benefit CFS patients, providing improvements both in symptoms and level of function. However, evidence related to many treatments is often too scant to provide firm conclusions.<sup>1084,1286,1783</sup> The most consistent treatment benefits for CFS have been demonstrated from studies of graded exercise and CBT.<sup>389,1233</sup> Studies of immune-related therapies have provided mixed findings<sup>1084,1783</sup> with the most promising results obtained from infusions of the drug Ampligen.<sup>1501,1510</sup> Studies indicate that antidepressant medications provide limited benefits for some CFS patients, with improvements in energy that are not related to the antidepressant effects of the drugs.<sup>606,1097</sup>

Studies have reported that glucocorticoids may provide some symptomatic benefit for CFS patients,<sup>257,1004</sup> but one concluded that adverse effects of these medications outweigh their benefits.<sup>1004</sup> Smaller studies have also suggested therapeutic benefit from antiviral drugs in CFS patients with evidence of herpes virus infection,<sup>825,888</sup> from the antibiotic azithromycin,<sup>1714</sup> and from a multimodal treatment that addresses endocrine and nutritional parameters identified in individual patients.<sup>1529</sup> Preliminary indications of benefit have also come from studies evaluating complementary therapies such as osteopathic treatment,<sup>1197</sup> massage therapy,<sup>437</sup> magnesium,<sup>286</sup> NADH,<sup>451</sup> and essential fatty acids.<sup>120</sup> The quality and size of these studies, however, were not sufficient to support firm conclusions concerning treatment effectiveness.

Graded exercise therapy and CBT have also been studied for their effectiveness in treating Gulf War illness in a large multicenter trial conducted by VA and DOD.<sup>354</sup> Cognitive behavioral therapy provided substantial improvement for just 18 percent of ill Gulf War veterans, compared to the 11 percent who improved with usual treatment, while graded exercise provided no benefit over usual treatment. Results indicated these treatments may be less helpful for veterans with Gulf War illness than for civilian patients with CFS and FM.<sup>639</sup>

Very little scientific information is available regarding treatments that are effective for MCS. Although not evaluated in formal trials, patients have reported that avoidance of chemicals and odors that exacerbate MCS-related symptoms has been most useful for them in reducing symptoms of this

condition.<sup>488</sup> Chemical avoidance has not been studied in ill Gulf War veterans, although one VA clinician has testified that her use of this approach, in conjunction with dietary modifications, provided improvement for her Gulf War veteran patients with chemical sensitivity.<sup>1399</sup>

**Summary. Gulf War illness in relation to multisymptom conditions in the general population.** Parallels are commonly drawn between Gulf War illness and symptom-defined conditions such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS) found in the general population. Research studies, however, have identified both similarities and differences between Gulf War illness and these conditions. The prevalence of CFS in Gulf War veterans is unique, and dramatically higher than CFS rates in nondeployed veterans and the general population. Rates of FM and MCS are also elevated in Gulf War veterans, but to a lesser degree. It is clear from multiple studies, however, that case definitions used to define CFS, FM, and MCS do not adequately describe the chronic symptom pattern that affects Gulf War veterans at excess rates. Only a fraction of veterans with Gulf War illness can be diagnosed with CFS, FM, or MCS. The epidemiologic profile of Gulf War illness is also unique. Unlike CFS and FM, Gulf War illness occurs in a pattern consistent with a common exposure, and affects female and male veterans at about the same rate.

Studies have also provided indicators of physiological similarities and differences between Gulf War illness and other multisymptom conditions. Many objective measures associated with CFS and FM in the general population, however, have not yet been evaluated in veterans with Gulf War illness. General similarities may be reflected in indicators of autonomic dysregulation and neurocognitive impairment in Gulf War illness, FM, and CFS, and by indications that Gulf War illness and MCS are linked to genetic variants of the PON1 enzyme. In contrast, studies have identified immune parameters that differ between veterans with Gulf War illness and civilians with CFS, and neuroimaging studies have not thus far identified specific abnormalities that are common to Gulf War illness and CFS or FM. Cognitive behavioral therapy and exercise were found to be less beneficial for Gulf War illness than for CFS and FM. But the extent to which other treatments useful in treating CM and CFS could improve symptoms and function in ill Gulf War veterans is not known.

Much remains to be learned about the pathophysiology of Gulf War illness, as well as the biological mechanisms that underlie conditions such as CFS, FM, and MCS that occur in the general population. Because of possible similarities in some physiological processes underlying these conditions, it is important that findings related both to biological abnormalities and treatments for these conditions be evaluated in veterans with Gulf War illness. But until Gulf War illness is better characterized physiologically, the degree to which it overlaps with other multisymptom conditions remains largely a matter of conjecture.

## Recommendations

Research studies have demonstrated both differences and similarities between Gulf War illness and multisymptom conditions found in the general population. Symptom complexes consistent with defined chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS) are found in Gulf War veterans at elevated rates, but account for only a fraction of the excess morbidity affecting Gulf War veterans. Research related to these conditions may provide useful insights regarding biological processes that underlie veterans' symptoms, treatment interventions that may benefit ill veterans, and research methodologies useful in studying syndromes defined primarily by symptoms. The Committee therefore recommends the following research:

- Studies that determine the extent to which objective measures that distinguish CFS, FM, and MCS patients from healthy controls are also associated with Gulf War illness. Such studies should include comprehensive evaluation of autonomic function and hypothalamic-pituitary-adrenal parameters in ill veterans, studies of immune and inflammatory parameters associated with multisymptom illnesses, evidence of infection by herpes viruses and enteropathogens, identification of cerebrospinal fluid levels of neuropeptides associated with central pain processing, and genomic and proteomic evaluation of blood and cerebrospinal fluid of veterans with Gulf War illness.
- Pilot studies and, where indicated by preliminary evidence, clinical trials to determine whether veterans with Gulf War illness benefit from therapies shown to improve the health of patients with FM and CFS.

The Committee also recommends that federal Gulf War illness research programs coordinate efforts with federal research programs that focus on other multisymptom conditions like CFS and FM.

## 4 | Federal Research on Gulf War Illness and the Health of Gulf War Veterans

In addition to reviewing scientific studies and government reports, the Committee is charged with reviewing federal research programs established to address health consequences of the 1991 Gulf War. As with other aspects of its work, the Committee's assessment of these programs is guided by the premise that the purpose of this research is, ultimately, to improve the health of ill Gulf War veterans. In its ongoing review of Gulf War research, the Committee has emphasized the importance of high quality studies that provide insights into biological processes underlying veterans' symptoms or contribute directly to identifying diagnostic tests and treatments. Although the government has sponsored some studies of this nature, these central objectives have not historically been the focus of federal Gulf War research programs.

Developing research programs capable of determining the nature and causes of Gulf War illness, and identifying effective treatments, has proven to be a difficult challenge for the agencies tasked with this responsibility. In the seventeen years since the war, hundreds of millions of federal dollars have been spent on Gulf War research. Many federally-funded studies have provided valuable insights regarding the health of Gulf War veterans. But much of the federal research has not usefully advanced understanding of Gulf War illness or other Gulf War-related health problems. Consequently, important questions have remained unanswered. The unsatisfactory pace of progress can be attributed to a variety of factors, including federal agencies' long-time emphasis on research that was peripheral to priority Gulf War health issues.

Some observers have suggested that the Departments of Defense and Veterans Affairs should not have been given primary responsibility for conducting and managing research on Gulf War-related health problems.<sup>137,1562,1684</sup> One reason relates to the scientifically complex nature of the required research and the need for a multifaceted, highly coordinated effort involving top investigators—the type of scientific program for which these agencies are not ideally suited. There is also a common perception that federal policy makers have not vigorously pursued key research in this area and that federal agencies have disincentives—whether political or fiscal—for providing definitive answers to Gulf War health questions. Historically, the situation parallels delayed federal responses to health problems stemming from hazardous exposures in earlier wars, such as consequences of radiation exposure in World War II and effects of herbicides in Vietnam. Although cynical, such views are reinforced by the slow progress made by federal agencies in addressing fundamental questions about the nature, causes, and treatments for Gulf War illness.

In its 2004 report, the Committee described systemic problems in the federal Gulf War research effort. Federal programs were not designed or managed to achieve identified research objectives related to Gulf War illness or other Gulf War health issues.<sup>1268</sup> The Committee has had continuing concerns about Gulf War research programs since 2004. Regrettably, seventeen years after the war, this research still has not provided tangible results in improving the health of ill Gulf War veterans. In 2006 and 2007 however, new developments in the management and federal funding of Gulf War research have provided positive indications that priority Gulf War research issues can now be more effectively addressed.

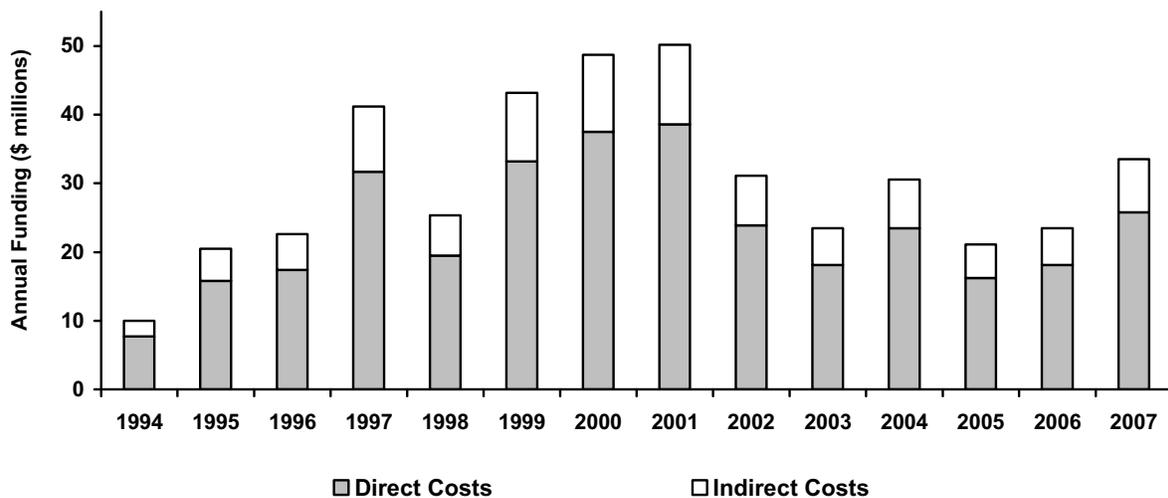
## Historical Funding and Management of Federal Gulf War Research

Since 1992, the U.S. federal government has reported expenditures of hundreds of millions of dollars for hundreds of individual research projects related to the health of Gulf War veterans.<sup>340</sup> This research has been funded by three agencies: the Department of Defense (DOD), the Department of Veterans Affairs (VA) and the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services. The Persian Gulf Veterans Coordinating Board, an interagency committee of representatives from the three agencies, was formed in 1994 to plan and coordinate the federal response to health problems affecting veterans of the 1991 Gulf War<sup>1274</sup> Since 1997, this board and its successor, the Deployment Health Working Group, have provided annual reports to Congress describing federally sponsored research on Gulf War veterans' illnesses. Although the reports identify substantial federal expenditures for Gulf War research, administration and use of these funds have historically been problematic.

As demonstrated throughout the present report, many individual federally-sponsored studies have been highly productive and provided extremely valuable insights into the nature and causes of Gulf War illness. Overall, however, there have been persistent shortcomings in federal Gulf War research programs. Foremost have been problems related to the specific types of studies selected for funding and the overall lack of cohesion and results-focused management of the federal Gulf War research effort. Many of the funded projects identified as "Gulf War research" in the federal portfolio have had little if anything to do with the health of Gulf War veterans. And a substantial proportion of funded studies have, historically, focused on stress and psychiatric disease as the central explanation for Gulf War illness, despite accumulated evidence to the contrary.

**Federal expenditures for Gulf War research.** The Deployment Health Working Group, each year in an annual report to Congress, identifies the amount of federal funding allocated for studies identified as research on Gulf War veterans' illnesses. As shown in Figure 1, total funding levels have varied from year to year, reaching their peak between 1999 and 2001, when total expenditures ranged from 43 to 50

**Figure 1. Total Funding For Studies Identified as Gulf War Research by Federal Agencies: 1994 – 2007**



Sources: Deployment Health Working Group Annual Reports to Congress, 2003-2007<sup>336-340</sup>

Note: References indicate that indirect costs were calculated as 30% of direct costs.<sup>336</sup>

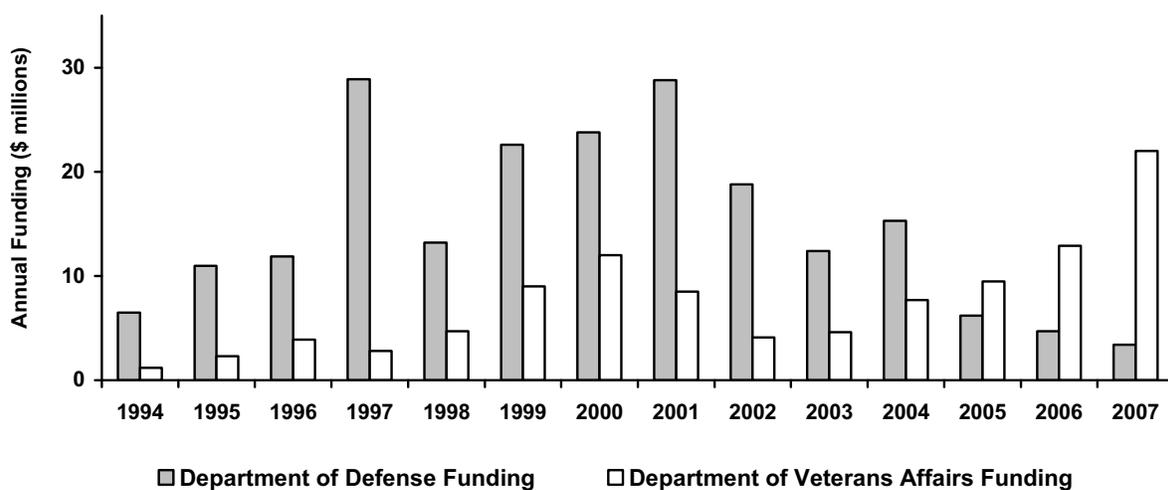
million dollars annually. In all, 345 distinct projects categorized as Gulf War research were sponsored by the federal government between 1992 and 2007.<sup>340</sup>

The exact amount spent by the U.S. government on Gulf War research has been obscured to some degree by differences in how federal funding has been calculated and presented to Congress from year to year. For example, early interagency reports identified annual funding totals, by year, from 1994 onward. Since 2004, funding details for projects funded more than 10 years earlier have been dropped from the reports, and expenditures for those projects no longer included in cumulative totals. In addition, reports in some years identified funding for both direct and indirect costs, but in other years included only direct costs. In some cases, total expenditures reported for a given year have varied. For example, federal Gulf War FY2005 research expenditures were reported as \$16.2 million in the 2005 Annual Report to Congress, but later reported as \$21.6 million in the 2006 Annual Report to Congress, and as \$20.1 million in the 2007 report.<sup>338-340</sup> Such year-to-year inconsistencies have introduced substantial uncertainty in identifying the precise amount spent by the federal government on Gulf War research.

Taking into account these uncertainties, estimated federal expenditures between 1994 and 2007 for projects identified as Gulf War Research have totaled \$340 million in direct costs, and \$442 million if indirect costs are considered at the historical rate of 30 percent, as indicated in some interagency annual reports to Congress. These summary estimates are based on figures provided in the Deployment Health Working Group's most recent Annual Report to Congress for fiscal years (FY) 1997 through 2007<sup>340</sup> and pre-1997 figures provided in the 2003 Annual Report to Congress.<sup>336</sup>

The Committee reported in 2004 that the majority of federal funding for Gulf War research had historically been provided by the Department of Defense. But as shown in Figure 2, DOD support for Gulf War illness research declined substantially after 2001. Few new Gulf War projects were funded by DOD between 2003 and 2006, although support continued for previously approved multiyear projects. Research funded by the U.S. Department of Health and Human Services has consistently represented only a small fraction of total Gulf War expenditures. Total expenditures have ranged from \$1.6 million annually between 1998 and 2000 to less than \$0.5 million annually between 2004 and 2007.

**Figure 2. Direct Funding for Studies Identified as Gulf War Research by the U.S. Department of Defense and U.S. Department of Veterans Affairs: 1994 - 2007**



Sources: Deployment Health Working Group, Annual Reports to Congress, 2003-2007<sup>336-340</sup>

Since 2002, VA has sponsored a steadily increasing proportion of federal Gulf War research, although this increase has not matched the dramatic decline in funding at DOD. The large majority of new Gulf War research projects initiated after 2003 have been funded by VA.

As pointed out in the Committee’s 2004 report, if progress in the Gulf War research effort were to be measured by the number of dollars spent, or the number of projects funded, it might be argued that the federal government has mounted an impressive research effort on behalf of ill Gulf War veterans. But the Committee is committed to assessing federal Gulf War research in terms of its scientific merit and progress made in improving the health of ill veterans. Although substantial funding has been allocated for studies identified as “Gulf War research” by federal agencies since 1994, the Committee has identified significant problems related to the effective use and management of these funds.

**Many “Gulf War” studies in the federal Gulf War research portfolio have not addressed Gulf War-related issues.** A prominent concern over the years has been that many of the studies identified as “Gulf War Research” in the federal research portfolio have been unrelated, or only marginally related to the health of veterans who served in the 1991 Gulf War. Representative examples are provided in Table 1.

**Table 1. Examples of Federally-Funded Studies Identified as “Gulf War Research” that have Little Relevance to Health Problems Resulting from Gulf War Service**

<i>Project Number</i>	<i>Year Initially Funded</i>	<i>Amount Funded</i>	<i>Study Title</i>
DOD-143	2000	\$18,224,000	Millennium Cohort Study
DOD-108	1999	\$ 1,107,996	Health Status of Current National Guard Members
VA-047	1997	\$ 1,089,060	Retrospective Verification of Mustard Gas Exposure
DOD-145	2001	\$ 800,000	Early Intervention Research Program to Enhance Soldier Resilience
DOD-140	2001	\$ 764,879	U.S. Department of Defense Surveillance for Neoplasms in Infancy
DOD-097	1999	\$ 626,244	Surveillance of B. Pertussis Among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Methods for Diagnosis of Pertussis
DOD-083	1997	\$ 299,700	Risk for Stress-Related Substance Abuse: Effects of Family History of Alcoholism

Sources: Deployment Health Working Group Annual Report to Congress, 2006-2007<sup>339,340</sup>

The Millenium Cohort study, for example, received over \$18 million in DOD funding between 2000 and 2007. This ambitious project involves long-term assessment of an initial sample of nearly 80,000 personnel serving in the military in and after October, 2000.<sup>522,1336</sup> The study includes relatively few personnel who served in the 1991 Gulf War—all presumably in good enough health to remain in the military 10 years after the war.<sup>1427</sup> Some other projects identified as “Gulf War Research” in interagency reports to Congress have even less connection to the health consequences of Gulf War service. These include studies of infectious diseases, such as pertussis, never identified in Gulf War veterans. It also includes studies to develop tests for mustard gas, although DOD has identified only one Gulf War veteran with a possible, but “indeterminate” exposure to mustard.<sup>1614</sup>

The Committee is not questioning the scientific merit or the need for the types of projects listed in Table 1. But labeling these studies as “Gulf War Research” in Congressional reports is misleading and has

given the impression to Congress and the general public that more federal funding has been provided for research on the health of Gulf War veterans than has actually been the case. Use of Gulf War research funds for studies with minimal connection to the health of Gulf War veterans has also meant less support for studies that do specifically address health consequences of the 1991 Gulf War.

**Excess emphasis on studies of stress and psychiatric illness in federally-funded Gulf**

**War research.** A second major concern relates to the use of substantial amounts of Gulf War research funding for studies focused exclusively on psychiatric disorders and psychological stress. Putative relationships between Gulf War illness, wartime stress, and psychiatric disorders were reasonable areas to investigate in the early years after the war, when little was understood about Gulf War-related conditions. The emphasis on studies focused on stress and psychiatric disorders in the federal Gulf War research portfolio has continued into recent years, however, long after multiple studies demonstrated that Gulf War illness is not explained by psychological stress and that relatively few Gulf War veterans have psychiatric disorders.

The Committee considers research on the effects of combat and war-related trauma to be extremely important for military populations in general. But such issues are notably less prominent among Gulf War-related health concerns, compared to other warzone deployments.<sup>689,969</sup> Among the many unique aspects of the 1991 Gulf War were the short duration of hostilities, the limited number of troops affected by combat and other traumatic experiences, and the relatively low number of Gulf War veterans who developed psychiatric disorders. The use of significant amounts of Gulf War research funding for studies focused on stress has been inappropriate, based on what is known about the Gulf War and the health of Gulf War veterans.

The Committee also noted that the prominence of psychological research in the federal Gulf War research portfolio has not been readily apparent in interagency reports to Congress. These reports categorize federal Gulf War research projects into five topic areas: (1) Brain and Nervous System Function, (2) Environmental Toxicology, (3) Immune Function and Infectious Diseases, (4) Reproductive Health, and (5) Symptoms and General Health.<sup>339,340</sup> There is no category for psychological or psychiatric research.

Instead, studies of this type are identified as “Brain and Nervous System Function” research, the category that has historically included the largest number of Gulf War projects. It includes all research—both clinical and basic laboratory studies—related to stress and psychiatric illness, along with research that is more commonly considered brain and nervous system research, such as neuroimaging and ALS studies. As shown in Table 2, examples include a nearly \$5 million study of cognitive behavioral therapy for posttraumatic stress disorder, primarily due to sexual trauma, that did not focus on Gulf War veterans,<sup>1364</sup> a \$1 million trial of two medical treatments for PTSD in OIF/OEF veterans, and a trial of a provider education program to improve treatment for major depression in primary care.

