Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013

Updated Scientific Findings and Recommendations

Research Advisory Committee on Gulf War Veterans' Illnesses

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Findings in Brief

This report was produced by the federal Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI), which was established by Congress under Public Law 105-368. Membership includes veterans of the 1990-91 Gulf War, scientists who have studied illnesses affecting these veterans, clinicians who care for ill Gulf War veterans and a member of the general public.

The Committee periodically releases reports that summarize research to date on the health of veterans of the 1990-1991 Gulf War. The most recent report was published in 2008, and the current report updates knowledge from that time by reviewing published scientific papers that appeared after the last report and through December 2013.

The present research review is divided into four sections. The first summarizes the new information available on rates of Gulf War illness and other illnesses and disabilities that affect groups of veterans from the Gulf War (Section 1, Epidemiologic Research). The second reviews the human and animal research that has been carried out to identify the causes of Gulf War illness and other health problems in Gulf War veterans (Section 2: Etiologic Investigations). The third section focuses on studies of the disruptions in normal body functions that underlie the symptoms of Gulf War illness and other health problems (Section 3: Pathobiology of Gulf War illness). And the fourth reviews clinical trials that are underway to treat Gulf War illness (Section 4: Gulf War Illness Treatment Research).

In this section, the findings of the report are described in brief.

General conclusions

Scientific research published since the 2008 Committee report supports and further substantiates the conclusions of the 2008 report that Gulf War illness is a serious physical disease, affecting at least 175,000 veterans of the 1990-1991 Gulf War, that resulted from hazardous exposures in the Gulf War theater. Important progress has been made in improving scientific understanding of Gulf War illness. Research has begun to identify probable underlying mechanisms, promising treatments and biomarkers. However, much work remains to be done.

We support the scientists and clinicians working to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures. Effective treatments for Gulf War illness could also lead to treatments for other exposure-related occupational health problems. The Committee recommends a robust federal research effort to monitor and improve the health of Gulf War veterans, with the identification of treatments for Gulf War illness the highest priority.

A wide-ranging scientific literature review of this problem published after 2008, the Institute of Medicine's 2010 *Gulf War and Health* report, also recommended a renewed federal research effort and concluded that treatments and hopefully preventions can likely be found with the right research.

What is Gulf War illness and how common is it?

Gulf War illness refers to the chronic symptoms that affect veterans of the 1990-1991 Gulf War at markedly elevated rates compared to other veteran groups and to the U.S. population as a whole. The individual symptoms experienced by ill Gulf War veterans can vary from person to person, but overall the types of symptoms reported are similar in the many groups of ill veterans that have been studied since the war. Symptoms typically include some combination of widespread pain, headache, persistent problems

with memory and thinking, fatigue, breathing problems, stomach and intestinal symptoms, and skin abnormalities.

In the early years after the war, this disorder was commonly called "Gulf War Syndrome" by the media and has since been referred to by a variety of names such as undiagnosed illness, Gulf War illness, chronic multisymptom illness and other terms. "Gulf War illness" is the term most commonly used by scientists, clinicians, veterans' groups and the Department of Defense and is used in this report to refer to the illness associated with military service in the 1990-1991 Gulf War.

Based on its review of the research that has been published since 2008, the Committee concludes that Gulf War illness has been consistently reported in all studies of Gulf War veterans and that it is seen in about 25-30% of Gulf War veterans, or about 175,000 to 250,000 of the 700,000 troops deployed to the war in 1990-91. The same conclusion was reached in 2008.

Little new information has become available on whether the health of ill Gulf War veterans has improved over time. The research published in the 2008 RACGWVI report suggests that there is little to no improvement among veterans with Gulf War illness. The effect that aging will have on this vulnerable population remains a matter of concern.

What other kinds of health problems are experienced by Gulf War veterans?

Studies published since 2008 continue to find that veterans from the 1990-91 Gulf War have poorer general health and greater disability than other veterans of the same era who did not deploy to the Gulf.

Studies reviewed in this report show that Gulf War veterans who were most exposed to the release of nerve gas by the destruction of the Khamisiyah Iraqi arms depot have significantly elevated rates of death due to brain cancer. Veterans who were exposed to the highest level of contaminants from oil well fires also have increased rates of brain cancer deaths. Studies conducted prior to 2008 show that Gulf War veterans experienced higher than expected rates of amyotrophic lateral sclerosis (ALS).

Very little other research has yet been conducted to determine rates at which Gulf War veterans have been affected by other medical conditions of possible concern, including neurological diseases such as multiple sclerosis or Parkinson's disease, cancers, sleep disorders, adverse pregnancy outcomes or rates of birth defects in veterans' children.

Persons with disorders like chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity have similar symptoms to veterans with Gulf War illness, but most Gulf War illness patients cannot be diagnosed with these disorders using standard diagnostic rules. Gulf War illness is a distinct disorder and Gulf War veterans who can be diagnosed with these disorders often differ significantly from non-veteran populations who are diagnosed with them.

Studies of psychological and psychiatric disorders in Gulf War veterans since 2008 continue to show that combat and other stressors are associated with post-traumatic stress disorder, anxiety, depression and alcohol abuse in Gulf War veterans but that these disorders are clinically distinct from Gulf War illness. They are typically reported to occur in less than 10% of Gulf War veterans, far below the rate of these disorders in veterans of other recent wars and far below the rate of Gulf War illness in Gulf War veterans.

Very little is known about whether service in the Gulf War or having Gulf War illness affects veterans' life expectancy. Much more needs to be learned about this. Despite specific recommendations over many years from both RACGWVI and Institute of Medicine panels, research in this area remains seriously inadequate.

Which exposures and experiences in the Gulf War theater caused ill health and functional disability in Gulf War veterans?

Once it became clear that veterans of the Gulf War had returned home with persistent health problems, the question immediately arose as to the cause or causes of ill health in this veteran group. Although a highly publicized initial argument was that their ill health was due to deployment related stressors and psychological trauma, scientific studies consistently demonstrated that Gulf War illness was associated with chemical, pharmaceutical and other environmental exposures in theater, rather than stress. Research in this area has expanded since 2008 and has included investigations of effects of veterans' exposures to specific chemicals and drugs during the war as well as extensive exploration of the persistent effects of single and combined Gulf War-related exposures in animal models. Further, many studies have shown that environmental and occupational exposure to pesticides in other populations are associated with health problems similar to Gulf War illness.

The research reviewed in this report supports and reinforces the conclusion in the 2008 RACGWVI report that exposures to pesticides and pyridostigmine bromide are causally associated with Gulf War illness. Evidence also continues to demonstrate that Gulf War illness is not the result of psychological stressors during the war.

Hazardous exposures in theater are also related to certain other health problems seen in Gulf War veterans. Exposure to the nerve gas agents sarin and cyclosarin has been linked in two more studies to changes in structural magnetic resonance brain imaging that are associated with cognitive decrements, further supporting findings on the nervous system effects of these agents reported in the 2008 report. New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. It is unclear if vaccine exposures may also be contributing to Gulf War veteran health symptoms, because current results have been conflicting and include weak associations. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear: studies on this substance have focused on small groups of individuals.

How are basic body functions affected in veterans with Gulf War illness?

Studies reviewed in the 2008 RACGWVI report and research published since then have shown that Gulf War illness is associated with changes in the brain, autonomic nervous system, endocrine system and immune system. Other health problems have also been demonstrated in subgroups of veterans who experienced exposures to specific chemicals in the Gulf War theater.

What effective treatments are available for patients with Gulf War illness and how should new treatments be developed?

Treatment research has increased significantly since 2008, particularly reflecting the efforts of the Gulf War Illness Research Program (GWIRP) of the Department of Defense (DoD)'s Office of Congressionally Directed Medical Research Programs (CDMRP) to fund such research. However, most of these studies are still underway, with few results yet available. Promising preliminary reports from the limited trials to date indicate possible benefits provided by coenzyme Q10 (a dietary supplement), acupuncture and use of continuous positive airway pressure (CPAP) during sleep in veterans with sleep apnea.

The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures.

Treatment approaches based on what is known about the underlying physiological changes that occur in veterans with Gulf War illness may be the most effective. Promising laboratory research is underway to develop cutting-edge treatment approaches by studying the effects of Gulf War exposures in animals and then targeting and testing treatments for these effects. Effective treatments of Gulf War illness could lead to treatments for exposure-related occupational and environmental health problems in other groups of people. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

Executive Summary

This report was produced by the federal Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI), established by Congress under Public Law 105-368. The Committee periodically releases reports that summarize research to date on the health of veterans of the 1990-1991 Gulf War. The most recent report was published in 2008, and the current report updates knowledge since that time by reviewing published papers that appeared after the last report and through December 2013.

The research review is divided into four sections that summarize the epidemiological issues and research on Gulf War illness, the human and animal research that has addressed causes of the illness and other health problems in Gulf War veterans, studies that focus on the underlying pathobiology of illness manifestations and the clinical trials that are underway to treat Gulf War illness.

In this Executive Summary, the Committee summarizes its conclusions about the findings from research to date on Gulf War illness and other health problems in Gulf War veterans and provides recommendations about how to further understand and, most importantly, how to identify and evaluate effective treatments.

General conclusions

Scientific research published since the 2008 Committee report supports and further substantiates the conclusions of the 2008 report that Gulf War illness is a serious physical disease, affecting at least 175,000 veterans of the 1990-1991 Gulf War, that resulted from hazardous exposures in the Gulf War theater. Important progress has been made in improving scientific understanding of Gulf War illness. Research is beginning to identify probable underlying mechanisms, promising treatments and biomarkers. However, much work remains to be done.

We support the scientists and clinicians working to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures. Effective treatments for Gulf War illness could also lead to treatments for other exposure-related occupational health problems. The Committee recommends a robust federal research effort to monitor and improve the health of Gulf War veterans, with the identification of treatments for Gulf War illness the highest priority.

A wide-ranging scientific literature review of this problem published after 2008, the Institute of Medicine's 2010 *Gulf War and Health* report, also recommended a renewed federal research effort and concluded that treatments and hopefully preventions can likely be found with the right research.

What is Gulf War illness and how prevalent is it?

As described in previous Committee reports, Gulf War illness refers to the chronic symptoms that affect veterans of the 1990-1991 Gulf War at markedly elevated rates compared to other veteran groups and to the U.S. population as a whole. The individual symptoms experienced by ill Gulf War veterans can vary from person to person, but overall the types of symptoms reported are similar in the many groups of ill veterans that have been studied since the war. Symptoms typically include some combination of widespread pain, headache, persistent problems with memory and thinking, fatigue, breathing problems, stomach and intestinal symptoms and skin abnormalities.

In the early years after the war, this disorder was commonly called "Gulf War Syndrome" by the media and has since been referred to by a variety of names such as undiagnosed illness, Gulf War illness, chronic multisymptom illness and various other terms. Gulf War illness, the term most commonly used

by scientists, clinicians, veterans' groups and the Department of Defense, is used throughout this report to refer to the chronic symptomatic illness associated with military service in the 1990-1991 Gulf War.

Based on its review of the data published since 2008, the Committee concludes that all population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans. The large majority of studies indicate that the prevalence of Gulf War illness is in the range of 25-30% in Gulf War veterans, as reported in 2008.

Little additional information on the long-term prognosis of Gulf War illness has become available since 2008. Prior data reported in 2008 suggest that there is little to no improvement in the health of ill Gulf War veterans over time. The effect that aging will have on this vulnerable population remains a matter of concern.

What other kinds of health problems are experienced by Gulf War veterans?

Studies published since 2008 continue to document poorer general health status and greater disability among Gulf War veterans than in contemporary veterans who did not deploy to the Gulf. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains seriously inadequate.

Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by many medical conditions of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess prevalence or incidence rates of most medical conditions. Disorders of concern reviewed in this report include the following:

1. Neurological disorders. Although neurological conditions are a prominent concern for Gulf War veterans and research has found an elevated incidence of amyotrophic lateral sclerosis (ALS), rates of multiple sclerosis, Parkinson's disease and other neurological diseases (e.g., seizures, stroke, migraines) in Gulf War veterans are currently unknown. Research studies on the prevalence of neurological diseases have not been conducted despite repeated recommendations by this Committee and the Institute of Medicine and explicit legislation by Congress. The prevalence of these disorders is particularly important because they can be expected to increase as the Gulf War veteran population ages.

2. Cancer. Since 2008, research using state cancer registries has suggested that there may be an increased rate of lung cancer in Gulf War veterans. Brain cancer mortality has been shown in two studies conducted by VA to be significantly increased in the subgroup of Gulf War veterans with greatest exposure to oil well fire smoke and to low-level nerve agents released by the destruction of Iraqi facilities at Khamisiyah. In general, cancer risk remains unknown and understudied.

3. Other diagnosed medical conditions reported at excess rates. Research since 2008 continues to indicate that Gulf War veterans report being diagnosed with a variety of medical conditions at significantly higher rates than nondeployed era veterans. These include chronic digestive disorders, respiratory conditions, heart disease and skin disorders. Although consistently reported by Gulf War veterans, these conditions have not been further evaluated or characterized by epidemiologic or clinical studies.

4. Sleep dysfunction. A single study published since 2008 has identified sleep abnormalities in a

group of Gulf War veterans compared to obesity-matched controls. Sleep disturbance is an extremely common symptom in veterans with Gulf War illness and continuous positive airway pressure (CPAP) has shown some promise for treating a range of symptoms in veterans with sleep apnea in a small treatment trial.

5. Adverse reproductive outcomes and birth defects. No definitive new information is available on birth defects in offspring of Gulf War veterans, and no research has ever been published concerning neurological or other medical conditions affecting veterans' children. It is important that medical and reproductive outcomes be assessed in children of veteran subgroups of interest (e.g. exposure, location, illness subgroups).

Multisymptom conditions, including chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity, share similar symptoms with Gulf War illness, but most Gulf War illness patients do not meet diagnostic criteria for them. Gulf War veterans who meet criteria for these disorders often differ significantly on tested parameters from non-veteran populations who are diagnosed with them. It may be necessary to consider people with these disorders who are and are not Gulf War veterans separately in research studies, including treatment research.

Studies of psychological and psychiatric morbidity in Gulf War veterans since 2008 continue to show that combat and other stressors are associated with post-traumatic stress disorder (PTSD), anxiety, depression and alcohol abuse but are not independently associated with Gulf War illness.

Lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans is an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 13 years for which no mortality figures are available represent more than half of the 23 years since Desert Storm. Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the latency periods associated with many chronic diseases of interest. Despite specific recommendations over many years from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remain seriously inadequate.

How can research on the health of Gulf War veterans be improved?

Case definition of Gulf War illness

In the absence of a consensus case definition of Gulf War illness 23 years after the appearance of this condition, it can be difficult to assess and compare research findings in epidemiological, pathobiological or treatment research on the disorder. The Committee recommends the following approaches to the development of such a definition.

1. An evidence-based, expert consensus-driven case definition for Gulf War illness should be developed. This process should include a) a review of the existing literature relevant to case definitions for Gulf War illness, b) in-depth statistical and epidemiologic assessment of the strengths and weaknesses of different case definition approaches using datasets that provide representative data on symptoms and medical conditions affecting 1990-1991 Gulf War era veterans and c) final case definition parameters and guidelines developed by an expert consensus panel that includes scientists experienced in Gulf War illness research and symptom-based case definitions in veterans affected by Gulf War illness (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf Section 5.3). The recent IOM panel on case definitions of Gulf War illness also commented that a data-based case definition of the disorder could be derived (Institute of Medicine, 2014). This effort should involve representatives from VA, a broad spectrum of scientists conducting research in Gulf War

veterans, clinicians knowledgeable about the problem and Gulf War veterans. It could be organized through the Gulf War Illness Research Program of the Department of Defense Congressionally Directed Medical Research Program (CDMRP) through its competitive grant proposal process with scientific review.

2. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War. This recommendation is also supported by the 2014 Institute of Medicine report on case definitions of the illness (Institute of Medicine, 2014).

Monitoring the effect of Gulf War service on long-term health

Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this veteran group ages. A strategy for such monitoring was included in a plan proposed by a VA Strategic Planning group composed of representatives from RACGWVI, the VA National Research Advisory Council and VA staff. Such surveillance should include outcomes described in this document, including Gulf War illness; neurological disorders, including Parkinson's disease; autoimmune conditions such as multiple sclerosis; brain, lung and other cancers; cardiovascular disorders and dysfunction; sleep dysfunction; adverse reproductive outcomes and birth defects; general ill health and disability; mortality, and other disorders and outcomes that emerge as important during the surveillance process. This effort must include the following elements.

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans is critical. VA's longitudinal survey currently in process should be extended to add a symptom inventory adequate to define the illness according to existing commonly-used case definitions, as previously recommended by the Committee: "[The current survey instrument] cannot determine the prevalence, progression, or correlates of this illness… [I]t is unthinkable that the largest national study of Gulf War veterans would not provide the data required to evaluate the signature problem of the 1991 Gulf War" (Research Advisory Committee on Gulf War Veterans' Illnesses, 2012).

2. VA's longitudinal survey can be effectively used to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans. Survey data should be used to flag conditions of possible importance and followed up with detailed investigation, including any clinical evaluations that are required to determine specific medical diagnoses affecting Gulf War veterans at excess rates.

3. A study on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans was required by Congress in 2008 (Public Law 110-389, 2008, Section 804) and should be carried out. These assessments should be repeated and published at a minimum of 5-year intervals.

4. Systematic assessment of overall and disease-specific mortality in all Gulf War veterans and in specific subgroups of interest is essential. The results of these assessments should also be published at 5-year intervals.

5. VA's longitudinal survey should be used to assess rates of medical conditions, including neurological and behavioral disorders and birth defects, in children of Gulf War era veterans. Survey data can be used to flag conditions of possible concern and followed up. It is also

important that VA publish results from studies of veterans' children that were conducted over 10 years ago.

6. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance is critical as some health outcomes are related to specific exposures and experiences in theater. These subgroups can be defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater or other predictors.

Improved methodology in Gulf War epidemiologic research
It is important that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.

2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.

3. Consideration of subpopulations with multiple health outcomes.

4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that control as fully as possible for confounding effects of multiple exposures and etiologic factors that may be associated both with the exposures and outcomes of interest. Consideration of the effects of mixed exposures is also key.

Which exposures and experiences in the Gulf War theater caused ill health and functional disability in Gulf War veterans?

Once it became clear that veterans of the Gulf War had returned home with persistent health problems, the question immediately arose as to the cause or causes of ill health in this veteran group. Although a highly publicized initial argument was that their ill health was due to deployment related stressors and psychological trauma, the evidence ultimately demonstrated that chemical, pharmaceutical and other environmental exposures in theater underlie the development of Gulf War illness. Research in this area has expanded since 2008 and has included research on exposure-outcome relationships in veterans as well as extensive use of animal models to explore the chronic, persistent effects of single and combined exposures to substances and conditions that occurred in theater.

Taken together, the scientific literature published since 2008 supports and reinforces the conclusion in the 2008 RACGWVI report that exposures to pesticides and pyridostigmine bromide are causally associated with Gulf War illness and that exposures to low-level nerve agents, oil well fires, receipt of multiple vaccines, and combinations of Gulf War exposures cannot be ruled out as contributing factors to this condition. Studies also continue to show that Gulf War illness is not caused by psychological stressors during the war.

Epidemiologic research
Overall, studies published since the 2008 report continue to show that exposures to pesticides and pyridostigmine bromide are etiologically important in the development of Gulf War illness and in the behavioral and cognitive dysfunction experienced by Gulf War veterans. The findings in Gulf War veteran populations are consistent with those seen in other occupational and environmental groups (see Appendix C). Exposure to the nerve gas agents sarin/cyclosarin has been linked in two more studies to changes in structural magnetic resonance brain imaging findings that are associated with cognitive

decrements, further supporting the conclusion from evidence reviewed in the 2008 report that exposure to these agents is etiologically important to the central nervous system dysfunction that occurs in some subsets of Gulf War veterans.

New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. It is unclear if vaccine exposures may also be contributing to Gulf War veteran health symptoms, because current results are conflicting and include weak associations. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear; studies on this substance have focused on small groups of individuals.

Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and mixed exposures would inform the assessment of mixed exposures, as would the development of biomarkers of exposures to specific chemicals that occurred in the past.

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they can help to determine treatment targets in subgroups of veterans with specific exposures for which there are known mechanistic pathways that cause illness and symptoms. Results from this work can be useful in protecting the health of future military personnel who will experience these exposures as well as non-military populations with occupational or environmental exposure to them. The Committee recommends that additional research in this area be carried out utilizing objective markers of exposure whenever feasible. These include environmental sampling and modeling of conditions in theater. Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for improving scientific understanding of the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic or metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness. Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection and other environmental stressors.

Animal studies

As noted in the RACGWVI 2008 report, animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown. The evidence concerning these effects has burgeoned since 2008, with new animal models of Gulf War illness and exposures in theater. It is axiomatic that animals are not humans and conclusions from animal studies must be used as clues that can be further investigated in appropriate human research. However, the outcomes from animal studies are important because data on exposure-outcome relationships can be collected rapidly and efficiently, with confidence in the exposures (since they are controlled). Animal models of Gulf War-relevant exposures to individual chemicals, chemical mixtures, and chemicals plus other stressors have demonstrated alterations in nervous system outcomes (behavior, cognition, neurotransmission, intracellular signaling, molecular and cellular disruptions of axonal transport); liver and cardiovascular function; genomic, proteomic, lipidomic and metabolomic profiles, and mitochondrial changes. These studies have confirmed hypotheses that exposures are important in the development and expression of Gulf War illness symptomatology, that health effects due to exposures and exposure mixtures can be delayed and occur after exposure has ended and that persistent effects can be seen following exposure cessation. Animal models are also critical for treatment research. The systemic alterations and physiological changes identified in exposure research can provide the targets for treatment approaches, and animal models can be used to pre-test promising treatments.

The Committee recommends that research using animal models of Gulf War illness continue to examine the immediate, delayed, and persistent effects of acute exposures to chemicals and chemical mixtures. Research in this area should include the following elements:

1. Future animal model research should focus on studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system, autonomic nervous system and peripheral target organs, including those that encompass mitochondrial dysfunction and accumulation of reactive oxygen species.

2. Studies that evaluate systemic immune and endocrine parameters in animal models, with an emphasis on those parameters that sensitize ill veterans to Gulf War illness, should also be informative.

3. Animal research to identify biomarkers indicative of past exposures to Gulf War-related toxic compounds that can be applied to Gulf War veterans is important. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s) and that identify persistent changes in the central nervous system and in autonomic function associated with Gulf War-related exposures and conditions. Exploratory biomarker research in animal models that assesses genomic, genetic, epigenetic, proteomic, metabolomic and lipidomic pathways of exposure effect may also be informative.

4. Animal models of Gulf War illness are recommended for rapid screening of potential therapeutics.

What are the physiological mechanisms that underlie Gulf War illness, ill health and functional disability in Gulf War veterans?

In order to understand the health problems seen in the Gulf War veteran population and to generate clues about how to treat their health conditions, is important to learn the underlying pathobiological changes associated with Gulf War illness and with exposures experienced in theater. This report reviews research on structure and function in the central nervous system (using brain imaging, electroencephalography (EEG) and cognitive assays) and work that assesses neuroendocrine, autonomic nervous system, and immunological functions.

Overall, the Committee concludes that the evidence to date continues to point to alterations in central and autonomic nervous system, neuroendocrine, and immune system functions in Gulf War illness and in subsets of Gulf War veterans with specific exposures in theater.

Consistent with evidence presented in the 2008 Committee report, new neuroimaging and EEG research has assessed veterans with Gulf War illness and veterans with sarin/cyclosarin exposure. Fourteen of fifteen new studies show structural and electrical abnormalities in the central nervous system associated with Gulf War illness or with exposure to the nerve gas agents sarin and cyclosarin.

Recent studies on cognitive function in Gulf War veterans provide further support for the conclusion of the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and for Gulf War veterans who experienced specific exposures in theater. These findings support the evidence from imaging and EEG probes that nervous system dysfunction is a key element in veterans' ill health.

Studies continue to support the conclusion from the 2008 report that neuroendocrine function, as assessed by altered hypothalamic pituitary axis (HPA) functioning in Gulf War veterans, is present and is not consistent with the typical pattern seen in post-traumatic stress disorder.

The 2008 RACGWVI report discussed a number of scientific publications documenting autonomic nervous system dysregulation in Gulf War veterans. Since 2008, the only published study that looked specifically at autonomic function in Gulf War veterans confirmed diminished night-time heart rate variability in all three Haley Syndrome Gulf War illness groups.

Six of eight studies conducted on immune system alterations in Gulf War veterans since 2008 showed immune dysregulation. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. Additionally, changes occurring during or following exercise reiterate that immunological (and other) manifestations of Gulf War illness may only become apparent in specific experimental or clinical settings under "challenge" conditions.

The Committee recommends that research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans continue to focus on the central and autonomic nervous systems and on immunological and neuroendocrine outcomes in this population in order to identify targets for treatment interventions and outcomes that should be improved during such treatments.

1. Clear, operationalized case definitions are important for this work. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, non-veteran patients with multisymptom illnesses like chronic fatigue syndrome or fibromyalgia may show different patterns of immunological or neurological function than veterans who have Gulf War illness and meet criteria for these disorders.

2. Similarly, Gulf War theater exposures, age and other variables likely moderate pathobiological effects and should be carefully addressed in research.

3. In some studies that have included female Gulf War veterans, it appears that gender differences may play a role in the pathobiological expression of Gulf War illness and its effects. Gender should be considered whenever possible in mechanistic and treatment research on Gulf War illness.

4. Since the pathobiological mechanisms underlying Gulf War illness are poorly understood, exploratory probes such as genomics, metabolomics and proteomics may yield useful information that can lead to more focused research.

5. Epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative.

6. In order to effectively pursue "omics" and genetic correlates of Gulf War illness, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standardized protocols for sample collections should be established and followed.

7. Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e. acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness

progression. Statistical analysis should be integrative and deployed across these interacting systems whenever possible using methodologies that formally acknowledge regulatory control.

8. Animal models may be appropriate to investigate some mechanistic hypotheses and illness or exposure effects.

What effective treatments are available for patients with Gulf War illness and how should new treatments be developed?

Treatment research has increased significantly since 2008, particularly reflecting the work of the Gulf War Illness Research Program (GWIRP) of the DoD Congressionally Directed Medical Research Program (CDMRP). However, most of these studies are underway, with results pending. Promising preliminary reports from the limited trials to date indicate possible benefits provided by coenzyme Q10 (a dietary supplement), acupuncture, and use of continuous positive airway pressure (CPAP) during sleep in veterans with sleep disorders.

Early results provide encouraging signs that the treatment goals identified in the 2010 Institute of Medicine report are achievable: "Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. The committee suggests a path forward to accomplish these goals and we believe that, through a concerted national effort and rigorous scientific input, answers can likely be found" (Institute of Medicine, 2010, p. x).

It will continue to be important to explore both conventional medical approaches (such as medications or devices) as well as alternative therapies. Treatments based on proposed mechanisms of illness presentation and on specific symptoms are currently under development through two CDMRP-funded collaborative consortia and through other trials by individual investigators. These projects have the potential to identify treatments that address the fundamental physiological alterations underlying the illness, rather than simply the symptoms.

The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures.

This research should include a number of critical elements.

1. Clear, operationalized case definitions for Gulf War illness and other diagnostic subgroups for whom treatments are designed are essential.

2. Clear, operationalized definitions of the clinical targets for treatment must be included in the research plan.

3. Treatment outcomes must be clearly defined so that it is possible to quantify improvements associated with interventions.

4. Where possible, treatment outcomes should include improvement in measures associated with expressions of underlying pathology (abnormal laboratory and functional assays).

Treatment approaches based on known mechanistic pathways of Gulf War illness should be pursued. Effective treatments of Gulf War illness could also lead to significant breakthroughs in the treatment of

other exposure-related occupational and environmental health problems. Funding agencies should support intervention development at the proof-of-concept level as well as large-scale clinical trials as they become appropriate. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

Although the perfect animal model of Gulf War illness has not yet been developed, preclinical animal models can and should be used to develop and test new treatments focused on pathobiological mechanisms of Gulf War illness and the effects of Gulf War theater exposures.

Center- and consortium based treatment research efforts can capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials. The CDMRP treatment consortia are an important step in developing integrated treatments for ill Gulf War veterans as an initial assessment of treatment safety and efficacy in Phase I/II trials. Since CDMRP has limited capacity to fund larger clinical trials, validation studies through the VA Cooperative Studies Program (CSP) or similar large, multi-site, government sponsored programs are necessary to provide validation of the safety and efficacy outcomes identified in initial Phase I/II trials. When a pilot treatment study funded by VA or CDMRP shows promising results and is judged to have scientific merit, VA should follow up with a larger trial or other systematic assessment of the treatment's potential benefits.

Data on effective treatments from VA's 2005 longitudinal survey should be published. Information from veterans with Gulf War illness and their treating physicians on treatments that they believe have been effective should be collected and published. This should include reconducting the IOM review of treatments by Gulf War veterans' medical practitioners ordered by Congress in 2010 (Public Law 111-275, 2010, Section 805). This study was transformed into a literature review of treatments for mainly mental health problems by a group with no experience in treating Gulf War illness.

VA Annual Reports to Congress on Gulf War illness research funded by VA should include only studies and treatment trials in which the health of Gulf War veterans is the central focus and in which the study participants are primarily Gulf War veterans.

Congress should maintain its funding to support the effective treatment-oriented Gulf War Illness Research Program at the DoD Office of Congressionally Directed Medical Research Programs for openly competed, peer-reviewed studies to identify:

1. Effective treatments for Gulf War illness,

2. Objective measures that distinguish veterans with Gulf War illness from healthy veterans, and

3. Underlying biological mechanisms potentially amenable to treatment.

Introduction

This document updates the reviews of research that were contained in prior reports from the Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI, generally referred to within the report as the Committee).

For the research review, the Committee considered published reports that appeared after those published in the 2008 RACGWVI report and before December, 2013. Results appearing during the 2008-2013 time period are compared to conclusions reached on parallel topics in the 2008 report where applicable. Published research studies are summarized in tables as well as text throughout this report.

The report is divided into four Research Review sections on Gulf War illnesses and health issues — Epidemiology, Etiology (Human and Animal Studies), Pathobiology and Treatment Research. Each section reviews research within specific subtopics, followed by Conclusions and Recommendations appropriate for the full section.

The Research Review is followed by a listing of research recommendations.

The report was drafted by Committee members and staff and reviewed by Committee members who were active at the time the report was begun in 2013 and active members in 2014.

Research Review and Update

Literature Review: The 2010 Institute of Medicine Report

There has been one review of the scientific literature related to Gulf War veterans' health since 2008. This review was conducted by the Institute of Medicine (IOM) in 2009 and 2010 and was released in April 2010, *Gulf War and Health: Volume 8: Update of Health Effects of Serving in the Gulf War* (Institute of Medicine, 2010).

The review was commissioned by the Department of Veterans Affairs. The IOM committee was charged with reviewing the literature since the 2006 IOM report, *Gulf War and Health, Volume 4: Health Effects of Serving in the Gulf War*, regarding health outcomes in cancer, ALS and other neurological diseases, birth defects and other adverse pregnancy outcomes, postdeployment psychiatric conditions, cause-specific mortality, and any other emerging health outcomes (Institute of Medicine, 2010, p. 2).

The IOM committee reviewed epidemiologic studies of health outcomes in Gulf War veterans since 2005. Over 1000 new citations were identified. The committee also reviewed the studies that had been included in Volume 4 as primary or secondary research. It did not review toxicologic, animal or experimental studies comprehensively but did evaluate "key epidemiologic and animal data cited in the [2008] RACGWVI report" (Institute of Medicine, 2010, p. 2).

The 2010 IOM report findings generally were in accordance with those of the 2008 RACGWVI report.

- "[C]urrent estimates [are] that more than 250,000 U.S. Gulf War veterans have persistent unexplained medical symptoms" (Institute of Medicine, 2010, p. 262).

- "The committee . . . accepted that multisymptom illness was a diagnostic entity" (Institute of Medicine, 2010, p. 204).

- "The committee concludes that there is sufficient evidence of association between deployment to [the] Gulf War and chronic multisymptom illness" (Institute of Medicine, 2010, p. 204).

- "The excess of unexplained medical symptoms reported by deployed Gulf War veterans cannot be reliably ascribed to any known psychiatric disorder" (Institute of Medicine, 2010, p.109).

A significant difference between the reports was that while the 2008 RACGWVI report found pesticides and pyridostigmine bromide pills to be causally associated with Gulf War illness and that several other exposures cannot be ruled out (including low-level nerve agents, close proximity to oil well fires, receipt of multiple vaccines, and effects of combinations of exposures), the 2010 IOM committee concluded that "current evidence is inadequate to determine whether an association exists between multisymptom illness and any specific battlefield exposure or exposures" (Institute of Medicine, 2010, p. x).

However, the IOM committee did observe that "it is likely that Gulf War illness results from an interplay of genetic and environmental factors" (Institute of Medicine, 2010, p. 261).

The major recommendations of the 2010 IOM report were similar to the major recommendations of the 2008 RACGWVI report.

- "The committee believes that the path forward for veterans has two branches. The first is continued surveillance of Gulf War veterans... [The] second branch of inquiry . . . consists of a renewed

research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans" (Institute of Medicine, 2010, p. 260).

The IOM committee chair, Dr. Stephen Hauser, a former president of the American Neurological Association, emphasized in his preface to the report that the committee considered these goals to be achievable:

"Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. The committee suggests a path forward to accomplish these goals and we believe that, through a concerted national effort and rigorous scientific input, answers can likely be found" (Institute of Medicine, 2010, p. x).

1| Epidemiologic Research: Gulf War Illness and Other Health Issues Affecting 1990-1991 Gulf War Veterans

Understanding the impact of Gulf War service on the health of military personnel requires data from well designed epidemiologic studies that address priority health questions. In its 2008 report, the Committee reviewed the extensive body of epidemiologic research conducted in multiple populations of Gulf War era veterans. Results of these studies, overall, indicated that Gulf War illness is the most prevalent condition affecting Gulf War veterans but is not the only serious health problem. Studies consistently found that Gulf War illness affects at least 25 percent of the nearly 700,000 veterans who served in theater and that few veterans had recovered over time. Research also indicated that Gulf War illness differs fundamentally from postwar stress conditions and that post-traumatic stress disorder (PTSD) and other psychiatric conditions affect a relatively low proportion of Gulf War veterans compared to veterans of other wars.

Epidemiologic studies reviewed for the 2008 report also showed that Gulf War veterans may suffer from excess rates of a number of medical conditions but that overall disease-related mortality did not appear to be elevated. Further, important questions remain about the degree to which Gulf War veterans are affected by most medical conditions of concern and about the possible impact of Gulf War service on the health of veterans' family members.

In this section, epidemiological research reviewed in the 2008 report is summarized for various topics, followed by extensive discussion of the relevant research that has been published since then.

A. Gulf War Illness: Update on Epidemiologic Research

As described in previous reports, Gulf War illness refers to the complex of chronic symptoms that affects veterans of the 1990-1991 Gulf War at excess rates. Although individual symptoms can vary from person to person, the overall profile of symptoms is consistent across populations of Gulf War veterans. Concurrent symptoms typically include some combination of widespread pain, headache, persistent memory problems and other cognitive difficulties, fatigue, respiratory symptoms, gastrointestinal problems and skin abnormalities.

In the early years after the war, this problem was commonly called "Gulf War Syndrome" by the media and has since been referred to by a variety of names such as undiagnosed illness, Gulf War illness, chronic multisymptom illness and various other terms. Gulf War illness, the term most commonly used by scientists, clinicians, veterans' groups, and the Department of Defense, is used throughout this report to refer to the chronic symptomatic illness, variously defined, associated with military service in the 1990-1991 Gulf War. The recent Institute of Medicine committee on Gulf War illness case definitions supported the use of this terminology (Institute of Medicine, 2014).

B. How Many Veterans Have Gulf War Illness?

In previous reports, the Committee reviewed available research that provided information concerning the number of veterans affected by Gulf War illness. Overall, the proportion of veterans with Gulf War illness identified by different studies was highly variable, ranging from 29 to 65 percent, depending on how the condition was defined. Case definitions that are very broad, for example, identify a larger number of veterans as having Gulf War illness, often 50 percent or more of those who deployed. More restrictive case definitions, in contrast, characterize fewer veterans as Gulf War illness cases.

In estimating the prevalence of this condition, the Committee focused on the burden of Gulf War illness that is specifically attributable to service in the 1990-1991 Gulf War. Medical research has long documented that some degree of symptomatology occurs in any population. The Committee therefore evaluated the *excess* rates of symptomatic illness in Gulf War veterans, that is, the proportion of 1991 Gulf War veterans who experienced multiple chronic symptoms, over and above the "background"

rate of these symptoms seen in contemporary veterans who did not deploy to the Gulf War theater. This approach produced a consistent estimate of the prevalence of symptomatic illness attributable to Gulf War service, independent of the case definition used.

As shown in Table 1, six of seven population-based estimates published before 2008 determined that Gulf War illness, variously defined, affected an excess of 26 – 32 percent of Gulf War veterans compared to nondeployed era veterans. The one exception was an excess rate of 13 percent, reported by a VA national study of 1,035 Gulf War era veterans assessed in 1999-2001 (Blanchard et al., 2006). In its 2008 report, the Committee speculated that this difference might be explained by the VA study's use of a restrictive modification of the Fukuda 1998 chronic multisymptom illness (CMI) case criteria (Fukuda et al., 1998), which appeared to reduce the number of identified cases disproportionately in Gulf War veterans compared to nondeployed era veterans.

Since 2008, a second VA study evaluated a much larger sample of 6,111 Gulf War veterans drawn from the same target population as the previous VA study and used a different multisymptom illness case definition (Kang et al., 2009). The later study identified an overall multisymptom illness prevalence of 37 percent in Gulf War veterans and an excess prevalence of 25 percent, consistent with most previous studies.

Two smaller national surveys, conducted by VA investigators in 2001 but published in 2008 and 2012, reported unweighted chronic multisymptom illness (CMI) prevalence estimates of 50 percent (mail survey; Smith et al., 2012) and 54 percent (telephone survey; King et al., 2008). Similarly, a population-based study of veterans residing in the greater Kansas City area reported that 45 percent of 646 Gulf War veterans surveyed by telephone screened positive for CMI as defined by Fukuda et al. (Steele et al., 2012). Two studies published since 2008 used entirely different approaches to defining Gulf War illness, with differing tabulation of symptoms in domains identified by factor analyses. These more restrictive case definitions identified a substantially lower overall prevalence of symptomatic illness (14-26%) in Gulf War veterans and a substantially lower excess prevalence (10%) in comparison to nondeployed veterans (Iannacchione et al., 2011; Kelsall et al., 2009).

Overall, all population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans. While prevalence estimates differ with the case definitions used, seven of ten population-based studies indicate that 25 – 32 percent of 1991 Gulf War veterans are affected by this illness, over and above symptom levels documented in nondeployed era veterans. Three studies, including two published since 2008, provided substantially lower estimates of excess prevalence (10 – 13%) in Gulf War veterans, compared to nondeployed veterans. These differences can largely be attributed to the case definitions used, since the three studies that provided lower prevalence estimates also used case definitions that were considerably more restrictive than definitions used by other studies. Differences are unlikely to be attributable to actual reductions in illness rates among Gulf War veterans, given the general consistency in prevalence estimates between earlier and more recent studies that used less restrictive case definitions. In addition, longitudinal studies consistently indicate that Gulf War illness rates and symptom frequencies reported by veterans have not declined with time (Hotopf et al., 2003; Ozakinci et al., 2006; Proctor et al., 1998; Wolfe et al., 2002).

Differences in excess prevalence rates reported by different studies provide a clear illustration of the importance of case definition in Gulf War illness research. The degree to which one prevalence estimate is more accurate than another depends on the degree to which the case definition used is sufficiently sensitive and specific in "capturing" the pattern of chronic excess symptoms associated with Gulf War service.

Table 1. Population-Based Prevalence Estimates: Chronic Symptomatic Illness in 1990-1991 Gulf War Veterans and Nondeployed Era Veterans

Study	*Gulf War Veterans Assessed*	*Year(s) of Assessment*	*Case Definition Used*	*Prevalence in Gulf War Veterans*	*Prevalence in Nondeployed Veterans*	*Excess Illness in Gulf War Veterans*
Prevalence estimates published before 2008						
Fukuda et al., 1998	1,155 Air Force veterans	1995	CMI	45%	15%	30%
Proctor et al., 2001	180 New England Army veterans	1994-1996	CMI (modified)	65%	33%	32%
Unwin et al., 1999	4,428 U.K. male veterans	1998	CMI (modified)	62%	36%	26%
Unwin et al., 2002	226 U.K. female veterans	1998	CMI (modified)	64%	35%	29%
Steele, 2000	1,548 Kansas veterans	1998	Kansas GWI CMI	34% 47%	8% 20%	26% 27%
Blanchard et al., 2006	1,035 U.S. veterans	1999-2001	CMI (modified)[1]	29%	16%	13%
Prevalence estimates published since 2008						
King et al., 2008	357 U.S. veterans	2001	CMI	54%	not evaluated	-
Kang et al., 2009	6,111 U.S. veterans	2005	VA-defined multisymptom illness[2]	37%	12%	25%
Kelsall et al., 2009	1,381 Australian veterans	2000-2002	Australian factor definition	26%	16%	10%
Iannacchione et al., 2011	5,699 U.S. veterans	2007-2009	Haley factor definition (3 syndromes combined)	14%	4%	10%
Steele et al., 2012	646 Kansas City area veterans	2000	CMI	45%	not evaluated	-
Smith et al., 2012	317 U.S. veterans	2001	CMI	50%[3] 34%[3]	not evaluated	-

Abbreviations: CMI = chronic multisymptom illness, as defined in Fukuda et al. (1998); Kansas GWI=Kansas Gulf War illness as defined in Steele (2000)

[1]CMI modification replaced fatigue criterion with fatigue lasting > 24 hours after exertion

[2]Unexplained multisymptom illness defined as multiple types of symptoms occurring together, not explained by medical/psychiatric diagnoses

[3]Unweighted sample prevalence = 50% (prevalence estimate weighted to reflect general population = 34%)

C. Gulf War Illness Prognosis: Are Veterans Getting Better or Worse with Time?
A question of great importance concerns the extent to which veterans' symptoms improve, stay the same or become progressively worse over time. In its 2008 report, the Committee reviewed results of longitudinal evaluations from four studies of Gulf War veterans, all of which indicated that the symptomatic illness affecting Gulf War veterans had not improved with time. This included published studies reporting results from two follow-up evaluations of the Fort Devens cohort (Proctor et al., 1998; Wolfe et al., 2002), a four year follow-up of British Gulf War veterans (Hotopf et al., 2003) and a five year follow-up (1995 – 2000) of 390 veterans enrolled in the VA's Gulf War Registry (Ozakinci et al., 2006).

The 2008 report also described preliminary results from a longitudinal assessment of Gulf War illness from the VA's national survey of Gulf War era veterans presented at a 2005 Committee meeting by Dr. Han Kang. At that time, Dr. Kang reported that 2,016 (35%) of 5,767 Gulf War veterans surveyed reported having "unexplained multisymptom illness lasting six months or longer" (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008, p. 36). Most Gulf War veterans (67%) indicated their condition had developed between 1991 and 1993, but relatively few had recovered or substantially improved since that time, as detailed in Table 2.

Table 2. Change in Unexplained Multisymptom Illness (MSI) Over Time: Gulf War Veterans Who Reported MSI Lasting 6 Months or Longer After January 1991

Status of Illness in 2005	Proportion of 2,016 Gulf War Veterans
Completely recovered	2 %
Much improved	7 %
Somewhat improved	14 %
About the same	36 %
Somewhat worse	25 %
Much worse	15 %

Source: Kang HK, Preliminary Findings: Reported Unexplained Multisymptom Illness Among Veterans Who Participated in the VA Longitudinal Health Study of Gulf War Era Veterans (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008, p. 36).

Taken together, studies evaluated through 2008 indicated that, on average, the frequency of symptoms reported by Gulf War veterans remained relatively stable over time. Preliminary longitudinal results from VA's national study indicated that few veterans with multisymptom illness had recovered or substantially improved as of 2005 and that 40 percent had become worse since the onset of their illness. These findings underscored the seriousness of the Gulf War illness problem and the urgent need to identify effective treatments for veterans who remained ill many years after their return from Desert Storm.

Little additional information on the long-term prognosis of Gulf War illness has become available since 2008. A 2002 follow-up of 362 veterans surveyed in the VA Gulf War Registry sample indicated that symptoms remained largely stable since the original 1995 evaluation (Brewer et al., 2008). Regrettably, although a variety of findings from VA's 2005 national longitudinal study of Gulf War era veterans have now been reported in several publications, results concerning the prognosis of Gulf War multisymptom illness, originally presented to the Committee in 2005, have not yet been published.

Boston investigators are currently conducting a follow-up assessment of the Fort Devens cohort, which will provide more current insights on the course and prognosis of Gulf War illness more than 23 years after the war. The third wave follow-up of the largest U.S. national cohort, the VA's National Survey of

Gulf War era veterans, is also currently underway. Unfortunately, this large national study does not include the questions necessary to assess Gulf War illness by any case definition. And unlike the 2005 survey, the 2013 survey does not collect data on the degree to which veterans with Gulf War illness may have improved or worsened over time.

D. Other Health Issues Associated with Gulf War Service

1) General Health Status of Gulf War Veterans

Studies conducted since the Gulf War have historically indicated that, when considered as a group, Gulf War veterans are in considerably poorer health overall than nondeployed veterans who served during the same period. Studies published since 2008 have continued to document poorer general health status and greater disability among Gulf War veterans (Table 3). These include a recent British report that compared health indicators in U.S. and U.K. Gulf War veterans who had been surveyed in 1995-1996 (U.S.) and 1997-1998 (U.K.). Overall, Gulf War veterans in both countries reported a greater number of symptoms and scored more poorly on the SF-36 General Health scale (Ware and Sherbourne, 1992) than nondeployed veterans of the same period (Ismail et al., 2011).

Table 3. Studies on GWI Symptom Reporting: 2009-2013

Study	*Groups Studied*	*Outcome(s)*	*Key Findings*
Horn et al., 2010	4,257 U.K. GWV and 4,295 U.K. IWV	HSC, GHQ-12	Symptom reporting increased over 7 years across all symptom dimensions for U.K. veterans, and increase was greater in analyses adjusting for psychological morbidity. Results not specific for deployment era.
Kang et al., 2009	6,111 GWV, 3,859 NDV	SF-12	GWV had significantly lower mean scores on both PF and MF summary scales.
Iannacchione et al., 2011	3,442 deployed GWV, 765 NDV	SF-12	Deployed GWV with GWI had significantly lower mean functional status than nonsymptomatic GWV.
Ismail et al., 2011	3,626 U.S. GWV and 5,573 U.K. GWV	SF-36, GHP and PF	PF scores did not differ between U.S. and U.K. GWV but GHP scores were significantly different.
Smith et al., 2013	311 deployed GWV	CMI symptoms	Most common symptom was fatigue, followed by memory impairment, joint issues, sleep difficulty, and mood lability.