The types of studies listed in Table 2 may have importance for military populations in general, but would more accurately be identified as psychological or psychiatric research than as research on the brain and nervous system. Further, these projects are not focused on Gulf War veterans or health issues that prominently affect Gulf War veterans. In identifying stress-related studies as brain research in interagency reports to Congress, the Deployment Health Working Group has obscured the historical emphasis on stress and psychiatric research in federal Gulf War research programs, and provided an inflated impression of the number of studies focused on central nervous system abnormalities in Gulf War veterans.

In its 2004 report, the Committee pointed out that 57 percent of VA’s projected 2003 Gulf War research expenditures would support studies of psychological factors and stress.<sup>335,1268</sup> In response, then-Secretary of Veterans Affairs Anthony Principi pledged that VA Gulf War research funding would no longer be used for studies focused on stress as the central cause of Gulf War illness.<sup>473,1644,1648</sup> Although previously

**Table 2. Examples of Psychiatric and Stress-Related Studies Identified as Gulf War Research on Brain and Nervous System Function in Reports to Congress**

<i>Project Number</i>	<i>Year First Funded</i>	<i>Amount Funded</i>	<i>Study Title</i>
DOD-125 VA-74	2001	\$4,892,743	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women
DOD-166	2005	\$1,000,000	A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance
DOD-144	1999	\$ 954,000	Psychological Health Screening: Methods and Metrics for Deployed Forces
VA-087	2002	\$ 572,271	Improving Outcomes of Depression in Primary Care
VA-086	2002	\$ 410,494	A Clinical Trial of Magnetic Stimulation in Depression
DOD-092	1997	\$ 249,700	Traumatic Experiences Persistently Enhance Cue-dependent Learning: toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
DOD-082	1997	\$ 172,000	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs

Source: Deployment Health Working Group Annual Report to Congress, 2006<sup>339</sup>

approved studies continued to be funded after the Secretary’s announcement, VA has now sharply reduced the number of newly-funded Gulf War studies focused on stress and psychiatric disorders.

**Lack of a cohesive federal Gulf War research program managed to achieve identified scientific objectives.** A pervasive problem, described over the years in reports from the U.S. General Accounting Office,<sup>1672,1677,1682</sup> and more recently in the Research Advisory Committee’s 2004 report,<sup>1268</sup> relates to the lack of management of the overall federal Gulf War research program to achieve identified research goals. Specifically, the federal Gulf War research effort has not been organized or managed to meet priority objectives such as identifying diagnostic markers and treatments for Gulf War illness, or determining its cause.

In 1993, the “Persian Gulf Interagency Research Coordinating Council” was established to plan and coordinate research on the health of Gulf War veterans. This task is now assigned to a successor group, the Research Subcommittee of the Deployment Health Working Group.<sup>1274</sup> The interagency group developed a working research plan in 1995 that was subsequently revised.<sup>1198</sup> The group’s plan initially targeted three priority research areas related to the health of Gulf War veterans, and later identified 21 priority research questions. These questions were reformulated into a corresponding list of 21 research topics in 2004.<sup>337</sup> Interagency annual reports to Congress point out that “the comprehensive Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published on each one.”<sup>339</sup> No assessment is provided, however, of the degree to which long-established priority questions have been answered or research objectives have been met by the federal Gulf War research effort.

The Committee recognizes that over the years, research studies have been funded that relate, in some way, to each of the 21 identified research categories. But this falls considerably short of a well-coordinated federal program with a management structure capable of achieving identified research objectives. Such a program requires that strategies be in place to identify and fund specific studies most capable of providing long-needed answers to priority questions. It also requires ongoing assessment of the degree to which identified objectives have been met or require revision.

Identifying funded projects according to which of 21 research categories they fall into is not the same as establishing and managing a research program to provide answers to priority scientific questions. The

interagency group tasked with coordinating the Gulf War research effort appears to have served primarily in the role of cataloguing and reporting federally-sponsored studies identified as “Gulf War research,” not as managers of an effective, well-coordinated federal research program.

In its 2004 report, the Committee’s initial programmatic recommendation was that VA, in conjunction with other federal agencies, develop a comprehensive federal research plan to address priority Gulf War research questions. Since the Committee’s 2004 report, a number of funding and management changes have taken place in the federal Gulf War research effort. For example, most newly-funded Gulf War research projects have been sponsored by VA, following commitments made by the Secretary of Veterans Affairs to support an expanded Gulf War research effort.<sup>1640,1644</sup> In contrast, the Department of Defense has greatly reduced funding for Gulf War-specific research. But over this period, regrettably, the federal Gulf War research portfolio has generally continued to reflect a haphazard mix of studies not indicative of a clear scientific plan or coordinated effort.

The overall focus and management of federal Gulf War research in recent years is described below for each of the three contributing agencies. A number of programmatic changes and improvements have been evident during this time, particularly at VA. The most significant changes in the direction and management of Gulf War research, however, have occurred as a result of Congressional actions in 2006, which provided funding for dramatic new directions in Gulf War research at both VA and DOD.

### **Gulf War Research at the Department of Veterans Affairs**

In 2004, the Committee described shortfalls in the types of studies that constituted VA’s Gulf War research portfolio, and problems in methods used by VA for soliciting and funding Gulf War research proposals. At that time, VA funding projections for 2003 indicated that the majority of VA’s Gulf War research spending would support studies related to stress and psychiatric illness.<sup>335,1268</sup> Since then, the Committee has continued to assess the focus of VA-funded Gulf War research studies and the processes used for funding research proposals.

**VA Gulf War programmatic changes and initiatives.** In its 2004 report, the Committee described administrative issues that had contributed, over the years, to an unacceptable profile of research projects in VA’s Gulf War research portfolio. One major problem related to the content of VA’s research funding announcements. Another was VA’s use of standing merit review panels for scientific review of Gulf War-related proposals. This meant that Gulf War research studies proposed by VA investigators were often judged for their scientific merit by scientists unfamiliar with research issues and findings on the health of Gulf War veterans. Since the 2004 report, both of these issues have been directly addressed by VA’s Office of Research and Development (ORD).

When it became apparent midway through FY2004 that VA had funded less than \$500,000 of Secretary Principi’s pledge of up to \$20 million in new Gulf War research that year,<sup>1640</sup> VA ORD issued a special request for applications (RFA) for Gulf War research in April, 2004. This was the first VA Gulf War-related solicitation to specifically prioritize research on physiological consequences of service in the 1991 Gulf War. The RFA indicated that VA was most interested in funding studies on immune and neurological processes associated with Gulf War illness, and neurological disorders in Gulf War veterans.<sup>1658</sup> The announcement attracted 49 proposals, which were reviewed by a special ad-hoc scientific panel that included scientists with expertise in Gulf War illness, epidemiology, neuropsychology, and neurotoxicology.<sup>497</sup> Fourteen new Gulf War projects were funded in response to the 2004 Gulf War RFA.

The Department of Veterans Affairs also issued a special Gulf War request for proposals (RFP) in June, 2005. This solicitation emphasized VA’s interest in funding projects focused on understanding and

treating Gulf War illness, on long-term health effects of Gulf War exposures, and on identification of biomarkers for Gulf War illness.<sup>1659</sup> Also for the first time, the announcement specified that proposals whose principle focus was psychological stress or psychiatric disorders would not be funded. Forty-four proposals were submitted in response to the RFP and again reviewed by a special panel of scientists with expertise relevant to Gulf War illness, resulting in the selection of 12 new projects for funding.<sup>846</sup>

The Committee commends VA ORD for improvements in the 2004 and 2005 Gulf War funding announcements. The Committee also applauds ORD's efforts to include scientists with expertise specifically relevant to Gulf War illness and effects of Gulf War exposures in the scientific review process. VA's expanded research effort dedicated to Gulf War illness and effects of Gulf War exposures, evident in 2005 and 2006, consisted largely of projects funded under the 2004 and 2005 funding announcements.

The Department of Veterans Affairs Office of Research and Development also informed the Committee in December, 2005, that VA would develop and fund a Gulf War brain tissue bank and DNA biorepository. The Gulf War Biorepository Trust would be managed by VA's Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) in Boston, which received nearly \$1 million in funding for the project in early FY2006. The Committee had recommended, in 2004, that VA develop a Gulf War brain tissue bank.<sup>1268</sup> It considered this an important initiative to allow study of brain tissues in deceased veterans whose health may have been affected by exposures and events of the Gulf War.

Preliminary plans for establishing the Gulf War Biorepository Trust were presented to the Committee in November, 2006.<sup>441,1225</sup> The Committee was impressed by the level of commitment and professionalism brought to the effort by the tissue bank management team. Committee members were concerned, however, to learn that all tissue and DNA samples to be collected for the planned "Gulf War" biorepository would come from the general population of veterans enrolled in VA's ALS Registry. In 2006, this included approximately 1,500 veterans with ALS in the VA system—deployed and nondeployed veterans of all ages and eras, about 50 of whom had served in the 1991 Gulf War. As a result, VA's "Gulf War" biorepository, as currently designed, will actually be an ALS biorepository. Although program administrators indicated their interest in expanding the effort to include tissues from Gulf War veterans with other conditions, including Gulf War illness, no such project has yet been developed or funded. As the Committee has previously pointed out, brain tissues of symptomatic Gulf War veterans could be a particularly valuable resource for determining the specific areas and types of neuropathology affecting veterans with Gulf War illness.

The Department of Veterans Affairs has not issued additional funding announcements focused on the health of Gulf War veterans since 2005. However, a significantly revised approach to sponsoring Gulf War research at VA occurred in 2006. The changes have the potential to address ongoing concerns regarding integration and management of a coordinated, multidisciplinary Gulf War research effort.

**Focus of VA Gulf War research: 2003 – 2006.** Table 3 identifies funding totals for projects identified as VA-sponsored Gulf War research in interagency reports to Congress from 2003 through 2006. Yearly amounts are further categorized according to the focus of the funded studies, as identified by the Committee. Overall, total funding for VA's Gulf War research portfolio increased from \$4.6 million in 2003 to \$12.9 million in 2006.

A number of VA research projects of note were funded during this period. These include the previously-described Gulf War Biorepository Trust, neuroimaging projects at the Boston and San Francisco VAMCs, studies of immune function in ill Gulf War veterans at the Miami VAMC and hypothalamic-pituitary-adrenal function in Gulf War veterans at the Bronx VAMC. Three studies were funded to evaluate treatments for ill Gulf War veterans. These included a trial of continuous positive airway pressure

**Table 3. Department of Veterans Affairs Gulf War Research: 2003-2006  
Funding Levels and Focus of Studies**

<i>Focus of VA Gulf War Research Studies<sup>†</sup></i>	<b>2003 Funding*</b> (% of 2003 funds)	<b>2004 Funding*</b> (% of 2004 funds)	<b>2005 Funding*</b> (% of 2005 funds)	<b>2006 Funding*</b> (% of 2006 funds)
Gulf War illness, effects of Gulf War exposures	\$ 1,101,310 (24%)	\$ 1,107,405 (14%)	\$ 2,726,875 (29%)	\$ 3,729,011 (29%)
Other health problems related to Gulf War service	\$ 72,700 (2%)	- (0%)	\$ 84,468 (1%)	\$ 336,582 (3%)
ALS research	\$ 458,829 (10%)	\$ 754,537 (10%)	\$ 3,309,588 (35%)	\$ 5,039,163 (39%)
Psychological stress, psychiatric illness	\$ 2,379,814 (51%)	\$ 3,239,545 (42%)	\$ 1,063,884 (11%)	\$ 1,235,409 (10%)
Peripheral or no clear relevance to Gulf War service	\$ 633,587 (14%)	\$ 2,570,284 (34%)	\$ 2,299,864 (24%)	\$ 2,601,898 (20%)
<b>Total VA Gulf War Research Funding, by Year*</b>	<b>\$ 4,646,510 (100%)</b>	<b>\$ 7,671,771 (100%)</b>	<b>\$ 9,484,679 (100%)</b>	<b>\$ 12,942,066 (100%)</b>

\*Direct costs, as reported in Deployment Health Working Group Annual Report to Congress for each year<sup>336-339</sup>

<sup>†</sup>Research focus of individual projects categorized by Research Advisory Committee on Gulf War Veterans' Illnesses

(CPAP) treatment for dysregulated sleep in ill Gulf War veterans, antibiotic therapy for irritable bowel syndrome in Gulf War veterans, and a telemedicine trial of cognitive behavioral therapy for veterans with Gulf War illness. Despite VA pledges in 2004 and 2005 to fund a research center devoted to evaluation of treatments for Gulf War illness, no such treatment research center was funded during this period.<sup>473,846,1648</sup>

Overall, the profile of studies included in VA's Gulf War research portfolio differed markedly between 2003 and 2006, as detailed in Table 3. This was due, in part, to completion of previously-funded projects and addition of new studies funded in connection with VA's 2004 and 2005 Gulf War research solicitations. But the most significant changes during this period were the result of administrative decisions made by VA ORD that determined which studies were identified as "Gulf War research" in a given year. Among the most prominent changes in VA's Gulf War research portfolio was the reduced level of funding for studies focused on stress and psychiatric disorders—from 51 percent of total funds in 2003 to just 10 percent in 2006. In 2003-2004, the single project that received the most funding in VA's Gulf War research portfolio was the clinical trial of behavioral therapy for PTSD in women. That project received \$3.3 million in 2003-2004, but no additional VA Gulf War research funding in 2005 and 2006.<sup>339</sup>

During the same period, both previously funded and recently approved ALS studies were newly identified as "Gulf War Research" by VA ORD. As a result, the amount allocated for ALS research in VA's Gulf War portfolio increased more than 10-fold, from less than \$500,000 in 2003 to over \$5 million in 2006. This had a dramatic impact on the total level of funding and overall profile of VA's Gulf War research portfolio. The largest single recipient of VA Gulf War research funding in 2005 and 2006 was VA's National ALS Research consortium, funded at nearly \$2 million over the two years. The second largest allocation was for VA's National Registry of Veterans with ALS, which received \$1.7 million in 2005-2006. Overall, 35-39 percent of total funding identified as "Gulf War research" in 2005 and 2006 was for ALS research. This supported 14 projects, only four of which included any Gulf War veterans or any element related to Gulf War service. And those four projects did not focus specifically on ALS in

connection with the Gulf War. They include, for example, VA's National ALS Registry program, which now includes over 2,000 veterans with ALS, only 60 of whom served in the Gulf War.

Research to better understand the causes of ALS and identify effective treatments is extremely important. This fatal condition has been found to affect Gulf War veterans at twice the rate of nondeployed era veterans.<sup>636</sup> But relatively few Gulf War veterans have ALS, and they represent only a small fraction of veterans in the VA system with ALS. The causes of ALS in Gulf War veterans cannot be presumed to be the same as those for inherited forms of ALS or age-associated ALS seen in the larger veteran population. In general, identifying the millions of dollars spent for all types of ALS research at VA as "Gulf War" research is misleading, and has provided an inflated impression of the amount of funding provided for research on the health of Gulf War veterans.

In recent years, VA also continued to identify other types of studies as "Gulf War research" that were not related to the health of Gulf War veterans, or only peripherally so. Examples include animal research evaluating effects of vaccines not used in the Gulf War, research on developmental factors in sensitivity to alcohol withdrawal, basic science research on proteins that may regulate progression of astrocytomas, genetic differences related to normal circadian sleep variation in mice strains, and preclinical studies that may provide insights concerning vaccine prevention of leishmaniasis.<sup>339</sup> Research questions addressed by such studies, while perhaps worthwhile, had no direct bearing on understanding the nature, causes, or treatments of health problems affecting veterans of the 1991 Gulf War. Studies of this type have constituted up to 34 percent of VA's Gulf War portfolio in recent years, and accounted for 20 percent of VA's Gulf War research expenditures in 2006.

The Committee was pleased to note the increase in total funding allocated in 2005 and 2006 for studies focused on Gulf War illness and effects of Gulf War exposures. Improving the health of Gulf War veterans requires that these Gulf War-specific areas be given high priority, since they are most relevant to the largest number of ill veterans. It was troubling, however, that the overall percentage of VA Gulf War research funding allocated to these areas remained relatively unchanged during this period. That is, from 2003 through 2006, just 24-29 percent of VA's Gulf War funding supported studies related to Gulf War illness and effects of Gulf War exposures. An additional three percent or less each year was for studies related to other Gulf War-specific health concerns, such as studies to identify cancer and mortality rates in Gulf War veterans. So as recently as 2006, a total of just 32 percent of VA's "Gulf War Research" funding was used for studies specifically focused on the health of Gulf War veterans. As the proportion of projects related to stress and psychiatric conditions in the portfolio decreased after 2003, those studies were largely replaced by ALS projects.

**Recent VA Gulf War research program developments.** The Committee's 2004 report recommended that Congress add an additional \$15 million to VA's research budget specifically for Gulf War research. The Committee also recommended that VA work with other federal agencies to develop a comprehensive plan to address Gulf War illness. This would include a strategic VA research program managed to address priority research questions related to the health of Gulf War veterans.

In 2006, Congress added \$19 million to VA's requested research budget, and specifically directed that at least \$15 million be used annually to support a center of excellence for Gulf War illness research.<sup>1685</sup> The new center was to be a joint collaboration between VA and the University of Texas Southwestern (UTSW) Medical School in Dallas. Since 1995, UTSW investigators have conducted an extensive Gulf War research program, under the direction of Dr. Robert Haley. This program produced a number of the neuroimaging results described in Section 3 of the present report, as well as other important findings related to the health of Gulf War veterans.

In response to the 2006 Congressional directive, VA has worked with UTSW to develop the "Gulf War Illness and Chemical Exposure Research Program" at UTSW. A memorandum of understanding between

VA and UTSW to establish the center was signed in 2006.<sup>1645</sup> In 2007, VA's Gulf War research funding included \$15 million for the UTSW research program, and multiple research proposals have been approved for funding. The Committee has reviewed information on the overall scope of the program and its major elements, studies underway in the program's initial year, and plans for additional research.<sup>559,560</sup> In April of 2008, it provided its initial findings and recommendations on the UTSW program to the Secretary.<sup>1272</sup>

The UTSW program will utilize a multidisciplinary approach focused on understanding the biological underpinnings of Gulf War illness and its association with hazardous exposures during the Gulf War. It is organized around four major, interrelated initiatives: (1) a national epidemiologic survey of Gulf War-era veterans, (2) a serum and DNA repository, (3) clinical studies to compare sick and healthy Gulf War veterans on a variety of objective measures, and (4) animal research to investigate biological effects of Gulf War-related exposures. The initial project is an epidemiologic study of a national, random sample of Gulf War-era veterans. Blood and DNA samples will be collected from survey participants and used to study specific hypotheses concerning biological differences between sick and healthy veterans. A smaller number of veterans will be brought to the UTSW Medical Center for clinical evaluation, using an extensive battery of neuroimaging, laboratory, and physiological tests. Parallel to the human studies, animal experiments are planned to evaluate molecular, cellular, and behavioral effects of exposures associated with Gulf War deployment.

The UTSW program is the first comprehensive Gulf War research center of its type funded by the federal government and is focused on issues long-identified by the Committee as having high priority. The Committee is enthusiastic about the potential for a multidisciplinary, coordinated research effort to achieve results not obtainable from federal Gulf War research programs of the past. It has offered recommendations concerning the overall scope of research addressed by the program, as well as more specific recommendations related to the design and conduct of program elements and individual studies.<sup>1272</sup> As the present report is being prepared, only the epidemiologic survey is underway, with clinical studies and toxicological research to follow. As the program moves forward, the Committee will continue to review the objectives, progress, and results of the UTSW research in detail, as it has reviewed previous VA-sponsored Gulf War research programs.

With the development and funding of the UTSW Gulf War research program in 2007, VA's Office of Research and Development substantially reorganized the remainder of the VA Gulf War research portfolio. Many of the ALS research projects included in the portfolio in 2005 and 2006, as well as other projects, were reassigned and no longer identified as "Gulf War research." In the Deployment Health Working Group's 2007 report to Congress on Gulf War research, VA reported total 2007 expenditures of nearly \$22 million dollars for Gulf War research: \$15 million for the UTSW program, and nearly \$7 million for additional research projects administered directly by VA ORD.<sup>340</sup> Most of the additional funding was for VA projects that had been funded in previous years, including the Gulf War/ALS tissue bank at the Boston VAMC (funded at \$1 million in 2007), and the large neuroimaging project at the San Francisco VAMC (funded at \$744,000 in 2007). Of the \$7 million funding for projects administered directly by VA in FY2007, 21 percent was for ALS research, seven percent for stress-related research, and eight percent for projects that were of peripheral or no relevance to Gulf War veterans. The remaining 64 percent of funding supported projects that addressed research questions related to Gulf War illness, effects of Gulf War exposures, or other health issues specific to the health of Gulf War veterans.

The Committee commends recent changes in the composition of VA's Gulf War research portfolio, and in how Gulf War research funding is reported to Congress. Overall, VA-reported funding for Gulf War research in 2007 more accurately reflected expenditures for research that was related to the health of Gulf War veterans than had previously been the case. This shift was the result of two changes: (1) allocation of \$15 million in 2007 for the Congressionally-mandated UTSW Gulf War research program, and (2) VA's withdrawal of many ALS studies and other projects unrelated to the health of Gulf War veterans

from the portfolio of studies identified as “Gulf War research” in agency reports to Congress. The Committee encourages VA to continue support for the multidisciplinary Gulf War research program at UTSW. It is also important that additional VA Gulf War research projects be supported in a strategic way that addresses priority issues identified in this report, as part of a coordinated federal Gulf War research effort.

## **Gulf War Research at the Department of Defense**

The U.S. Department of Defense historically provided the largest share of funding for federal Gulf War research.<sup>335,1268</sup> This has changed markedly in recent years, with DOD Gulf War research funding declining from about \$30 million in direct costs in 1997, to less than \$4 million in 2007. Interagency annual reports from 2003 through 2006 indicated that just three new Gulf War projects were funded by DOD in 2003, and no new studies funded between 2004 and 2006.<sup>336-339</sup>

**Focus of DOD Gulf War research: 2003 – 2006.** As shown in Table 4, most research funded by DOD in 2003 and 2004 related to Gulf War illness and biological effects of Gulf War exposures. Several studies also focused on other Gulf War-related health issues, including rates of hospitalization and motor vehicle accidents in Gulf War veterans. Between 2004 and 2006, however, the proportion of DOD “Gulf War research” projects that had little or no direct relevance to the health of Gulf War veterans increased dramatically.