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; NDV = nondeployed Gulf War era veterans; IWV = Iraqi War Veterans; HSC = Hopkins Symptom Checklist; GHQ-12 = General Health Questionnaire; SF-12 = Short-Form Health Survey 12; SF-36= Medical Outcomes Survey Short Form 36; GHP = General Health Perception; PF = physical functioning; MH = mental functioning; CMI = chronic multisymptom illness, as defined in Fukuda et al. (1998)

British veterans reported lower general health status and more health symptoms than U.S. veterans but not more medical diagnoses (Ismail et al., 2011). The Department of Veterans Affairs longitudinal assessment, published in 2009, compared a variety of health indicators in 6,111 Gulf War veterans and 3,589 era veterans (Kang et al., 2009). Only 35 percent of Gulf War veterans considered their general health to be “very good” or “excellent,” compared to 54 percent of nondeployed veterans of similar age. Gulf War veterans also reported, on average, significantly more sick days and physician visits than era veterans who did not serve in the Gulf War. In addition, two national surveys conducted in 2005 and 2008 reported that Gulf War veterans scored significantly worse than comparison veterans and the general

population on the SF-12 summary measure of physical health status, indicating a substantial reduction in health-related quality of life among Gulf War veterans (Iannacchione et al., 2011; Kang et al., 2009).

2) Other Medical Conditions Affecting Gulf War Veterans

As noted in the 2008 Committee report, few studies have evaluated the degree to which Gulf War veterans suffer from excess rates of medical conditions other than Gulf War illness. Epidemiologic studies available at that time indicated that amyotrophic lateral sclerosis (ALS) was significantly more prevalent in Gulf War veterans than in nondeployed era veterans. In addition, a VA mortality study reported that Gulf War veterans potentially exposed to low levels of nerve agents in connection with the Khamisiyah demolitions had died from brain cancer at twice the rate of other veterans in theater. Several surveys also provided indications that Gulf War veterans may have elevated rates of diagnosed migraines, seizures, gastrointestinal conditions, respiratory conditions and skin disorders (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008).

However, despite the extensive number of studies conducted in Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains inadequate. Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by medical conditions of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess rates of most medical conditions. This lack of scientific evidence undermines the ability of the Secretary of Veterans Affairs to make informed determinations concerning conditions for which veterans should be service-connected for purposes of disability compensation.

Neurological Conditions in Gulf War Veterans

Studies reporting a significant excess of amyotrophic lateral sclerosis (ALS) diagnoses in veterans of the 1990-1991 Gulf War were summarized in the 2008 report. New onset ALS cases occurred at higher rates in deployed Gulf War veterans than in nondeployed controls (Coffman et al., 2005; Horner et al., 2008), possibly with an earlier age at onset (Haley, 2003). However, this excess of new cases appears to have occurred only in the first five years after the war (Horner et al., 2008), suggesting a time-delimited ALS "outbreak" associated with Gulf War service. In addition, ALS risk was found to be related to location in specific geographic areas in theater (Miranda et al., 2008), possibly indicating an association with events or exposures in those areas. Since 2008, two studies addressed ALS in Gulf War veterans (Table 4). Evaluating 109 cases, Kasarskis and colleagues (2009) found that while ALS age, site of onset, and symptom presentation were similar for Gulf War and nondeployed era veterans, ventilator-free survival time after initial diagnosis was significantly shorter in Gulf War deployed veterans (Kasarskis et al., 2009). And, as described in more detail below, a VA study reported in 2009 that Gulf War veterans did not have an excess rate of death due to ALS compared to nondeployed era veterans (Barth et al., 2009).

However, this and a previous VA mortality study identified excess rates of brain cancer deaths among the subgroup of Gulf War veterans who had potentially been exposed to low levels of nerve agents resulting from munitions demolitions in theater (Barth et al., 2009; Bullman et al., 2005). These studies are described later in this report.

Although neurological conditions are a prominent concern for Gulf War veterans, very little research is available that identifies rates of most neurological disorders in this population: rates of multiple sclerosis, Parkinson's disease and other neurological diseases are currently unknown. This Committee and the Institute of Medicine have long recommended that VA conduct studies to determine if Gulf War veterans have experienced increased rates of multiple sclerosis and other neurological disorders since the war. In 2008, Congress enacted legislation requiring VA to contract with the IOM to conduct a study "to identify incidence and prevalence of diagnosed neurological diseases, including multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in 1991 Gulf War veterans, in Post 9/11 Global Operations veterans, and in nondeployed

comparison groups. To date, however, no research studies have been conducted to evaluate prevalence rates of these conditions in Gulf War veterans.

Preliminary information on a number of other neurological conditions was provided from data collected for VA's 2005 national longitudinal survey of nearly 9,000 Gulf War era veterans published in 2009 (Kang et al., 2009). Gulf War veterans reported being diagnosed by their doctors with a number of neurological conditions at significantly higher rates than nondeployed era veterans. These included repeated seizures, neuralgia or neuritis, and stroke. Most of these conditions had also been reported at excess rates by Gulf War veterans in VA's 1996 national survey, along with migraines (which were not assessed in 2005; Kang et al., 2000). Although these conditions were self-reported, medical record reviews for both the 1996 and 2005 VA national surveys indicated a high degree of concordance (93 – 96%) between medical records and veteran-identified reasons for clinic visits and hospital stays (Kang et al., 2009; Kang et al., 2000).

Previous indications of significantly increased rates of migraines among Gulf War veterans (Gray et al., 2002; Kang et al., 2000; Steele, 2000; Unwin et al., 1999) were supported by a recent clinical study that evaluated 50 Gulf War veterans meeting case criteria for chronic fatigue syndrome (CFS; Rayhan et al., 2013b). A large proportion (64%) of Gulf War veterans in the study were diagnosed with migraines, similar to nonveteran subjects with CFS, and significantly higher than sedentary controls.

Rates of multiple sclerosis (MS) were explored in all veterans who served in the military between 1990-2007 (Wallin et al., 2012). Incidence rates of MS were three times higher in female veterans compared to male veterans, regardless of race, which has been found in the general population (Baum and Rothschild, 1981). Black servicemen and women showed significantly higher incidence rates of MS compared to white, Latino and Asian veterans, which is the reverse for prevalence rates in the U.S. (Baum and Rothschild, 1981). However, the results were not broken out to show if veterans who deployed to the 1990-1991 war had an excess rate of MS compared to other 1990-2007 veterans, although this study was funded under the VA Gulf War research portfolio.

Despite concerns raised by veterans' groups in relation to MS rates in Gulf War veterans, as well as Congressional directives and previous RACGWVI and IOM recommendations, the only MS study that included veterans of this era was not designed to determine if Gulf War veterans are affected by excess rates of MS. The 2012 VA study included individuals who had applied for VA disability benefits for MS and had served in the military between 1990 and 2007 (Wallin et al., 2012). The study did not include veterans with MS who had not applied for disability compensation, nor did it distinguish 1990-1991 Gulf War veterans from veterans who did not serve in a warzone or those who served in other periods through 2007.

A large national VA survey, currently underway, will provide some insight concerning the degree to which Gulf War veterans are affected by excess rates of neurological diseases. This longitudinal survey of VA's national sample of 30,000 Gulf War era veterans will, for the first time, include a more comprehensive assessment of physician-diagnosed neurological diseases, as reported by Gulf War and nondeployed era veterans. A second national survey, recently funded by DoD, will also query veterans about physician-diagnosed neurological and other diseases. Neither of these surveys, however, is a substitute for the rigorous epidemiological study ordered by Congress or recommended by past RACGWVI and IOM reports.

Table 4. Studies Reporting on Neurological Conditions in Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Outcome(s)*	*Key Findings*
Barth et al., 2009	621,902 GWV, 746,248 NDV	Mortality due to brain cancer, MS, PD, and ALS	GWV potentially exposed to nerve agents over multiple days and GWV with greatest exposure to oil well fires had significantly higher rates of brain cancer mortality. Overall, mortality due to brain cancer, PD, MS, ALS similar in GWV and NDV.
Kang et al., 2009	6,111 GWV, 3,859 NDV	Diagnosed medical conditions reported by veterans	Compared to NDV, GWV reported significantly higher rates of repeated seizures, neuralgia/neuritis, and stroke.
Kasarskis et al., 2009	43 deployed GWV with ALS, 66 nondeployed GWV with ALS	ALS age of onset, site of onset, atypical symptom features, ventilator-free survival time	No differences between ALS symptoms, age and site of onset similar for deployed GWV vs. nondeployed. Ventilator-free survival time post-diagnosis was significantly shorter in deployed GWV.
Rayhan et al., 2013	50 symptomatic GWV, 39 CFS patients, 45 sedentary controls	Structured headache evaluation	Statistically similar proportions of GWV (64%) and CFS (82%) patients affected by migraines; both significantly greater than controls (13%)
Wallin et al., 2012	2,691 veterans who served in the military between 1990 and 2007, and had applied for VA benefits for MS	MS incidence by age, sex, race and branch of service	No determination of MS rates specifically in relation to 1991 Gulf War era or deployment. MS incidence was significantly higher in females than males, blacks vs. other races, and in Air Force and Army veterans vs. other branches.

Abbreviations: GWV = Gulf War veterans; NDV = Nondeployed veterans; ALS= amyotrophic lateral sclerosis; PD = Parkinson's disease, MS = multiple sclerosis; CFS= chronic fatigue syndrome

Cancer in Gulf War Veterans

As described in the 2008 Committee report, only limited research has been conducted to determine cancer rates in Gulf War veterans. As of 2008, information from two studies provided no evidence of significantly increased cancer morbidity among Gulf War veterans (Macfarlane et al., 2003; McCauley et al., 2002). However, preliminary data from one pilot study indicated a significant proportional excess of testicular cancer and non-Hodgkin's lymphoma among deployed Persian Gulf War veterans identified in specific state cancer registries (Levine et al., 2005).

In addition to the increase in brain cancer deaths related to nerve agent and oil fire exposures described elsewhere in this chapter (Barth et al., 2009, see Table 4), two studies since 2008 have evaluated cancer morbidity in Gulf War veterans. In VA's national longitudinal study, Gulf War veterans reported similar rates of both skin cancer and other cancers compared to nondeployed era veterans. In addition, Young et al. (Young et al., 2010) utilized data from 28 state cancer registries to evaluate proportional incidence ratios of specific cancer types among Gulf War and era veterans. Overall, a significantly higher proportion of lung cancer cases was identified in 1991 Gulf War veterans compared to nondeployed era veterans (Table 5). No other cancers were significantly increased, while Gulf War veterans had significantly lower proportional rates of testicular cancer and Kaposi's sarcoma compared to nondeployed era veterans.

Overall, cancer studies have identified a significant proportional excess of lung cancer rates and increased brain cancer mortality among Gulf War veterans, although cancer data in this population are limited. The continued paucity of data on specific types of cancer among Gulf War veterans is problematic. Data on cancer rates among veteran subgroups associated with deployment exposures, locations, and branches of

service are of particular importance, as illustrated by studies of brain cancer mortality in Gulf War veterans. These studies have reported that proximity to the plume of nerve agent released by the destruction of the Iraqi storage facility at Khamisiyah was associated with increased brain cancer. And, since many cancers have long latencies prior to diagnosis, research to determine cancer rates in this cohort remains a high priority.

Table 5. Studies Reporting on Cancer in Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Outcome(s)***	***Key Findings***
Kang et al., 2009	6,111 GWV, 3,859 NDV	Self-reported diagnosed cancer	GWV and NDV report similar rates of skin cancer (12%) and "other" cancer (10%).
Young et al., 2010	8,211 GWV with cancer, 12,864 NDV with cancers	Proportional incidence ratios of cancer diagnoses from 28 state cancer registries	Proportional incidence of lung cancer significantly higher in GWV compared to NDV. Proportional incidence of testicular cancer and Kaposi's sarcoma significantly lower in GWV.

Abbreviations: GWV = Gulf War veterans; NDV = nondeployed Gulf War era veterans

Sleep dysfunction in Gulf War veterans

Historically, studies reporting on sleep dysfunction find that Gulf War veterans report greater rates of sleep and circadian disturbances relative to controls (Haley et al., 2004; Peacock et al., 1997; White, 2003). Sleep apnea results from two previous studies were inconsistent: Peacock et al. (1997) reported increased sleep apnea in Gulf War veterans, while Haley et al.(2004) did not. Animal studies modeling exposures experienced by Gulf War veterans showed sleep abnormalities in depleted uranium (Houpert et al., 2005; Lestaevel et al., 2005) and sarin exposed groups (Burchfiel et al., 1976; van Helden et al., 2004).

One study published since 2008 addressed sleep disturbances in symptomatic Gulf War veterans compared to age and obesity-matched asymptomatic Gulf War veteran controls (Table 6). Amin et al. (2011a) found a significantly increased occurrence of sleep apneas, hypopneas and mild inspiratory airflow limitation in symptomatic veterans. Treatments utilizing continuous positive airway pressure (CPAP; see Treatments section) have shown early promise as treatments in symptomatic veterans with sleep disordered breathing (Amin et al., 2011b).

Table 6. Studies Reporting on Sleep Disturbances in Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Outcome(s)***	***Key Findings***
Amin et al., 2011a	18 GWV with GWI, 11 healthy GWV controls	Sleep apnea, hypopnea, airflow limitation	When compared to matched healthy controls, symptomatic GWV showed significantly increased numbers of arousals, sleep disordered breathing and flow-limited breathing during NREM stage 2 sleep, indicating more collapsible upper airways.

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; NREM = Non-rapid eye movement

Self-reported Rates of Other Medical Conditions Affecting Gulf War Veterans
As described previously, in the 23 years since the Gulf War, relatively little research has been conducted to determine if service in the 1990-1991 Gulf War is associated with excess rates of most medical conditions of possible concern in this population. Previous recommendations by the Committee and by the Institute of Medicine have called for in-depth surveillance of health outcomes affecting Gulf War veterans over time. Data from such research is essential to provide adequate healthcare for Gulf War veterans and for making scientifically informed determinations regarding disability compensation. As described in the Committee's 2008 report, multiple large population surveys of Gulf War era veterans have provided preliminary indications that Gulf War veterans have been affected by a variety of medical conditions at significantly higher rates than nondeployed era veterans. These include veteran-reported diagnoses of migraines, seizures, digestive disorders, respiratory conditions, skin disorders and symptom-defined conditions, including fibromyalgia and chronic fatigue syndrome.

Since 2008, one national study has provided additional information on veteran-reported medical diagnoses. The large VA longitudinal survey, conducted in 2005, found that Gulf War veterans reported being diagnosed by their doctors with a variety of medical conditions at significantly higher rates than nondeployed era veterans. These include excess rates of seizures, stroke, emphysema, asthma, gastritis, irritable bowel syndrome, skin disorders and heart disease (Kang et al., 2009). The project also included validation studies conducted in a subgroup of 572 veterans and found a high degree of accuracy (93%) in veteran-reported reasons for clinic visits and hospitalizations.

Adverse Reproductive Outcomes and Birth Defects in Gulf War Veterans
Studies of birth defects and adverse reproductive outcomes in deployed Gulf War veterans have reported mixed results. As described in the 2008 Committee report, a number of early studies found no association between Gulf War service and birth defects (Cowan et al., 1997; Cowan et al., 2002; Penman et al., 1996). A later study looked specifically at Goldenhar Syndrome, a rare congenital defect. Excess cases of Goldenhar Syndrome were seen in children of deployed veterans (Araneta et al., 1997); however the rarity of the condition made results difficult to interpret, despite the large sample size. U.K. veterans showed a significant increase in birth defects in children born to Gulf War veterans, specifically related to genitourinary and musculoskeletal systems (Doyle et al., 2004) and higher reported rates of male infertility (Maconochie et al., 2004). American Gulf War veterans reported significantly higher rates of miscarriage and birth defects (Araneta et al., 2003; Doyle et al., 2004; Kang, 2003; Kang and Bullman, 2001). Significantly higher rates of heart defects and urethral opening defects were also found in the children of male veterans (Araneta et al., 1997). However, the 2008 report noted that although statistically significant small increases in birth defect rates were found, overall rates of birth defects are within the range of those found in the general population.

Three studies have provided information on reproductive outcomes since the 2008 report (Table 7). In the large VA longitudinal survey of Gulf War era veterans conducted in 2005, women Gulf War veterans reported difficulty conceiving at significantly higher rates (10%) than nondeployed era veterans (4%) but no differences in rates of miscarriage over the previous six months (Kang et al., 2009). Although VA's 1996 national survey of Gulf War era veterans had identified significantly increased rates of birth defects among children of Gulf War veterans (Kang, 2003; Kang et al., 2001), birth defects were not assessed in the 2005 follow-up survey.

Investigators at the Naval Health Research Center utilized data from the Department of Defense Birth and Infant Health Registry to assess birth defect rates among infants born between 1998 and 2004 to parents who remained in the military and previously served in the 1990-1991 Gulf War (Bukowinski et al., 2012). Provided separately for children of male and female Gulf War veterans, results identified no significant differences between Gulf War and nondeployed era veterans overall or for eight specific types of birth defects. Birth defect rates also did not differ in relation to several deployment characteristics, including

exposure to oil fire smoke and fallout from the Khamisiyah demolitions. Only paternal deployment duration between 153 and 200 days was associated with a significantly increased rate of birth defects compared to shorter duration deployment (Bukowinski et al., 2012). This major study is particularly noteworthy for its evaluation of birth defect rates in veteran subgroups associated with exposures and experiences during the Gulf War. Limitations relate to the study's inclusion only of births to Gulf War era veterans who remained in the military after 1998 (excluding births among 60 – 75% of Gulf War veterans during that period). And despite the large size of the study population, most individual types of birth defects were rare, providing limited power to determine the significance of findings related to specific types of birth defects.

Additional information is provided by a study conducted in French Gulf War veterans. Overall and individual birth defect rates among children born to 5,666 French Gulf War veterans were generally similar to those in the general French population, although the rate of Down's syndrome was significantly lower in children of Gulf War veterans (Verret et al., 2008).

Table 7. Studies Reporting on Adverse Reproductive and Birth Outcomes in Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Outcome(s)*	*Key Findings*
Bukowinski et al., 2012	178,766 infants born to deployed GWV	Birth defects	No increased overall risk of birth defects; paternal deployment length between 153 and 200 days was significantly associated with higher birth defect rate when compared to paternal deployment length <92 days.
Verret et al., 2008*	5,666 French GWV	Fertility disorders, miscarriage, birth defects, preterm birth	No evidence of an association between paternal GW deployment and adverse reproductive or birth outcomes.
Kang et al., 2009	1,225 women GWV and 851 women NDV	Fertility disorders, miscarriage	Significantly higher rates (10%) of fertility disorders in women GWV than NDV (4%) but no difference in miscarriage rates during prior 6 months.

Abbreviations: GWV = Gulf War veterans; NDV = nondeployed Gulf War era veterans
* Papers published in 2008 after the 2008 RACGWVI report release have been included.

3) Multisymptom Illnesses: Chronic Fatigue Syndrome, Fibromyalgia, Multiple Chemical Sensitivity

In its 2008 report, the Committee reviewed Gulf War studies that assessed rates of symptom-defined illnesses found in the general population based on established case definitions for fibromyalgia (FM), chronic fatigue syndrome (CFS) and multiple chemical sensitivity (MCS). Taken together, these studies indicated that a relatively small proportion of veterans who meet Gulf War illness criteria, by any case definition, also meet defining criteria for FM, CFS or MCS. Epidemiologic studies, however, did commonly find that a higher proportion of Gulf War veterans than nondeployed era veterans met criteria for these syndromes, particularly for CFS. The largest study that utilized clinical evaluations of veterans reported that 1.6 percent of Gulf War veterans met CFS criteria, compared to only 0.1 percent of nondeployed era veterans, a nearly 41-fold greater CFS risk among Gulf War veterans. The prevalence of CFS in Gulf War veterans is also substantially higher than in the general population, where CFS affects approximately 0.2 percent of adults (Jason et al., 1999; Reyes et al., 2003).

Since 2008, studies have provided additional information on CFS in Gulf War veterans but few insights concerning FM, MCS, or other symptom-defined conditions (Table 8). In the large VA study of over 6,000 veterans evaluated in 2005, investigators reported that 37 percent of Gulf War veterans report "unexplained multisymptom illness" but only nine percent met study criteria for a "CFS-like" illness based on reported symptoms (Kang et al., 2009; Li et al., 2011a). British investigators also reported that among 111 disabled U.K. Gulf War veterans, 18 percent met CFS criteria, compared to just three percent of disabled Gulf War era and Bosnia veterans (Ismail et al., 2008). Fibromyalgia was diagnosed in 2.7 percent of disabled Gulf War veterans but was not significantly more prevalent than in veteran comparison groups (Ismail et al., 2008). While there is some overlap between Gulf War illness symptoms and symptoms reported by CFS and FM patients, studies continue to indicate that criteria for these conditions do not adequately describe Gulf War illness and do not account for the large majority of cases.

The Committee's 2008 report described results from seven studies that compared ill Gulf War veterans to civilian patients with CFS or FM on specific biological measures. Two studies reported similarities between Gulf War and civilian patients and five studies reported differences. Since 2008, several additional studies have compared illness characteristics of Gulf War veterans who meet CFS criteria to civilian patients with CFS. New Jersey investigators compared 45 male Gulf War veterans meeting CFS criteria to 84 male civilians with CFS. Although identical CFS case criteria were used in both groups, patients' illnesses differed in a number of important respects. Gulf War veterans were significantly less likely to have comorbid FM, to be physically disabled, and to report sudden illness onset compared to civilians with CFS (Ciccone et al., 2008). The authors pointed out that, although both groups satisfied the same case defining criteria, they may nonetheless have different disorders. As described in later sections of this report, additional studies have reported differences between Gulf War veterans and civilian CFS patients in relation to several immune parameters (Broderick et al., 2012; Smylie et al., 2013). Studies have reported similarities between Gulf War veterans and CFS patents in relation to the prominence of migraine headaches in both groups (Rayhan et al., 2013b), as well as similarities between Gulf War veterans and FM patients on measures associated with pain response (Cook, 2012).

Table 8. Studies Reporting on Other Multisymptom Conditions in Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Outcome(s)***	***Key Findings***
Other multi-symptom conditions (FM, CFS, MCS)			
Ciccone et al., 2008 *	45 CFS GWV and 84 matched male civilians	CFS screening questionnaire	CFS characteristics differed between GWV and civilian controls. Civilian CFS more likely to have sudden flu-like onset and be comorbid with FM and psychiatric disorders.
Ismail et al., 2008 *	111 disabled deployed GWV, 133 disabled BWV and nondeployed veteran controls	CFS, FM	Disabled GWV more likely to meet CFS criteria, but similar rates of FM to comparison group.
Kang et al., 2009	6,111 deployed GWV, 3,859 NDV	MSI, CFS, FM	Deployed GWV reported significantly higher rates of MSI, CFS, FM.
Li et al., 2011	6,111 deployed GWV, 3,859 NDV	CFS-like illness	GWV had significantly higher prevalence of CFS-like illness, and greater increase in CFS-like illness between 1995 and 2005.

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; NDV = nondeployed Gulf War era veterans; CFS = chronic fatigue syndrome; FM = fibromyalgia; BWV = Bosnian War veterans; MSI= multisymptom illness;
* Papers published in 2008 after the 2008 RACGWVI report release have been included.

4) Psychiatric and Psychological Disorders in Gulf War Veterans

When ill soldiers returned from the first Gulf War, a debate began over whether reported symptoms could be attributed to psychological factors versus hazardous exposures. Extensive research was accordingly focused on psychiatric outcomes. As discussed in the 2008 Committee report and the Committee's previous 2004 report, by the early 2000's this extensive body of research had demonstrated that while Gulf War veterans exhibited higher rates of post-traumatic stress disorder (PTSD) and other psychiatric conditions than their nondeployed counterparts, their rates of psychiatric illness were far below the rates of such conditions seen in other wars and far below their rate of Gulf War illness.

Rates of PTSD in Gulf War veterans were consistently found to be about 3-6%, compared to a rate of 25-32% for Gulf War illness. When stress reactions and exposures to stressful events in theater were quantified, these variables did not explain or predict diagnosis of Gulf War illness (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008, p. 78). The 2010 IOM report reached the same conclusion indicating that, "The excess of unexplained medical symptoms reported by deployed Gulf War veterans cannot be reliably ascribed to any known psychiatric disorder" (Institute of Medicine, 2010, p. 109).

Since 2008, a number of studies have been published reporting on psychiatric and psychological morbidity in Gulf War veterans (Table 9). In a 2011 study, Gade and colleagues found that exposure to war casualties was associated with increased mental health decline (Gade and Wenger, 2011). Veterans on active duty and National Guard/Reservists scored higher on rating scales for PTSD symptoms and reported perceived threats and difficult working and living environments while deployed more often than comparison service men and women (Vogt et al., 2008). Post-traumatic stress disorder symptom severity was associated with worse physical health post-deployment (Wachen et al., 2013). PTSD, symptoms of depression and alcohol abuse were associated with combat exposure (Hassija et al., 2012), and problem drinking was associated with PTSD, major depressive disorder and multisymptom illness (Coughlin et al., 2011).

Veterans diagnosed with PTSD showed anatomical brain and hormonal changes. Apfel et al. (2011) found that Gulf War veterans with chronic PTSD showed significantly reduced hippocampal volumes compared to veterans without PTSD diagnoses and that current PTSD symptoms were associated with smaller hippocampal volume. Hippocampal volume and metabolic activity changes were also seen in Gulf War veterans diagnosed with PTSD, who additionally identified significantly greater stress hormone suppression (Yehuda et al., 2010). In another MRI study, veterans diagnosed with combat-related PTSD showed smaller volume, area and thickness values in the hippocampal gyrus, superior temporal cortex, lateral orbital frontal cortex and pars orbitalis brain regions when compared to veterans without PTSD (Woodward et al., 2009).

In summary, follow up studies on deployed Gulf War veterans and psychological and psychiatric morbidity since 2008 continue to show that combat and other stressors are associated with PTSD, anxiety, depression and alcohol abuse in this population. However, these disorders do not explain Gulf War illness and occur at far lower rates than Gulf War illness in Gulf War veterans.

Table 9. Studies Reporting on Psychiatric and Psychological Disorders in Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Outcome(s)*	*Key Findings*
Apfel et al., 2011	82 GWV with lifetime PTSD, 44 GWV with current PTSD, 38 GWV with MDD, 80 PTSD- GWV	Hippocampal volume measured using MRI	GWV with chronic PTSD had smaller hippocampal volume than GWV without current PTSD. Current PTSD symptoms were associated with significantly reduced hippocampal volume.
Coughlin et al., 2011	6,111 deployed GWV, 3,859 nondeployed GWV controls	Alcohol use, PTSD, MDD, MSI, CFS-like illness	Problem drinking was significantly and positively associated with PTSD, MDD, unexplained MSI and CFS.
Gade et al., 2011	1035 GWV, 3452 VV	MCS	Exposure to war casualties but not combat overall was associated with mental health decline. Negative effects of combat were larger for GWV compared to VV.
Hassija et al., 2012	87 GWV and 43 OIF/OEF veterans	PSS, DSS, alcohol misuse	Combat exposure was significantly associated with PSS, DSS and alcohol misuse.
Vogt et al., 2008*	81 active duty GWV and 230 NG/R GWV	DRRI, PTSS	High PT and DLWE scores on the DRRI and PTSS were significantly stronger for active duty women and NG/R men.
Wachen et al., 2013	317 GWV	PSS, PCL, PHS	Significant associations between post-deployment physical health and PSS in all symptom categories. PSS score was more strongly related to physical health for subjects with lower warzone exposures, but also significant for high warzone exposures as well.
Woodward et al., 2009	50 PTSD+ (13 GWV and 37 VV) and 47 PTSD- (23 GWV and 24 VV)	Cortical volume measured using MRI	Subjects with combat-related PTSD showed significantly smaller cerebral cortical volume, thickness and area compared to PTSD- controls.
Yehuda et al., 2010	12 PTSD+ GWV and 9 PTSD- GWV	Plasma ACTH changes, declarative memory, MRI, PET, DST	PTSD+ group showed significantly greater cortisol and ACTH suppression. Hippocampal volume difference and greater hippocampal metabolic activity seen in PTSD+ GWV. No memory differences were seen.

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; MDD = major depressive disorder; PTSD = Post-traumatic Stress Disorder; PTSD+ = meets the criteria for current PTSD resulting from one or more military trauma; PTSD- = did not meet criteria for PTSD, either current or lifetime; MRI = Magnetic Resonance Imaging; CFS = chronic fatigue syndrome; MSI = multisymptom illness; BMI = Body Mass Index; MCS = Mental Component Summary; VV = Vietnam veterans; OEF= Operation Enduring Freedom; OIF = Operation Iraqi Freedom, PSS = Post-traumatic Stress Disorder symptom severity; DSS = depressive symptom severity; SF-12 = Short-Form Health Survey 12 item; GHQ-12 = General Health Questionnaire; PTSS = Post-traumatic stress symptomatology; DRRI = Deployment Risk and Resilience Inventory; PT = perceived threat; DLWE = difficult living and working environment; NG/R = National Guard/Reserve; PCL = Post-traumatic Stress Disorder Checklist; PHS = physical health symptoms; ACTH = adrenocorticotropic hormone; PET = positron emission tomography; DST = dexamethasone suppression test

* Papers published in 2008 after the 2008 RACGWVI report release have been included.

5) Hospitalization Rates

In 2008, the Committee reviewed results of 14 studies that compared hospitalization rates among Gulf War veterans with those of veteran comparison groups. Overall, few differences were identified in disease-specific hospitalizations, although individual studies found that Gulf War veterans had higher hospitalization rates due to fibromyalgia, musculoskeletal conditions, respiratory conditions and gastrointestinal conditions (Gray et al., 2000). In addition, one study reported that veterans downwind from the Khamisiyah demolitions had experienced significantly more hospitalizations for cardiac dysrhythmias (Smith et al., 2002).

One study of hospitalizations among Gulf War veterans has been published since the Committee's 2008 report (Table 10). Hooper et al. (2008) evaluated Gulf War veterans who remained on active duty in 1994 and were assessed at three-year intervals over a 10-year period. Hospitalization data included primary and secondary inpatient diagnoses at military facilities or admissions at civilian facilities that were paid for by the military. The largest proportions of hospitalizations were associated with musculoskeletal/connective tissue disorders (33%), diseases of the digestive system (23%), injuries (21%) and symptoms/ill-defined conditions (19%). Hospitalization rates increased over time for circulatory disorders, symptoms/ill-defined conditions and digestive disorders. Notably, hospitalization for mental disorders was substantially less common among 1990-1991 Gulf War veterans than for the U.S. Armed Forces overall. No associations were seen between hospitalizations and specific war-related exposures, including Khamisiyah munitions, oil fire smoke and anthrax or botulinum vaccines. However, personnel hospitalized in theater during the Gulf War were also more likely to be hospitalized after the war.

It is important to underscore that hospitalization studies would generally not be informative for detecting excess rates of conditions, like Gulf War illness, for which few patients are ever hospitalized. Further, the majority of Gulf War hospitalization studies relied on DoD administrative data, that is, data assembled from U.S. military hospital records, which provide information only on individuals currently on active military duty. For studies conducted many years after the war, this would exclude the majority of Gulf War veterans. For example, over 90% of Gulf War veterans had left military service by 2007 (U.S. Department of Veterans' Affairs, 2007). Service members in poor health after the war would have separated from the military at even higher rates and so would be particularly underrepresented in studies of military hospitalizations.

Table 10. Studies on Hospitalization Rates Among Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Outcome(s)***	***Key Findings***
Hooper et al., 2008*	264,409 GWV	Hospitalization rates	Most common hospitalizations involved musculoskeletal, digestive, injury related, ill-defined and circulatory conditions. Hospitalizations related to mental health disorders were under-represented in this study population compared to U.S. Armed Forces overall.

Abbreviations: GWV = Gulf War veterans;
* Paper published in 2008 after the 2008 RACGWVI report release.

E. Mortality in Gulf War Veterans

One of the most important health issues for Gulf War veterans concerns whether they have experienced excess deaths since their return from Desert Storm. In its 2008 report, the Committee emphasized the importance of monitoring the mortality of Gulf War veterans over time and recommended that VA provide cause-specific mortality reports at minimum, at five-year intervals. The Committee further emphasized the need for assessing mortality rates in Gulf War veteran subgroups identified by deployment and/or exposure characteristics of importance. This was essential, since excess mortality due to specific events or exposures in theater can be obscured if all Gulf War veterans are assessed together and compared as a single group to nondeployed era veterans.

At the time of the 2008 report, the most recent year for which mortality data had been published for U.S. Gulf War era veterans was 2000. Earlier studies that evaluated mortality data prior to 1997 had shown that Gulf War veterans, overall, had lower rates of deaths due to diseases but higher mortality due to accidental causes. These differences had largely disappeared by 1997 (Kang and Bullman, 2001).

A study conducted by VA and published since the 2008 RACGWVI report (Table 4; Barth et al., 2009) found that when Gulf War veterans were compared to nondeployed era veterans, no significant differences in deaths due to any neurological disease were identified, including deaths due to brain cancer, amyotrophic lateral sclerosis (ALS) and Parkinson's disease. However, when brain cancer mortality rates were evaluated in subgroups of veterans who were potentially exposed to nerve agents resulting from the Khamisiyah demolitions and Kuwaiti oil fires, both were associated with significantly increased risk for brain cancer deaths in exposed Gulf War veterans. In addition, veterans located in areas downwind from the Khamisiyah demolitions for two days or longer experienced a significantly greater risk of brain cancer death than those who were in those areas only one day. This difference was significant and supports the dose-response effect previously reported for brain cancer mortality observed through 2000 by Bullman et al. (2005). Investigators obtained medical records for 236 of the 372 brain cancer deaths identified on death certificates and were able to confirm brain cancer as the cause of death in 204 (86%) of those cases. No significant differences in mortality risks were observed when the Khamisiyah associations were reanalyzed to include only confirmed brain cancer deaths (Barth et al., 2009).

The 2009 VA mortality study was an impressive undertaking in its use of large datasets from different sources to address questions concerning differing mortality rates in Gulf War veteran subgroups. Study results provide a clear example of the importance of assessing mortality and other health outcomes in veteran subgroups defined by deployment locations, exposures and other characteristics of importance. Important health effects of Gulf War service are easily obscured in studies that evaluate all Gulf War veterans as a single group for comparison to nondeployed era veterans. This occurred in VA's study of neurological mortality rates, which did not differ, overall, when Gulf War veterans were compared with nondeployed era veterans.

Although VA's 2009 study of neurological mortality provided useful insights, the outcomes included were limited in scope. Other than brain cancer deaths, there were very few identified deaths attributed to neurological diseases in Gulf War veterans (e.g. six deaths due to multiple sclerosis, three due to Parkinson's disease). Concerns have been raised, based on evidence from amyotrophic lateral sclerosis (ALS) prevalence studies in Gulf War veterans, that ALS deaths may have been under-ascertained in the 2009 study (Horner et al., 2010). In any case, deaths due to neurological diseases are relatively rare, overall, and particularly in the age groups most represented in the Gulf War era veteran cohort. Therefore, even a complete and detailed assessment of neurological mortality characterizes only a small fraction of deaths in this population.

In addition to the scientific literature, there are two additional sources of mortality information for 1990-1991 Gulf War veterans. The Department of Veterans Affairs' *Gulf War Era Veterans Report: Pre-9/11*, issued in February 2011, is a compilation of statistical information available in VA databases (U.S. Department of Veterans Affairs, 2011). This report provides summary data but is not sufficiently detailed to adequately evaluate mortality rates in Gulf War veterans. Crude mortality rates are provided for U.S. Gulf War veterans through 2009, however, and suggest that military personnel who were in Al Jubayl, Saudi Arabia, on January 19, 1991, may have experienced a greater overall mortality rate (2.6%) than other veterans in theater during Desert Storm (1.6%). Similarly, figures indicate higher crude mortality rates among units downwind from the Khamisiyah demolitions (2.0%) compared to other personnel in theater in the post-Desert Storm period (1.5%). These figures cannot be clearly interpreted, however, without additional data needed to adjust for age and other possible differences of importance. [Note: VA Pre-9/11 report online at:http://www.va.gov/vetdata/docs/SpecialReports/GW_Pre911_report.pdf].

The U.K. Ministry of Defence (MOD) issues annual reports on deaths among British veterans who served in the 1990-1991 Gulf War. The most recent report available online March 28, 2013, provides mortality information through December 31, 2012 (U.K. Ministry of Defence, 2013). This report provides current data on overall mortality, as well as cause-specific mortality rates for both Gulf War veterans and a comparison group of era veterans who did not serve in the Gulf War. Figures indicate no statistically significant differences between the two groups. An important limitation of the MOD mortality reports, however, is that no information is provided for veteran subgroups of interest; mortality rates are reported only for all Gulf War veterans as a single group. As demonstrated by the 2005 and 2009 U.S. mortality studies, evaluations that combine Gulf War veterans into a single group can mask important mortality differences that are identifiable when important subgroups are evaluated and compared—for example, subgroups affected by the Khamisiyah demolitions or sustained exposure to oil fire smoke. Although the MOD mortality reports provide an exemplary resource for ongoing surveillance of overall mortality in Gulf War veterans, they would be considerably more valuable if they provided mortality data in relation to exposures and/or veteran subgroups of interest. [Note: MOD Gulf War veteran mortality through 2012 online at: http://www.dasa.mod.uk/index.php/publications/health/veterans/gulf-1-deaths/2012-12-31].

Taken together, the overall picture of mortality among U.S. Gulf War veterans remains unclear and poorly documented. Issues of current concern include apparent increases in brain cancer deaths among veterans exposed to oil fire smoke and low-level nerve agents. Additional areas of possible concern, raised by crude mortality data reported in VA's 2011 *Gulf War Era Veterans Report: Pre 9/11,* relate to whether overall mortality through 2009 was higher among Gulf War personnel in particular locations in theater (U.S. Department of Veterans Affairs, 2011).

In summary, a primary issue of concern is the lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 14 years for which no mortality figures are available represents more than half of the 23 years since Desert Storm. Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the latency periods often associated with chronic diseases of interest. Despite specific recommendations, over many years, from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remain seriously inadequate.

F. Methodological Issues for Epidemiologic Research on Gulf War Illness: Data Collection Techniques

Two studies published since the 2008 Committee report have focused on improving study methodology in data collection techniques and cross-study survey assessments (Table 11). In the first, Erickson et al. (2013) compared low-cost recruitment techniques that included free advertising resources, support and

veteran service groups and physician outreach. They learned that targeted media campaigns recruited the greatest percentage of Gulf War veterans (52%), followed by referrals (13%) and local physician outreach (11%). In the other, survey instruments across 12 epidemiological studies and two registries were compared for consistency and generalizability (McNeil et al., 2013). The authors found that questions about deployment-related exposures were most similar and therefore easier to pool, whereas cognitive and psychological testing were most variable. Physical or clinical examinations, specimen storage and biomedical assessments were not commonly used in Gulf War illness studies. These results have important implications for future studies that aim to address current knowledge gaps and also utilize surveys and other design tools optimized for comparisons with previously published results.

Table 11. New Reports on Methodological Findings of Importance in Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Outcome(s)*	*Key Findings*
Erickson et al., 2013	46 symptomatic GWV	Study enrollment via recruitment approach	Directed media campaign produced the highest number of enrolled GWV study subjects, with all other strategies together producing similar enrollment numbers.
McNeil et al., 2013	12 GWV studies and 2 GW registries	Survey and sampling consistency	Exposure-related survey questions showed the greatest cross-study consistency; neurocognitive and psychological tests were the most variable tools.

Abbreviations: GWV = Gulf War veterans

G. Conclusions and recommendations

Based on its review of the epidemiological evidence published since its 2008 report, the Committee offers the following conclusions and recommendations for future directions of research efforts.

Research findings

- Prevalence of Gulf War illness. All population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans. A large majority of studies indicate Gulf War illness prevalence in the 25-30% range.

- Prognosis for veterans with Gulf War illness. Little additional information on the long-term prognosis of Gulf War illness has become available since 2008. Prior data suggest that there is little to no improvement in the health of ill Gulf War veterans over time. The effect that aging will have on this vulnerable population remains a matter of concern.

- General health among Gulf War veterans. Studies published since 2008 continue to document poorer general health status and greater disability among Gulf War veterans. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance of this population remains seriously inadequate.

- Medical conditions in Gulf War veterans. Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by medical conditions of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess rates of most medical conditions. Disorders of concern reviewed in this report include the following:

    1. Neurological disorders. Although neurological conditions are a prominent concern for Gulf

War veterans, and research has found an elevated incidence of amyotrophic lateral sclerosis (ALS), rates of multiple sclerosis, Parkinson's disease and other neurological diseases (e.g., seizures, stroke, migraines) in Gulf War veterans are currently unknown. Research on the prevalence of neurological diseases has not been conducted despite repeated recommendations by this Committee and the Institute of Medicine and explicit legislation by Congress. The prevalence of these disorders is particularly important because they can be expected to increase as the Gulf War veteran population ages.

2. Cancer. Since 2008, research using state cancer registries has suggested that there may be an increased rate of lung cancer in Gulf War veterans. Brain cancer mortality has been shown in two studies conducted by VA to be significantly increased in the subgroup of Gulf War veterans with greatest exposure to oil well fire smoke and to low-level nerve agents released by the destruction of Iraqi facilities at Khamisiyah. In general, cancer risk remains unknown and understudied.

3. Other diagnosed medical conditions reported at excess rates. Research since 2008 continues to indicate that Gulf War veterans report being diagnosed with a variety of medical conditions at significantly higher rates than nondeployed era veterans. These include chronic digestive disorders, respiratory conditions, heart disease and skin disorders. Although consistently reported by Gulf War veterans, these conditions have not been further evaluated or characterized by epidemiologic or clinical studies.

4. Sleep dysfunction. A single study published since 2008 has identified sleep abnormalities in a group of Gulf War veterans compared to obesity-matched controls. Sleep disturbance is an extremely common symptom in veterans with Gulf War illness and continuous positive airway pressure (CPAP) has shown some promise for treating a range of symptoms in veterans with sleep disorders in a small treatment trial.

5. Adverse reproductive outcomes and birth defects. No definitive new information is available on birth defects in offspring of Gulf War veterans, and no research has ever been published concerning neurological or other medical conditions affecting veterans' children. It is important that medical and reproductive outcomes be assessed in children of veteran subgroups of interest (e.g. exposure, location, illness subgroups).

- Multisymptom conditions: chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity. These disorders share similar symptoms with Gulf War illness, but most Gulf War illness patients do not meet criteria for them. Gulf War veterans who meet criteria for these disorders often differ significantly on tested parameters from non-veteran populations who are diagnosed with them. It may be necessary to consider people with these disorders who are and are not Gulf War veterans separately in research studies, including treatment research.

- Psychiatric disorders. Studies of psychological and psychiatric morbidity in Gulf War veterans since 2008 continue to show that combat and other stressors are associated with PTSD, anxiety, depression and alcohol abuse in Gulf War veterans but are not independently associated with Gulf War illness.

- Mortality. Lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans is an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 14 years for which no mortality figures are available represent more than half of the 23 years since Desert Storm. Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the

latency periods associated with many chronic diseases of interest. Despite specific recommendations over many years from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remain seriously inadequate.

Methodological issues

Collecting data on Gulf War illness has been hampered by a number of methodological issues relating to case definitions, concurrent disorders and conditions in ill veterans, multiple exposures, subject recruitment, subject follow-up and survey tools. For example, as raised in both the 2004 and 2008 Committee reports, it is important to assess health outcomes in identifiable Gulf War veteran subgroups, as opposed to grouping all veterans with heterogeneous exposures and experiences together. Whether these groupings are based on exposure, unit membership, symptom profiles, deployment location or a combination of factors, comparisons of subgroups with healthy controls will be more informative than assessing all deployed veterans as a single group.

- Case definitions. Case definitions currently include the Haley syndrome criteria, chronic multisymptom illness (CMI), the Kansas definition and other adaptations of these approaches to defining Gulf War illness. Each of these definitions has advantages and drawbacks. The Haley syndromes are quite narrow and underestimate the occurrence of the disorder but may allow highly specific characterization of veterans who meet criteria for a syndrome; the mild form of CMI is very broad and over inclusive, resulting in high prevalence rates even in control populations, and the Kansas criteria predict Gulf War illness at rates that appear to be consistent with those seen across multiple Gulf War populations but exclude veterans with some concurrent medical disorders who may also have Gulf War illness. Many research papers and proposals do not clearly define the criteria used for identifying veterans with Gulf War illness at all, an even greater problem. In the absence of a consensus case definition 23 years after the appearance of this condition, it remains difficult to assess and compare research findings in epidemiological, pathobiological or treatment research on Gulf War illness.

- Surveillance. Relatively little data are available that provide a clear understanding of the impact of Gulf War service on the current health of Gulf War veterans. This includes data on the clinical course and prognosis of veterans with Gulf War illness, rates of other medical conditions and the mortality profile of Gulf War veterans many years after the war. As noted above, very little is known about prognosis of veterans with Gulf War illness and other health issues such as poor general health, neurological disorders, other medical conditions, sleep dysfunction, multisymptom illnesses such as chronic fatigue syndrome and fibromyalgia, adverse reproductive outcomes, hospitalizations, and mortality. In addition, there are few available data on birth defects and other health outcomes in the offspring of Gulf War veterans. Some of these issues are addressed in the VA longitudinal survey that is currently underway, but the survey instrument does not allow identification of veterans with Gulf War illness and other outcomes of interest, despite urging from the RACGWVI and despite recommendations in the 2010 IOM report for improved surveillance of this population. Information about Gulf War illness prevalence and prognosis as well as other medical disorders is key to healthcare planning for this population.

Recommendations

- Case definition of Gulf War illness. As noted above, the absence of a consensus case definition of Gulf War illness 23 years after the appearance of this condition impedes the assessment and comparison of research findings in epidemiological, pathobiological or treatment research on the disorder. The Committee recommends the following approaches to the development of such a definition.