The largest single allocation of DOD funding between 2003 and 2006 was \$9.7 million provided to the Naval Health Research Center for the Millenium Cohort Study. As previously described, this is an ongoing longitudinal study of a large cohort of military personnel serving during and after the year 2000. Other major DOD allocations during this period included \$7.6 million to the University of Michigan for studies of multisymptom illness, \$4.9 million to Intracellular Therapies, Inc., for research on molecular signaling pathways activated by nerve agents, and \$3.9 million provided to the University of Texas Southwestern for neuroimaging research.<sup>336-339</sup>

By 2006, the DOD Gulf War research portfolio included only three studies. Nearly all funding allocated for “Gulf War” research—93 percent—was for research that had little direct relevance to the health of Gulf War veterans. Department of Defense studies funded between 2004 and 2006, in large part, focused on military personnel who served after Desert Storm. Although identified as “Gulf War Research” in interagency reports to Congress, these projects would more accurately be considered research related to “Deployment Health,” a term used by federal agencies to refer to health issues stemming from military deployment in general, as opposed to issues associated with any specific war or deployment.

The funding levels and studies summarized in Table 4 reflect information provided by DOD in annual reports to Congress from 2003 through 2006. In 2006, however, DOD retroactively added additional studies that were funded in 2001, 2003, and 2005 to Gulf War research portfolios for those years.<sup>339</sup> These included two ALS studies, funded at over \$2 million, and two PTSD treatment studies, also totaling about \$2 million. Had these additional studies been included in annual reports to Congress for 2003 and 2005, total funding levels for those years would appear greater than those indicated in Table 4, and the profile of the DOD Gulf War research portfolio would have reflected substantial funding for studies focused on ALS and psychiatric disorders.

**Recent program developments in DOD Gulf War research.** Recognizing the decline in DOD’s support for Gulf War research after 2002, Congress appropriated \$5 million for new DOD Gulf War research in FY2006. Congressional language specifically directed that the funds be used for research that provided insights into biological mechanisms that underlie Gulf War illness and for studies to evaluate promising treatments for Gulf War illness.<sup>586,842</sup>

**Table 4. Department of Defense Gulf War Research: 2003—2006  
Funding Levels and Focus of Studies**

<i>Focus of DOD Gulf War Research Studies<sup>†</sup></i>	<i>2003 Funding* (% of 2003 funds)</i>	<i>2004 Funding* (% of 2004 funds)</i>	<i>2005 Funding* (% of 2005 funds)</i>	<i>2006 Funding* (% of 2006 funds)</i>
Gulf War illness, effects of Gulf War exposures	\$ 7,230,104 (58%)	\$ 11,272,424 (73%)	\$2,694,894 (44%)	\$ 326,570 (7%)
Other health problems related to Gulf War service	\$ 2,031,950 (16%)	\$ 1,750,000 (11%)	- (0%)	- (0%)
Peripheral or no clear relevance to Gulf War service	\$ 3,134,072 (26%)	\$ 2,318,687 (15%)	\$ 3,484,372 (56%)	\$ 4,393,452 (93%)
Total DOD Gulf War Research Funding, by Year*	\$ 12,396,126 (100%)	\$ 15,341,111 (100%)	\$ 6,179,266 (100%)	\$4,720,022 (100%)

\*Direct costs, as reported in Deployment Health Working Group Annual Report to Congress for each year <sup>336-339</sup>

<sup>†</sup>Research focus of individual projects categorized by Research Advisory Committee on Gulf War Veterans' Illnesses

In previous years, Gulf War research at DOD was managed by the Military Operational Medicine Research Program in the U.S. Army Medical Research and Materiel Command (USAMRMC). Funding allocated in FY2006, however, was directed to USAMRMC's Office of Congressionally Directed Medical Research Programs (CDMRP). This multifaceted program was established in 1993 to manage research conducted in areas of special Congressional and public interest.(CDMRP) CDMRP programs emphasize innovative research studies of high scientific merit that have the potential for providing breakthroughs in understanding and treating diseases and protecting the health of military personnel. The CDMRP issued a funding announcement for its newly-established Gulf War Veterans' Illnesses Research Program in October, 2006.<sup>1634</sup> The solicitation identified two funding priorities: (1) studies to identify and evaluate treatments for Gulf War illness, and (2) studies to identify objective measures that distinguish ill from healthy veterans. A total of 80 letters of intent and preproposals were submitted to CDMRP in response to the announcement. Full proposals were invited for 34 of the projects, nine of which were ultimately funded in 2007.<sup>586</sup> The selection process involved scientific merit review of proposals and an additional review to evaluate the projects' relevance to identified research priorities. Both stages of the review process included Gulf War veterans with Gulf War illness.

With the initial \$5 million funding provided to CDMRP in the first year of the new Gulf War research program, three of the nine funded studies focused on treatments for Gulf War illness, two focused on objective biological measures that distinguish ill from healthy veterans, and three projects included both treatment and biomarker components.<sup>737</sup> This represents a clear departure from previous federal Gulf War research programs. The Committee commends the results-oriented direction and management of the program, now referred to as the Gulf War Illness Research Program (GWIRP). The GWIRP's success, with its initial \$5 million allocation, in attracting and funding research studies focused on treatments and objective biological measures for Gulf War illness is impressive, especially in comparison to the very small number of studies funded in these areas during the entire previous history of federal Gulf War research.

The CDMRP GWIRP program has clearly addressed Congressional directives and has also funded Gulf War studies in areas given highest priority by the Committee, that is, identification of treatments and objective biological markers for Gulf War illness. The program's support of smaller treatment studies to identify suitable candidates for larger clinical trials is also compatible with Committee recommendations. In its 2004 report, the Committee called for lower-cost studies to provide preliminary data on currently

available, potentially promising treatments before allocating millions of dollars for large multi-center clinical trials, as had previously been done by VA and DOD.<sup>1268</sup>

The Committee also applauds CDMRP’s inclusion of veterans with Gulf War illness, and scientists with expertise in Gulf War illness, in reviewing research proposals. It is also of great importance that CDMRP funding for Gulf War research is available to all investigators from academic and government institutions, and can enlist the best ideas from the most qualified scientists, wherever they are found. In contrast, VA research funding can only be provided to VA researchers, imposing significant restrictions on the expertise brought to bear on Gulf War research issues and the types of studies done. The Committee was favorably impressed, overall, with the general approach used by CDMRP, including its emphasis on innovative studies that have the potential to yield clinically useful results in the near term.

Based on CDMRP’s initial success in attracting substantial scientific interest and its support of Gulf War research projects in areas of highest priority, Congress allocated \$10 million for the CDMRP Gulf War research program in FY2008. The GWIRP research solicitation, issued in May, 2008, attracted 113 preproposals. The announcement again emphasized the program’s support of research focused on treatment, diagnosis, and understanding of Gulf War illness, with highest priority given to identification of treatments.<sup>737</sup> Submitted proposals will be reviewed in late 2008, and approved studies will receive funding in 2009.<sup>737</sup> The Committee commends the early successes of the CDMRP program, and will continue to monitor the progress and productivity of the program, as it has reviewed previous federal Gulf War research programs.

A limited number of additional projects, outside the CDMRP Gulf War research program, continued to be identified by DOD as “Gulf War research” in the 2007 interagency report to Congress. Funding continued to reflect trends of recent years. Ninety-five percent of the \$3.4 million funding identified by DOD as “Gulf War Research” in FY2007 was allocated for the Millenium Cohort Study which, as previously described, represents “Deployment Health” research that has little relevance to the health of veterans of the 1990-1991 Gulf War.<sup>340</sup>

**Table 5. Centers for Disease Control and Prevention Gulf War Research: 2003—2006  
Funding Levels and Focus of Studies**

<i><b>Focus of CDC Gulf War Research Studies<sup>†</sup></b></i>	<i><b>2003 Funding*</b></i> (% of 2003 funds)	<i><b>2004 Funding*</b></i> (% of 2004 funds)	<i><b>2005 Funding*</b></i> (% of 2005 funds)	<i><b>2006 Funding*</b></i> (% of 2006 funds)
Gulf War illness, effects of Gulf War exposures	- (0%)	- (0%)	- (0%)	- (0%)
Other health problems related to Gulf War service	\$ 164,291 (17%)	- (0%)	- (0%)	- (0%)
ALS research	- (0%)	\$ 461,951 (100%)	\$ 462,071 (100%)	\$ 466,000 (100%)
Peripheral or no clear relevance to Gulf War service	\$ 799,814 (83%)	- (0%)	- (0%)	- (0%)
<b>Total CDC Gulf War Research Funding, by Year*</b>	<b>\$ 964,105 (100%)</b>	<b>\$ 461,951 (100%)</b>	<b>\$ 462,071 (100%)</b>	<b>\$ 466,000 (100%)</b>

\*Direct costs, as reported in Deployment Health Working Group Annual Report to Congress for each year<sup>336-339</sup>

<sup>†</sup>Research focus of individual projects categorized by Research Advisory Committee on Gulf War Veterans’ Illnesse

## **Gulf War Research at the Centers for Disease Control and Prevention**

The U.S. Centers for Disease Control and Prevention (CDC) has, for many years, participated as a cooperating agency in the ongoing federal effort to address health consequences of the 1991 Gulf War. But CDC has consistently funded only a small percentage of federal Gulf War research. In recent years, Gulf War research funding at CDC has declined from nearly \$1 million in 2003 to about half that amount in 2006, as shown in Table 5.<sup>336-339</sup>

None of the CDC studies funded since 2003 have specifically addressed questions related to Gulf War illness or the effects of Gulf War exposures. One study funded in 2003 addressed another important Gulf War health issue, however, evaluating cancer rates in Gulf War veterans. Two additional studies funded in 2003 had little relevance to the health of 1991 Gulf War veterans. Both involved identification of strategies to improve health risk communications related to military deployments. In addition, CDC has funded one ALS research project between 2004 and 2007, which is evaluating genetic and environmental risk factors among veterans enrolled in VA's ALS Registry. Although the \$1.8 million funding provided for the project over this period has been identified as "Gulf War Research" in the Deployment Health Working Group's reports to Congress, the study includes relatively few Gulf War veterans and does not address scientific questions specific to Gulf War service.<sup>339</sup>

## **Additional VA Programs Relevant to Gulf War Research**

Years ago, I left the VA healthcare system, after being prescribed a powerful medication by VA 'Obecalp'—a medication to be used with extreme caution. However, it did not work very well. Spelled backward, it is simply 'Placebo.' To answer your questions [before you ask], I have never participated in a study, much less one at the VA. After leaving the VA and seeking private medical care, I found a good doctor and neurologist who managed to control my declining health.

... Recently, we sold our home in Florida and moved back to our home state of Kentucky, at which time I returned to the VA for my health care. My wife and I felt, after everything that had been done over the years, that surely the VA healthcare system has improved for Gulf War veterans. But to my surprise, returning to VA was like going back in time. I was once again told there is nothing wrong with Gulf War veterans. Even worse, the doctor I saw on my last visit even stated that she cannot believe veterans receive compensation for Gulf War illnesses, because there is nothing really wrong with them that is related to their service.

... I cannot believe, after all the work that has been done on this issue, that this is still the normal response from VA doctors.

--Gulf War veteran, 2005 Congressional Testimony<sup>1809</sup>

The Committee is charged with reviewing research studies and programs related to the health of Gulf War veterans. There are additional programs and services provided by VA that, although not specifically research programs, are connected to and affected by scientific research on the health of Gulf War veterans. These include VA programs that provide information to healthcare providers caring for Gulf War veterans, programs that provide clinical evaluations of Gulf War veterans, and programs that provide disability benefits to ill veterans.

Veterans with Gulf War illness commonly inform the Committee in public testimony and in private that their VA healthcare providers have little to offer for their conditions, do not take their illness seriously, or believe their symptoms to be psychological. Veterans also question why their providers seem not to know about the types of scientific research discussed in Committee meetings and reports. There are no

recent data that characterize VA healthcare providers' attitudes about Gulf War illness or their familiarity with Gulf War research. However, the Committee has reviewed sources of research information provided to VA healthcare providers, and found them to be both selective and out-of-date. These include continuing education materials provided to VA physicians through the Veterans Health Initiative (VHI), clinical practice guidelines provided for chronic multisymptom illness, as well as other VA documents and public statements made by VA officials. Information from these sources commonly ignores or minimizes Gulf War illness and the wide-ranging scientific evidence that it is not a psychiatric condition and that it affects a substantial number of veterans. This pattern of denying or minimizing the problem of Gulf War illness is exemplified by the following paragraphs from physician education materials currently in use at VA:

Most Gulf War veterans who come to VA for health care or to participate in the VA health registry receive conventional diagnoses and treatments. Most have health problems similar to those experienced by veterans of other eras. However, some veterans report chronic multisymptom illnesses that often are difficult to diagnose. Thus, most of the symptoms reported by veterans in VA registry examinations were found to be caused by conventional illnesses.

... Considerable progress has been made in evaluating and treating illnesses among Gulf War veterans and in determining the prevalence of symptoms. Most Gulf War veterans are healthy today and have successfully readjusted to post-war life, or they have diagnosable health problems. VA has been able to respond to the complexity of veterans' health problems; most are readily diagnosed and effective treatments are available.

--VA Continuing Medical Education Program<sup>1649</sup>

**Information on Gulf War research provided to VA clinicians.** The Veterans Health Initiative, VA's continuing medical education program, provides information on the health of Gulf War veterans to VA clinicians. The independent study course, *A Guide to Gulf War Veterans' Health*, was first prepared in 1997 by VA's Employee Education System in cooperation with VA's Office of Public Health and Environmental Hazards.<sup>1649</sup> The currently-used guide was revised in 2001 and released in March 2002. It provides general information from VA's Gulf War Registry and from selected types of Gulf War epidemiologic research available at that time, most prominently information on symptoms, hospitalizations, and mortality rates. It also provides guidelines for clinical risk communications, to assist clinicians in explaining causality information to veterans with Gulf War illness, as demonstrated by the following excerpts:

Frequently, the veteran seems to overestimate or overvalue the apparently low chance that a rare, improbable cause (e.g., in theater vaccinations or biological weapons exposures) is responsible for symptoms than more ordinary and likely causes (e.g. early degenerative joint disease in an airborne infantry soldier).

... discussing chronic illness with a Gulf War veteran or a woman with silicone breast implants is a different matter from discussing it with the average patient. Of course, this is because the Gulf War and silicone implants have been the focus of intense scientific, governmental and media scrutiny as possible sources of illness.

--VA Continuing Medical Education Program<sup>1649</sup>

The course provides no information on many of the most significant research findings related to the health of Gulf War veterans. That is, VA physicians trained using the Veterans' Health Initiative course are not informed about: (1) epidemiologic research showing high rates of multisymptom illness in Gulf War veterans, significant associations between Gulf War illness and hazardous exposures during the Gulf War, and elevated rates of ALS in Gulf War veterans, (2) clinical findings of objective indicators of

neurological alterations and other biological abnormalities in ill veterans, or (3) toxicological studies showing persistent neurological effects of low-level Gulf War-related exposures, and synergistic effects of combined exposures. In short, Gulf War research information provided to VA clinicians through the Veterans Health Initiative is unacceptably limited and out-of-date.

**Information provided to VA clinicians on clinical management of Gulf War illness.** As previously described, VA and DOD commissioned expert panels to develop two sets of clinical practice guidelines related to the health of Gulf War veterans. These guidelines, finalized in 2001, were informed by available scientific research and by the clinical experience of panel members. One set of guidelines provides information to assist clinicians in evaluating patients with “post-deployment health concerns” but does not provide specific treatment recommendations.<sup>1656</sup>

The second set of practice guidelines provides information on evaluation and management of veterans with chronic unexplained illness, specifically symptoms of chronic pain and fatigue.<sup>1656</sup> Information provided on recommended treatments is based on the limited number of clinical trials published by 2001 that evaluated therapies for fibromyalgia and chronic fatigue syndrome. Information on other potentially useful treatments is also provided, based on more preliminary research findings and the clinical experience of panel members. The guidelines emphasize the use of cognitive behavioral therapy (CBT), graded exercise, and antidepressant medications. Although exercise and CBT have been shown to provide improvements for fibromyalgia and chronic fatigue syndrome patients, studies have found them to be less helpful for ill Gulf War veterans.<sup>226,354,406</sup> The clinical practice guidelines are also seriously outdated in terms of the many studies of treatments for multisymptom conditions published since 2001, particularly treatments for fibromyalgia.

**VA clinical programs relevant to Gulf War health research.** VA has long maintained a national Gulf War Registry that provides clinical evaluations to Gulf War veterans at no cost and serves, for some veterans, as a gateway to other VA healthcare and benefits programs. Participating veterans complete detailed questionnaires and are given standardized medical examinations.<sup>1654</sup> Although not designed to provide scientific research information, the registry relates to the federal Gulf War research effort in a number of ways. Summary data from the registry are reported in medical journals and frequently cited in government reports and testimony. In addition, VA’s Gulf War Registry is sometimes used as a resource to identify veterans for Gulf War research projects. The Committee was informed by VA’s Office of Environmental Hazards that, as of November 1, 2007, a total of 102,215 veterans of the 1990-1991 Gulf War had enrolled in VA’s Gulf War Registry. Figures from recent years indicate that additional Gulf War veterans have continued to come forward with health concerns, even 17 years after Desert Storm. According to VA’s Office of Environmental Hazards, 3400-4400 Gulf War veterans have received VA Gulf War Registry exams in each of the last three years.

The Department of Veterans Affairs also maintains a national referral program that provides more in-depth clinical evaluations at specialty clinics for veterans with difficult-to-diagnose conditions.<sup>1653</sup> The War-Related Illness and Injury Study Centers (WRIISCs) were established in 2001 and initially located at VA Medical Centers in Washington, D.C., and East Orange, New Jersey.<sup>1642</sup> A third WRIISC was recently established in Palo Alto, California.<sup>1657</sup> Multidisciplinary clinical evaluations at the WRIISCs require between two and five days and include detailed medical and psychological evaluations, as well as other types of specialty testing, as indicated for individual patients. This might include environmental exposure assessments, neurological testing, balance testing, neuropsychological assessments, or other evaluations. The program is provided for veterans who served in a theater of combat operations and are affected by undiagnosed or difficult-to-diagnose conditions. Veterans are referred by their local VA clinicians, and all medical services, travel, and local accommodations are provided at no cost to the veteran.<sup>1657</sup>

The WRIISCs were established both to provide multidisciplinary clinical evaluations for ill veterans, and as research centers.<sup>1653</sup> Investigators based at the Washington and New Jersey WRIISCs have conducted dozens of studies on diverse topics related to Gulf War illness and other Gulf War health issues. Relatively few veterans, however, have participated in the WRIISC clinical evaluation programs. A published report indicated that, in their first two years of operation, the New Jersey and Washington WRIISCs combined had evaluated a total of 53 combat veterans with difficult-to-diagnose conditions, only 42 of whom had served in the Persian Gulf War.<sup>907</sup> Figures provided to the Committee by VA's Office of Environmental Hazards indicate that a total of 168 Gulf War veterans were evaluated at the two WRIISCs between 2001 and 2007.

**VA disability benefits in relation to Gulf War research.** The Department of Veterans Affairs provides financial compensation to veterans of all eras who have disabling health problems in connection with their military service. Disability compensation programs are administered by the Veterans Benefits Administration (VBA) within VA. Department of Veterans Affairs regulations identify specific requirements that must be met in order for veterans of a particular era or veterans with certain health problems to receive disability benefits. There are special provisions, for example, that allow Gulf War veterans disabled by chronic symptoms that are not explained by a specific diagnosis to receive disability compensation for "undiagnosed illnesses."<sup>1643</sup> Although VBA does not sponsor scientific research studies, decisions and regulations concerning disability benefits rely on scientific research.

As of February, 2008, VBA's Gulf War Veterans Information System (GWVIS) reported that 33 percent of the 631,477 service members who separated from military service after serving in the 1991 Gulf War had filed disability claims and were found by VBA to have a service-connected disability. Among personnel potentially exposed to low-level nerve agents in relation to the Khamisiyah demolitions in March of 1991, 39 percent have a service-connected disability.<sup>1650</sup> By comparison, 29 percent of military personnel who deployed to Southwest Asia *after* 1991, and are now separated from service, have a service-connected disability. Although crude figures provided for different groups in the GWVIS reports cannot be directly compared without proper adjustments, available figures do suggest that veterans of the 1990-1991 Gulf War have a high rate of service-connected disabilities, especially considering the brevity of the 1991 Gulf War and the low rate of injuries during the war.<sup>1607,1633</sup>

It is also important to note that very few Gulf War veterans have applied for disability compensation for "undiagnosed illness." As of February, 2008, just two percent of Gulf War veterans had filed disability claims for undiagnosed illness and only 0.5 percent had been service-connected for undiagnosed illness.<sup>1650</sup> The very low number of claims for Gulf War-related undiagnosed illness is somewhat unexpected, given the much larger number of veterans identified with multisymptom illness in research studies. The explanation for this is not known, but may relate to several factors. VBA statistics suggest that undiagnosed illness claims have been difficult for veterans, veterans service officers, and VA to successfully execute. Eighty-seven percent of all disability claims filed by veterans who served since 1990 have been granted service-connection by VBA. In sharp contrast, only 26 percent of claims filed for undiagnosed illness have been granted service-connection.<sup>1650</sup> This may explain, in part, why few veterans, or veterans' service officers, have filed this type of claim. In any case, the very small number of veterans who have applied for disability benefits for undiagnosed illness belies inferences made that Gulf War veterans might be inclined to report difficult-to-diagnose symptoms for purposes of financial gain.<sup>379,466</sup>

As described in an earlier section of this report, Congress directed VA, in 1998, to commission the Institute of Medicine (IOM) to conduct comprehensive scientific reviews to assist the Secretary in making decisions about service-connected disability compensation for Gulf War veterans in relation to Gulf War service and Gulf War exposures. Congress specified that VA direct IOM to: (1) identify diagnosed and undiagnosed conditions that affect Gulf War veterans at excess rates, and (2) evaluate scientific evidence from human and animal studies concerning associations between those conditions and a detailed list of

Gulf War exposures.<sup>1242,1243</sup> As previously detailed, the resulting *Gulf War and Health* series of reports have not fulfilled the purpose directed by Congress. As commissioned by VA, these reviews have either excluded, or only superficially considered, key areas of research essential for understanding associations between Gulf War illness and hazardous exposures in the Gulf War. Although intended by Congress to provide support to the VA Secretary in making decisions about Gulf War-related disability benefits, the *Gulf War and Health* reports have provided little information relevant to the most prominent Gulf War health and disability issues. This includes Gulf War illness and ALS, for which no conclusions related to Gulf War-related exposures have been provided.<sup>685,686</sup> In the present report, the Committee has recommended that the IOM Gulf War reviews be redone to reflect the purpose and content directed by Congress.