    1. An evidence-based, expert consensus-driven case definition for Gulf War illness (GWI) should be developed. This process should include 1) a review of the existing literature relevant

to case definitions for GWI, 2) in-depth statistical and epidemiologic assessment of the strengths and weaknesses of different case definition approaches using datasets that provide representative data on symptoms and medical conditions affecting 1990-1991 Gulf War era veterans and 3) final case definition parameters and guidelines developed by an expert consensus panel that includes scientists experienced in GWI research and symptom-based case definitions and veterans affected by GWI (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf). The recent IOM panel on case definitions of Gulf War illness also commented that a data based case definition of the disorder could be derived (Institute of Medicine, 2014). This effort should involve representatives from VA, a broad spectrum of scientists conducting research in Gulf War veterans, clinicians knowledgeable about the problem, and Gulf War veterans. It could be organized through the Gulf War Illness Research Program of the Department of Defense Congressionally Directed Medical Research Program (CDMRP) through its competitive grant proposal process with scientific review.

2. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War. This recommendation is also supported by the 2014 Institute of Medicine report on case definitions of the illness (Institute of Medicine, 2014).

- Surveillance. Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this veteran group ages. A strategy for such monitoring was included in the plan proposed by a VA Strategic Planning group composed of representatives from RACGWVI, the VA National Research Advisory Council and VA staff (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf Section 5.2). Such surveillance should include outcomes described in this document, including Gulf War illness; neurological disorders, including Parkinson's disease; autoimmune conditions such as multiple sclerosis; brain, lung and other cancers; cardiovascular disorders and dysfunction; sleep dysfunction; adverse reproductive outcomes and birth defects; general ill health and disability; mortality and other disorders and outcomes that emerge as important during the surveillance process. This effort must include the following elements.

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans is critical. VA's longitudinal survey currently in process should be extended to add a symptom inventory adequate to define the illness according to existing commonly-used case definitions, as previously recommended by the Committee: "[The current survey instrument] cannot determine the prevalence, progression, or correlates of this illness. . . [I]t is unthinkable that the largest national study of Gulf War veterans would not provide the data required to evaluate the signature problem of the 1991 Gulf War" (Research Advisory Committee on Gulf War Veterans' Illnesses, 2012).

2. VA's longitudinal survey can be effectively used to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans. Survey data should be used to flag conditions of possible importance and followed up with detailed investigation, including clinical evaluations that are required to determine specific medical diagnoses affecting Gulf War veterans at excess rates.

3. A study on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans was required by Congress in 2008 (Public Law 110-389, 2008, Section 804) and should be carried out. These assessments should be repeated and published at a minimum of 5-year intervals.

4. Systematic assessment of overall and disease-specific mortality in all Gulf War veterans and in specific subgroups of interest is essential. The results of these assessments should also be published at 5-year intervals.

5. VA's longitudinal survey should be used to assess rates of medical conditions, including neurological and behavioral disorders and birth defects, in children of Gulf War era veterans. Survey data can be used to flag conditions of possible concern and followed up. It is also important that VA publish results from studies of veterans' children that were conducted over 10 years ago.

6. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance is critical as some health outcomes are related to specific exposures and experiences in theater. These subgroups can be defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater or other predictors.

- Improved methodology in Gulf War epidemiologic research. It is important that VA work with the DoD Congressionally Directed Medical Research Program (CDMRP) to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.

2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.

3. Consideration of subpopulations with multiple health outcomes.

4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that control as fully as possible for confounding effects of multiple exposures and etiologic factors that may be associated both with the exposures and outcomes of interest. Consideration of the effects of mixed exposures is also key.

2| Etiological Investigations: Research on Persistent Health Effects of Gulf War Experiences and Exposures

Once it became clear that veterans of the Gulf War had returned home with persistent health problems, the question immediately arose as to the cause or causes of ill health in this veteran group. Although a highly publicized initial argument was that their ill health was due to deployment related stressors and psychological trauma, scientific studies consistently demonstrated that Gulf War illness was associated with chemical, pharmaceutical and other environmental exposures in theater, rather than stress. Research in this area has expanded since 2008 and has included research on effects of veterans' exposures to specific chemicals and drugs during the war as well as extensive exploration of the persistent effects of single and combined Gulf War-related exposures in animal models. This section summarizes research in both of these domains.

A. Research on Persistent Health Effects in Gulf War Veterans in Relation to Deployment Experiences and Exposures

In its 2008 report, the Committee reviewed available evidence related to the diverse experiences and exposures encountered by military personnel during the 1990-1991 Gulf War. This included information provided by government reports, investigations, and modeling efforts to determine veterans' exposures to psychological stress and trauma, pesticides, depleted uranium munitions, airborne contaminants from the Kuwaiti oil fires, chemical nerve agents, the anthrax vaccine and other vaccinations, widespread use of pyridostigmine bromide as a prophylactic measure against possible nerve agent exposure and other potential hazards. Essential information was provided from the many epidemiologic and clinical studies that investigated associations between exposures in theater and a variety of health measures and outcomes in Gulf War veterans. In addition, the Committee reviewed studies that provide insights from other human populations concerning health effects of exposures similar to those encountered by military personnel during the Gulf War.

Research on associations between deployment experiences and the health of Gulf War veterans reviewed through 2008 provided the most significant and consistent results in relation to three exposures of concern. The first, veterans' experiences related to psychological stressors in theater, was not found to be associated with Gulf War illness. The second, exposure to pesticides, was found to be causally associated with Gulf War illness. The third, the use of pyridostigmine bromide pills as prophylaxis against nerve agent exposure, was also found to be causally associated with Gulf War illness.

The largest number of Gulf War studies available prior to 2008 evaluated long-term effects of psychological stressors during deployment—experiences such as serving in combat and seeing other troops badly wounded or killed. Studies consistently found no association between Gulf War illness and combat or other war-related stressors, after adjusting for effects of other deployment exposures. As expected, studies identified increased rates of post-traumatic stress disorder and psychiatric diagnoses among veterans who experienced psychological trauma and stressors during the Gulf War, but at rates substantially below rates of psychiatric illness seen in other wars and rates of Gulf War illness (Richardson et al., 2010).

Overall, the Committee's review of the many Gulf War studies published through 2008 identified only two types of exposures—pyridostigmine bromide and pesticides—that were consistently associated with a significantly increased risk for Gulf War illness. In addition, dose-response relationships between severity of exposure and probability of development of Gulf War illness were identified for both exposures. The two exposures were also associated with significant differences in objectively measured health outcomes in Gulf War veterans, including alterations in neurocognitive function and hypothalamic-pituitary-adrenal measures. Taken together, the consistency of the epidemiological associations, the significant dose-response effects, and observed associations with objective biological measures led the

Committee to conclude that the evidence strongly supported a causal role for both pyridostigmine bromide and pesticide exposures in the development of Gulf War illness.

Research available through 2008 provided limited and/or mixed results concerning associations between Gulf War illness and exposure to low levels of nerve agents released by the destruction of Iraqi facilities, smoke from oil well fires and the number of vaccines received. There was little evidence or support for a primary or widespread association between Gulf War illness and depleted uranium, fuels and solvents, CARC paint or the anthrax vaccine.

In reviewing these studies, the Committee pointed out the importance of assessing health outcomes in Gulf War veteran subgroups, identified according to deployment locations and exposures. This issue has profound implications for studies of Gulf War veterans, since combining all veterans into a single "deployed" group in research studies can potentially obscure important differences between exposure subgroups. The Committee also pointed out a serious problem commonly seen in studies that evaluated health outcomes in relation to the many potential hazards associated with Gulf War deployment. Gulf War studies commonly evaluated 20 or more different wartime exposures as risk factors for Gulf War illness and other health outcomes—exposures that frequently co-occurred in the same individuals and groups. Analytic assessment of associations between health outcomes and multiple correlated exposures introduces serious potential for confounding error, that is, results that confuse the effects of different exposures with one another. The Committee noted that studies evaluating deployment exposures as risk factors for health outcomes in Gulf War veterans often did not appropriately control for effects of concurrent exposures. Though not explicitly described in that report, the issue of exposures to multiple chemicals is inherent to the Gulf War experience and is difficult to address in epidemiologic studies.

One of the central challenges in evaluating risk factors for Gulf War-related health outcomes involves limitations in what is known about which individuals experienced specific exposures in theater and at what levels. Studies often rely on veterans' own reports of their experiences and exposures during deployment, reports which have been shown to have varying degrees of reliability. To address this concern, the Department of Defense has sponsored a number of intensive efforts to provide simulations, modeled estimates and detailed investigations to better characterize wartime exposures in different locations and different units. These include modeled estimates of nerve agent exposures following demolitions at the massive munitions depot at Khamisiyah, Iraq, in March of 1991. Additional in-depth investigations have provided modeled estimates of levels of airborne contaminants from the Kuwaiti oil fires in different locations, determinations of radiation and heavy metal exposures associated with depleted uranium munitions and insights concerning patterns of use of pesticides and pyridostigmine bromide during the Gulf War.

Details of research studies through 2008 that evaluated veterans' risk for Gulf War illness in relation to deployment experiences and exposures are itemized in an extended appendix provided as part of the Committee's 2008 report. Since 2008, additional studies have been published on the extent and patterns of exposures during the war, research on persistent effects of exposures experienced by military personnel during the war and insights obtained from studies conducted in other exposed human populations.

1) Additional information on possible chemical exposures during the Gulf War
Since the Committee's 2008 report, exposure-related studies of Gulf War veterans have most extensively evaluated health outcomes in relation to possible exposure to chemical weapons in theater.

The detailed modeling efforts by DoD and CIA to estimate nerve agent exposures following weapons demolitions near Khamisiyah, Iraq, in March of 1990-1991 have been extensively reviewed, as described, in the Committee's 2008 report. Since that time, two reports have provided information and insights

concerning the potential for chemical weapons exposures thought to have occurred in other locations and times, in addition to the areas affected by the Khamisiyah demolitions.

A 2012 paper from A. Brimfield, of the U.S. Army Medical Research Institute of Chemical Defense, proposed a mechanism that may have contributed to the development of Gulf War illness (Brimfield, 2012). The putative mechanism built on the assumption that U.S. troops were potentially exposed to low levels of multiple types of chemical agents during the Gulf War, including both nerve agents and blister agents such as sulfur mustard. Citing recent work elaborating the mechanisms associated with mustard toxicity, the author detailed the potential for mustard exposures to interact with other exposures in theater, including chlorpyrifos, permethrin, N,N-diethyl-meta-toluamide, and pyridostigmine bromide.

Prior to this report, the only information confirming likely exposure to blister agents in theater came from a DoD case report on Private David Fisher, whose skin abnormalities during the war were attributed to blister agent exposure by military physicians (U.S. Department of Defense Office of the Special Assistant for Gulf War Illnesses, 2000a). Although useful for the detailed insights provided concerning possible mechanisms contributing to Gulf War illness, the Brimfield paper did not provide documentation of mustard gas exposures in theater or research demonstrating adverse health outcomes in Gulf War veterans in relation to possible mustard gas exposure in theater.

A second study, published by Tuite and Haley in 2012, provided information concerning the potential for Gulf War veterans to have been exposed to nerve agents in January of 1991 as a consequence of U.S. and Coalition bombing campaigns that destroyed multiple Iraqi chemical manufacturing and storage sites in the early days and nights of the air war (Tuite and Haley, 2012). The paper evaluated weather patterns during that period using meteorological records, satellite imagery data, and technical or intelligence information from multiple government sources. Plume height predictions, weather charts, weather satellite images showing transit of a hot air mass, effects of solar mixing of atmospheric layers, and observations of a stationary weather front and thermal inversion in the region provide evidence supporting the conclusion that in the wake of munitions bombings in January 1991, plumes carrying chemical agents rose rapidly upwards, were blown southward, and were deposited in northern Saudi Arabia on 19 January 1991, resulting in the sounding of nerve agent detection alarms and repetitive exposure to low level nerve agents for troops in affected areas.

This possibility had previously been raised by multiple sources, including Czech and other Coalition partners who reported chemical detections in northern Saudi Arabia in January of 1991 (U.S. Department of Defense Office of the Special Assistant for Gulf War Illnesses, 1998; U.S. General Accounting Office, 2004). Additional support for more widespread chemical agent releases and troop exposures has been provided by a number of other investigations and reports, (Eddington, 1997; Tucker, 1997), including a 2004 report from the U.S. Government Accountability Office that outlined evidence concerning the potential for other chemical exposures, in addition to those resulting from the Khamisiyah demolitions, to have occurred during the Gulf War (U.S. General Accounting Office, 2004).

A comment published on the Tuite and Haley paper raised objections to its meteorological analysis (Chang, 2013). However, the points raised in the comment appear to be explained in the paper. For example, Chang states that satellite infrared images are typically presented with white as colder and black as warmer, and that Haley and Tuite were thus incorrect in interpreting bright areas as warmer. However, Tuite and Haley state in the paper that they chose to present white areas as warmer. The comment further suggests that Tuite and Haley mistakenly interpreted the data as showing a temperature inversion, but the temperature inversion notation was made directly on the National Oceanic and Atmospheric Administration (NOAA) pressure chart by NOAA itself.

The Tuite and Haley paper adds to prior evidence that Gulf War veterans experienced low level chemical agent exposures, in addition to those resulting from the March 1991 Khamisiyah demolitions, and that low level exposure related to the destruction of Iraqi weapons facilities remains a possible contributing factor to the development of Gulf War illness. Results of studies published since 2008 that provide additional exposure information are summarized in Table 1.

2) Health Outcomes in Relation to Exposures in Theater
a. Studies Evaluating Effects of Exposures in Gulf War Veterans: Nerve gas agents, chemical weapons, vaccines, pyridostigmine bromide, pesticides, and Kuwaiti oil fires

Prior to 2008, studies conducted by Boston investigators found that exposure to sarin/cyclosarin nerve agents, as determined by DoD models, was significantly correlated with reduced neurocognitive performance (Proctor et al., 2006) and that exposed veterans had significantly less white matter volume on structural magnetic resonance imaging (MRI; Heaton et al., 2007). Both associations occurred in a dose-response pattern, that is, greater exposure was associated with larger differences in brain structure and function. As shown in Table 1, two studies by Chao et al. have reported significant differences in MRI volumetric measures of brain structures in relation to modeled nerve agent exposures. In a 2010 study, using a 1.5 Tesla MRI, they reported significantly less total gray matter and hippocampal volume in exposed veterans (Chao et al., 2010). In exposed veterans, reduced white matter volume was associated with reduced performance on cognitive tests that assess executive function and visuospatial abilities. Their 2011 study reported significantly less total gray matter and total white matter volume in exposed veterans compared to unexposed veterans (Chao et al., 2011). Significant differences in cognitive function were seen in exposed and unexposed groups in the 2011 study, but the results were inconsistent: exposed veterans performed worse on a continuous performance attention test but better on two psychomotor functions tests than unexposed veterans. This is surprising because exposure was associated with structural brain changes that would be expected to adversely affect psychomotor function. Toomey et al. (2009) reported decrements in test performance in several cognitive domains related to deployment, as well as specific exposures in theater, including nerve agents (see Section 3 of Research Review, Pathobiology, Neurocognitive findings, p. 63 and Table 2).

In addition, two studies have reported that veterans identified by DoD models as being located downwind from the Khamisiyah demolitions for two or more days have died from brain cancer at significantly higher rates than unexposed veterans. The earlier study, reporting on mortality through 2000, identified a nearly two-fold increase in brain cancer deaths in exposed veterans (Bullman et al., 2005). The observed increase was further supported by a 2009 VA study that evaluated mortality rates through 2004, which found a nearly three-fold increased brain cancer rate in veterans who were exposed to oil well fires and nerve agents near the Khamisiyah plume (Barth et al., 2009).

Haley and colleagues found that veterans who reported hearing chemical alarms were at significantly greater risk for Gulf War illness as defined by either the Center for Disease Control and Prevention chronic multisymptom illness (CMI) criteria (Fukuda et al., 1998) or the Haley factor case definition (Haley et al., 1997b). They noted a significant dose-response effect whereby veterans who reported hearing more alarms had greater risk for Gulf War illness (Haley et al., 2013). In contrast, a study of Gulf War veterans in the Midwest reported that hearing chemical alarms, depleted uranium exposure and vaccines received during deployment were not associated with increased risk for Gulf War illness (Steele et al., 2012). However, personal pesticide use was significantly associated with Gulf War illness for veterans who were in Iraq or Kuwait and for veterans in support areas during the war. Pyridostigmine bromide prophylaxis and oil well fire exposure were associated with an increased risk of Gulf War illness for veterans in forward areas during the war (Steele et al., 2012).

Squalene antibodies, which are believed by some investigators to have developed in reaction to the presence of squalene in vaccines received during deployment (Asa et al., 2000), were not associated with chronic multisymptom illness (CMI) diagnosis in a study of U.S. Seabees who served in the Gulf War (Phillips et al., 2009), although overall health status and symptom number were associated with number of self-reported vaccines in a study of Australian Gulf War veterans (Kelsall et al., 2009).

Overall, studies published since the 2008 report continue to show that exposures to pesticides and pyridostigmine bromide are etiologically important in the development of Gulf War illness and in the behavioral and cognitive dysfunction experienced by Gulf War veterans. The findings in Gulf War veteran populations are consistent with those seen in other occupational and environmental groups (see Appendix C). Exposure to the nerve gas agents sarin/cyclosarin has been linked in two more studies to changes in structural magnetic resonance brain imaging findings and cognitive decrements, further supporting the conclusion from evidence reviewed in the 2008 report that exposure to these agents is etiologically important to the central nervous system dysfunction that occurs in some subsets of Gulf War veterans. The Chao studies did not provide clear evidence on whether sarin exposure was associated with Gulf War illness (Chao et al., 2011; Chao et al., 2010).

New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. In addition, a recent study showed that soldiers wearing uniforms treated with the pesticide permethrin showed urinary permethrin excretion to be higher in those with longer wear-times (Proctor et al., 2013), providing evidence for another route of pesticide exposure and subsequent absorption and possible health effects. It is unclear if vaccine exposures may also be contributing to GW veteran health symptoms, because current results have been conflicting and include weak associations.

Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and combined exposures would inform the assessment of mixed exposures, as would the development of biomarkers of past exposures to specific chemicals of interest.

Table 1. Studies Assessing Exposures Associated with Health Outcomes in Gulf War Veterans: 2009 – 2013

Study	*Groups Studied*	*Exposure(s)*	*Method(s)*	*Key Findings*
Neurological and neuropsychological				
Chao et al., 2010	40 exposed GWV, 40 unexposed GWV	Sarin and cyclosarin	MRI, neuropsychological testing	Significantly reduced gray matter and hippocampal volumes in sarin and cyclosarin exposed subjects. White matter volume was associated with executive function and visuospatial abilities in exposed veterans.
Chao et al., 2011	64 exposed GWV, 64 unexposed GWV	Sarin and cyclosarin	MRI, neuropsychological testing	Sarin/cyclosarin exposed GWV showed sign. reduced total gray and white matter volumes compared to unexposed controls. GWI/CMI diagnosis sign. predicted gray and white matter volumes in sarin/cyclosarin exposed subjects. Exposed GWV performed sign. worse on a continuous performance test of attention, but better on psychomotor function (Trailmaking Test A and Grooved Pegboard).

Study	*Groups Studied*	*Exposure(s)*	*Method(s)*	*Key Findings*
Toomey et al., 2009	1,061 deployed GWV; 1,128 nondeployed GWV	PB, pesticides, vaccines, IG injections, oil well fire smoke	Neuropsychological testing	Deployed GWV had sign. lower scores on tests of verbal memory, verbal learning, motor speed, and attention than nondeployed. Specific exposure in Khamisiyah was negatively correlated with motor speed.
Cancer mortality				
Barth et al., 2009	621,902 GWV, 746,248 non-GWV	Sarin/cyclosarin Oil well fire contaminants	Brain cancer mortality, brain cancer, ALS, MS, PD	Significant increase in brain cancer mortality among GWV in sarin exposure area ≥ 2 days; sign. dose response effect for number of days of exposure. Oil fire associated with sign. increase in brain cancer mortality among exposed Army GWV, compared to non-exposed. No interaction found between oil well fires and sarin exposure.
Health status				
Kelsall et al., 2009	698 Australian GWV	Vaccines	Total symptom number, SF-12 physical component, GHQ-12 case status	Number of self-reported vaccines weakly associated with total number of symptoms and poorer health; relationship not seen with recorded vaccination number.
GWI and CMI				
Haley et al., 2013	8,020 GWV	Chemical alarms, DoD-modeled Khamisiyah exposure area	GWI	GWI was significantly associated with hearing chemical alarms but not with exposure to Khamisiyah plume
Phillips et al., 2009	175 male U.S. Navy Seabees GWV	Vaccines (squalene antibodies)	CMI	Similar proportions of CMI (55%) and healthy (51%) GWV were positive for squalene antibodies ($p = 0.71$).
Steele et al., 2012	304 Kansas City area GWV	PB, pesticides, vaccines, oil well fire smoke	GWI	Pesticide use significantly associated with GWI for veterans who were in Iraq or Kuwait and for veterans in support areas. Use of PB, close proximity to exploded SCUD missile and exposure to oil well fire smoke significantly associated with GWI for personnel in forward areas only; GWI not associated with serving in combat, hearing chemical alarms.

Abbreviations: GWV = Gulf War veterans; GWI = Gulf War illness; PB = pyridostigmine bromide pills; MRI = magnetic resonance imaging; IG = immunoglobulin; ACTH = adrenocorticotropic hormone; CRF = corticotrophin-releasing factor; sign. = significant; CMI = chronic multisymptom illness; SF-12 = Short-Form Health Survey 12 items; PCS = Physical Component Summary Score; GHQ-12 = General Health Questionnaire; DoD = Department of Defense, ALS= amyotrophic lateral sclerosis; PD = Parkinson's disease; MS = multiple sclerosis

b. Studies Evaluating Depleted Uranium Exposure in Gulf War Veterans

Depleted uranium (DU) is a byproduct that is created when natural uranium is converted to enriched uranium. It retains approximately 60% of the radioactivity of natural uranium. DU is extremely effective for armor-piercing weapons and as armoring material for tanks because of its high density and pyrophoric (flammable) properties. DU poses both a chemical and radioactive risk. Although radioactivity emanates from DU shrapnel, ingestion and dust, dangers associated with DU radioactivity are considered to be relatively less than that of the chemical risks (Parkhurst et al., 2004). Most uranium that has entered the

body is excreted via the kidneys and through digestion, and cells involved in these systems are considered to be the most vulnerable to DU. Because DU ammunitions ignite upon target impact, subsequent fires and explosions were especially effective when aimed at fuel tanks or munitions caches. Fires resulting from DU explosions contained DU dust, exposing nearby soldiers and civilians through dermal contact, respiration and ingestion.

The Gulf War was the first conflict in which DU was utilized in weapons and armaments, despite the fact that little was known about the long-term health outcomes associated with its use. Soldiers came into contact with burning vehicles hit by DU weaponry in recovery efforts and in exploring bomb sites. In friendly fire incidents, American soldiers mistakenly hit with DU rounds were exposed to DU in the air or internally exposed after being hit with DU bullets or shrapnel, which may or may not have been removed (Parkhurst et al., 2004). High levels of DU exposure would have also been seen in U.S. troops and personnel who were responsible for cleaning up damaged vehicles or damage after the Camp Doha fire, when an ammunition carrier caught fire and spread to nearby munitions vehicles and storage units (Scherpelz et al., 2000). Cleanup and decontamination efforts took months to complete, during which little protective gear was used (Fahey, 1998). Many of the Gulf War ground troops were unaware that DU was present and, in some circumstances, rescue operations after friendly fire incidents resulted in high levels of exposure for soldiers.

DU-related health effect studies summarized in the 2008 Committee report showed conflicting results. Kidney damage and renal changes were noted in a number of studies (Royal Society, 2001; Royal Society, 2002; World Health Organization, 2001), while an IOM report found insufficient evidence to conclude that DU was associated with cancers or nonmalignant renal disease (Institute of Medicine, 2000; Institute of Medicine, 2008). Disparate conclusions have been reached about whether DU levels during the Gulf War were high enough to cause adverse outcomes: two reports cited high DU Level I exposures (Squibb and McDiarmid, 2006; U.S. Army Center for Health Promotion and Preventive Medicine, 2000) in theater, while the DoD Environmental Exposure report concluded that DU levels during the Gulf War were not high enough to cause health effects (U.S. Department of Defense Office of the Special Assistant for Gulf War Illnesses, 2000b).

As described in the 2008 Committee report, the most extensive DU research in Gulf War veterans was conducted as a joint study between Veterans Affairs and the Department of Defense. This longitudinal study was intended to monitor the health of Gulf War veterans exposed to DU during friendly fire incidents, of whom 25% continued to carry embedded DU fragments in 2008 (Squibb and McDiarmid, 2006). To summarize the results from numerous studies published prior to 2008, elevated urine uranium was found in veterans with embedded shrapnel (Hooper et al., 1999; McDiarmid et al., 2001b). Poorer cognitive performance was associated with higher excreted uranium (McDiarmid et al., 2007), as were some measures of renal function (McDiarmid et al., 2004; McDiarmid et al., 2001a). Sperm count and concentration was found to be significantly or nearly significantly higher (McDiarmid et al., 2001a), and measures of chromosomal aberrations and gene mutations were significantly increased with DU exposure (McDiarmid et al., 2001a). Endocrine function was also altered in higher DU populations; the 1997 Baltimore VA Longitudinal Evaluation found significantly higher prolactin levels in Gulf War veterans exposed to friendly fire (McDiarmid et al., 2000).

Since 2008, a number of follow-up studies have assessed Gulf War veterans with embedded DU fragments. Todorov et al. (2013) reported that the highest levels of semen uranium were found in the DU exposed veterans. Similarly, only subjects who continued to carry embedded DU fragments showed detectable DU signatures in urine (Dorsey et al., 2009). In a number of studies, no health effects were found to be associated with urine uranium levels (Squibb et al., 2012), nor were any biomarkers of genotoxicity (Bakhmutsky et al., 2013; McDiarmid et al., 2011) or pulmonary effects found (Hines et al., 2013; McDiarmid et al., 2013). One study looked at renal effects of DU exposure, reporting elevated

urine creatine in Gulf War veterans with multiple embedded fragments (McDiarmid et al., 2013). Finally, uranyl acetate patch testing revealed no significant differences between exposed veterans or a control group, indicating the absence of immune hypersensitivity to uranium (McDiarmid et al., 2013). These differences are notable but not currently associated with known diagnoses or long-term health outcomes. The studies were conducted on small numbers of exposed soldiers, limiting power to detect statistically significant differences.

Table 2. Studies Assessing Exposure to Depleted Uranium in Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Parameter(s) Evaluated***	***Key Findings***
Bakhmutsky et al., 2013	35 DU-exposed GWV	^{235}U:^{238}U in urine and cytogenic endpoints	Chromosomal damage was not associated with urinary uranium levels.
Dorsey et al., 2009	404 GWV and 1,365 post-GWV	KPA Isotopic ratio of U (^{235}U:^{238}U) in urine	Subjects with DU embedded fragments showed detectible depleted isotopic uranium signatures in urine. Those without embedded fragments had urine U levels comparable to the U.S. population.
Hines et al., 2013	80 DU-exposed GWV	Total urine uranium and ^{235}U:^{238}U urine ratio	No differences in pulmonary or respiratory function were seen between high and low uranium groups.
McDiarmid et al., 2011	35 DU-exposed GWV	ICP-DRC-MS urine U/g creatinine	No statistically significant differences in biomarkers of genotoxicity or cognitive function between high and low U groups. Subjects with DU fragments showed significantly reduced urine calcium and sodium (measures of bone metabolism), and significantly decreased PTH.
McDiarmid et al., 2013	37 DU-exposed GWV	ICP-MS total U/g creatinine, isotopic ratio of uranium (^{235}U:^{238}U) in urine, PET-CT	DU-related effects on renal function seen only in subjects with multiple metal fragments; pulmonary function in clinically normal range; PET-CT test not well-suited to identify DU fragment breakdown or early lesions.
Shvartzbeyn et al., 2011	40 DU-exposed GWV or IWV and 46 dermatology patients controls	Uranyl acetate and extended metal match testing	No uranyl acetate patch test reactions were observed in veterans or control group, indicating few memory effector T-cells sensitive to dermal DU exposure.
Squibb 2012 et al.,	79 GWV and 5 DU-exposed	ICP-MS total U/g creatinine; isotopic ratio of uranium (^{235}U:^{238}U) in urine	Urine U concentration in most DU-exposed GWV similar to U.S. adults; 42% showed excreted U concentrations above normal U excretion cutoff values. No clinically significant health effects found in DU-exposed GWV. Nearly significant increase in retinol binding protein in high DU exposure group.
Todorov et al., 2013	10 GWV and 6 DU-exposed GWV	ICP-MS U quantification in semen	Wide variation in semen uranium in DU-exposed GWV and GWV with unknown exposure; highest exposure seen in DU-exposed GWV.

Abbreviations: GWV = Gulf War veteran; IWV = Iraq War veteran; DU: Depleted uranium; U: Uranium; KPA: kinetic phosphorescence analysis; ICP-MS: inductively coupled plasma mass spectrometry, PET-CT: positron emission tomography- computed tomography; ICP-DRC-MS: inductively coupled plasma-dynamic reaction cell-mass spectrometry; PTH: parathyroid hormone.

Conclusions: Human exposures

Overall, studies published since the 2008 report continue to show that exposures to pesticides and pyridostigmine bromide are etiologically important in the development of Gulf War illness and in the behavioral and cognitive dysfunction experienced by Gulf War veterans. The findings in Gulf War veteran populations are consistent with those seen in other occupational and environmental groups (see Appendix C). Exposure to the nerve gas agents sarin/cyclosarin has been linked in two more studies to changes in structural MRI findings and with cognitive decrements, further supporting the conclusion from evidence reviewed in the 2008 report that exposure to these agents is etiologically important to the central nervous system dysfunction that occurs in some subsets of Gulf War veterans.

New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. It is unclear if vaccine exposures may also be contributing to Gulf War veteran health symptoms, because current results have been conflicting and include weak associations. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear: studies on this substance have focused on small groups of individuals.

Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and mixed exposures would inform the assessment of mixed exposures, as would the development of biomarkers of exposures to specific chemicals that occurred in the past.

B. Studies Using Animal Models of Gulf War Illness and Related Diseases

Animal models have advanced science and improved public health. While it may not be possible to develop a "perfect" animal model that reflects all features of Gulf War illness, animal models can readily be used to characterize the wide variety of effects associated with exposures that may underlie the pathogenesis of Gulf War illness in ill veterans. Animal models have the advantage of providing post-exposure evidence obtained directly from any organ or target tissue. Modeling the persistence of effects due to exposures presumably occurring years earlier in ill veterans can be achieved in a short time frame using rodent (rats/mice) models. Finally, a very wide variety of effect "domains," from molecular to cellular changes, from genomic to proteomic, from structural to functional alterations in physiology and behavior, can readily be assessed in experimental animals. Agents and conditions that may underlie Gulf War illness can be used in animal models as an ideal means to assess the relevance of these exposures, with the goal of better understanding Gulf War illness and for devising and testing potential treatments. No one organ system has been singled out and, given the multisymptom basis of Gulf War illness, it is not surprising that effects of candidate exposures involve diverse effects on diverse targets in multiple organ systems. Since the last RACGWVI report, progress has been achieved in identifying targets and effects of Gulf War illness-related exposure using several animal models.

Animal models have been used to characterize the persistent molecular, cellular and functional effects associated with individual and combined exposures encountered by veterans in theater during the Gulf War. The 2008 Committee report summarized a number of animal studies evaluating exposures such as pesticides, pyrostigmine bromide (PB), insect repellants, nerve agents and stress, either administered alone or in combination. Animal models of PB showed that this drug adversely affected nerve function (Drake-Baumann and Seil, 1999; Hudson et al., 1985) and had gastrointestinal (Kluwe et al., 1990), muscular (Adler et al., 1992), immune (Peden-Adams et al., 2004) and cardiovascular (Bernatova et al., 2006) effects. Rodents given PB over time showed a number of locomotor, learning and behavioral deficits (Abou-Donia et al., 2002; Abou-Donia et al., 2001; van Haaren et al., 2001), despite showing no overt signs of cholinergic toxicity or illness. Three studies in rodent models found that the adverse effects

of PB were enhanced by stressors (Abdel-Rahman et al., 2004; Abdel-Rahman et al., 2002; Friedman et al., 1996). Other studies showed reduced levels of acetylcholinesterase in the brains of animals given PB and exposed to stressors (Baireddy et al., 2007; Sinton et al., 2000). PB administered with the nerve agent sarin produced locomotor deficits (Abou-Donia et al., 2002; Scremin et al., 2003), EEG abnormalities (van Helden et al., 2004), changes in heart rate variability (Scremin et al., 2003) and increased signs of oxidative stress in urine (Shih et al., 2006).

The British Ministry of Defense sponsored a series of studies that used animal models of multiple vaccines administered with and without PB pills. Injection of high doses of the anthrax and pertussis vaccines in mice caused reduced body weight, enlargement of the spleen, and illness, while lower doses produced fewer adverse effects (Rijpkema et al., 2005). In a series of experiments in small primates called marmosets, animals that received PB and/or diluted vaccines showed reduced cognitive function and electroencephalography (EEG) alpha wave activity and beta-2 waves (Stevens et al., 2006). In another study, marmosets receiving multiple vaccines did not show compromised immune function or other adverse effects (Hornby et al., 2006).

The 2008 RACGWVI report outlined two animal studies on the pulmonary effects of exposure to the Kuwaiti oil fires. When hamsters were exposed to concentrations of particulates similar to those released during the Kuwaiti oil fires, significantly greater numbers of white blood cells involved in inflammatory processes were found in lung tissue (Brain et al., 1998). Similarly, feral cats captured in Kuwait after eight months of exposure in areas downwind from the fires had histopathological lesions in the lungs, with hyperplasia and other cell changes noted in the bronchioles and other tracheal and pulmonary tissues (Moeller et al., 1994).

Rodent models of depleted uranium (DU) exposure have also been used to explore whether DU may be related to symptoms of Gulf War illness. Studies on inhaled DU dust in rodent models showed uranium deposits in the olfactory bulb, hippocampus, cortex and cerebellum in the brain, which was associated with impaired locomotion and spatial working memory (Monleau et al., 2005). Uranyl acetate injected into rats produced sensorimotor deficits and alterations in nitric oxide and acetylcholinesterase distribution in the brain (Abou-Donia et al., 2002) and reduced appetite and sleep (Lestaevel et al., 2005). Finally, DU ingested through drinking water has been shown to also accumulate in the brain (Bussy et al., 2006; Houpert et al., 2005), alter behavioral task performance and sleep (Briner and Murray, 2005; Houpert et al., 2005; Lestaevel et al., 2005) and decrease neurotransmitter levels in the brain (Bussy et al., 2006).

Taken together, the studies outlined in the 2008 Committee report have laid the framework for how exposures experienced in theater during the first Gulf War could be related to symptoms reported by veterans. Since the last RACGWVI report, further progress has been achieved in identifying targets and effects of GWI-related exposure using several animal models. These are detailed here.

Altered behavior, cognitive function, neurotransmission and intracellular signaling
Organophosphates are a class of chemicals that are well established as inhibitors of the enzyme acetylcholinesterase (AChE). Organophosphates are highly reactive compounds and can covalently bind organophosphorylate serine residues throughout the body. Mice exposed to low doses of pyridostigmine bromide (PB, an organophosphate-like medication that is an AChE inhibitor) and permethrin (PER; a pyrethroid-based pesticide) showed elevated levels of the phosphocholine reservoir compounds phosphatidylcholine and sphingomyeline, which are necessary for acetylcholine synthesis (Abdullah et al., 2013). Exposure after only three days to chlorpyrifos (CPF) in combination with PB and PER produced an overall increase in basal acetylcholine levels in the brains of 6-month old mice, astrogliosis, vascular injury markers, altered cell differentiation in the dentate gyrus and reduced concentration of the synaptic vesicle protein synaptophysin (Ojo et al., 2013). Organophosphates and other pesticides can also

produce changes at the behavioral level. When CPF, PER and PB were given to rats, behavioral changes were seen that indicated spatial navigation and memory impairment (Parihar et al., 2013). Exposure to stressor stimuli in addition to the pesticide protocol produced significant increases in glial-related inflammation, reduced neuronal growth in the hippocampus and reduced overall hippocampal volume (Parihar et al., 2013).

Alterations in synaptic transmission have been observed in mice exposed to CPF at dosages that do not result in overt symptoms of cholinergic toxicity. Direct electrophysiological evidence for suppression of hippocampal synaptic transmission was observed at three months post CPF exposure (Speed et al., 2012). These deficits in signaling were associated with large decrements in hippocampal spine density in a subfield of this structure, i.e. evidence for subtle structural damage underlying the observed changes in neurotransmission. Thus, relatively short lasting exposures to CPF at dosages that do not produce cholinergic toxicity can lead to long lasting changes in an area of the brain linked to cognitive functions, as observed in animal models and consistent with some of the symptoms of Gulf War illness. A study by Nutter et al. (2013) showed that exposure to CPF, PER and PB produced changes in K^+ channel kinetics and excitability in muscle pain receptors, even though no changes were seen at the behavioral level between exposed and control animals. In addition to alterations of neuronal signals from cell to cell, Gulf War-relevant exposures of mice disrupt intracellular signaling. Exposure of mice to PB and DEET for two weeks followed by exposure to the sarin surrogate, diisopropylfluorophosphate (DFP), or exposure to one week of CPF, resulted in deficits in signaling through glutamatergic receptors in the striatum (Torres-Altoro et al., 2011). These effects in turn were linked to alterations in phosphorylation of the key intracellular signaling protein of striatal medium spiny neurons, DARPP-32, and the protein kinase CDK5. In aggregate, these studies suggest that subtle changes in neuronal signaling, perhaps as a consequence of or leading to subtle changes in neuronal structure, could serve as the basis of some of the symptoms of Gulf War illness.

Evidence for mood and cognitive deficits in an animal model of Gulf War illness also have been reported using a month-long exposure to permethrin, PB and DEET with and without a brief exposure to restraint stress (Parihar et al., 2013). This dosing paradigm resulted in behavioral, histochemical and neuroanatomical changes consistent with neuroinflammation in the hippocampal formation, a brain area responsible for maintenance of cognitive function. Even a brief stressor exposure exacerbated the effects observed across all domains evaluated. While the long-term persistence of these effects was not established, the data suggest that anti-inflammatory treatments may improve the mood and cognitive deficits associated with neuroinflammation in Gulf War illness.

Molecular and cellular disruptions of axonal transport

Organophosphates (OPs) have been shown to disrupt multiple functions beyond those linked strictly to acetylcholinesterase (AChE). While acetylcholinesterase inhibition by exposures that occurred in the Gulf War (e.g. sarin and CPF) have been implicated in the etiology of Gulf War illness (Golomb, 2008), more recent studies have identified additional secondary pathways of OP effects apparently unrelated to inhibition of AChE (see review; Terry, 2012). A notable non-cholinergic target of OPs is the process of axonal transport, a key nervous system function for transporting molecules (e.g. RNA and proteins) and subcellular organelles (e.g. mitochondria and synaptic vesicles) through the cytoplasm of axons (Terry, 2012). OPs can affect axonal transport directly by altering microtubule structure by binding to tubulin required for transport function (Grigoryan et al., 2008). This and similar covalent interaction of OPs with proteins to alter their function is not limited to binding to serine residues, because tyrosine is also bound by OP esters (Grigoryan et al., 2009). The direct consequences of OP binding (e.g. CPF) on transport has been visualized in vitro and shown to affect movement of mitochondria within the axon at concentrations below those that inhibit AChE (Middlemore-Risher et al., 2011). Effects of OPs on axonal transport were accompanied by changes in behavior associated with impairments in attention, memory and other aspects of cognition after exposure of rats to the OP CPF and the sarin surrogate DFP (Terry, 2012).

Thus, axonal transport disruption by OPs relevant to exposures in the 1991 Gulf War can result in deficits in cognition in animal models that resemble symptoms in ill veterans. As with most animal models of Gulf War illness studied to date, future evaluations of Gulf War exposures on axonal transport would benefit from combined exposures at low levels. Nevertheless, studies that have been conducted since the 2008 RACGWVI report clearly indicate that low levels of OPs can adversely affect a key CNS process that may serve as a partial mechanistic explanation for symptoms associated with Gulf War illness.

Genomic and proteomic profiling to identify novel targets of Gulf War exposure
While many animal studies of Gulf War illness have focused on particular effect "domains," genomics and proteomic technology offers a means to identify and characterize novel targets affected by Gulf War-related exposures that have not previously been examined. Such an approach recently was implemented to examine chronic exposures to PB, permethrin, DEET and restraint stress to recapitulate exposures that occurred in the Gulf War in a mouse model (Abdullah et al., 2011; Abdullah et al., 2012). Both the genomic and proteomic surveys revealed novel effect domains. More specifically, phospholipids key to lipid metabolism, axonal transport and endocrine and immune function were implicated. These effects were accompanied by behavioral findings indicating sensory, motor and memory impairments as well as subtle effects on glial morphology suggestive of underlying neuropathology and/or neuroimmune alterations. Together these data show the value of obtaining a broader perspective of the effect domains associated with exposure to Gulf War-related agents. While not revealing specific nervous system targets amenable to therapeutic intervention, these studies serve as a template to discover additional pathways and systems disrupted by Gulf War-related exposures.

Liver and cardiovascular effects
In addition to studies of Gulf War-related exposures on the central nervous system, animals were used to evaluate liver and cardiovascular changes with dichlorvos and sarin, respectively (Binukumar et al., 2010). Rats dosed for 12 weeks with dichlorovos showed disrupted liver mitochondrial electron transport and ATP synthesis. These effects were associated with increased mitochondrial calcium uptake and an increase in reactive oxygen species; mitochondrial morphology changes were linked to functional deficits in this key energy producing cellular organelle. These findings were suggestive of impaired mitochondrial bioenergetics underlying liver dysfunction following chronic exposure to dichlorvos. Cardiac structure and function were affected in mice exposed to the Gulf War illness-linked nerve agent sarin (Shewale et al., 2012). At three months post exposure of mice to sarin, left ventricular enlargement was observed along with a corresponding reduction in left ventricular contractility. These findings appeared to reflect a cardiomyopathy as heart weight ratios to body and kidney weight were significantly increased in sarin-treated mice.

Depleted uranium: Mitochondria and oxidative stress
Only one animal study on the effects of depleted uranium has been published since 2008. In a study from Shaki et al. (2013), brain mitochondria isolated from rats and exposed to uranyl acetate showed enhanced production of reaction oxygen species (ROS) through alterations in enzyme expression in the electron transport chain, specifically complexes I and II. Increased ROS caused further downstream effects, such as elevated lipid peroxidation and glutathione oxidation, mitochondrial swelling and cytochrome C release (Shaki et al., 2013).

Conclusions: Animal exposure studies evaluating biological effects of exposures
In aggregate, the data obtained using animal models of Gulf War illness (GWI) are suggestive of the involvement of multiple organ systems and pathways in its etiology. Although the exact pathobiological mechanism(s) have yet to be fully understood, effects from single and combined Gulf War-relevant exposures have implications for the lasting health problems experienced by a significant proportion of Gulf War veterans. Further characterization of adverse effects of these exposures on the multiple targets and systems already identified, as well as the identification of additional novel targets affected by Gulf

War exposures, will provide a more global view of the etiology of this illness and lead to effective therapeutic interventions.

Table 3. Studies Using Animal Models of Gulf War Illness and Related Diseases: 2009-2013

Study	*Model*	*Parameter(s) Evaluated Exposure*	*Key Findings*
Abdullah et al., 2011	Mouse	PB, PER	Exposed mice demonstrated significantly increased anxiety behavior, memory impairment and psychomotor dysfunction. After 150 days of exposure, significant increases in astrogliosis were seen in exposed mice. Proteomic analysis showed significant expression alterations for proteins that regulate lipid metabolism, molecular transport, and endocrine and immune function.
Abdullah et al., 2012	Mouse	PB, PER, DEET, stress	Significant increases in ether PC, diacyl, PC and SM lipids, indicating altered transport, uptake, storage and synthesis in ACh pathways in the brain. Anxiety-like behavior was increased in exposed mice, especially in females. Sensorimotor deficits were also significantly associated with exposure, as was astrogliosis.
Abdullah et al., 2013	Mouse	PB, PER	In mice exposed to PB and PER, phosphocholine precursors PC and SM were elevated compared to controls. Lyso-platelet activating factors were significantly decreased in exposed animals.
Arfsten et al., 2009	Rat	Implanted DU pellets	Gestational duration in F1 females bred from F0 mid-dose mating pairs was significantly longer than controls. More pups who died post-weaning were bred from DU-exposed mating pairs. Heart and liver weights in F1 females significantly higher in descendants of DU exposed rats compared to controls. No other reproductive or neurodevelopmental differences seen.
Binukumar et al., 2010	Rat	Dichlorvos	Significant increase in liver enzymes in exposed rats compared to controls. Mitochondrial calcium increases and enzymatic activity impairment involved in the mitochondrial electron transport chain were also significantly associated with dichlorvos exposure.
Bozkurt et al., 2010	Rat	CPF	Single CPF dose showed significant short term (12 hour) changes in glial and neuronal markers in serum. Immediate significant changes in body weight and temperature persisted for approximately 168 hours.
Cardona et al., 2013	Rat	CPF	CPF significantly inhibited AChE and APF enzymatic activity even when signs of acute toxicity are absent. Striatum and brainstem areas showed slowed AChE recovery after CPF exposure.
Corbel et al., 2009	Insect and mouse cultured tissue	DEET	DEET application to insect CNS neuronal preparation produced significant initial increase in neuronal electrophysiological activation, followed by a significant decrease, indicating changes in synaptic transmission and inhibition of cholinesterase activity.
Grigoryan et al., 2008*	Bovine protein isolate	Sarin, soman, CPO, DFP, FP-biotin	Pesticide agents bind covalently to tubulin, a protein required for neuronal transport, putatively creating axonal transport deficits.