In 2001, former VA Secretary Principi announced that VA would provide service-connected disability compensation to all Gulf War veterans who had been identified at that time with a diagnosis of ALS.<sup>1639</sup> The decision was based on emerging findings from epidemiologic research indicating that Gulf War veterans had a significantly higher rate of ALS than their nondeployed counterparts. However, VBA did not establish a regulation at that time that provided presumptive service-connection for all Gulf War veterans with ALS. New claims related to ALS in Gulf War veterans continued to be adjudicated on a case-by-case basis.<sup>1028,1639</sup> This changed in September, 2008, when VA Secretary James Peake announced that all U.S. veterans, of all eras, would be given presumptive service connection for ALS.<sup>1647</sup> The decision was based, primarily, on an IOM 2006 report on ALS, which concluded that there was limited, suggestive evidence supporting an association between military service, overall, and development of ALS.<sup>685</sup>

In summary, multiple issues have been raised concerning VA programs that are not specifically focused on research, but are closely linked to scientific research on the health of Gulf War veterans. These include programs that provide research information to VA clinicians, programs that provide clinical assessments of ill Gulf War veterans, and programs that provide benefits to disabled Gulf War veterans. In 2007, the Committee formally recommended that VA update and improve information on Gulf War research provided to VA clinicians.<sup>1271</sup> This included both the Veterans' Health Initiative continuing education program on the health of Gulf War veterans, and the VA/DOD Clinical Practice Guidelines for Unexplained Symptoms.

The Committee also recommended that the Secretary establish a separate advisory committee to consider issues related to clinical care and benefits for Gulf War veterans.<sup>1271</sup> In April 2008, Secretary Peake appointed a new public advisory panel, the Advisory Committee on Gulf War Veterans, and charged it with an assessment of the full spectrum of VA healthcare and benefits issues that affect veterans who served in the 1990-1991 Gulf War.<sup>1646</sup> The Committee welcomes this development and looks forward to working cooperatively with the new panel.

### **Summary. Federal research on Gulf War illness and the health of Gulf War veterans.**

Since 1994, the federal government has reported spending hundreds of millions of dollars for projects identified as Gulf War research, but prominent shortcomings have slowed federal progress in addressing Gulf War-related health issues. Studies identified as federally-sponsored "Gulf War research" have often been unrelated, or only marginally related, to the health of Gulf War veterans. In addition, a substantial portion of Gulf War research funding has been used for studies focused on psychological stress and psychiatric disorders. The federal Gulf War research effort has not, historically, been designed or managed to achieve high-priority scientific objectives. Specifically, federal programs have not been managed to resolve fundamental questions concerning the nature, causes, and treatments for Gulf War illness. Consequently, federal Gulf War research programs have not, as yet, succeeded in improving the health of ill Gulf War veterans.

Congressional actions have brought about major changes in Gulf War research programs at both VA and DOD in recent years. In 2006, Congress allocated an additional \$15 million annually for Gulf War research at VA to support a center of excellence for Gulf War research at the University of Texas Southwestern (UTSW) in Dallas. The VA UTSW program is focused on identifying biological abnormalities associated with Gulf War illness and effects of hazardous exposures during the Gulf War. In addition, Congress appropriated \$5 million in 2006 and \$10 million in 2008 for an innovative Gulf War research program managed by DOD's Office of Congressionally Directed Medical Research Programs. The new DOD Gulf War research program is focused on identifying effective treatments and objective biological markers for Gulf War illness, and funded multiple studies in these areas in 2007.

Early indications suggest that changes at both VA and DOD represent promising new directions in the federal Gulf War research effort that have the potential to make a significant difference in the health of Gulf War veterans. Despite these positive developments, overall funding for federal Gulf War research has declined dramatically since 2001. A renewed federal research commitment is urgently needed to restore Gulf War research funding to pre-2001 levels in support of research focused on identifying beneficial treatments for Gulf War illness and other priority Gulf War research issues identified in this report.

## Recommendations

The Committee welcomes recent programmatic developments related to federal Gulf War research, and urges the federal government to allocate no less than \$60 million annually in the federal budget for Gulf War research programs. This is consistent with annual funding levels committed for federal Gulf War research between 1999 and 2001, adjusted for inflation. Specifically, the Committee recommends:

- That the Administration request and Congress appropriate a minimum of \$40 million annually to the Department of Defense for the Gulf War Illness Research Program managed by DOD's Office of Congressionally Directed Medical Research Programs. This funding should support openly-competed, peer-reviewed studies focused on identifying: (1) effective treatments for Gulf War illness, (2) objective measures that distinguish ill from healthy veterans, and (3) underlying biological mechanisms potentially amenable to treatment, in accordance with the priorities identified by the Committee.
- That the Administration request and Congress appropriate a minimum of \$20 million annually to the Department of Veterans Affairs for Gulf War illness research. This should include \$15 million annually to support the Gulf War illness research center at the University of Texas Southwestern through FY2010, with the balance to fund additional Gulf War research studies, through Gulf War-specific and general solicitations for peer-reviewed proposals consistent with research recommendations in this report.
- That VA continue to fund the ALS Registry and the Gulf War Biorepository, focused more specifically on projects related to Gulf War era veterans. The biorepository should be expanded to include Gulf War era veterans with other diagnosed medical diseases and difficult-to-diagnose conditions.
- That the Department of Defense and the Department of Veterans Affairs collaborate in establishing a comprehensive federal Gulf War research plan and a strategy to coordinate and manage federal programs to ensure that priority research objectives are satisfactorily achieved.



## 5 | Research Priorities and Recommendations

Veterans of the 1990-1991 Gulf War had the distinction of serving their country in a military operation that was a tremendous success, achieved in short order. But many had the misfortune of developing lasting health consequences that were poorly understood and, for too long, denied or trivialized. The extensive body of scientific research now available consistently indicates that Gulf War illness is real, that it is the result of neurotoxic exposures during Gulf War deployment, and that few veterans have recovered or substantially improved with time. Addressing the serious and persistent health problems that affect Gulf War veterans as a result of their military service remains the obligation of the federal government and all who are indebted to the men and women who risked their lives in Iraq, Kuwait, and Saudi Arabia 17 years ago. This obligation is made more urgent by the length of time veterans have waited for answers and assistance.

The Committee was directed to determine what has been learned about the health consequences of military service in the 1990-1991 Gulf War and to recommend research directed toward improving the health of Gulf War veterans. As described throughout this report, an extensive amount of research has provided important progress and improved understanding of the nature and causes of Gulf War illness and, more generally, the health of Gulf War veterans. Important questions remain, however. In reviewing the broad range of studies and topics related to the health of Gulf War veterans, the Committee identified many scientific issues for which additional research is needed and provided specific recommendations for each topic considered. Those research recommendations are brought together and summarized below, listed by categories of priority. Guidelines are also provided for improvements in clinical and epidemiologic research on Gulf War veterans, based on limitations commonly identified in existing studies.

While the Committee believes that all of the recommended research is important, it places highest priority on research that can most directly contribute to the objective of improving the health of Gulf War veterans. The corollary objective, of achieving a clearer and more comprehensive understanding of the health consequences of the Gulf War, also remains essential both to assist Gulf War veterans and their families, and to avoid similar consequences in future military deployments.

### **Highest Priority Gulf War Research**

**1. Identification of effective treatments for Gulf War illness.** Highest priority is given to research conducted to identify beneficial treatments for Gulf War illness. The primary objective is the conduct of well-designed clinical trials of treatments that hold promise for providing substantial benefit for veterans with Gulf War illness or identifiable subgroups. This research should include:

- Studies that identify and systematically evaluate the effectiveness of currently available treatments used for Gulf War illness or conditions with similarities to Gulf War illness. Preliminary research should include pilot trials and/or observational studies capable of identifying promising treatments suitable for evaluation in larger clinical trials.

- Research to identify specific pathophysiological mechanisms underlying Gulf War illness that are potentially amenable to treatment interventions.
- Research to evaluate novel therapies based on scientific findings as they emerge.

**2. Identification of objective measures that distinguish veterans with Gulf War illness from healthy veterans.** The Committee places a high priority on identification of biological markers for Gulf War illness and measurable differences between groups of symptomatic and healthy Gulf War veterans. In light of findings from current and ongoing studies describing associations between Gulf War illness and neurological, immune, endocrine, genetic, and biochemical alterations, the Committee recommends the following research:

- Studies that utilize state-of-the-art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish veterans with Gulf War illness, including illness or exposure subgroups, from healthy Gulf War veterans.
- Comprehensive evaluation of autonomic nervous system function associated with Gulf War illness, as well as illness and exposure subgroups.
- Research that investigates biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, including studies that evaluate associations between Gulf War illness and genetic polymorphisms and activity levels of enzymes associated with uptake and metabolism of neurotoxic exposures.
- Studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans affected by Gulf War illness.
- Comprehensive evaluation of immune parameters associated with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Comprehensive evaluation of hypothalamic-pituitary-adrenal axis and other neuroendocrine parameters in association with Gulf War illness, including parameters that may differ among illness and/or exposure subgroups.
- Studies that determine the extent to which other physiological characteristics that distinguish CFS, FM, and MCS patients from healthy controls are also associated with Gulf War illness.
- Studies that use the most reliable methods available to determine rates of latent or active leishmania (particularly *L. tropica*) and mycoplasma infection in veterans with Gulf War illness and healthy controls.
- Studies that utilize new technologies (proteomic, genomic, and metabolomic methods) capable of identifying unique molecular characteristics of Gulf War illness, and of illness and exposure subgroups.

**3. Studies that characterize effects of neurotoxic exposures associated with Gulf War illness.** Due to the consistency of findings relating Gulf War illness to neurotoxic exposures during the war, the Committee gives high priority to studies that further characterize specific effects of Gulf War-related neurotoxic exposures, and recommends the following research:

- Studies that utilize animal models to characterize persistent molecular, cellular, systemic, and behavioral effects of individual and combined exposure to pyridostigmine bromide, pesticides and insect repellants used in the Gulf War, and low-level sarin.
- Studies that utilize animal models to characterize persistent effects of Gulf War-related exposures, alone and in combination, on central proinflammatory processes and their biological mediators in the central nervous system and target organs.
- Studies that identify markers indicative of past exposure to Gulf War-related neurotoxic compounds that can be applied to Gulf War veterans. This might include studies that utilize technologies capable of detecting toxins or secondary metabolites retained for many years following exposure, studies that identify persistent or “downstream” changes in biochemical processes in relation to past neurotoxicant exposure, and studies that identify persistent changes in the central nervous system and autonomic function associated with exposure to Gulf War-related neurotoxicants.

**4. Research to determine if Gulf War veterans are affected by excess rates of neurological diseases and to further characterize neurological abnormalities in Gulf War veterans.** Research studies indicating that Gulf War veterans have a significantly higher rate of amyotrophic lateral sclerosis (ALS) than their nondeployed peers raise concerns about other chronic neurological conditions for which no studies have been conducted. The committee therefore recommends the following research:

- Epidemiologic studies to identify rates of diagnosed neurological diseases (including multiple sclerosis, Parkinson’s disease, ALS, and brain cancers), as well as central nervous system conditions that are difficult to precisely diagnose, in Gulf War veterans and appropriate comparison groups.
- Greater focus of VA’s ALS Registry and Gulf War brain tissue bank on projects related to Gulf War veterans, and expansion of both programs to include Gulf War veterans with other diagnosed neurological diseases and difficult-to-diagnose neurological conditions. In addition, the brain tissue bank should be expanded to specifically include veterans with Gulf War multisymptom illness and appropriate controls.

## **Other Research Areas of Importance for Addressing Gulf War Health Issues**

**Epidemiologic research: general.** The Committee considers information provided by VA's national longitudinal study of Gulf War veterans and continued monitoring of the health of Gulf War veterans over time to be extremely important. It therefore recommends that VA:

- Make results from the national longitudinal study of Gulf War veterans publicly available at the earliest possible time, including comprehensive findings related to multisymptom illness, treatments and practices used by veterans to address their symptoms, and reported rates of medical diagnoses. Results should include outcomes assessed according to the guidelines for epidemiologic research provided below.
- Continue current research evaluating cancer rates in Gulf War era veterans, and assess cancer rates among subsets of veterans identified as being exposed to chemical nerve agents, depleted uranium, and smoke from the Kuwaiti oil well fires.
- Provide current information on overall and cause-specific mortality rates in Gulf War veterans, and update this information, at minimum, at five year intervals. This should include information on mortality in subgroups of Gulf War veterans identified by deployment locations, branch of service, and exposures reported in the National Survey of Gulf War Era Veterans and Their Families.
- Conduct additional analyses of available data from existing large population-based studies to more thoroughly evaluate rates of Gulf War illness, cancer, respiratory conditions, and other health outcomes in relation to self-reported and modeled exposures, individually and in combination, appropriately controlling for effects of other exposures in theater.
- Make available comprehensive information on family members of Gulf War veterans from the national study of Gulf War era veterans and family members. This should include information on diagnosed conditions, multisymptom illness, behavioral problems, and birth defects. Health parameters should also be assessed in subgroups of interest, such as family members of veterans with/without Gulf War illness and subgroups defined by characteristics of veterans' wartime service.
- Continue to monitor health and disease outcomes among veterans assessed in the National Survey of Gulf War Era Veterans and Their Families, conducting longitudinal surveys and appropriate clinical follow-up studies at five year intervals.
- Further evaluate indications of possible increased risk of specific types of birth defects, as well as other health problems in children of Gulf War veterans, using innovative study designs.

### **Studies to further characterize effects of Gulf War exposures**

- Conduct an epidemiologic investigation to evaluate health outcomes in an expanded cohort of Gulf War veterans who had the greatest exposure to depleted uranium during deployment, and an appropriate comparison group. Evaluated health outcomes should include detailed information on symptoms, Gulf War illness, functional status, diagnosed medical conditions, and reproductive outcomes.

- Commission a case-control study to determine whether Gulf War illness is associated with elevated levels of squalene antibodies.
- Evaluate the association of anthrax vaccine adsorbed (AVA) with chronic symptoms, multisymptom illness, and diagnosed disease by conducting a retrospective cohort study of military personnel known to have received/not received AVA during the Gulf War and/or in the early years of the AVIP program.
- Conduct an epidemiologic investigation to determine if personnel who served with the Army National Guard's 325<sup>th</sup> Maintenance Company in the Gulf War suffer excess health problems associated with exposure to CARC paint during deployment, alone or in combination with other Gulf War-related exposures.

### **Guidelines for Clinical and Epidemiologic Research on Gulf War Veterans**

- Studies of Gulf War veterans should use well-constructed and clearly-described case definitions for Gulf War illness and illness subgroups. Pending more widespread acceptance of an established case definition, preferred case definitions are those that most clearly distinguish the pattern of symptoms in Gulf War veterans from those in nondeployed era veterans, such as the Kansas Gulf War illness case definition.
- In addition to general comparisons between Gulf War and nondeployed veterans, Gulf War research studies should analyze results in relation to Gulf War veteran subgroups of interest, including ill vs. well veterans and subgroups defined according to veterans' locations in theater, exposures, and other military and deployment characteristics potentially relevant to the outcomes evaluated.
- Associations between deployment-related exposures and health outcomes in Gulf War veterans should be evaluated using analytic methods that appropriately control for the effects of confounding introduced by multiple exposures during deployment.
- Research studies whose principal focus is on psychiatric disorders such as posttraumatic stress disorder or effects of psychological stressors are not directly relevant to Gulf War illness and should not be considered Gulf War illness research.



## | Acknowledgements

Since its inception, the work of the Committee has relied on the assistance and input provided by research scientists, veterans, government officials, and members of the general public. The Committee could not have executed its charge in the comprehensive manner required had it not been for this support. We have been continually gratified by the generosity with which individuals from many sectors have enthusiastically provided their expertise and time in this important endeavor.

We would first like to acknowledge former members of the Committee who have contributed greatly to its work in the years since the last major report, but whose names do not appear as authors of the present report. These past members include Mr. Adrian Atizado, Dr. Nicola Cherry, Dr. Robert Haley, Dr. Pierre Pellier, Mr. Steve Robinson, and Dr. Hugh Tilson. This report, in no small part, reflects their contributions. We also welcome new members LTC Adam Such and Dr. Dedra Buchwald, who recently joined the Committee. Because they did not participate in discussions and approval of the present report, neither former members nor new members are responsible for the report's specific findings or content.

The Committee was mandated by Congress, and charged with advising the federal government on Gulf War research, directing its advice specifically to the Secretary of Veterans Affairs, who chairs the interagency group on the health of Gulf War veterans, the Deployment Health Working Group. We express our thanks to the Secretaries of Veterans Affairs we have advised and under whom we have served: Secretary Anthony J. Principi, Secretary R. James Nicholson, and Secretary James B. Peake. We appreciate their support and continuing interest in our work and, more broadly, in issues concerning the health of Gulf War veterans. We have also appreciated inquiries from members of Congress, and their ongoing interest in and support of the Committee's work.

There are many individuals, both officials and staff members, in the Department of Veterans Affairs (VA) and the Department of Defense (DOD) who have been most helpful in providing information and assistance to the Committee. Within VA, we express our gratitude to officials at the Office of Research and Development: Chief Research and Development Officer Dr. Joel Kupersmith, Director of the Clinical Science Research and Development Service Dr. Timothy O'Leary, and portfolio manager for VA's Gulf War illness research program Dr. William Goldberg, who also serves as the Committee's Designated Federal Officer. We also thank Mr. Phil Riffin, Special Assistant to the Secretary, who oversees VA's Office of Advisory Committees. Within the Department of Defense, we are grateful for the assistance of Dr. Michael Kilpatrick, Deputy Director of the Office of Force Health Protection and Readiness and Dr. Francis O'Donnell, medical consultant in that office. We also thank COL Janet Harris and CAPT Melissa Kaime, past and current directors of the Army's Office of Congressionally Directed Medical Research Programs.

The Committee recognizes, with special appreciation, the Gulf War veterans and other members of the public who have attended our meetings. We have considered their experiences and ideas—shared in public testimony and in private conversations—to be extremely useful in charting our course, and keeping us on course. Many veterans who have attended our meetings have themselves been chronically ill and their participation has often required considerable personal effort and expense. Their continuing efforts on behalf of their fellow veterans, 17 years after the war, have been an inspiration and a valuable asset in the Committee's work. Here we acknowledge veterans and members of the public who have offered public testimony at Committee meetings since 2004: Mr. Mark Anderson, Ms. Lauren Billings, Mr. Edward Bryan, Mr. Ed Butler, Ms. Becky Cann, Mr. Wesley Crawford, Mr. Albert Donnay, Ms. Julia Dyckman, Mr. Andrew Eddowes, Mr. Dan Fahey, Ms. Connie Gonzales, Mr. Mike Hood, Ms. Alison Johnson, Ms. Kathi Krome, Mr. Kirt Love, Dr. Ruth McGill, Dr. Meryl Nass, Mr. Harold Nelson,

Ms. Angela Newbold, Mr. Kevin Smith, Mr. Erwin Steffen, Mr. James Thew, Ms. Venus Val-Hammack, and Mr. Cheyne Worley. We would like to single out for special acknowledgement Ms. Denise Nichols, retired Air Force Major, nurse, and Desert Storm veteran, for her tireless participation in nearly every meeting held by the Committee since its inception.

One of the most valuable assets in the Committee's work has been our small but dedicated research staff. Their work in providing both scientific and administrative support to the Committee's activities has been exemplary and we are grateful for their commitment and efforts. Our thanks to Ms. Laura Palmer, Ms. Barbara LaClair, Dr. Kim Sullivan, and Ms. Callie Comtois. We also thank Dr. Jeff Levin for his assistance with staff activities, including technical assistance in preparing this report.

We give special recognition and thanks to Dr. Lea Steele, who served as the Committee's Scientific Director throughout most of the period of review and deliberations covered by this document. We appreciate her prodigious contribution in overseeing the scientific activities of the Committee during this period, including preparation of this report.

The Committee is also greatly indebted to the scientists and government officials who have generously provided presentations to our meetings, taken part in scientific discussions, and often provided helpful insights and suggestions after their meeting participation. Their names are listed below, and the Committee could not have conducted its work without their expertise and thoughtful assistance. We are also grateful to the countless other scientists who have conferred with the Chair, Scientific Director, and Committee members on a wide variety of scientific matters in relation to this work. Their insights have helped to shape our consideration of important topics and identify useful resources. Although it is not possible to name them all here, we are most grateful for their input and advice.

We thank the scientists and government officials listed below who have provided presentations at Committee meetings since 2004. Detailed information on presentations and discussions is provided in each meeting's minutes, which can be found on the Committee's website: [www.va.gov/RAC-GWVI](http://www.va.gov/RAC-GWVI).