Study	*Model*	*Parameter(s) Evaluated Exposure*	*Key Findings*
Grigoryan et al., 2009	Bovine, human, porcine and murine protein isolate	FP-biotin	OP esters bind to tyrosine in proteins across different species. OP- reactive proteins include enzymes with and without active serine sites.
Grigoryan et al., 2009	Bovine, human, porcine, murine protein isolate	DFP, CPO	OP esters covalently bond to lysine in albumin, keratin, actin, tubulin and transferrin in a number of mammalian species.
Jiang et al., 2010	Mouse	CPF, CPO	Microtubules isolated from brain tissue from exposed mice showed fewer associated proteins than control mice, and microtubules from exposed mice were significantly smaller in comparison to controls. Mice brains show CPO-labeled tubulin after injections of nontoxic doses of CPF or CPO.
Middlemore-Risher et al., 2011	Rat	CPF, CPO	Mitochondrial length, number and axonal movement was decreased in central nervous system neurons in rats exposed to CPF or CPO when compared to controls.
Nutter et al., 2013	Rat	CPF, PER, PB	After exposure, K^+ channel kinetics were altered in vascular pain receptors, with significant increases in electrophysiological excitability. No behavioral differences were noted between exposed and control animals, nor were significant effects seen in Na^+ channel activity.
Ojo et al., 2013	Mouse	CPF, PB, PER	Exposure to CPF alone or in combination with PB and PER reduced synaptic function by reducing hippocampal synaptophysin and impairing cell differentiation in the dentate gyrus, with altered basal ACh levels throughout the brain.
Parihar et al., 2013	Rat	DEET, PER, PB, stress	Exposure to low doses of DEET, PER and PB increased disordered mood and cognitive behaviors. Rats exposed to pesticides and stress showed significantly reduced hippocampal volume and neuron growth, and increased glial inflammation.
Shaki et al., 2013	Rat	DU	Uranyl acetate exposure caused elevations in ROS production in brain mitochondria via disruptions via complexes I and II.
Shawale et al., 2012	Mouse	Sarin	Mice exposed to sarin showed increased LV dilation when compared to unexposed mice, with a nearly significant reduction in LV contractility. Heart weight ratios to body and kidney weight were significantly higher in sarin-treated mice, consistent with LV remodeling. Adrenal TH mRNA and CORT were significantly reduced in sarin exposed mice.
Speed et al., 2012	Mouse	CPF	Mice injected with CPF showed a short term increase in synaptic transmission in the CA3-CA1 hippocampal region. After three months, decreased spine density in the hippocampus and reduced synaptic activity was seen in exposed vs. control mice.
Torres-Altoro et al., 2011 torries	Mouse	CPF, sarin, PB, DEET, DFP	CFP and PB altered dopaminergic and glutamatergic synaptic transmission in vivo and slice preparations. Combined PB/DEET/DFP exposure stimulated aberrant brain specific protein expression in the striatum and hippocampus.

Abbreviations: PB= Pyridostigmine bromide, PER = permethrin, DEET = *N,N*-diethyl-meta-toluamide, PC = phosphatidylcholine, SM = sphingomyelin, ACh= acetylcholine, DU = depleted uranium, CPF = chlorpyrifos, CNS = central nervous system, CPO = chlorpyrifos oxon, DFP = diisopropylfluorophosphate, FP-biotin = 10-fluoroethoxyphosphinyl-*N*-biotinamidopentyldecanamide, OP = organophosphorus, AChE = acetylcholinesterase, APF = acylpeptide hydrolase, LV = left ventricular, TH = tyrosine hydroxylase, PC = phosphatidylcholine, SM = sphingomyelin, DU = depleted uranium, ROS = reactive oxygen species, CORT = corticosterone

* Papers published in 2008 after the 2008 RACGWVI report release have been included.

C. Conclusions and Recommendations

Research findings

- Human exposure studies. The research reviewed in this report supports and reinforces the conclusion in the 2008 RACGWVI report that exposures to pesticides and pyridostigmine bromide are causally associated with Gulf War illness. The findings in pesticide-exposed Gulf War veteran populations are consistent with those seen in other occupational and environmental groups (see Appendix C). Evidence also continues to demonstrate that Gulf War illness is not the result of psychological stressors during the war.

Hazardous exposures in theater are also related to certain other health problems seen in Gulf War veterans. Exposure to the nerve gas agents sarin/cyclosarin has been linked in two more studies to changes in structural magnetic resonance imaging (MRI) findings and cognitive decrements, further supporting the conclusion from evidence reviewed in the 2008 report that exposure to these agents is etiologically important to the central nervous system dysfunction that occurs in some subsets of Gulf War veterans.

New evidence has emerged suggesting that oil well fire exposures may be important in the development of Gulf War illness and brain cancer. It is unclear if vaccine exposures may also be contributing to Gulf War veteran health symptoms, because current results have been conflicting and include weak associations. Although exposure to depleted uranium has been demonstrated, with continuing levels in body tissue, its contribution to ill health is unclear; studies on this substance have focused on small groups of individuals.

Most veterans experienced exposures to chemical mixtures in theater and effects of these complex exposures remain unknown. Improved modeling of contributions of individual and mixed exposures would inform the assessment of mixed exposures, as would the development of biomarkers of exposures to specific chemicals in the past.

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they can help to determine treatment targets in subgroups of veterans with specific exposures for which there are known mechanistic pathways that cause illness and symptoms. Results from this work can be useful in protecting the health of future military personnel who will experience these exposures as well as non-military populations with occupational or environmental exposure to them. The Committee recommends that additional research in this area be carried out utilizing objective markers of exposure whenever feasible. These include environmental sampling and modeling of conditions in theater. Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for understanding the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic and metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness. Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection and other environmental stressors.

- Animal studies. As noted in the RACGWVI 2008 report, animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown. The evidence concerning these effects has burgeoned since 2008, with new animal models of Gulf War illness and exposures in theater. It is axiomatic that animals are not humans and conclusions from animal studies

must be used as clues that can be further investigated in appropriate human research. However, the outcomes from animal studies are important because data on exposure-outcome relationships can be collected rapidly and efficiently to provide such clues. Animal models of Gulf War-relevant exposures to individual chemicals, chemical mixtures, and chemicals plus other stressors have demonstrated alterations in nervous system outcomes (behavior, cognition, neurotransmission, intracellular signaling, molecular and cellular disruptions of axonal transport); liver and cardiovascular function; genomic, proteomic, lipidomic and metabolomic profiles, and mitochondrial changes. These studies have confirmed hypotheses that exposures are important in the development and expression Gulf War illness symptomatology, that health effects due to exposures and exposure mixtures are often delayed and that persistent effects can be seen after exposure has ended. Even more importantly, animal models are critical for treatment research. They have identified systemic alterations and physiological changes that can be the targets of treatment approaches. And animal models can be used to pre-test promising treatments.

Recommendations

Based on human studies:

- Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they clarify the physiological basis of the disorder and may help to determine treatment targets for Gulf War illness and other health problems in Gulf War veterans. Research in this area should include the following elements.

1. Objective markers of exposure should be utilized whenever possible. These include environmental sampling and modeling of conditions in theater.

2. The Committee recommends that additional research in this area be carried out utilizing objective biomarkers of exposure whenever feasible. Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for understanding the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic and metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness.

3. Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection and other environmental stressors.

Based on animal studies:

- Studies that utilize animal models (multiple types of species and genetically altered rodents) 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, as well as low-level sarin or sarin surrogate, and environmental stressors such as heat and dehydration, all have been informative to date. Research using animal models in Gulf War illness should continue to examine the immediate, delayed, and persistent effects of acute exposures to chemicals and chemical mixtures. Future animal model research should focus on:

1. Studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system, autonomic nervous system and peripheral target organs, including those that encompass mitochondrial dysfunction and accumulation of reactive oxygen species.

2. Studies that evaluate systemic immune parameters in animal models, with an emphasis on those parameters that sensitize ill veterans to Gulf War illness, will also be informative.

3 Animal research to identify biomarkers indicative of past exposures to Gulf War-related toxic compounds that can be applied to Gulf War veterans is important. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s) and that identify persistent changes in the central nervous system and in autonomic function associated with Gulf War-related exposures and conditions. Exploratory biomarker research in animal models that assesses genomic, genetic, epigenetic, proteomic, metabolomic and lipidomic pathways of exposure effect may also be informative.

4. Animal models of Gulf War illness are recommended for rapid screening of potential therapies.

3| Pathobiology of Gulf War Illness: Biological Findings in Gulf War Veterans and Mechanistic Hypotheses

As outlined in the last section of this report, exposures in theater were critical to the occurrence of Gulf War illness and certain other health effects associated with service in the Gulf War. In order to understand the health problems seen in the Gulf War veteran population and to generate clues about how to treat their health conditions, is important to learn the underlying pathobiological changes associated with Gulf War illness and with exposures experienced in theater. This report reviews research on structure and function in the central nervous system (using brain imaging, electroencephalography and cognitive assessments and work that assesses neuroendocrine, autonomic nervous system, and immunological functions.

A. Nervous System functioning in Gulf War Veterans

Cognitive complaints, fatigue, and headaches are common symptoms of veterans with Gulf War illness and were identified very early when veterans began to complain of being ill. In addition, many of the chemicals to which veterans were exposed in theater are well established neurotoxicants, including nerve gas agents, pesticides and other organophosphate-like chemicals such as pyridostigmine bromide. For these reasons, a focus of research in this area has been the nervous system. The outcomes discussed in this section are probes into the nervous system through structural, functional and electrical assays. Most focus on the central nervous system (CNS), though research has also implicated the autonomic nervous system.

1. Neuroimaging and Electroencephalogram (EEG) Findings in Gulf War Veterans

Brain imaging techniques include several rapidly developing tools that have been used in both clinical and research evaluations of Gulf War veterans. Scanning technology such as magnetic resonance imaging (MRI), computerized tomography (CT), electroencephalography (EEG) and positron emission tomography (PET) have been used to study the neurophysiological basis of Gulf War illness and its symptoms. In 2008, this Committee reported that early brain imaging studies showed no significant differences between symptomatic Gulf War veterans and controls (Amato et al., 1997; Haley et al., 1997a; Lee et al., 2005; Levine et al., 2006; Newmark and Clayton, 1995). Since the release of the previous RACGWVI report, sixteen additional peer-reviewed neuroimaging articles on Gulf War veterans have been published, providing further insight into some of the pathologies and mechanisms that underlie Gulf War illness and the importance of the CNS in Gulf War illness pathobiology (Table 1).

Metabolic brain changes seen using MRI and SPECT

Magnetic resonance imaging (MRI) is a technology that measures cerebral blood flow (CBF), white or gray matter atrophy and other metabolic activity and tissue changes. The 2008 Committee report described a number of studies that used MR techniques to measure metabolic changes in the brains of symptomatic Gulf War veterans. To summarize, Haley et al. (2000) used proton magnetic resonance spectroscopy (H-MRS) to measure the relative abundance of neural metabolic products such as choline, creatine and N-acetylaspartate (NAA), which can serve as markers of neuron loss or dysfunction. Their study found significantly lower ratios of the metabolites in the brainstem and basal ganglia of Gulf War veterans who met the Haley case definition criteria. Significant reductions in NAA/creatine ratios were also seen in Meyerhoff et al.'s basal ganglia study (Meyerhoff, 2001) and in a similar study that explored hippocampal NAA/creatine changes (Menon et al., 2004). In a preliminary report, Weiner et al. (2005) found significant differences in choline/creatine ratios in Gulf War veterans who met the Haley Syndrome 2 case definition (confusion-ataxia; Haley et al., 1997b) compared to healthy controls in a preliminary report.

Since 2008, three imaging studies were published that followed up on brain metabolic changes in Gulf War veterans. Weiner et al. (2011) found no significant results in a study that measured NAA, creatine and choline in Gulf War veterans (Weiner et al., 2011). However, another study examined lactate metabolite levels in the prefrontal cortex prior to exercise and after exercise challenge (Rayhan et al., 2013a). Lactate levels were correlated with memory function tested after the exercise challenge but not

before (Rayhan et al., 2013a). A study at the University of Texas Southwestern Medical Center (UTSW) used single-photon emission computer tomography (SPECT), which injects a radioactive tracer to provide clinicians with a 3-D representation of metabolic activity in the brain. In 21 subjects diagnosed with Haley Syndrome 2 (confusion-ataxia), significantly lower cerebral blood flow in the caudate, globus pallidus, putamen and posterior hypothalamus was reported for the ill Gulf War veterans than in 17 military controls (Haley et al., 2009).

Cholinergic neurotransmitter dysfunction

While on duty in the Persian Gulf, many Gulf War veterans were exposed to pesticides, nerve agents and anti-chemical agent prophylaxes that act on cholinergic neurotransmitter systems in the brain and body. Examples of such agents include cyclosarin, sarin, organophosphate pesticides and the pyridostigmine bromide pills given to soldiers to protect against chemical agent exposure. In some imaging studies, physostigmine infusions are given to patients to test or "challenge" the cholinergic system in the brain as a test for transmission dysfunction. As described in the 2008 Committee report, in response to a physostigmine challenge, global cerebral blood flow was significantly different in Gulf War veterans who met the criteria for the Haley Syndrome 2 (confusion-ataxia) when compared to healthy controls and to Gulf War veterans in the other two Haley syndrome groups (Haley, 2006). Haley Syndrome 2 Gulf War veterans also showed significantly lower cerebral blood flow in the insula and frontal cortex when compared to controls using a modified method of analysis; standard analytic methods did not show significant differences (Haley, 2006).

Since 2008, several studies have used the physostigmine challenge test and magnetic resonance spectroscopy (MRS) to explore cholinergic brain changes. Subjects diagnosed with Gulf War illness showed abnormal cerebral blood flow through the hippocampus before the physostigmine challenge (Li et al., 2011b). After the physostigmine injection Gulf War veterans with Haley Syndrome 2 (confusion-ataxia) and 3 (neuropathic pain) showed significantly abnormal increases in regional cerebral blood flow in the hippocampus of both hemispheres (Li et al., 2011b). In another physostigmine study, Liu et al. (2011) failed to see an expected decrease in brain activity in symptomatic Gulf War veterans. Instead, Gulf War veterans diagnosed with Gulf War illness showed either no change or increased cerebral blood flow after injection, with changes being statistically significantly different from sedentary control veterans. Differences between Gulf War veterans and controls were most significant in the hippocampus, amygdala, caudate and thalamic areas after physostigmine injection. Similar elevated cerebral blood flow results in a physostigmine study were also seen by Haley et al. (2009).

Structural magnetic resonance imaging (MRI)

MRI studies published since 2008 that focused solely on neuroanatomical changes associated with Gulf War illness have consistently shown reduced white and gray matter volume in cortical areas in symptomatic Gulf War veterans and in sarin/cyclosarin-exposed Gulf War veterans (Chao et al., 2011; Chao et al., 2010; Rayhan et al., 2013d; Rosenzweig et al., 2012). Reduced signaling was seen in the thalamus, caudate, hippocampus, globus pallidus and putamen (Calley et al., 2010; Haley et al., 2009; Li et al., 2011b). Two studies published after 2008 followed up on whether specific wartime exposures to nerve gas agents were associated with neuroanatomical changes in Gulf War veterans. Sarin-exposed Gulf War veterans showed significantly reduced gray matter and hippocampal volume compared to unexposed controls in an MRI study carried out at the San Francisco Veterans Affairs Medical Center (Chao et al., 2010); no changes were seen in white matter volume. A follow-up study by the same group using a larger sample size showed reductions in gray and white matter, although the extent of atrophy was not correlated with estimated exposure dose (Chao et al., 2011). Chao et al. (2011) also found that Gulf War illness and chronic multisymptom illness diagnoses significantly predicted volume changes in sarin and cyclosarin-exposed subjects.

Alterations seen in functional MRI (fMRI)
Functional MRI (fMRI) can be used to measure blood flow changes in real time, usually during a task or in response to a probe. Since 2008, a number of studies used fMRI to collect information on functional changes occurring in Gulf War illness and other related illnesses. Increases in axial diffusivity—a measure of axonal neuropathology and white matter integrity in the brain measured by diffusion tensor imaging (DTI) using fMRI--was found to be associated with fatigue, pain and hyperalgesia (Rayhan et al., 2013d). This study further showed that axial diffusivity in the right inferior fronto-occipital fasciculus predicted chronic multisymptom illness (CMI) classification. In another study, when civilian controls and Gulf War veterans were exposed to exercise, two distinct Gulf War veteran phenotypes emerged (Rayhan et al., 2013c). Additionally, changes in axial diffusivity were significantly higher in Gulf War veterans diagnosed with CMI and chronic fatigue syndrome and were correlated with pain, fatigue and other symptoms. In response to exercise, the first subgroup displayed orthostatic tachycardia while the other developed hyperalgesia (Rayhan et al., 2013c). Both groups showed signs of brain atrophy when compared to controls and altered working memory compensation in brain areas that were different from controls. Another University of Texas Southwest study used fMRI to scan 53 symptomatic Gulf War veterans and found significant signal changes in the thalamic and caudate regions in Haley Syndrome 2 (confusion-ataxia) subjects when compared to other symptomatic veterans and healthy controls (Calley et al., 2010). Additionally, the Haley Syndrome 2 group's performance on a semantic learning task was significantly associated with signal change in bilateral caudate areas.

fMRI was used to measure responses to an innocuous heat stimulus in symptomatic and control Gulf War veterans (Gopinath et al., 2012). Compared to Haley Syndrome 3 (neuropathic pain) patients and controls, Gulf War veterans diagnosed with Haley Syndromes 1 (impaired cognition) and 2 (confusion-ataxia) showed significantly reduced brain activity in the insula, somatosensory areas S1 and S2, the medial prefrontal cortex, supplementary motor area, premotor cortex and dorsolateral prefrontal cortex. In a working memory task, symptomatic Gulf War veterans showed distinct prefrontal cortical activity during a working memory task when compared to civilian controls, indicating impairments in central executive processing (Hubbard, 2013).

Electroencephalogram (EEG) studies
EEG records electrical activity in the brain using electrodes that affix to the scalp and face. While having limited spatial resolution, the EEG can nevertheless show abnormal responses to certain sensory stimuli and delays during processing tasks. EEG specifically measures event related potentials (ERPs), which are bursts of electrical activity in the brain in response to a stimulus and are measured at the scalp. This wave of electrical activity is divided into particular epochs, such as P1 and P3, which represent different positive deflections with measurable amplitudes and latencies. In an EEG study performed at the Center for Brain Health at the University of Texas, Tillman et al. (2012) found significant associations between Haley Syndrome diagnoses 2 (confusion-ataxia) and 3 (neuropathic pain) and P1 latency and amplitude during a task that measures hyperarousability, when compared to healthy controls and Haley Syndrome 1 (impaired cognition) subjects. Gulf War veterans with Syndromes 1 (impaired cognition) and 2 (confusion-ataxia) showed P3a amplitudes that were significantly different from controls and Syndrome 3 (neuropathic pain) subjects. In a follow-up study, significantly lower P3b amplitudes were seen in all three syndrome groups when compared to controls (Tillman et al., 2013).

Overall, studies of veterans with Gulf War illness defined in various ways and of veterans with sarin/cyclosarin exposure that utilize varying imaging and EEG probes consistently identify structural and electrical abnormalities in the central nervous system: 14 of the 15 papers summarized in Table 1 support this conclusion.

Table 1. EEG and Brain Imaging Findings in Symptomatic Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Method(s)*	*Key Findings*
MRI and SPECT			
Haley et al., 2009	21 GWV with Haley syndromes, 17 veteran controls	SPECT	Syndrome 2 showed significantly lower resting nrCBF compared to controls and other syndrome groups. Reduction most apparent in caudate head, globus pallidus, putamen and posterior thalamus. Subjects with Syndrome 2 showed elevated nrCBF while other groups showed reduced nrCBF after physostigmine stimulation.
Rayhan et al., 2013	15 symptomatic GWV, 11 veteran and civilian controls	fMRI, MRS	Prefrontal lactate levels prior to exercise predicted whether symptomatic GWV showed increased or decreased memory test scores.
Weiner et al., 2011	81 symptomatic GWV, 101 intermediate GWV, 97 deployed veteran controls	MRI, MRS	No significant differences in NAA and NAA metabolites in the basal ganglia and pons between symptomatic and control veterans.
Physostigmine challenge test			
Li et al., 2011	35 GWV with Haley syndromes, 13 veteran controls	MRI-based ASL	Abnormal hippocampal CBF persists in symptomatic GWV at baseline. Patients with Syndromes 2 and 3 showed significantly increased bilateral rCBF in hippocampi after physostigmine stimulation.
Liu et al., 2011	33 GWV with Haley syndromes, 14 nonsymptomatic veteran controls	MRI-based ASL	Expected physostigmine decrease in CBF was absent in symptomatic GWV, who showed either no change or increased CBF after cholinergic challenge. Physostigmine response differences between GWV and controls most pronounced in amygdala, hippocampus, caudate and thalamus.
Structural MRI			
Chao et al., 2010	40 GWV with suspected sarin or cyclosarin exposure matched to 40 unexposed GWV	MRI	Significantly reduced gray matter and hippocampal volumes in sarin and cyclosarin exposed subjects. No significant differences in white matter or CSF volume.
Chao et al., 2011	64 GWV with suspected sarin or cyclosarin exposure matched to 64 unexposed GWV	MRI	Sarin and cyclosarin exposed GWV showed significantly reduced total gray and white matter volumes compared to unexposed controls. GWI/CMI diagnosis significantly predicted gray and white matter volumes in sarin and cyclosarin exposed subjects. No dose-response relationships seen.
Rayhan et al., 2013	31 GWV with CFS or CMI, 12 sedentary control veterans	fMRI	In GWV diagnosed with CMI or CFS, white matter integrity loss was identified in cortico-cortical and corticospinal areas. Changes in axial diffusivity in the IFOF significantly different between controls and CFS/CMI GWV.
Rosenzweig et al., 2012	1 GWV with MS exposed to long term smoke fume	MRI	Asymmetric frontotemporal atrophy focused in left hemisphere, periventricular white matter lesions.

Study	*Groups Studied*	*Method(s)*	*Key Findings*
Calley et al., 2010	53 GWV with Haley syndromes, 16 nonsymptomatic deployed GWV	fMRI	Significant signal change increase in the thalamic region and signal change decrease in the caudate in Syndrome 2 subjects compared to Syndrome 1 and controls. Syndrome 2 subjects showed significantly positive association between reaction time on SORT task and percent signal change in bilateral caudate heads. Syndrome 1 and 3 subjects performed significantly worse on SORT compared to deployed controls.
FMRI			
Gopinath et al., 2012	40 GWV with Haley syndromes, 14 veteran controls	fMRI	In response to innocuous heat, subjects with Syndromes 1 and 2 showed significantly reduced activation in the insula, S1, S2, SMA, medial PPC, IPL, premotor cortex and DMPFC in compared to controls. Syndrome 1 and 2 exhibited significantly more activation to innocuous heat in the ventral anterior cingulate.
Rayhan et al., 2013	28 symptomatic GWV, 10 civilian controls	fMRI	The GWI post-exercise orthostatic tachycardia subgroup showed brainstem atrophy and baseline working memory compensation in the vermis. The other GWI subgroup exhibited hyperalgesia in response to exercise, and had baseline working memory compensation in the basal ganglia when compared to controls. GWV showed impaired working memory compared to controls.
Hubbard 2013	96 symptomatic GWV, 44 matched controls	fMRI	Significant differences were seen between groups for prefrontal cortex activity during a working memory task, indicating that GWVs allocate high demand working memory loads differently from controls.
EEG			
Tillman et al., 2012	20 GWV with Haley syndromes, 8 deployed asymptomatic GWV	ERP from EEG	Haley syndrome group predicted P1 amplitude, P1 latency, with longer latencies in syndromes 2 and 3 compared to controls and Syndrome 1. Mean P3a amplitudes significantly different between syndromes 1 and 2 compared to controls and syndrome 3.
Tillman et al., 2013	22 GWV with Haley syndromes, 8 deployed asymptomatic GWV	ERP from EEG	Significantly lower P3b amplitudes in 3 syndrome groups compared to controls in an oddball attention task.