February 23-24, 2004 (Washington, D.C.):

Dr. John Concato	West Haven VA, Yale University
Mr. Roger Kaplan, Mr. Joe Gough, Ms. Preeti Hans	VA Office of Research and Development
Dr. Alan Magill	Walter Reed Army Institute of Research
Dr. Ya Fang Liu	Boston University School of Medicine
Dr. Mohan Sopori	Lovelace Respiratory Research Institute
Dr. John Ottenweller	East Orange, NJ, VA War-Related Illness and Injury Study Center
Dr. Mark Peakman	King's College School of Medicine
Mr. Al Marshall	Sandia National Laboratories
Dr. Terry Pellmar	DOD Armed Forces Radiobiology Research Institute
Dr. Johnnye Lewis	University of New Mexico
Dr. Melissa McDiarmid	Baltimore VA Depleted Uranium Program
Dr. Sam Donta	Boston VA (retired), Donta Infectious Diseases

June 28-29, 2004 (East Orange, New Jersey)

Dr. Benjamin Natelson, East Orange, NJ, VA War-Related Illness and Injury Study Center  
Dr. Tom Findley, Dr. John Ottenweller, Dr. Dane Cook,  
Dr. Kevin Beck, Dr. Karen Quigley,  
Dr. Liesel Copeland, Dr. Drew Helmer, Dr. Gudrun Lange, Dr. Helena Chandler, Dr. Don Ciccone,  
Dr. Ronald Teichman  
Mr. Roger Kaplan VA Office of Research and Development  
Dr. John Concato West Haven VA, Yale University  
Dr. Paul Greengard, Dr. Sharon Mates, Dr. Allen Fienberg Intra-Cellular Therapies, Inc.

October 25-26, 2004 (Washington, D.C.)

Dr. Jack Heller, Mr. Warren U.S. Army Center for Health Promotion and Preventive Medicine  
Wortman, Mr. Jeff Kirkpatrick,  
MAJ Christine Moser  
CAPT Eugene Goodwin U.S. Navy Medical Service Corps  
Dr. David Cowan Walter Reed Army Institute of Research  
Dr. Charles Engel Walter Reed Army Medical Center  
Dr. Stephan Fihn VA Office of Research and Development  
Dr. Quentin Deming  
Mr. Bill Weiss

April 6-8, 2005 (Washington, D.C.)

Dr. Iris Bell University of Arizona School of Medicine  
Dr. William Reeves U.S. Centers for Disease Control and Prevention  
Dr. Daniel Clauw University of Michigan School of Medicine  
LTC Mark Melanson USACHPPM Health Physics  
Ms. Mary Ann Parkhurst Battelle Pacific Northwest National Laboratory  
Dr. Wayne Briner University of Nebraska  
Dr. David Barber University of Florida  
COL John Grabenstein Military Vaccine Agency, U.S. Army Medical Command  
Dr. Phillip Pittman U.S. Army Medical Research Institute of Infectious Diseases  
Dr. Brian Schuster VA Office of Research and Development

September 19-21, 2005 (Washington, D.C.)

Dr. Gary Friedman Texas Lung Institute  
Dr. Bellina Veronesi U.S. Environmental Protection Agency  
Dr. Mark Witten University of Arizona College of Medicine

September 19-21, 2005 (Washington, D.C.) (cont.)

Dr. Glen Ritchie	Battelle
Dr. Susan Proctor	Boston VA
Dr. Mihaela Aslan, Dr. Peter Peduzzi	West Haven VA
Mr. Tim Bullman	Washington, D.C., VA
Dr. Paul Levine	George Washington University
Dr. Joel Kupersmith, Dr. Timothy O'Leary	VA Office of Research and Development
Dr. Han Kang	Washington, D.C., VA

December 12-13, 2005 (Washington, D.C.)

Dr. Joel Kupersmith, Dr. William Goldberg	VA Office of Research and Development
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May 15-16, 2006 (Washington, D.C.)

Dr. Mohamed Abou-Donia	Duke University Medical Center
Dr. Robert Haley	University of Texas Southwestern School of Medicine
Secretary James Nicholson	U.S. Department of Veterans Affairs
Dr. James Baraniuk	Georgetown University School of Medicine
Dr. William Goldberg	VA Office of Research and Development

August 14-15, 2006 (Washington, D.C.)

Dr. Kevin Tracey	Feinstein Institute for Medical Research
Dr. Nancy Klimas	Miami VA, University of Miami School of Medicine
Dr. Mariana Morris	Wright State University Boonshoft School of Medicine
Dr. Mohan Sopori	Lovelace Respiratory Research Institute
Dr. Jau-Shyong Hong	National Institute for Environmental Health Sciences
Dr. Tomas Guilarte	Johns Hopkins School of Hygiene and Public Health
Dr. Michael Kussman	VA Principal Deputy Undersecretary for Health
COL Janet Harris	U.S. Army Congressionally Directed Medical Research Programs
Dr. Joseph Francis, Dr. William Goldberg	VA Office of Research and Development

November 6-7, 2006 (Dallas, Texas)

Ms. Kathleen Considine, Mr. Vince Iannacchione	Research Triangle Institute
Dr. Robert Haley, Dr. Jeffrey Spence, Dr. Richard Briggs, Dr. Christopher Sinton, Dr. James Bibb,	University of Texas Southwestern School of Medicine

November 6-7, 2006 (Dallas, Texas) (cont.)

Dr. George DeMartino, Dr. Philip Thomas, Dr. Ilya Bezprozvanny University of Texas Southwestern School of Medicine  
Dr. Louis Fiore Boston VA MAVERIC Program  
Dr. Anil Prasad Tucson VA  
Dr. Joel Kupersmith, Dr. William Goldberg VA Office of Research and Development

April 24-25, 2007 (Washington, D.C.)

Dr. Douglas Wallace University of California at Irvine  
Dr. Julia Golier Bronx VA  
Dr. Kristin Heaton U.S. Army Research Institute of Environmental Medicine  
Dr. William Goldberg VA Office of Research and Development  
COL Janet Harris U.S. Army Congressionally Mandated Medical Research Programs

July 18-19, 2007 (Dallas, Texas)

Dr. Jonathan Kerr St. George's University of London  
Dr. Robert Haley, Dr. Wendy Ringe, Dr. Richard Briggs, Dr. Tom Ferree, Dr. Sergei Cheshkov, Dr. Roderick McColl, Dr. K.S. Gopinath, Dr. Michael Motes University of Texas Southwestern School of Medicine  
Dr. John Hart, Dr. James Bartlett University of Texas at Dallas  
Dr. William Goldberg VA Office of Research and Development

April 7-8, 2008 (Boston, Massachusetts)

Dr. Ronald Bach Minneapolis VA  
Dr. Ashok Tuteja Salt Lake City VA  
Dr. Fred Gorelick, Dr. Avlin Imaeda West Haven VA, Yale University  
General Richard Valente Rhode Island Persian Gulf War Information and Relief Commission  
Dr. Allen Fienberg Intra-Cellular Therapies, Inc.  
Dr. William Goldberg VA Office of Research and Development  
Dr. Louis Fiore VA Boston MAVERIC Program

September 15-16, 2008 (Washington, D.C.)

Dr. Edward Kasarskis Lexington VA  
Dr. Ronnie Horner University of Cincinnati  
Dr. Eugene Oddone Durham VA, Duke University Medical Center  
Dr. Marie Lynn Miranda Duke University Medical Center  
Dr. Paul Levine George Washington University

September 15-16, 2008 (Washington, D.C.) (cont.)

Dr. William Goldberg	VA Office of Research and Development
Dr. Robert Haley	University of Texas Southwestern School of Medicine
Dr. Mitchell Wallin	Washington, D.C., VA
CAPT Melissa Kaime	U.S. Army Congressionally Directed Medical Research Programs
Dr. Han Kang	Washington, D.C., VA
Dr. Karen Quigley, Dr. Helena Chandler, Dr. Gudrun Lange	East Orange, NJ, VA War-Related Illness and Injury Study Center
Secretary James Peake	U.S. Department of Veterans Affairs

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# **| Appendices**



**Association of Gulf War Experiences and Exposures  
with Chronic Symptoms and Multisymptom Illness:**

**Results from Studies of Gulf War Veterans**



**Appendix A-1. CARC (Chemical Agent Resistant Coating) Paint: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with CARC Exposures During Deployment			
	Veterans Studied	Exposure Assessed	Health Outcome	Adjusted for other deployment exposures
				Crude (no adjustments)
Haley 1997	249 Seabees,	Near enough to smell	Haley Syndrome 1	RR (CI) = 0.9 (0.1-6.9)
	24th NMCB	CARC paint sprayed	Haley Syndrome 2	RR (CI) = 3.2 (1.3-8.0)*
			Haley Syndrome 3	RR (CI) = 1.6 (0.5-5.1)
Kang 2002	10,423 U.S. GWV	CARC paint	GW-unique neurological symptom complex	OR (CI) = 5.4 (4.2-6.9)* †
Spencer 2001	1,119 GWV from OR, WA	Painted with CARC	CMI	OR (CI) = 1.9 (0.7-5.0)
			GWUI (study-defined)	OR (CI) = 2.1 (0.9-5.0)

CARC = Chemical Agent Resistant Coating; GW = Gulf War; GWV = Gulf War veterans; CMI = chronic multisymptom illness;<sup>464</sup> GWUI = Gulf War unexplained illness; OR = odds ratio; RR = risk ratio; CI = 95% confidence interval; p = p value; \* statistically significant; † calculated from reported data



**Appendix A-2. Chemical Agent-related Variables: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Possible Chemical Agent Exposures	
				Crude (no adjustments)	Adjusted for military, demographic variables Adjusted for other deployment exposures
Blanchard 2006	1,035 GWV veterans	In DOD-modeled Khamisiyah exposure area	CMI-any CMI-severe	OR (CI) = 1.6 (1.0-2.6) sign *	
Boyd 2003	978 GWV in GW Registry	Days gas mask worn at least 4 hours Days gas mask worn at all Chemical/biological warfare	High symptom vs. low symptom groups	p < 0.01* p = 0.12 p < 0.01*	
Goss Gilroy 1998	3,113 Canadian GWV	Chemical warfare agents	Cognitive symptoms Chronic fatigue symptoms Fibromyalgia symptoms	ns ns ns	
Gray 2002	3,831 U.S. Navy Seabees	Use of gas masks	GWV (study-defined)	OR (CI) = 2.6 (2.1-3.1)*	OR(CI) = 1.4 (1.1-1.8)*
Haley 1997	249 Seabees, 24th NMCB	Experienced likely chemical attack	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	RR (CI) = 1.3 (0.4-3.9) RR (CI) = 7.8 (2.4-25.9)* RR (CI) = 2.3 (1.0-5.3)	*p < 0.001*
		In sector 7 on 20 Jan 1990	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	undefined RR (CI) = 4.3 (1.9-10.0)* undefined	*p = 0.004*
		Saw explosion suspected chemical land mine	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	RR (CI) = 2.2 (0.3-15.2) RR (CI) = 5.6 (2.3-13.6)* RR (CI) = 1.1 (0.2-7.6)	ns
		Found enemy's chemical or biological weapons	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	RR (CI) = 6.0 (1.6-23.1)* RR (CI) = 3.2 (0.9-11.4) RR (CI) = 1.4 (0.2-9.4)	

**Appendix A-2. Chemical Agent-related Variables: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with Possible Chemical Agent Exposures					
	Veterans Studied	Exposure Assessed	Health Outcome	Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Iowa 1997	1,896 Iowa GWV	Chemical warfare agents	Cognitive symptoms Fibromyalgia symptoms	Prev diff = 6.8, p < 0.001* Prev diff = 8.1, p < 0.001*		
Ishoy 1999	686 Danish GWV	Nerve gas Other chemical warfare Mustard gas	Gastrointestinal symptoms	ns trend test, p < 0.05* ns		ns
Kang 2002	10,423 U.S. GWV	Nerve gas	GW-unique neurological symptom complex	OR(CI) = 15.1 (11.6-19.7)†		
Kelsall 2004		Chemical weapons area	Number of symptoms		ARM (CI) = 1.3 (1.2-1.5)*	
McCaughey 2001	2,918 U.S. GWV	Within 50 km. of Khamisiyah (DOD determined) Participated in or within sight of Khamisiyah	24 symptoms		ns 6 of 24 symptoms sign., ORs = 1.6-2.0	
Nisenbaum 2000	1,002 U.S. Air Force GWV	Thought biological or chemical weapons used	CMI-Mild/moderate CMI-Severe	OR (CI) = 2.5 (1.8-3.5)* OR (CI) = 6.1 (3.4-10.7)*		OR (CI) = 2.3 (1.5-3.3)* OR (CI) = 3.5 (1.7-6.9)*
Page 2006	5,234 U.S. Army GWV	In DOD-modeled Khamisiyah exposure area	mild-moderate symptoms severe symptoms		ns 2 of 47 symptoms sign.	
Proctor 1998	252 U.S. GWV	Chemical, biological warfare agents	Dermatological symptoms Musculoskeletal symptoms Neurological symptoms Neuropsych symptoms Psychiatric symptoms		ns sign corr, p = 0.001* sign corr, p = 0.013* sign corr, p = 0.009* sign corr, p = 0.001*	p = 0.015* sign corr* sign corr* sign corr*

**Appendix A-2. Chemical Agent-related Variables: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Possible Chemical Agent Exposures		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Reid 2001	3,531 U.K. GWV	Chemical nerve gas attack	CFS	OR (CI) = 1.7 (0.9-3.4)	OR (CI) = 1.5 (0.7-3.1)	
			MCS	OR (CI) = 3.8 (1.9-7.6)*	OR (CI) = 3.2 (1.5-6.7)*	
		Mustard gas	CFS	OR (CI) = 2.5 (0.9-7.1)	OR (CI) = 1.4 (0.4-4.6)	
			MCS	OR (CI) = 4.2 (1.4-12.0)*	OR (CI) = 2.5 (0.8-7.9)	
Schumm 2005	650 Ohio GWV reservists	Located in areas potentially affected by Khamisiyah	CMI	sign.*		
			GW (Kansas definition)	ns		
Spencer 2001	1,119 GWV from OR, WA	Inadequate protection during chemical/SCUD alarms	CMI	OR (CI) = 3.2 (1.3-7.8)*		
			GWUJ (study-defined)	OR (CI) = 2.4 (1.0-5.6)*		
		Worked around chemical warfare agents	CMI	OR (CI) = 1.9 (0.7-5.3)		
Steele 2000	1,548 Kansas GWV	Notified by DOD of possible Khamisiyah exposure	GW (Kansas definition)	OR (CI) = 1.5 (1.1-1.9)*	OR (CI) = 1.3 (0.9-1.7)	
Suadicani 1999	667 Danish GWV	Nerve gas	Neurological symptoms	ns		
			Other chemical warfare	ns		
		Mustard gas	trend test, p < 0.05*			ns
			SCUD explosion w/in 2 km	ns		
Unwin 1999	2,735 U.K. GWV	NBC suits Heard chemical alarms Chemical nerve gas attack	CMI		OR (CI) = 2.7 (2.3-3.3)*	
					OR (CI) = 2.2 (1.9-2.6)*	
					OR (CI) = 2.6 (1.9-3.5)*	
Wolfe 1998	2,119 U.S. Army GWV	Poison gas exposure	More than 5 symptoms reported		OR (CI) = 6.3 (1.2-33.3)*	

**Appendix A-2. Chemical Agent-related Variables: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Possible Chemical Agent Exposures		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Wolfe 2002	945 U.S. Army GWV	Placed on formal alert for chemical attack 3-10 times	CMI-Mild-mod. CMI-Severe CMI - Mild, mod, severe	OR (CI) = 1.2 (0.8-1.8) OR (CI) = 1.1 (0.7-1.7)		ns
		more than 10 times	CMI-Mild-mod. CMI-Severe CMI - Mild, mod, severe	OR (CI) = 1.9 (1.4-2.7)* OR (CI) = 2.7 (2.0-3.7)*		ns

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; ARM = adjusted ratio of means; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † calculated from reported data; ‡ limited number of selected exposures in model

**Appendix A-3. Contaminated and Local Food and Water: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Local or Contaminated Food/Water		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Boyd 2003	978 GWV in GW Registry	Ate/drank local food or water	High symptom vs. low symptom groups		p < 0.01*	
Gray 2002	3,831 U.S. Navy Seabees	Drank contaminated water Food poisoning in unit Water from desert bag Got food poisoning Bathed in local pond/river/Gulf Ate local food	GWV (study-defined)	OR (CI) = 3.8 (3.1-4.7)* OR (CI) = 2.1 (1.8-2.6)* OR (CI) = 2.0 (1.7-2.4)* OR (CI) = 2.5 (1.9-3.3)* OR (CI) = 1.8 (1.5-2.1)* OR (CI) = 1.3 (1.1-1.6)*		OR (CI) = 1.7 (1.3-2.2)* OR (CI) = 1.4 (1.1-1.8)* OR (CI) = 1.4 (1.1-1.7)* ns ns ns
Haley 1997	249 Seabees, 24th NMCB	Drinking water had petroleum taste	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	RR (CI) = 2.6 (0.9-7.7) RR (CI) = 2.8 (1.3-6.3)* RR (CI) = 2.6 (1.2-5.6)*		
Ishoy 1999	686 Danish GWV	Ingested contaminated food Ingested local food Bathed in or drank contaminated water Brushed teeth with contaminated water Bathed/swam in local lake, pond, Gulf	Gastrointestinal symptoms	trend test, p < 0.001* trend test, p < 0.01* trend test, p < 0.001* trend test, p < 0.001* ns		ns ns ns ns
Kang 2002	10,423 U.S. GWV	Ate food contaminated with smoke, oil Bathed in or drank contaminated water	GW-unique neurological symptom complex	OR (CI) = 10.6 (8.1-13.9)*† OR (CI) = 6.3 (4.9-8.1)*†		
Reid 2001	3,531 U.K. GWV	Ate local food	CFS MCS	OR (CI) = 0.8 (0.5-1.4) OR (CI) = 0.8 (0.4-1.6)		OR (CI) = 0.9 (0.5-1.6) OR (CI) = 0.9 (0.5-1.7)

**Appendix A-3. Contaminated and Local Food and Water: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Local or Contaminated Food/Water		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Spencer 2001	1,119 GWV from OR, WA	Drank local alcohol	CMI GWUJ (study-defined)	OR (CI) = 0.5 (0.2-1.6) OR (CI) = 0.8 (0.3-1.8)		
Suadicani 1999	667 Danish GWV	Ingested contaminated food (fumes, oil, chemicals) Bathed in/drank contam water (fumes, oil, chemicals) Ingested local food Brushed teeth using contaminated water	Neurological symptoms	trend test, p < 0.001* trend test, p < 0.001* trend test, p < 0.001* trend test, p < 0.001*	ns OR (CI) = 2.9 (1.8-4.6)* ns ns	
Unwin 1999	2,735 U.K. GWV	Ate local food	CMI			OR (CI) = 1.1 (0.9-1.3)

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † calculated from reported data

**Appendix A-4. Depleted Uranium: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with Depleted Uranium Exposure				
	Veterans Studied	Exposure Assessed	Health Outcome	Adjusted only for military, demographic variables Adjusted for other deployment exposures	
Haley 1997	249 Seabees, 24th NMCB	Any exposure to DU	Haley Syndrome 1	Crude (no adjustments)	RR (CI) = 0.7 (0.1-5.2)
			Haley Syndrome 2		RR (CI) = 2.4 (0.9-6.0)
			Haley Syndrome 3		RR (CI) = 0.8 (0.2-3.1)
	Walked past DU munitions	Haley Syndrome 1			RR (CI) = 0.8 (0.1-5.6)
			Haley Syndrome 2		RR (CI) = 2.6 (1.0-6.5)
			Haley Syndrome 3		RR (CI) = 0.8 (0.2-3.3)
	Stood 6 feet from DU munitions	Haley Syndrome 1			RR (CI) = 0.9 (0.1-6.9)
			Haley Syndrome 2		RR (CI) = 1.7 (0.6-5.4)
			Haley Syndrome 3		RR (CI) = 1.0 (0.3-4.1)
Ishoy 1999	686 Danish GWV	Inside destroyed Iraqi tanks	Gastrointestinal symptoms	trend test, p < 0.01*	ns
Kang 2002	10,423 U.S. GWV	DU exposure	GW-unique neurological symptom complex	OR (CI) = 5.7 (4.4-7.6) <sup>†</sup>	
Kelsall 2004	1,456 Australian GWV	DU	Number of symptoms	ARM (CI) = 1.0 (0.9-1.1)	
Spencer 2001	1,119 GWV from OR, WA	DU exposure	CMI	OR (CI) = 4.5 (1.7-11.4)*	
			GWUJ (study-defined)	OR (CI) = 3.7 (1.5-8.8)*	
Suadicani 1999	667 Danish GWV	Inside destroyed Iraqi tank DU exposure	Neurological symptoms	trend test, p < 0.01* trend test, p < 0.001*	OR (CI) = 2.3 (0.9-5.7)

DU = depleted uranium; GW = Gulf War; GWV = Gulf War veterans; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> OR = odds ratio; RR = risk ratio; ARM = adjusted ratio of means; CI = 95% confidence interval; p = p value; ns = not significant; \* statistically significant; † calculated from reported data



**Appendix A-5. Fuel Exposures: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Fuel Exposures During Deployment		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Gray 2002	3,831 U.S. Navy Seabees	Jet fuel burned in tent heaters	GWV (study-defined)	OR (CI) = 2.1 (1.8-2.5)*		ns
		Oil sprayed on ground		OR (CI) = 2.2 (1.9-2.6)*		ns
Haley 1997	249 Seabees, 24th NMCB	Burned jet fuel in stove or lantern in tent	Haley Syndrome 1	RR (CI) = 0.7 (0.2-2.2)		
			Haley Syndrome 2	RR (CI) = 0.9 (0.4-2.1)		
			Haley Syndrome 3	RR (CI) = 0.7 (0.3-1.7)		
Iowa 1997	1,896 Iowa GWV	Worked on sand sprayed with petroleum	Haley Syndrome 1	RR (CI) = 1.8 (0.6-5.6)		
			Haley Syndrome 2	RR (CI) = 2.1 (0.9-4.9)		
			Haley Syndrome 3	RR (CI) = 0.9 (0.4-2.0)		
Ishoy 1999	686 Danish GWV	Solvents/petrochemicals	Cognitive symptoms	Prev diff = 8.6, p < 0.001*		
		Diesel, kerosene, other fumes	Fibromyalgia symptoms	Prev diff = 6.7, p < 0.001*		
Proctor 1998	252 U.S. GWV	Evaporated fuel on ground to suppress dust	Gastrointestinal symptoms	ns		ns
		Skin contact with fuel		trend test, p < 0.01*		ns
		Vehicle exhaust	Cardiac symptoms	trend test, p < 0.001*	sign corr, p = 0.026*	ns
		Smoke from tent heaters	Neuro symptoms	sign corr, p = 0.024*	sign corr, p = 0.011*	ns
			Cardiac symptoms	sign corr, p < 0.001*	sign corr, p = 0.001*	p = 0.011*
			Neuro symptoms	sign corr, p = 0.001*	sign corr, p = 0.001*	ns
			Pulmonary symptoms	sign corr, p < 0.001*	sign corr, p < 0.001*	p = 0.007*

**Appendix A-5. Fuel Exposures: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Fuel Exposures During Deployment		
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures	
Reid 2001	3,531 U.K. GWV	Exhaust from heaters	CFS	OR (CI) = 1.3 (0.7-2.3)	OR (CI) = 1.4 (0.7-2.6)	
			MCS	OR (CI) = 2.0 (0.9-4.8)	OR (CI) = 2.8 (1.1-7.5)*	
		Diesel on skin	CFS	OR (CI) = 2.1 (1.2-3.6)*	OR (CI) = 1.8 (1.0-3.5)*	
			MCS	OR (CI) = 1.7 (0.9-3.2)	OR (CI) = 1.7 (0.8-3.6)	
Spencer 2001	1,119 GWV from OR, WA	Kerosene tent heater	CMI	OR (CI) = 1.9 (0.9-4.0)		
			GWUJ (study-defined)	OR (CI) = 2.1 (1.1-4.0)*		
		Diesel tent heater	CMI	OR (CI) = 1.8 (0.9-3.4)		
			GWUJ (study-defined)	OR (CI) = 1.6 (0.9-2.9)		
		Potbelly tent heater	CMI	OR (CI) = 2.3 (1.1-4.7)*		
			GWUJ (study-defined)	OR (CI) = 2.0 (1.1-3.7)*		
		Cleaned tent heater	CMI	OR (CI) = 2.4 (1.3-4.5)*		
			GWUJ (study-defined)	OR (CI) = 2.2 (1.2-3.8)*		
		Direct contact with diesel/petroleum fuel				
			1-5 times	CMI	OR (CI) = 1.5 (0.8-3.0)	
6+ times			OR (CI) = 3.8 (2.0-7.1)*			
1-5 times						
	6+ times			OR (CI) = 1.5 (0.9-2.8)		
				OR (CI) = 3.6 (2.0-6.3)*		
Suadicani 1999	667 Danish GWV	Diesel, kerosene or other fumes Evaporated diesel oil used on ground Skin contact with diesel, other petrochemical fuel	Neurological symptoms	trend test, p < 0.01*	ns	
				trend test, p < 0.01*	ns	
				trend test, p < 0.001*	ns	

**Appendix A-5. Fuel Exposures: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Fuel Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Unwin 1999	2,735 U.K. GWV	Diesel or petrochemical fumes	CMI	OR (CI) = 1.9 (1.4-2.6)*	OR (CI) = 2.1 (1.7-2.5)*
		Exhaust from heaters or generators	CMI	OR (CI) = 2.7 (1.9-3.9)*	OR (CI) = 1.9 (1.6-2.2)*
		Diesel or petrochemical on skin	CMI		OR (CI) = 1.8 (1.5-2.1)*
Wolfe 2002	945 U.S. Army GWV	Diesel fuel odor	CMI-Mild-moderate CMI-Severe CMI-Mild,mod,severe	OR (CI) = 1.1 (0.8-1.5) OR (CI) = 1.6 (1.1-2.2)*	ns
		Heater in tent	CMI-Mild-moderate CMI-Severe CMI-Mild,mod,severe	OR (CI) = 1.4 (1.0-1.8)*	

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; GWUI = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † calculated from reported data



**Appendix A-6. Oil Well Fires: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Oil Well Fire Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Cherry 2001	7,791 U.K. GWV	Days exposed to oil fire smoke	Overall symptom severity		sign. corr, $p < 0.001^*$
Gray 1999	527 U.S. Navy Seabees	Oil fire smoke	23 individual symptoms	15 of 23 symptoms sign; ORs = 2.1-5.7	
Gray 2002	3,831 U.S. Navy Seabees	Oil fire smoke Oil fire smoke (modeled: yes/no)	GW (study-defined)	OR (CI) = 2.2 (1.9-2.7)* OR (CI) = 1.5 (1.3-1.8)*	ns OR (CI) = 0.4 (0.3-0.7)*
Haley 1997	249 Seabees, 24th NMCB	Lived/worked in air filled with oil well smoke	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	RR (CI) = 0.9 (0.1-6.3) RR (CI) = 1.6 (0.2-11.0) RR (CI) = 1.6 (0.2-11.5)	
		Scaled smoke exposure	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	trend test, $p = 0.854$ trend test, $p = 0.021^*$ trend test, $p = 0.072$	
Iowa 1997	1,896 Iowa GWV	Smoke/combustion products	Cognitive symptoms Fibromyalgia symptoms	Prev diff = 5.1, $p < 0.001^*$ Prev diff = 5.7, $p < 0.001^*$	
Ishoy 1999	686 Danish GWV	Fumes from burning oil wells	Gastrointestinal symptoms	ns	
Kang 2002	10,423 U.S. GWV	Food contaminated with oil, smoke	GW-unique neurological symptom complex	OR (CI) = 10.6 (8.1-13.9)* <sup>†</sup>	
Nisenbaum 2000	1002 U.S. Air Force GWV	Direct contact with smoke/ crude oil from oil well fires	CMI - Mild-moderate CMI - Severe	OR (CI) = 1.3 (1.0-1.7) OR (CI) = 2.0 (1.2-3.5)*	OR (CI) = 1.3 (0.9-1.8) OR (CI) = 1.6 (0.8-3.4)

**Appendix A-6. Oil Well Fires: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Oil Well Fire Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Proctor 1998	252 U.S. GWV	Oil fire smoke	Cardiac symptoms Neuro symptoms Pulmonary symptoms	ns ns ns	
Reid 2001	3,531 U.K. GWV	Oil fire smoke	CFS MCS	OR (CI) = 0.9 (0.5-1.4) OR (CI) = 4.3 (1.6-12.2)*	OR (CI) = 1.1 (0.6-2.0) OR (CI) = 4.6 (1.6-13.3)*
Spencer 2001	1,119 GWV from OR, WA	Eye irritation from burning oil wells 1-5 days 6+ days	GWUJ (study-defined)	OR (CI) = 1.5 (0.9-2.8) OR (CI) = 3.6 (2.0-6.3)*	
Unwin 1999	2,735 U.K. GWV	Oil fire smoke	CMI	OR (CI) = 2.6 (1.3-5.2)* OR (CI) = 4.5 (2.1-9.6)*	OR (CI) = 1.8 (1.5-2.1)*
Wolfe 2002	945 U.S. Army GWV	Oil fire smoke odor	CMI - Mild-moderate CMI - Severe CMI - Mild, mod, severe	OR (CI) = 2.1 (1.5-2.9)* OR (CI) = 2.9 (2.1-4.1)*	OR (CI) = 1.6 (1.2-2.1)*

GW = Gulf War; GWV = Gulf War veterans; GWUJ = Gulf War illness; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † calculated from reported data

**Appendix A-7. Pesticides and Insect Repellants: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with Pesticide Exposures During Deployment			
	Veterans Studied	Exposure Assessed	Health Outcome	Adjusted for other deployment exposures
Cherry 2001	7,971 U.K. GWV	Days handling pesticide	Overall symptom severity	sign. corr, p < 0.001*
			Peripheral symptoms	sign. corr, p < 0.002*
			Neurological symptoms	sign. corr, p < 0.003*
			Peripheral neuropathy	OR = 1.3, p < 0.001*
		Widespread pain		Ns
		Days using insect repellent	Overall symptom severity	sign. corr, p < 0.005*
			Peripheral symptoms	sign. corr, p < 0.006*
			Neurological symptoms	sign. corr, p < 0.007*
			Peripheral neuropathy	sign. corr, p < 0.008*
		Widespread pain		OR = 1.2, p < 0.001*
Gray 2002	3,831 U.S. Navy Seabees	Pesticides Wore flea collar Wore treated uniform	GW (study-defined)	OR (CI) = 3.5 (2.5-4.9)*
				OR (CI) = 3.8 (2.7-5.2)*
				OR (CI) = 3.4 (2.7-4.2)*
Haley 1997	249 Seabees, 24th NMCB	Wore flea collar	Haley Syndrome 1	RR (CI) = 8.7 (3.0-24.7)*
			Haley Syndrome 2	RR (CI) = 2.9 (1.1-7.6)*
			Haley Syndrome 3	RR (CI) = 2.7 (1.0-7.2)
	DEET scale, govt. repellent users	Haley Syndrome 1	trend test, p = 0.14	
		Haley Syndrome 2	trend test, p = 0.4	
		Haley Syndrome 3	trend test, p = 0.004*	
	DEET scale, Offl users	Haley Syndrome 1	trend test, p = 0.06	
		Haley Syndrome 2	trend test, p = 0.19	
		Haley Syndrome 3	trend test, p = 0.06	
DEET scale, Skin-so-soft users	Haley Syndrome 1	trend test, p = 0.01*		
	Haley Syndrome 2	trend test, p = 0.40		
	Haley Syndrome 3	trend test, p = 0.19		

**Appendix A-7. Pesticides and Insect Repellants: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Pesticide Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Haley (cont.)	Wore treated uniform	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	Haley Syndrome 1	RR (CI) = 6.0 (1.6-23.1)*	
			Haley Syndrome 2	undefined	
			Haley Syndrome 3	RR (CI) = 1.4 (0.2-9.4)	
	Sprayed pesticides	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	Haley Syndrome 1	RR (CI) = 3.0 (0.9-10.3)	
			Haley Syndrome 2	RR (CI) = 2.8 (1.1-7.0)*	
			Haley Syndrome 3	RR (CI) = 2.0 (0.7-5.4)	
	Residence sprayed with pesticides	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	Haley Syndrome 1	RR (CI) = 7.3 (0.9-55.4)	
			Haley Syndrome 2	RR (CI) = 0.5 (0.2-1.1)	
			Haley Syndrome 3	RR (CI) = 1.0 (0.4-2.2)	
Personally sprayed residence with pesticides	Haley Syndrome 1 Haley Syndrome 2 Haley Syndrome 3	Haley Syndrome 1	RR (CI) = 2.5 (0.8-7.6)		
		Haley Syndrome 2	RR (CI) = 0.6 (0.2-1.5)		
		Haley Syndrome 3	RR (CI) = 1.2 (0.5-2.8)		
Iowa 1997	1,896 Iowa GWV	Pesticides	Cognitive symptoms Fibromyalgia symptoms	Prev diff = 14.2, p < 0.001* Prev diff = 11.0, p < 0.001*	
Ishoy 1999	686 Danish GWV	Lotions, sprays against fleas Insecticides against cockroaches	Gastrointestinal symptoms	trend test, p < 0.001* trend test, p < 0.001*	ns OR(CI) = 2.3 (1.2-4.4)*
Kelsall 2004	1,456 Australian GWV	Pesticides Insect repellents	Number of symptoms		ARM (CI) = 1.3 (1.2-1.4)* ARM (CI) = 1.2 (1.1-1.3)*
Kelsall 2005	1,424 Australian GWV	Pesticides Insect repellents	Number of neurological symptoms		ARM (CI) = 1.7 (1.4-2.0)* ARM (CI) = 1.3 (1.1-1.5)*

**Appendix A-7. Pesticides and Insect Repellants: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with Pesticide Exposures During Deployment			
	Veterans Studied	Exposure Assessed	Health Outcome	Crude (no adjustments) Adjusted only for military, demographic variables Adjusted for other deployment exposures
Nisenbaum 2000	1,002 U.S. Air Force GWV	Used insect repellent on regular basis	CMI- Mild to moderate	OR (CI) = 2.0 (1.5-2.6)* OR (CI) = 1.7 (1.2-2.3)*
			CMI- Severe	OR (CI) = 3.4 (2.0-6.0)* OR (CI) = 2.4 (1.3-4.5)*
Proctor 1998	252 U.S. GWV	Pesticides	Dermatological symptoms	ns
			Gastrointestinal symptoms	ns
			Musculoskeletal symptoms	sign. corr, p = 0.001*
			Neurological symptoms	sign. corr, p = 0.007*
			Neuropsych symptoms	ns
			Psychiatric symptoms	ns
				p = 0.011*
Reid 2001	3,531 U.K. GWV	Personal pesticides	CFS	OR (CI) = 1.2 (0.7-2.1) OR (CI) = 1.0 (0.6-1.8)
			MCS	OR (CI) = 10.6 (2.6-43.9)* OR (CI) = 10.9 (2.6-45.8)*
Schumm 2005	650 Ohio GWV reservists	Pesticides on clothing	CFS	OR (CI) = 1.4 (0.9-2.2) OR (CI) = 1.2 (0.7-3.1)
			MCS	OR (CI) = 11.3 (4.8-27.0)* OR (CI) = 12.3 (5.1-30.0)*
Schumm 2005	650 Ohio GWV reservists	Frequency of pesticides sprayed in billeting area	CMI	sign.*
			GWJ (Kansas definition)	ns
Spencer 2001	1,119 GWV from OR, WA	Frequency of personal pesticide use	CMI	sign.*
			GWJ (Kansas definition)	sign.*
Spencer 2001	1,119 GWV from OR, WA	DEET	CMI	OR (CI) = 3.3 (1.8-6.3)*
			GWUJ (study-defined)	OR (CI) = 2.7 (1.5-4.7)*
			CMI	OR (CI) = 3.6 (1.8-6.9)*
			GWUJ (study-defined)	OR (CI) = 3.1 (1.7-5.7)*
			CMI	OR (CI) = 2.3 (0.7-7.6)
Spencer 2001	1,119 GWV from OR, WA	Burned surplus insecticide	CMI	OR (CI) = 2.9 (1.0-8.3)
			GWUJ (study-defined)	OR (CI) = 2.9 (1.0-8.3)
Spencer 2001	1,119 GWV from OR, WA	Sprayed pesticide	CMI	OR (CI) = 1.5 (0.8-2.8)
			GWUJ (study-defined)	OR (CI) = 1.5 (0.8-2.8)

**Appendix A-7. Pesticides and Insect Repellants: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Pesticide Exposures During Deployment		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Suadicani 1999	667 Danish GWV	Lotions or spray against e.g. fleas Insecticides against cockroaches	Neurological symptoms	trend test, $p < 0.001^*$  trend test, $p < 0.001^*$		ns  ns
Unwin 1999	2,735 U.K. GWV	Personal pesticides Pesticides on clothing or bedding	CMI		OR (CI) = 2.2 (1.9-2.6)* OR (CI) = 1.9 (1.6-2.2)*	
Wolfe 2002	945 U.S. Army GWV	Insecticide odor	CMI - Mild-moderate CMI - Severe CMI - Mild, mod, severe	OR (CI) = 1.4 (1.0-2.1) OR (CI) = 3.1 (2.2-4.3)*		ns

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval;  $p$  =  $p$  value; sign. = statistically significant; ns = not significant; \* statistically significant; † limited number of selected exposures in model

**Appendix A-8. Psychological Stressors: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Psychological Stressors During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Australia DVA 2003	1,456 Australian GWV	MSE score = 0-4 MSE score = 5-8 MSE score = 9-12 MSE score ≥ 12 Dose response	Total number of symptoms	ARM = 1.0 ARM (CI) = 1.3 (1.2-1.5)* ARM (CI) = 1.8 (1.6-2.0)* ARM (CI) = 2.5 (2.3-2.8)* p < 0.001*	
Blanchard 2006	1,035 U.S. GWV	Mean combat exposure score	CMI	p < 0.001*	
Boyd 2003	978 GWV in GW Registry	Traumatic event Battle experiences	High symptom vs. low symptom groups	p = 0.03* p = 0.15	
Cherry 2001	7,971 U.K. GWV	Combat	Overall symptom severity Peripheral symptoms Neurological symptoms Respiratory symptoms Gastrointestinal symptoms		ns ns ns ns ns
Ford 2001	237 cases, 113 controls	Combat exposure score	Unexplained illness case, confirmed by physician exam	OR (CI) = 1.0 (1.0-1.1)*	
Goss Gilroy 1998	3,112 Canadian GWV	Psychological stressors	Cognitive symptoms Chronic fatigue symptoms Fibromyalgia symptoms	POR (CI) = 2.1 (1.7-2.5)* POR (CI) = 2.2 (1.5-3.1)* POR (CI) = 1.9 (1.5-2.4)*	
Gray 2002	3,831 U.S. Navy Seabees	Seeing someone killed Seeing dead bodies Direct combat	GWV (study-defined)	OR (CI) = 3.1 (2.4-4.1)* OR (CI) = 2.6 (2.2-3.1)* OR (CI) = 2.6 (2.1-3.2)*	OR(CI) = 1.6 (1.1-2.2)* ns ns

**Appendix A-8. Psychological Stressors: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Psychological Stressors During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Haley 1997	249 Seabees, 24th NMCB	Combat stress index	Haley Syndrome 1	trend test, p=0.024*	
			Haley Syndrome 2	trend test, p=0.260	
			Haley Syndrome 3	trend test, p=0.892	
		Iraqi artillery shell exploded w/in 1 km	Haley Syndrome 1	RR (CI) = 2.0 (0.5-8.4)	ns
			Haley Syndrome 2	RR (CI) = 4.9 (2.2-10.9)*	
			Haley Syndrome 3	RR (CI) = 0.5 (0.1-3.3)	
		Saw explosion, suspected chem land mine	Haley Syndrome 1	RR (CI) = 2.2 (0.3-15.2)	ns
			Haley Syndrome 2	RR (CI) = 5.6 (2.3-13.6)*	
			Haley Syndrome 3	RR (CI) = 1.1 (0.2-7.6)	
		Scud missile exploded w/in 5 km	Haley Syndrome 1	RR (CI) = 1.0 (0.2-4.5)	
			Haley Syndrome 2	RR (CI) = 4.1 (0.6-29.4)	
			Haley Syndrome 3	RR (CI) = 2.0 (0.5-8.4)	
Iowa 1997	1,896 Iowa GWV	Psychological stressors	Fibromyalgia symptoms	Prev diff = 3.4, p =0.003*	
Ishoy 1999	686 Danish GWV	SCUD explosion within 2 km	Gastrointestinal symptoms	ns	
Kang 2002	10,423 U.S. GWV	Sexual assault	GW-unique neurological symptom complex	OR (CI) = 8.3 (3.9-17.9)*†	
		Sexual harassment		OR (CI) = 6.7 (4.7-9.6)*‡	
Nisenbaum 2000	1,002 U.S. Air Force GWV	Came under attack	CMI - Mild-moderate	OR (CI) = 1.1 (0.9-1.5)	OR (CI) = 0.7 (0.5-1.0)
			CMI - Severe	OR (CI) = 2.4 (1.3-4.3)*	OR (CI) = 1.2 (0.5-3.1)
		Saw casualties	CMI - Mild-moderate	OR (CI) = 1.3 (0.8-2.0)	OR (CI) = 1.0 (0.6-1.7)
			CMI - Severe	OR (CI) = 2.2 (1.0-4.6)	OR (CI) = 1.1 (0.4-2.8)

**Appendix A-8. Psychological Stressors: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Psychological Stressors During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Nisenbaum (cont.)		Family member had significant health event	CMI - Mild-moderate CMI - Severe	OR (CI) = 1.7 (1.0-2.8)	OR (CI) = 1.6 (0.9-2.9)
				OR (CI) = 2.8 (1.2-6.5)*	OR (CI) = 2.2 (0.8-5.7)
		Change in marital status	CMI - Mild-moderate CMI - Severe	OR (CI) = 1.1 (0.7-1.6)	OR (CI) = 0.9 (0.6-1.5)
				OR (CI) = 1.7 (0.8-3.7)	OR (CI) = 1.3 (0.6-3.2)
Reid 2001	3,531 U.K. GWV	Dismembered bodies Maimed soldiers Witnessed death SCUD explosion Small arms fire Artillery close by	CFS	OR (CI) = 1.9 (1.1-3.4)*	OR (CI) = 1.6 (0.8-3.0)
				OR (CI) = 2.1 (1.3-3.5)*	OR (CI) = 2.0 (1.2-3.6)*
				OR (CI) = 2.3 (1.4-3.6)*	OR (CI) = 2.2 (1.3-3.8)*
				OR (CI) = 2.2 (1.4-3.6)*	OR (CI) = 2.6 (1.5-4.6)*
				OR (CI) = 1.3 (0.8-2.1)	OR (CI) = 1.3 (0.8-2.3)
				OR (CI) = 1.8 (1.2-2.9)*	OR (CI) = 2.4 (1.4-4.1)*
				OR (CI) = 4.5 (1.8-11.4)*	OR (CI) = 4.2 (1.6-11.0)*
				OR (CI) = 3.8 (1.9-7.6)*	OR (CI) = 3.2 (1.6-6.5)*
Spencer 2001	1,119 GWV from OR, WA	CES subscore (continuous) CES: low-mod stress mod-heavy stress Heard SCUD alarms 1-5 times 6-30 times 31+ times	CMI GWUI (study-defined) GWUI (study-defined) CMI	OR (CI) = 1.1 (1.0-1.2)*	OR <sup>±</sup> (CI) = 1.3 (0.7-2.5)
				OR (CI) = 1.1 (1.0-1.1)*	OR <sup>±</sup> (CI) = 2.4 (0.8-7.6)

**Appendix A-8. Psychological Stressors: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Psychological Stressors During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Spencer (cont)		Heard SCUD alarms 1-5 times 6-30 times 31 + times	GWUJ (study defined)	OR (CI) = 1.3 (0.6-2.8)	
				OR (CI) = 1.3 (0.7-2.4)	
				OR (CI) = 1.4 (0.8-2.5)	
		Saw SCUD detonate 1-5 times 6-30 times 31 + times	CMI	OR (CI) = 1.1 (0.6-2.1)	
				OR (CI) = 1.9 (0.9-3.9)	
				OR (CI) = 2.3 (0.8-6.0)	
		Saw SCUD detonate 1-5 times 6-30 times 31 + times	GWUJ (study-defined)	OR (CI) = 1.0 (0.6-1.8)	
				OR (CI) = 1.9 (1.0-3.6)	
				OR (CI) = 1.6 (0.7 - 4.1)	
Suadicani 1999	667 Danish GWV	Witnessed combat	Neurological symptoms	trend test, p < 0.01*	
		Saw assaults on civilians		trend test, p < 0.01*	
		Saw wounded/ dead		trend test, p < 0.05*	
		Threatened with arms		trend test, p < 0.01*	
		Saw colleagues threatened or shot at		trend test, p < 0.001*	ns
		Was shot at Pointed gun/shot other		trend test, p < 0.01* trend test, p < 0.001*	
Unwin 1999	2,735 U.K. GWV	Dismembered bodies	CMI	OR (CI) = 2.0 (1.7-2.3)*	
		Maimed soldiers		OR (CI) = 1.7 (1.5-2.0)*	
		Combat injury		OR (CI) = 2.9 (2.1-4.2)*	
		Witness death		OR (CI) = 1.6 (1.4-1.9)*	
		SCUD exploded w/in 1 mile		OR (CI) = 1.6 (1.4-1.9)*	
		Under small arms fire		OR (CI) = 1.5 (1.3-1.7)*	

**Appendix A-8. Psychological Stressors: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Psychological Stressors During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Wolfe 1998	2,119 GWV	High combat exposure score	High symptom endorsement	OR (CI) = 3.2 (2.3-4.4)*	ns
Wolfe 2002	945 U.S. Army GWV	Score > 6 on expanded combat exposure scale	CMI - Mild-moderate	OR (CI) = 1.5 (1.1-2.1)*	
			CMI - Severe	OR (CI) = 1.5 (1.1-2.1)*	
			CMI - Mild, mod, severe		ns

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; MSE = Military Service Experience score; CES = Keane Combat Exposure Scale; DVA = Department of Veterans Affairs; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † limited number of selected exposures in model; ‡ calculated from reported data



**Appendix A-9. Pyridostigmine Bromide: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

		Association of Health Outcomes with Use of Pyridostigmine Bromide				
Study	Veterans Studied	Exposure Assessed	Health Outcome	Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Boyd 2003	978 GWV in GW Registry	Days taking any PB	High symptom vs. low symptom groups		p = 0.07	
		Days taking > 3 PB pills			p = 0.08	
Cherry 2001	7,971 U.K. GWV	Days used NAPs	Overall symptom severity			sign. corr; p < 0.001*
		Side effects from NAPs	Overall symptom severity			sign. corr; p < 0.001*
			Peripheral symptoms			sign. corr; p < 0.001*
			Gastrointestinal symptoms			sign. corr; p < 0.001*
			Peripheral neuropathy			OR = 1.4, p < 0.001*
Widespread pain			OR = 1.5, p < 0.001*			
Gray 2002	3,831 U.S. Navy Seabees	Took PB tablets	GWV (study defined)	OR (CI) = 3.0 (2.4-3.7)*		OR (CI) = 1.4 (1.1-1.9)*
Haley 1997	249 Seabees, 24th NMCB	Took PB tablets	Haley Syndrome 1	RR (CI) = 0.6 (0.1-4.3)		
			Haley Syndrome 2	undefined		
			Haley Syndrome 3	RR (CI) = 0.6 (0.1-2.1)		
		Scale of advanced side effects of PB	Haley Syndrome 1	trend test, p = 0.413		p* < 0.001*
			Haley Syndrome 2	trend test, p < 0.001*		p* < 0.001*
			Haley Syndrome 3	trend test, p < 0.001*		
		Scale of mild side effects of PB	Haley Syndrome 1	trend test, p= 0.670		ns
			Haley Syndrome 2	trend test, p= 0.003*		
			Haley Syndrome 3	trend test, p= 0.067		
Iowa 1997	1,896 Iowa GWV	PB tablets used	Cognitive symptoms Fibromyalgia symptoms	Prev diff = 12.0, p < 0.001* Prev diff = 16.4, p < 0.001*		

**Appendix A-9. Pyridostigmine Bromide: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Association of Health Outcomes with Use of Pyridostigmine Bromide			
	Veterans Studied	Exposure Assessed	Health Outcome	Crude (no adjustments) Adjusted only for military, demographic variables Adjusted for other deployment exposures
Kelsall 2004	1,456 Australian GWV	Any PB 1-80 PB tablets 81-180 PB tablets >180 PB tablets Dose-response	Number of symptoms	ARM (CI) = 1.4 (1.2-1.5)*
				ARM (CI) = 1.3 (1.1-1.5)*
				ARM (CI) = 1.4 (1.2-1.6)*
				ARM (CI) = 1.4 (1.2-1.7)*
				ARM (CI) = 1.1 (1.1-1.2)*
Kelsall 2005	1,424 Australian GWV	Any PB 1-80 PB tablets 81-180 PB tablets >180 PB tablets Dose-response	Number of neurological symptoms	ARM (CI) = 1.5 (1.2-1.8)*
				ARM (CI) = 1.4 (1.0-1.8)
				ARM (CI) = 1.6 (1.2-2.1)*
				ARM (CI) = 1.6 (1.2-2.1)*
				ARM (CI) = 1.2 (1.1-1.3)*
Nisenbaum 2000	1,002 U.S. Air Force GWV	Took PB to protect from nerve gas	CMI - Mild-moderate CMI - Severe	OR (CI) = 1.4 (1.1-1.8)*
				OR (CI) = 3.0 (1.7-5.2)*
Proctor 1998	252 U.S. GWV	Anti-nerve gas pills	Dermatological symptoms Gastrointestinal symptoms Musculoskeletal symptoms Neurological symptoms Neuro-psych symptoms Psychiatric symptoms	ns
				ns
Reid 2001	3,531 U.K. GWV	PB	CFS MCS	OR (CI) = 1.6 (0.8-3.2)
				OR (CI) = 1.5 (0.6-3.4) OR (CI) = 1.6 (0.6-4.0)
Schumm 2005	650 Ohio GWV reservists	Amount of PB taken	CMI GWI (Kansas definition)	sign.* sign.*

**Appendix A-9. Pyridostigmine Bromide: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Use of Pyridostigmine Bromide		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Spencer 2001	1,119 GWV from OR, WA	≤21 PB pills 22+ PB pills	CMI	OR (CI) = 3.2 (1.7-5.8)*		
				OR (CI) = 4.4 (2.1-9.4)*		
		≤21 PB pills 22+ PB pills	GWUJ (study-defined)	OR (CI) = 2.2 (1.3-3.8)*		OR <sup>±</sup> (CI) = 1.6 (0.9-2.9)
				OR (CI) = 3.8 (2.0-7.4)*		OR <sup>±</sup> (CI) = 2.2 (1.0-4.6)*
Unwin 1999	2,735 U.K. GWV	PB	CMI		OR (CI) = 2.6 (2.2-3.1)*	
Wolfe 2002	945 U.S. Army GWV	1-21 PB pills  >21 PB pills	CMI - Mild-moderate	OR (CI) = 1.9 (1.4-2.7)*		
			CMI - Severe	OR (CI) = 2.3 (1.6-3.3)*		OR (CI) = 1.4 (1.0-1.9)*
			CMI - Mild, mod, severe			
			CMI - Mild-moderate	OR (CI) = 2.5 (1.6-3.9)*		
			CMI - Severe	OR (CI) = 3.7 (2.4-5.6)*		OR (CI) = 2.1 (1.4-3.1)*
			CMI - Mild, mod, severe			

PB = pyridostigmine bromide; NAPs = nerve agent pretreatment sets; GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; GWUJ = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; RR = risk ratio; corr = correlation; prev diff = prevalence difference; CI = 95% confidence interval; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant; † limited number of selected exposures in model



**Appendix A-10. Sand-related Variables: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Sand Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Gray 1999	527 U.S. Navy Seabees	Sandstorms	23 symptoms	7 of 23 symptoms sign.; ORs 2.3-4.1	
Gray 2002	3,831 U.S. Navy Seabees	Sandstorms	GW (study-defined)	OR (CI) = 2.6 (2.1-3.3)*	OR (CI) = 1.7 (1.3-2.3)*
Ishoy 1999	686 Danish GWV	Sand or dust storm	Gastrointestinal symptoms	trend test, p < 0.01	ns
Nisenbaum 2000	1,002 U.S. Air Force GWV	Sandbagging/digging	CMI - Mild-moderate CMI - Severe	OR (CI) = 1.8 (1.4-2.4)* OR (CI) = 3.1 (1.7-5.5)*	OR (CI) = 1.4 (1.0-1.9) OR (CI) = 1.5 (0.7-2.9)
Suadcani 1999	667 Danish GWV	Walk/hike in sand Sand or dust storm	CMI - Mild-moderate CMI - Severe Neurological symptoms	OR (CI) = 1.6 (1.1-2.4)* OR (CI) = 6.4 (1.5-26.7)* trend test, p < 0.01*	OR (CI) = 1.1 (0.7-1.7) OR (CI) = 2.6 (0.6-11.7) ns

GW = Gulf War; GWV = Gulf War veterans; GWI = Gulf War illness; CMI = chronic multisymptom illness;<sup>464</sup> OR = odds ratio; CI = 95% confidence interval; sign. = statistically significant; ns = not significant; \* statistically significant



**Appendix A-11. Solvents: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Solvent Exposures During Deployment	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Iowa 1997	1,896 Iowa GWV	Solvents/petrochemicals	Cognitive symptoms Fibromyalgia symptoms	Prev diff = 6.6, p < 0.001* Prev diff = 4.6, p < 0.001*	
Ishoy 1999	686 Danish GWV	Other paint, solvents or kerosene products	Gastrointestinal symptoms	trend test, p < 0.05*	ns
Kelsall 2005	1,424 Australian GWV	Solvents	Neurological symptoms		ARM (CI) = 1.8 (1.3-2.5)*
Reid 2001	3,531 U.K. GWV	Other paints or solvents	CFS MCS	OR (CI) = 1.3 (0.8-2.2) OR (CI) = 2.2 (1.1-4.4)*	OR (CI) = 1.4 (0.8-2.5) OR (CI) = 2.4 (1.1-5.1)*
Spencer 2001	1,119 GWV from OR, WA	Vehicle repair Battery repair Generator repair Refrig service Electronic/ radio repair Degreasing machinery Cleaned hydraulic leaks Weapons repair	CMI GWUJ (study-defined) CMI GWUJ (study-defined) CMI GWUJ (study-defined) CMI GWUJ (study-defined) CMI GWUJ (study-defined) CMI GWUJ (study-defined) CMI GWUJ (study-defined)	OR (CI) = 3.3 (1.9-5.8)* OR (CI) = 3.0 (1.8-4.9)* OR (CI) = 2.7 (1.3-5.5)* OR (CI) = 2.1 (1.1-4.1)* OR (CI) = 2.1 (1.2-3.9)* OR (CI) = 1.6 (1.0-2.8) OR (CI) = 2.9 (0.9-9.2) OR (CI) = 2.1 (0.7-6.3) OR (CI) = 1.2 (0.6-2.2) OR (CI) = 1.3 (0.7-2.2) OR (CI) = 2.4 (1.3-4.2)* OR (CI) = 2.5 (1.5-4.1)* OR (CI) = 2.5 (1.3-4.6)* OR (CI) = 2.5 (1.4-4.3)* OR (CI) = 1.2 (0.5-2.9) OR (CI) = 1.5 (0.7-3.1)	

**Appendix A-11. Solvents: Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Solvent Exposures During Deployment		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Unwin 1999	2,735 U.K. GWV	Other paints or solvents	CMI		OR (CI) = 1.7 (1.5-2.0)*	

GW = Gulf War; GWV = Gulf War veterans; GWUI = Gulf War unexplained illness; CMI = chronic multisymptom illness;<sup>464</sup> CFS = chronic fatigue syndrome; MCS = multiple chemical sensitivity; OR = odds ratio; CI = 95% confidence interval; p = p value; prev diff = prevalence difference; sign. = statistically significant; ns = not significant; \* statistically significant

**Appendix A-12a. Vaccines (Individual Types): Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Vaccine/Shot Assessed	Health Outcome	Association of Health Outcomes with Individual Types of Vaccines	
				Crude (no adjustments)	Adjusted for military, demographic variables Adjusted for other deployment exposures
Boyd 2003	978 GWV in GW Registry	Botulism	High symptom vs. low symptom groups		OR = 1.8, p = 0.02*
		Meningococcus			OR = 1.6, p = 0.10
		Anthrax			OR = 1.7, p = 0.03*
		Plague			OR = 1.3, ns
		Typhoid			OR = 1.4, ns
		IgG			OR = 1.2, ns
Goss Gilroy 1998	3,113 Canadian GWV	Non-routine immunizations	Cognitive symptoms		OR (CI) = 1.3 (1.1-1.5)*
		(anthrax, plague)	Chronic fatigue symptoms		OR (CI) = 1.9 (1.5-2.5)*
			Fibromyalgia symptoms		ns
Gray 1999	527 U.S. Navy Seabees	Anthrax	23 individual symptoms	12 of 23 symptoms sign.; ORs 2.0-4.5	
		IgG		11 of 23 symptoms sign.; ORs 2.1-8.1	
		Botulism		16 of 23 symptoms sign.; ORs 2.7-5.2	
Gray 2002	3,831 U.S. Navy Seabees	Meningococcus	GWV (study-defined)	OR (CI) = 3.6 (2.5-5.2)*	OR (CI) = 1.3 (1.0-1.6)*
		Botulism		OR (CI) = 4.9 (3.5-7.0)*	ns
		Anthrax		OR (CI) = 3.7 (2.6-5.4)*	ns
		Plague		OR (CI) = 3.2 (2.2-4.8)*	ns
		IgG		OR (CI) = 1.9 (1.4-2.5)*	ns
		Typhoid		OR (CI) = 2.3 (1.5-3.6)*	ns

**Appendix A-12a. Vaccines (Individual Types): Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Vaccine/Shot Assessed	Health Outcome	Association of Health Outcomes with Individual Types of Vaccines			
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures	
Hotopf 2000	923 U.K. GWV with vaccine records	Received predeployment	CMI				
		Anthrax		OR (CI) = 1.3 (0.8-2.0)			
		Plague		OR (CI) = 1.2 (0.6-2.2)			
		Pertussis		OR (CI) = 1.0 (0.5-1.7)			
		Tetanus		OR (CI) = 0.9 (0.6-1.3)			
		Cholera		OR (CI) = 0.9 (0.6-1.2)			
		Hepatitis A		OR (CI) = 1.3 (0.8-2.1)			
		Hepatitis B		OR (CI) = 0.8 (0.5-1.3)			
		Polio		OR (CI) = 0.7 (0.5-1.2)			
		Yellow fever		OR (CI) = 1.3 (0.9-1.9)			
		Typhoid		OR (CI) = 1.0 (0.7-1.4)			
		Kang 2002	10,423 U.S. GWV	Received during deployment	CMI		
				Anthrax		OR (CI) = 1.3 (0.9-2.0)	
				Plague		OR (CI) = 0.9 (0.6-1.4)	
Pertussis				OR (CI) = 1.3 (0.9-2.0)			
Tetanus				OR (CI) = 2.7 (1.0-7.2)*			
Cholera				OR (CI) = 2.9 (1.0-7.9)*			
Hepatitis A				OR (CI) = 1.3 (0.5-3.2)			
Hepatitis B				OR (CI) = 0.7 (0.3-1.4)			
Polio				OR (CI) = 1.2 (0.3-4.3)			
Yellow fever				OR (CI) = 0.8 (0.2-3.7)			
Typhoid				OR (CI) = 0.7 (0.3-2.0)			
Mahan 2004	11,441 U.S. GWV			Botulism vaccine	GW-unique neurological symptom complex	OR (CI) = 3.5 (2.7-4.7)†	
				Anthrax vaccine (verified by DOD records)	10 severe symptoms		5 of 10 symptoms sign.; ORs = 1.5-1.6

**Appendix A-12a. Vaccines (Individual Types): Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Vaccine/Shot Assessed	Health Outcome	Association of Health Outcomes with Individual Types of Vaccines	
				Crude (no adjustments)	Adjusted only for military, demographic variables Adjusted for other deployment exposures
Schumm 2005	650 Ohio GWV reservists	Anthrax	GWV (Kansas definition)	sign.*	
Unwin 1999	2,735 U.K. GWV	Anthrax Plague Pertussis Any biological vaccine Hepatitis A Hepatitis B Yellow fever Typhoid Poliomyelitis Cholera Tetanus Any routine vaccine	CMI		OR (CI) = 1.5 (1.3-1.7)* OR (CI) = 1.3 (1.1-1.6)* OR (CI) = 1.1 (0.9-1.4) OR (CI) = 1.5 (1.3-1.7)* OR (CI) = 1.1 (0.8-1.5) OR (CI) = 1.0 (0.8-1.3) OR (CI) = 1.3 (1.1-1.7)* OR (CI) = 1.0 (0.8-1.3) OR (CI) = 1.2 (1.0-1.5) OR (CI) = 1.1 (0.9-1.4) OR (CI) = 1.3 (1.1-1.5)* OR (CI) = 1.2 (1.1-1.4)*
Wolfe 2002	945 U.S. Army GWV	Anthrax	CMI - Mild-moderate CMI - Severe CMI - Mild, mod, severe	OR (CI) = 1.5 (1.1-2.1)* OR (CI) = 1.9 (1.4-2.6)*	OR (CI) = 1.5 (1.1-2.0)*

GW = Gulf War; GWV = Gulf War veterans; CMI = chronic multisymptom illness;<sup>464</sup> OR = odds ratio; CI = 95% confidence interval; sign. = statistically significant; ns = not significant; \* statistically significant; † calculated from reported data



**Appendix A-12b. Vaccines (Number Received): Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Number of Vaccines Received		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Cherry 2001	7,971 U.K. GWV	Number of inoculations	Overall symptom severity Peripheral symptoms			sign. corr; p < 0.001* sign. corr; p < 0.001*
Hotopf 2000	923 U.K. GWV with vaccine records	<u>Received predeployment</u> 0/1 vaccine 2 vaccines 3 vaccines 4 vaccines 5+ vaccines	CMI	OR = 1.0 OR (CI) = 1.0 (0.6-1.6) OR (CI) = 0.8 (0.5-1.4) OR (CI) = 1.3 (0.8-2.2) OR (CI) = 1.1 (0.6-2.0) trend test, p = 0.38		
		<u>Received during deployment</u> 0/1 vaccine 2 vaccines 3 vaccines 4 vaccines 5+ vaccines		OR = 1.0 OR (CI) = 2.2 (1.3-3.7)* OR (CI) = 2.4 (1.4-4.0)* OR (CI) = 2.2 (1.4-3.4)* OR (CI) = 5.0 (2.5-9.8)* trend test, p < 0.001		
Kelsall 2004	1,456 Australian GWV	Any immunization 1-4 immunizations 5-9 immunizations 10+ immunizations >5 in one week Dose response	Number of symptoms	ARM (CI) = 1.0 (0.9-1.2) ARM (CI) = 0.9 (0.7-1.0) ARM (CI) = 1.0 (0.9-1.2) ARM (CI) = 1.3 (1.1-1.6)* ARM (CI) = 1.1 (1.0-1.2) ARM (CI) = 1.0 (1.0-1.1)*		

**Appendix A-12b. Vaccines (Number Received): Association with Symptoms and Multisymptom Illness in Studies of Gulf War Veterans**

Study	Veterans Studied	Exposure Assessed	Health Outcome	Association of Health Outcomes with Number of Vaccines Received		
				Crude (no adjustments)	Adjusted only for military, demographic variables	Adjusted for other deployment exposures
Kelsall 2005	1,424 Australian GWV	Any immunization	Number of neurological symptoms		ARM (CI) = 1.1 (0.8-1.5)	
		1-4 immunizations			ARM (CI) = 0.8 (0.6-1.1)	
		5-9 immunizations			ARM (CI) = 1.1 (0.8-1.5)	
		10+ immunizations			ARM (CI) = 1.5 (1.1-2.3)*	
		>5 in one week			ARM (CI) = 1.1 (0.8-1.5)	
		Dose response			ARM (CI) = 1.1 (1.0-1.1)*	
Unwin 1999	2,735 U.K. GWV	<u>All veterans</u>	CMI		OR (CI) = 0.9 (0.7-1.2)	
		1-2 vaccinations			OR (CI) = 1.2 (1.0-1.4)	
		3-6 vaccinations			OR (CI) = 1.8 (1.5-2.2)*	
		7+ vaccinations			trend test, p < 0.001	
		<u>Veterans with shot records</u>	CMI		OR (CI) = 1.2 (0.7-2.0)	
		1-2 vaccinations			OR (CI) = 1.1 (0.8-1.6)	
		3-6 vaccinations			OR (CI) = 1.9 (1.3-2.8)*	
		7+ vaccinations			trend test, p < 0.001	

GW = Gulf War; GWV = Gulf War veterans; CMI = chronic multisymptom illness;<sup>464</sup> OR = odds ratio; CI = 95% confidence interval; ARM = adjusted ratio of means; p = p value; sign. = statistically significant; ns = not significant; \* statistically significant

| **Appendix B**

**Charter of the Research Advisory Committee  
on Gulf War Veterans' Illnesses**



# | Committee Charter

## DEPARTMENT OF VETERANS AFFAIRS CHARTER OF THE RESEARCH ADVISORY COMMITTEE ON GULF WAR VETERANS' ILLNESSES

A. OFFICIAL DESIGNATION: Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI).

B. OBJECTIVES AND SCOPE OF ACTIVITY: The Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses shall provide advice and make recommendations to the Secretary of Veterans Affairs on proposed research plans and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theater of operations during the 1990-1991 Gulf War (Operations Desert Shield and Desert Storm). The Committee shall not conduct scientific research or review research proposals submitted to VA prior to funding. VA may, however, request individual Committee members with appropriate scientific expertise to participate in the review of such proposals.

The guiding principle for the work of the Committee shall be the premise that the fundamental goal of Gulf War-related government research, either basic or applied, is to ultimately improve the health of ill Gulf War veterans, and that the choice and success of research efforts shall be judged accordingly. The Committee shall assess the overall effectiveness of government research to answer central questions on the nature, causes, and treatments for health consequences of military service in the Southwest Asia theater of operations during the 1990-1991 Gulf War.

The Committee shall meet in public session to review all relevant funded research, investigations, and processes for funding research conducted previously and assess their methods, results, and implications. The Committee shall review all proposed Federal research plans, initiatives, procurements, grant programs, and other activities in support of research projects on health consequences of military service in the Southwest Asia theater of operations during the 1990-1991 Gulf War. The Committee, consistent with law, shall have access to all VA documents and other sources of information it finds relevant to such review.

C. PERIOD OF TIME NECESSARY FOR THE COMMITTEE TO CARRY OUT ITS PURPOSE: The Committee was established in compliance with statutory instructions contained in § 104 of Public Law 105-368. It has no termination date.

D. OFFICIAL TO WHOM THE COMMITTEE REPORTS: The Committee shall report to the Secretary of Veterans Affairs.

E. OFFICE RESPONSIBLE FOR PROVIDING THE NECESSARY SUPPORT TO THE COMMITTEE: The Veterans Health Administration of the Department of Veterans Affairs will provide support for the Committee. A VA employee shall be the Designated Federal Officer. Technical support for the Committee shall be provided by a staff that reports to the Committee chair, who may appoint a technical director for the staff to supervise its operation. Staff members may be VA employees, employees of other government agencies, or independent agents employed as temporary VA employees.

F. DUTIES OF THE COMMITTEE: The Committee shall provide to the Secretary of Veterans Affairs, not later than December 1 of each year, an annual report summarizing its activities for the preceding year. The Committee is authorized to develop additional reports and recommendations regarding relevant research. During its review of such research and in compliance with governing law, the Committee shall have access to all VA documents and

other information sources it finds relevant to such review. Recommendations contained within a formal Committee report shall be submitted to the Secretary and other appropriate officials, as directed by the Secretary. All such reports shall be approved by the Committee, meeting in open public session, prior to submission to the Secretary.

The Secretary shall, to the extent provided by law, seek support from other Federal departments and agencies to provide the Committee with information and research findings it may require for purposes of carrying out its functions. To augment the expertise of the Committee, the Secretary may, at the request of the chair of the Committee, contract through VA for the services of non-governmental consultants who may prepare reports and background papers or prepare other materials for consideration by the Committee, as appropriate.

The Committee shall be comprised of members of the general public, including Gulf War veterans, representatives of such veterans, and members of the medical and scientific communities representing appropriate disciplines such as, but not limited to, biomedicine, epidemiology, immunology, environmental health, neurology, and toxicology.

Members shall be appointed for two- or three-year terms. The Secretary may renew the terms of members. The Secretary shall appoint the chair of the Committee. The term of office for the chair shall be two years, also renewable by the Secretary. The Committee will be composed of approximately fifteen (15) members. Several members may be Regular Government Employees (RGE), but the majority of the Committee's membership will be Special Government Employees (SGE).

The Committee may establish subcommittees to carry out specific projects or assignments. The Committee chair shall notify the Secretary, through the Designated Federal Officer for the Committee, upon the establishment of any subcommittee, including its function, membership and estimated duration.

The Secretary may establish a panel of experts representing appropriate medical and scientific disciplines to assist the Committee in its work. Panelists may be called on by the Secretary for advice and consultation, and may advise the Committee on research or conduct other appropriate activities for the Committee, at the request of the Committee chair. Panelists shall report directly to the chair or such Committee members designated by the chair, but they shall not be members of the Committee. Panelists will be nominated by the Committee chair and appointed by the Secretary.

G. ESTIMATED ANNUAL OPERATING COSTS IN DOLLARS AND STAFF-YEARS: The estimated annual cost for operating the Committee and its support staff is \$400,000 and 4 FTE. All members will receive travel expenses and a per diem allowance in accordance with the Federal Travel Regulation for any travel made in connection with their participation in Committee meetings.

H. ESTIMATED NUMBER AND FREQUENCY OF MEETINGS: The Committee is expected to meet not less than twice annually. Meetings of the subcommittee(s) shall be convened as necessary. The Designated Federal Officer (DFO), a full time VA employee, will approve the schedule of Committee meetings. The DFO or a designee will be present at all meetings, and each meeting will be conducted in accordance with an agenda approved by the DFO. The DFO is authorized to adjourn any meeting when he or she determines it is in the public interest to do so.

I. COMMITTEE TERMINATION DATE: None.

J. DATE CHARTER IS FILED:

APPROVED: James B. Peake, M.D.  
Secretary of Veterans Affairs

Date: 05/08/08

## | **Appendix C**

### **Members of the Research Advisory Committee on Gulf War Veteran's Illnesses**



## | Committee Members

### **James H. Binns (Committee Chair)**

Mr. Binns is former Principal Deputy Assistant Secretary of Defense for International Security Policy, and a Vietnam veteran. He is also former chairman of Parallel Design and past president of A.D.R. Ultrasound, two medical imaging manufacturing companies which he led from startup to merger with major corporations. He is a graduate of Stanford University and Harvard Law School.

### **Carrolee Barlow, MD, PhD**

Dr. Barlow is Vice President of Research for BrainCells, Inc., and previously conducted neuroscience research at the National Institutes of Health, the Salk Institute of Biological Studies, and Merck Research Laboratories. Dr. Barlow is an expert in neuroscience and clinical applications of basic research to neurological and neuropsychiatric diseases. She has authored numerous articles and book chapters in areas ranging from neurogenomics to the implications of basic research for understanding genetic diseases affecting the brain.

### **Floyd E. Bloom, MD**

Dr. Bloom is Professor Emeritus in the Molecular and Integrative Neuroscience Department at The Scripps Research Institute. He is a distinguished neuroscientist who pioneered the use of modern molecular biological and database techniques in brain research. Dr. Bloom is a past president of the American Association for the Advancement of Science (AAAS) and a member of the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society, and the Royal Swedish Academy of Science. He has authored or co-authored over 700 scientific articles and was Editor-in-Chief of Science Magazine from 1995 – 2000.

### **Daniel J. Clauw, MD**

Dr. Clauw is Assistant Dean for Clinical and Translation Research and Professor of Medicine at the University of Michigan. He is director of the Chronic Pain and Fatigue Research Center and the Center for the Advancement of Clinical Research. His primary research interest focuses on overlapping chronic pain syndromes such as fibromyalgia and Gulf War illness and the role of central nervous system dysfunction in the development of these syndromes. He leads a multidisciplinary team of collaborators committed to identifying chronic pain syndrome risk factors and the establishment of programs aimed at the most effective treatment and prevention of this spectrum of illnesses.

### **Beatrice A. Golomb, MD, PhD**

Dr. Golomb is Associate Professor of Medicine and of Family and Preventive Medicine at the University of California at San Diego, Research Associate Professor of Psychology at the University of Southern California, and a Robert Wood Johnson Generalist Physician Faculty Scholar. Her research focuses on the risks and benefits of medical interventions, especially cholesterol drugs, and on Gulf War veterans' illnesses. As a RAND scientist she traveled to the Middle East on a fact finding mission related to this issue, and has authored several RAND reports on the relation of exposures to illness in Gulf War veterans. Dr. Golomb served as Scientific Director of the Committee in 2002 and 2003.

**Joel C. Graves, DMin**

Rev. Graves is a Lutheran minister, hospice chaplain and Gulf War veteran. He retired from the U.S. Army in 1997 as a captain, after serving as enlisted for nine years and an armor officer for nine years. During the war, he was a member of the 1st Battalion, 67th Armored Battalion, 1st "Tiger" Brigade Independent Task Force, which took the northern part of Kuwait City. He has Gulf War illness.

**Anthony Hardie**

Mr. Hardie is Executive Assistant of the Wisconsin Department of Veterans Affairs where he oversees the agency's relations with the state legislature, Congress, the media, stakeholders, and the public. He is a Gulf War and Somalia veteran and is a former officer with the National Gulf War Resource Center. He has worked extensively on policy issues related to Gulf War veterans' illnesses and deployment health. He is a former Congressional staff member, a graduate of the University of Wisconsin, and the 2005 recipient of Wisconsin's Disabled American Veterans Department Distinguished Service Award.

**Marguerite L. Knox, MN, NP**

LTC Knox serves on the South Carolina Army National Guard's Medical Command and is a senior sales representative for Teva Neuroscience. During the Gulf War she served with the 251st Evacuation Hospital at King Khalid Military City, Saudi Arabia. During her tenure as Assistant Professor at the University of South Carolina College of Nursing, she served on the Presidential Advisory Committee on Gulf War Veterans' Illnesses (1995-1998).

**William J. Meggs, MD, PhD**

Dr. Meggs is Professor and Chief of the Division of Toxicology, Department of Emergency Medicine at the Brody School of Medicine at East Carolina University, where he also serves as Senior Vice Chair for Academic Affairs. His research interests include the role of neurogenic inflammation in chemical sensitivity, and the effects of low-level exposures to organophosphorous compounds. Dr. Meggs is a fellow of the American College of Medical Toxicology and the American College of Emergency Medicine, and served on the National Academy of Science's subcommittee on immunotoxicology.

**Mary Dekker Nettleman, MD, MS**

Dr. Nettleman is the Chair of the Department of Medicine at Michigan State University. She is dually boarded in Internal Medicine and Infectious Diseases, with a Master's Degree in Preventive Medicine. Her research focuses on disease epidemiology, with special emphasis on nosocomial infections, sexually transmitted diseases, and early pregnancy. She has served on national committees, study sections, and editorial boards related to infectious diseases, quality of care, and general internal medicine.

**James P. O'Callaghan, PhD**

Dr. O'Callaghan is Distinguished Consultant and Head of the Molecular Neurotoxicology Laboratory in the Toxicology and Molecular Biology Branch of the Health Effects Laboratory Division at the U.S. Centers for Disease Control and Prevention (CDC). Prior to joining CDC, Dr. O'Callaghan founded the molecular and cellular neurotoxicology program in the Neurotoxicology Division, U.S. Environmental Protection Agency in Research Triangle Park, North Carolina. He directs a research program dedicated to the discovery and implementation of biomarkers of neurotoxicity.

**Steve Smithson**

Mr. Smithson is Deputy Director for Claims Services for the American Legion, where he oversees matters related to the Veterans Benefits Administration. He served on active duty in the United States Marine Corps from 1988-92, including a seven-month tour of duty in Saudi Arabia and Kuwait during the Gulf War. Mr. Smithson was previously an Assistant Director for Gulf War and deployment-related issues with the American Legion.

**Lea Steele, PhD**

Dr. Steele is Adjunct Associate Professor in the College of Human Ecology at Kansas State University. She is an epidemiologist and human ecologist whose research interests focus on the study of complex medical conditions that are difficult to diagnose and treat. Dr. Steele previously directed the Kansas Persian Gulf War Veterans Health Initiative, a state-sponsored research and service program, and was principal investigator of the Kansas Gulf Veterans Health Study. She served as Scientific Director of the Committee from 2003 through early 2008.

**Roberta F. White, PhD**

Dr. White is Professor and Chair of the Department of Environmental Health at Boston University School of Public Health. She is a neuropsychologist with expertise in environmental and occupational epidemiology. Author of numerous scientific publications, her research interests include evaluation of chronic effects of exposure to neurotoxicants, the use of imaging in behavioral toxicology, and environmental factors that influence the development of neurodegeneration. Dr. White currently serves as Scientific Director of the Committee.

**Consultant to the Committee****Jack Melling, PhD**

Dr. Melling is former Chief Executive of the U.K. Microbiological Research Authority. He was previously Director of the Salk Institute of Biologicals Development Center, Director of the Karl Landsteiner Institute for Vaccine Development, and a Senior Program Manager at the Battelle Memorial Institute. He is currently a consultant to the United States Government Accountability Office.



## **Abbreviations and Acronyms**



## | Abbreviations and Acronyms

ACE	angiotensin converting enzyme
ACh	acetylcholine, a neurotransmitter
AChE	acetylcholinesterase, an enzyme that breaks down acetylcholine
ACTH	adrenocorticotropic hormone
AFRRI	U.S. Armed Forces Radiobiology Research Institute
AFTAC	Air Force Technical Assistance Center, U.S. Air Force
ALS	amyotrophic lateral sclerosis, also known as Lou Gehrig's disease
ANS	autonomic nervous system
ARM	adjusted ratio of means
ATP	adenosine triphosphate
AVA	anthrax vaccine adsorbed
AVEC	Anthrax Vaccine Expert Committee, U.S. Department of Health and Human Services
AVIP	Anthrax Vaccine Immunization Program, U.S. Department of Defense
BChE	butyrylcholinesterase
BDRC	Birth Defect Research for Children
BIRLS	Beneficiary Identification and Records Locator Subsystem, U.S. Department of Veterans Affairs
BT	botulinum toxoid
CAM	chemical agent monitor
CAPS	Clinician-Administered PTSD Scale
CARC	chemical agent resistant coating
CATI	computer assisted telephone interview
CBT	cognitive behavioral therapy
CBW	chemical and biological warfare agents
CCEP	Comprehensive Clinical Evaluation Program, U.S. Department of Veterans Affairs
CDC	U.S. Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Program, U.S. Department of Defense
CENTCOM	Central Command, U.S. Department of Defense
CFS	chronic fatigue syndrome
CI	confidence interval
CIA	U.S. Central Intelligence Agency
CIDI	Composite International Diagnostic Interview
CMI	chronic multisymptom illness
CMV	Cytomegalovirus
CN	chloroacetophenone, a form of tear gas
CNS	central nervous system
CO	carbon monoxide
CO <sub>2</sub>	carbon dioxide

corr	correlation
CPAP	Continuous Positive Airway Pressure, used to treat sleep apnea
CRH	corticotropin-releasing hormone
CS	chlorobenzylidenemalononitrile, tear gas
CT	computed tomography scan
DC	District of Columbia
DEET	N,N-diethyl-meta-toluamide, an insect repellent
DEX	dexamethasone, a synthetic glucocorticoid
DFP	diisopropylfluorophosphate
DHWG	Deployment Health Working Group, U.S. federal interagency group
DMSS	Defense Medical Surveillance System
DNA	deoxyribonucleic acid
DOD	U.S. Department of Defense
DS <sub>2</sub>	decontamination solution 2
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DU	depleted uranium
EEG	electroencephalogram
EBV	Epstein-Barr virus
EEG	electroencephalogram
EF	edema factor, a protein in the anthrax vaccine
ELISA	Enzyme-Linked ImmunoSorbent Assay
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
FVC	forced vital capacity
FY	fiscal year
GABA	gamma aminobutyric acid, a neurotransmitter
GAO	U.S. General Accounting Office, renamed the U.S. Government Accountability Office in 2004
GFAP	glial fibrillary acidic protein
GH	growth hormone
GIS	geographical information systems
GW	Gulf War
GWI	Gulf War illness
GWUI	Gulf War-related unexplained illness
GWV	Gulf War veterans
GWVIS	Gulf War Veterans Information System, U.S. Department of Veterans Affairs
HDI	hexamethylene diisocyanate, a hardening compound in CARC paint
HHS	U.S. Department of Health and Human Services
HHV	human herpes virus

HHV6	human herpes virus 6
5-HIAA	5-hydroxyindoleacetic acid, a metabolite of serotonin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
<sup>1</sup> H MRS	proton magnetic resonance spectroscopy
HPA	hypothalamic-pituitary-adrenal axis
HPRT	hypoxanthine-guanine phosphoribosyl transferase, used to assay genetic mutations
HRV	heart rate variability
HSC	Health Symptom Checklist
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine, or serotonin
HVA	homovanillic acid, a dopamine metabolite
IAEA	International Atomic Energy Agency
IBS	irritable bowel syndrome
IFN	interferon
IG	Inspector General
IgE	immunoglobulin E
IgG	immunoglobulin G
IL-2	interleukin 2
IL-10	interleukin 10
IM	intramuscular
IND	investigational new drug
IOM	Institute of Medicine, National Academy of Sciences
IP	intraoperative
ISG	Iraq Survey Group
IV	intravenous
JP-4, JP-5, JP-8	jet propulsion fuel types 4, 5, and 8
KKMC	King Khalid Military City, Saudi Arabia
KLH	keyhole limpet hemocyanin
km	kilometer
KS GWI	Kansas case definition for Gulf War illness
L	leucine, an amino acid
LD <sub>50</sub>	dosage that is lethal to 50 percent of exposed animals
LF	lethal factor, a protein in the anthrax vaccine
LSD	lysergic acid diethylamide, a hallucinogenic drug
M	methionine, an amino acid
M1, M2, M3	types of acetylcholine muscarinic receptors
MAP	Medical Assessment Program, U.K. Ministry of Defence
MAVERIC	Massachusetts Veterans Epidemiology Research and Information Center (VA)
MBPI	Michigan Biological Products Institute

MCS	multiple chemical sensitivity
MDA	malondialdehyde
MDPH	Michigan Department of Public Health
2ME	ethylene glycolmonomethyl ether, a solvent
MEG	magnetoencephalography
MF59	a vaccine adjuvant that contains squalene
MHPG	3-methoxy-4-hydroxyphenylglycol
MOD	Ministry of Defence, U.K.
MOPP	Mission Oriented Protective Posture, protective garments worn at different levels of chemical threat
MPTP	1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
NAA/Cr	N-acetyl-aspartate/creatine ratio
NADH	nicotinamide adenine dinucleotide
NAPPs	nerve agent pyridostigmine pretreatment sets
NAPs	nerve agent pretreatment sets
NAS	The National Academy of Sciences
NATO	North Atlantic Treaty Organization
NBC	nuclear, biological, and chemical
NCO	noncommissioned officer
NHRC	Naval Health Research Center, U.S. Navy
NIH	National Institutes of Health
NK cells	natural killer cells
NMH	neurally mediated hypotension
NO <sub>x</sub>	oxides of nitrogen
NTE	neuropathy target esterase
O <sub>3</sub>	ozone
ODS	Operation Desert Storm
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OP	organophosphate
OPIDN	organophosphate induced delayed neuropathy
OR	odds ratio, a measure of association between a risk factor and health outcome
ORD	Office of Research and Development, U.S. Department of Veterans Affairs
OSAGWI	Office of the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses
p	p value, a test of statistical significance
PA	protective antigen, immunogenic component of the anthrax vaccine
PAC	Presidential Advisory Committee on Gulf War Veterans' Illnesses

PAHs	polycyclic aromatic hydrocarbons
2-PAM	2-pralidoxine chloride, used as an antidote following nerve agent exposure
PB	pyridostigmine bromide
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PET	positron emission tomography
PGVCB	Persian Gulf Veterans Coordinating Board
PL	public law
PM10	particulate matter, 10 microns or smaller
PON1	paraoxonase
Prev diff	prevalence difference
PSOB	Presidential Special Oversight Board for Department of Defense Investigations of Chemical and Biological Incidents
PTSD	post traumatic stress disorder
Q	glutamine, an amino acid
R	arginine, an amino acid
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RAND	RAND National Defense Research Institute
RCT	randomized, controlled trial
REM	rapid eye movement, a stage in the sleep cycle
RFA	Request for Applications
RFP	Request for Proposals
ROS	reactive oxygen species
RR	risk ratio, a measure of association between a risk factor and health outcome
SCID	Structured Clinical Interview for DSM-III-R
SCUD	Subsonic Cruise Unarmed Decoy
SF36	Medical Outcomes Study Short Form Survey
SF36 PCS	Physical component score of the Medical Outcomes Study Short Form Survey
sign.	statistically significant
SIU	Special Investigation Unit on Gulf War Illnesses, U.S. Senate
SO <sub>2</sub>	sulfur dioxide
SO <sub>x</sub>	oxides of sulfur
SPECT	single photon emission tomography
SR	self-reported
SRI	Stanford Research Institute
SSG	Staff Sergeant (U.S. Army)
SSgt	Staff Sergeant (U.S. Air Force)
subQ	subcutaneous
TCPs	tricresyl phosphates
Th1	T-helper cells associated with cell-mediated immunity and phagocyte-dependent inflammation

Th2	T-helper cells associated with humoral immunity and allergy
TNF	tumor necrosis factor
TSPs	total suspended particulates
U.K.	United Kingdom
U.N.	United Nations
UNSCOM	United Nations Special Commission on Iraq
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine (formerly USAEHA)
USAEHA	U.S. Army Environmental Hygiene Agency
USAMRMC	U.S. Army Medical Research and Materiel Command
UTSW	University of Texas Southwestern Medical School
VA	U.S. Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VAMC	VA Medical Center
VBA	Veterans Benefits Administration, U.S. Department of Veterans Affairs
VHA	Veterans Health Administration, U.S. Department of Veterans Affairs
VHI	Veterans Health Initiative, U.S. Department of Veterans Affairs
VOCs	volatile organic compounds
VZV	varicella zoster virus
WMD	weapons of mass destruction
WRAIR	Walter Reed Army Institute of Research
WRIISC	War Related Injury and Illness Study Center, U.S. Department of Veterans Affairs