Abbreviations: GWV= Gulf War veterans, PTSD= post-traumatic stress disorder, SORT = Semantic object retrieval test, MRI = magnetic resonance imaging, fMRI = functional magnetic resonance imaging, GWI= Gulf War illness, CMI = chronic multisymptom illness, CSF = cerebrospinal fluid, S1 = Primary somatosensory cortex, S2 = Secondary somatosensory cortex, SMA = supplementary motor area, PPC = posterior parietal cortex, IPL= inferior parietal lobule, DMPFC = dorsomedial prefrontal cortex, SPECT = Single Photon Emission Computed Tomography, noCBF = normalized regional cerebral blood flow, rCBF = regional cerebral blood flow, ASL = arterial spin labeling. CFS= chronic fatigue syndrome, IFOF= inferior fronto-occipital fasciculus, MRS = magnetic resonance spectroscopy, MS = multiple sclerosis, EEG = electroencephalogram, ERP = event related potential, NAA = N-acetyl aspartate, VV = Vietnam veterans, PHG = parahippocampal gyrus, STC = superior temporal cortex, OFC = orbital frontal cortex, PO= pars orbitalis.

2. Neurocognitive Findings in Gulf War Veterans

Gulf War veterans reported cognitive symptoms such as memory problems, concentration difficulties and dysregulated mood upon returning from deployment, with many reporting continued dysfunction and impairment. These symptoms have been systematically investigated in this population through neuropsychological assessments, which allow objective, quantified and standardized measurement of behavioral function. Neuropsychological tests generally focus on specific cognitive and affective domains, including learning and memory, attention, executive functioning, visuospatial functioning, motor skills, performance effort and mood. Because a great deal is known about the relationships between performance on neuropsychological tests and functioning of specific brain structures and neural systems, data from them can be used to generate conclusions about existence and sites of brain damage in patients and in populations with brain insults. Neuropsychological assessments are used both in research and clinical settings to provide information on the presence and extent of cognitive dysfunction and to inform treatment and future research.

The 2008 RACGWVI report summarized cognitive findings among Gulf War veterans according to deployment status, presence of Gulf War illness and exposure to specific chemicals in theater. Studies comparing deployed versus nondeployed veterans frequently found differences in mood or emotional functioning, but few detected any cognitive differences. Studies examining veterans with Gulf War illness and veterans with specific exposures – nerve agents, pesticides, and the prophylactic anti-chemical warfare medication pyridostigmine bromide (PB) – yielded more significant results. Veterans with Gulf War illness demonstrated poorer performance on tasks of attention, executive functioning, memory, visuospatial function and psychomotor skills, as well as mood alterations (Anger et al., 1999; Axelrod and Milner, 1997; Binder et al., 1999; Bunegin et al., 2001; Lange et al., 2001; Storzbach et al., 2000; Storzbach et al., 2001; Sullivan et al., 2003). Furthermore, a subgroup of slower psychomotor symptomatic veterans was identified, suggesting that subgroups exist within ill veterans (Anger et al., 1999; Storzbach et al., 2001). Exposure to pyridostigmine bromide (PB) was associated with poorer performance on executive functioning tasks, as well as dysphoric mood (Sullivan et al., 2003; White et al., 2001). Veterans self-reporting exposure to chemical and biological warfare demonstrated problems with memory, attention and mood. Finally, veterans exposed to sarin and cyclosarin from the Khamisiyah demolition had slowed performance on psychomotor and visuospatial tasks (Proctor et al., 2006).

Four studies investigating neuropsychological functioning in GW veterans since 2008 are summarized in Table 2. Each study examined a unique cohort of Gulf War veterans, with two studies examining several cognitive domains and one study focusing only on executive functioning. Tillman et al. (2010) utilized a GO-NOGO task while participants underwent an EEG; they found that veterans who reported cognitive problems demonstrated difficulty with inhibition compared to control Gulf War veterans (Tillman et al., 2010). Odegard et al. (2013) also employed a single task, a face-name paradigm (Odegard et al., 2013). Veterans who met criteria for Haley Syndrome 3 (neuropathic pain) performed significantly worse than veterans who met criteria for Haley Syndrome 1 (impaired cognition) and healthy veterans. Toomey et al. (2009) evaluated a large sample of deployed Gulf War veterans (1,061) and nondeployed controls (1,128), finding poorer motor speed and sustained attention in the deployed Gulf War veterans (Toomey et al., 2009). Specific self-reported exposures were significant predictors of performance in some cognitive domains: contaminated food and water for sustained attention, Khamisiyah exposure for verbal memory, CARC/paint and immunoglobulin (IG) for visual memory, and Scud missiles and vaccines for motor speed (Toomey et al., 2009). Wallin et al. (2009) found no significant differences on cognitive tests in a small sample of 25 deployed and 16 nondeployed veterans but noted significant differences in measures of mood and quality of life (Wallin et al., 2009). As noted in the Etiology section of this Research review, two studies from Chao et al (2010, 2011; see Table 1 above) on Gulf War veterans with Khamisyah exposures noted decrements in cognitive function related to brain volumetric depletions in one study (2010), though cognitive results were inconsistent in a second study (2011), with exposed

veterans performing better than controls on two tasks and worse on two other tasks. As noted previously, this is a surprising finding considering the exposure-related structural brain changes identified in the exposed subjects.

Overall, studies on cognitive function in Gulf War veterans continue to support the conclusion from the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and with specific exposures in theater. Four new studies support this conclusion. The Chao (2011) study, which found inconsistent results, is difficult to interpret given the fact that structural brain changes that would be expected to result in cognitive dysfunction in Khamisyah exposure were clearly identified. The sixth study (Wallin et al., 2009) assessed a very small sample and was too underpowered to support any conclusions about cognitive dysfunction in Gulf War veterans.

Table 2. Neurocognitive Findings in Gulf War Veterans: 2009-2013

Study	***Groups Studied***	***Key Findings***
Odegard et al., 2013	10 GWV Haley Syndrome 1; 12GWV Haley Syndrome 2; 11 GWV Haley Syndrome 3; 14 GWV well controls	Control GWV and GWV with Haley Syndrome 1 provided significantly more recall responses to face-name items than GWVs with Haley Syndrome 3. Memory performance was related to activation in the left hippocampus.
Tillman et al., 2010	25 GWV with major cognitive complaints; 23 matched GWV controls	The experimental group had significantly more false positives and significantly less hits than the control group suggesting inhibition difficulties. The mean P3 amplitude of the patient group was significantly lower than the control group, and also demonstrated a condition effect with decreased amplitude during the NOGO condition.
Toomey et al., 2009	1,061 deployed GWV; 1128 nondeployed GWV	Eight factors were generated accounting for 68% of variance including verbal memory, attention/working memory, visual memory, executive functioning, perceptual motor speed, visual organization, motor speed, and sustained attention. With a cutoff of 2 SD below the mean the deployed group performed worse on motor speed and sustained attention. The deployed group performed significantly worse on Trails B compared to the nondeployed group. Self-reported exposure to contaminated food or water was a significant predictor of performance in sustained attention. Khamisiyah exposure was a significant predictor in verbal memory, CARC/paint and IG of visual memory performance, and scud missiles and vaccines of motor speed performance.
Wallin et al., 2009	25 deployed GWV with CDC defined GWI; 16 deployed GWV without CDC defined GWI	No significant differences were found between GWI cases and controls for any cognitive domains. GWI cases and controls mean scores were both within normal limits compared to population based normative samples. GWI cases mean scores were all lower than controls. GWI cases were significantly more impaired on measures of mood and quality of life.

Abbreviations: GWV = Gulf War Veteran; CARC = chemical agent resistant coating; IG = immunoglobulin; SD = standard deviation

B. Neuroendocrine Functioning in Gulf War Veterans

Elevated rates of endocrine disorders have not been identified in Gulf War veterans, but altered hypothalamic-pituitary adrenal (HPA) axis function has been shown in disorders that affect Gulf War veterans such as post-traumatic stress disorder (PTSD) and chronic fatigue syndrome (CFS). Studies of other populations with PTSD have revealed increases in glucocorticoid levels and corticotropin releasing factor (CRF), as well as enhanced cortisol and adrenocorticotropic hormone (ACTH) suppression in response to dexamethasone (DEX) challenge (Yehuda, 2001; Yehuda, 2005; Yehuda et al., 2004).

The 2008 RACGWVI report discussed multiple studies investigating endocrine and HPA axis functioning in Gulf War veterans. A small sample had lower salivary cortisol levels 18 months after returning from theater (Kellner et al., 1997). Kellner et al. (1997) also demonstrated that Gulf War veterans had an enhanced cortisol suppression response after being administered dexamethasone (DEX). Golier and colleagues (Golier et al., 2006a; Golier et al., 2006b; Golier et al., 2007) investigated HPA parameters in Gulf War veterans. No differences were found in veterans with PTSD, without PTSD, and healthy controls for baseline measures of cortisol, ACTH, or glucocorticoid receptors. Gulf War veterans demonstrated a greater suppression of ACTH and cortisol in response to DEX. Musculoskeletal symptoms were significantly related to the degree of ACTH suppression. Cortisol suppression was also significantly related to musculoskeletal symptoms and found to be more pronounced in Gulf War veterans reporting pyridostigmine bromide (PB) use (Golier et al., 2006a; Golier et al., 2006b). Furthermore, Gulf War veterans without PTSD had reductions in twenty-four hour ACTH levels. Lowered ACTH levels were also associated with reported use of pesticides and PB, especially in veterans reporting acute symptoms at the time of exposure. Cortisol to ACTH ratios were significantly elevated in Gulf War veterans and correlated with cognitive and mood symptoms (Golier et al., 2007).

Since 2008 Golier and colleagues have continued their work investigating HPA-axis functioning in Gulf War veterans (Table 3). Gulf War veterans with and without PTSD and healthy controls demonstrated equal baseline levels of cortisol, 11-deoxycortisol, and ACTH. When administered a metyraprone stimulation challenge, Gulf War veterans without PTSD demonstrated a lower ACTH response and also had significantly lower ACTH levels after the challenge compared to Gulf War veterans with PTSD and healthy controls. Gulf War veterans' ACTH response significantly correlated with health symptom scales (Golier et al., 2009). Golier et al. (2012) measured ACTH response to a corticotropin-releasing factor (CRF) stimulation test in Gulf War veterans, Vietnam veterans and OEF/OIF veterans, some veterans with PTSD, some without PTSD, and a group of nondeployed controls (Golier et al., 2012). A group difference was only demonstrated in Gulf War veterans; veterans with PTSD demonstrated a significantly higher level of ACTH compared to the non-exposed group. Peak change in ACTH response was associated with self-reported exposure to PB (Golier et al., 2012).

Studies continue to support altered HPA-axis functioning in Gulf War veterans that is not consistent with the pattern seen in PTSD. Recently, it was shown that ACTH response trends differed between Gulf War veterans, Vietnam veterans and OEF/OIF veterans, indicating a unique change in Gulf War veterans (Golier et al., 2012). Further studies are warranted to determine the exact nature of the alteration, which may lead to treatment options.

Table 3. Studies Assessing Neuroendocrine Function in Symptomatic Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Parameter(s) Evaluated*	*Key Findings*
Golier et al., 2009	18 GWV PTSD+, 11 GWV PTSD-, 15 Non-Gulf healthy controls (8 veteran, 7 non-veteran)	Metyrapone stimulation, cortisol, 11-deoxycortisol, ACTH	PTSD- group had significantly lower ACTH response to metyrapone stimulation and significantly lower post-metyrapone ACTH levels compared to PTSD+ and healthy controls. ACTH response to metyrapone was significantly associated with six health symptom scales (neurological, psychological, musculoskeletal, neuropsychological, pulmonary, cardiac) for both GWV groups, but not healthy controls. Baseline ACTH levels were similar across all groups.
Golier et al., 2012	21 VV, 16 GWV, 14 OEF/OIF (16 PTSD+, 25 PTSD-, 10 non-exposed)	CRF stimulation, ACTH, cortisol, DHEA, CBG	PTSD- group from OEF/OIF showed elevated ACTH compared to non-exposed group, but not in GWV. PTSD+ ACTH levels were higher than non-exposed in GWV and OIF/OEF. Robust differences between PTSD+, PTSD- and non-exposed were found in GWV ACTH response greater in PTSD+ GWV than PTSD- or non-exposed GWV, and also greater than VV and OEF/OIF PTSD+ subjects. ACTH AUC was associated with self-reported exposure to PB.

Abbreviations: GWV= Gulf War veterans, PTSD= post-traumatic stress disorder, VV= Vietnam veterans, OIF= Operation Iraqi Freedom, OEF= Operation Enduring Freedom, PTSD+= diagnosed with PTSD, PTSD-= not diagnosed with PTSD, CRF = corticotrophin-releasing factor, ACTH = adrenocorticotropin hormone, CBG= cortisol binding globulin, DHEA = dehydroepiandrosterone, AUC = area under the curve, PB = pyridostigmine bromide.

C. Autonomic Nervous System Alterations in Gulf War Veterans

The human nervous system is divided into two parts. The central nervous system encompasses the brain and spinal cord which together control behavior, memory, cognition, and deliberate movement. Alternatively, the autonomic nervous system (ANS) operates below the level of consciousness to control "automatic" physiological processes such as heart rate, respiration, circulation, digestion, and temperature control. The ANS is further subdivided into three categories: the sympathetic, parasympathetic and enteric nervous systems. Simply put, the sympathetic nervous system is responsible for "flight or fight" responses, whereas the parasympathetic nervous system operates in "rest and digest" activities. Finally, the enteric nervous system describes neurons that orchestrate areas of digestion and excretion. Signaling between and within these systems is primarily carried through neurotransmitters such as acetylcholine and norepinephrine, in addition to others.

Given the broad range of functions controlled by the ANS, it is not surprising that ANS pathology is associated with a diverse set of symptoms that may include digestive disorders, weakness, sexual dysfunction, fatigue and nausea. At the disease level, autonomic dysfunction has also been implicated in diabetes, cardiovascular disease, hypertension, chronic fatigue syndrome and fibromyalgia. Because symptoms of autonomic dysfunction can cluster in many ways, it can only be diagnosed using specific

tests that measure distinct systems or functions. There is scientific evidence for autonomic dysfunction in Gulf War veterans or Gulf War illness.

The 2008 RACGWVI report summarized several papers that documented autonomic nervous system dysregulation in Gulf War veterans. Most studies that included baseline measures of autonomic function were unable to distinguish between Gulf War veterans and controls, with the exception of significantly lower 24-hour heart rate variability (HRV; Haley et al., 2004; Stein et al., 2004). However, in response to exercise, postural changes and other challenges, statistically significant differences were seen between Gulf War veterans and controls: heart rate variability was blunted compared to controls after exposure to diesel vapors (Fiedler et al., 2004), blood pressure and heart rate responses were altered in Gulf War veterans during and after tilt table testing (Clauw, 2001; Davis et al., 2000; Lucas et al., 2005; Sastre and Cook, 2004) and cardiovascular responses to cognitive stressors were reduced (Peckerman et al., 2003; Peckerman et al., 2000). Only one study found no statistical differences between Gulf War veterans and controls when examining sympathetic skin responses, airway pressure changes and HRV (Sharief et al., 2002). Taken together, these findings suggest that the autonomic nervous system function is dysregulated across a number of organ systems in symptomatic Gulf War veterans.

Since 2008, the only published study that looked specifically at autonomic function in Gulf War veterans was by Haley et al. (2013). Haley and colleagues found that Gulf War veterans who met any of the three Haley case definitions for Gulf War illness (Haley et al., 1997b) received higher scores on the Autonomic Symptom Profile questionnaire, driven by higher self-reports of gastrointestinal distress, sleep and urinary dysfunction and orthostatic intolerance (Haley et al., 2013). Gulf War veterans who met the Haley Gulf War illness case definitions (Haley et al., 1997b) also received higher Composite Autonomic Severity scores when compared to controls. Specifically for this test, Syndrome 2 (confusion-ataxia) veterans showed significantly reduced sweat response. This study also confirmed diminished night-time heart rate variability in all three syndrome groups.

Table 4. Studies of Autonomic Function in Symptomatic Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Autonomic Tests*	*Key Findings*
Haley et al., 2013	66 GWV with Haley syndromes, 16 healthy deployed GWV, 15 nondeployed veterans	ASP, CAS, 24-hour HRV with ECG	GWV in all symptom groups reported significantly more symptoms on the ASP than controls. CAS varied significantly between syndrome groups and controls, and was highest in Haley syndrome 2. Syndrome groups had significantly reduced sudomotor function. High frequency increases in HRV was significantly blunted in syndrome groups.

Abbreviations: GWV= Gulf War veterans, ASP= autonomic symptom profile, CAS= composite autonomic severity, HRV = heart rate variability, ECG= echocardiogram

D. Immunological Functioning in Gulf War Veterans

The immune system is the body's first response to bacterial or viral pathogens, as well as internally controlling and eliminating cancerous or unhealthy cells. An immune response involves coordinating lymphocytes and other cells, chemical messengers and protein signaling to coordinate complicated defenses to such internal and external challenges. In addition, the immune system must maintain its ability to adapt in the face of evolving threats. When the immune system is compromised, the body is less able to guard against disease and distinguish between pathogens and its own healthy tissue. Immune

system dysfunction can also compromise functioning of multiple body systems, including the nervous system.

Studies on immune dysfunction outlined in the 2008 Committee report revealed a number of altered immune parameters in symptomatic Gulf War veterans in several investigations, while other studies showed no effect. In two studies that did not differentiate asymptomatic Gulf War veterans from those suffering from Gulf War illness, no significant differences were seen in natural killer (NK) or other cytokines (Bregenholt et al., 2001) or in total leukocytes or erythrocyte sedimentation rates (Eisen et al., 2005). However, another study showed that a higher proportion of symptomatic Gulf War veterans had elevated T and B cells, decreased NK cells activity and other signs of altered immune function (Vojdani and Thrasher, 2004).

One hypothesis relating Gulf War illness and immune function is known as the Rook hypothesis, developed by Drs. Graham Rook and Alimuddin Zumla of University College in London. They argued that Gulf War illness was associated with shifts in two major classes of CD4 cells, known as T-helper (Th) cells. Th-1 cells are responsible for fighting bacteria and other organisms that have made their way inside cells and are triggered by IL-2 and IFN-γ. Th-1 cell overactivation is believed to underlie diseases such as Type 1 diabetes, rheumatoid arthritis and multiple sclerosis. Th-2 cells protect the body against larger, multi-cellular threats like parasitic worms and are associated with production of IL-4, IL-5, IL-6, IL-9 and IL-13. Overactivation of Th-2 cells is thought to be responsible for heightened allergic and asthmatic reactions.

The Rook hypothesis originally gained traction when two studies found that Gulf War veterans who had received higher numbers of vaccines were more symptomatic than those receiving fewer (Cherry et al., 2001; Unwin et al., 1999). Looking more closely at markers of Th-1 and Th-2 dysfunction, Zhang et al. (1999) found significantly higher levels of mRNA for a number of Th-1 markers such as IFN-γ, TNF-α, IL-2 and IL-10 in Gulf War veterans diagnosed with chronic fatigue syndrome (CFS; Zhang et al., 1999). This study did not find evidence of Th-2 mediated immune dysfunction, nor did a 2002 Birmingham VA study show evidence of Th-2 overactivation (Everson et al., 2000). Elevated levels of IL-2 and IFN-γ producing cells were seen in symptomatic Gulf War veterans by Skowera et al. (2004), furthering the Th-1 but not Th-2 portion of the Rook hypothesis. No differences were seen in another study by the same group on antinuclear antibodies (ANA; Skowera et al., 2002).

Since the 2008 Committee report, the immune-related outcome studies in Gulf War veterans have been primarily performed by Klimas, Broderick and colleagues, who examined immune alterations during and after exercise challenges in symptomatic Gulf War veterans (Table 5). Whistler et al. (2009) and Broderick (Broderick et al., 2013; Broderick et al., 2012; Broderick et al., 2011) measured immune parameters in Gulf War veterans following an exercise challenge. Symptomatic veterans demonstrated immune alterations in response to a bicycle ergometric exercise challenge, including significantly decreased cytotoxicity in subsets of natural killer (NK) cells and altered CD4/CD8 ratios. Furthermore, symptomatic and healthy veterans were distinguishable based on hierarchical clustering of prolactin (PRL) and killer cell lectin-like complex receptors (Whistler et al., 2009). Altered CD4 cell functioning has been suggested as a potential mechanism for autoimmune dysregulation in symptomatic Gulf War veterans (Moss, 2012; Moss, 2013).

Subsequently, Broderick et al. (2011) also demonstrated significantly lower NK cell activity following a graded exercise test, as well as persistent elevations of CD2+/CD26+ and CD8+/CH26+ T cell counts. Higher production of IFN-c and IL-5 in vitro and higher plasma IL-6 was observed (Broderick et al., 2011). Measures of IL-1α, IL-10 and neuropeptide Y (NPY) were not observed in symptomatic veterans potentially indicating immune exhaustion. Differences in immune networking were also noted, with symptomatic veterans demonstrating a higher number of immune connections but also higher rates of

disorganization. These dysregulated immune network patterns were negatively enhanced during exercise with notable restructuring around immune nodes distinguishable from healthy controls (Broderick et al., 2011).

Broderick et al. (2013) further investigated immune differences between ill Gulf War veterans, healthy Gulf War veterans and patients with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) (Broderick et al., 2013). Blood was drawn from each participant prior to a graded exercise challenge, during peak velocity performance and four hours after the challenge ended. Differences in immunological gene expression pathway activation were observed between each group. Ill Gulf War veterans had altered PRL/NF-κB signaling, as well as decreased apoptotic signaling. Elevations of PRL/ NF-κB, T and NK cells, IL-10 and IL-12, and CD2+ cells were related to symptom severity (Broderick et al., 2013). Smylie et al. (2013) investigated differences in immune parameters between males and females in healthy sedentary controls, CFS/ME subjects, and ill Gulf War veterans during an exercise challenge (Smylie et al., 2013). Healthy males were distinguishable from Gulf War illness males at rest and post-exercise, while male CFS/ME participants were only distinguishable from healthy controls during peak effort. No differences were seen between male Gulf War illness and CFS/ME participants. Female Gulf War illness participants had significantly different immune parameters than female controls at peak effort and post-exercise, while female CFS/ME participants were only distinguishable from controls at peak effort. Female Gulf War illness participants demonstrated an opposite pattern of female CFS/ME participants at rest (Smylie et al., 2013).

Johnson and colleagues (2013) demonstrated evidence of an underlying inflammatory state in Gulf War veterans while investigating platelet function in ill and healthy Gulf War veterans. There was no evidence of ill veterans having impaired platelet functioning compared to healthy veterans. However, ill Gulf War veterans demonstrated higher platelet counts and also had a higher rate of spontaneous platelet aggregation when compared to healthy Gulf War veterans. Higher rates of platelet aggregation in response to thrombin receptor agonist peptide 6 and C-reactive protein were also seen in ill Gulf War veterans (Johnson et al., 2013).

In 2000, Asa and colleagues found that symptomatic veterans were more likely to show IgG antibodies to squalene, a contaminant found in a series of anthrax vaccines given to Gulf War veterans (Asa et al., 2000). However, a follow up study by Phillips et al. (2009) failed to find an association between squalene antibody status and multisymptom illness.

Six of eight studies conducted on immune system alterations in Gulf War veterans showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines, while seemingly ruling out earlier hypothetical mechanisms of immune dysfunction, including the Rook hypothesis. Additionally, changes occurring during exercise indicate that immunological manifestations of Gulf War illness may be state specific, i.e., evidence of underlying immune differences between symptomatic and asymptomatic veterans may only become apparent in specific experimental or clinical settings under “challenge” conditions that surpass the individual’s capacity for homeostatic compensation.

Table 5. Studies Assessing Immunological Function in Symptomatic Gulf War Veterans: 2009-2013

Study	*Groups Evaluated*	*Immune Findings*
Bakhmutsky et al., 2011	35 GWV, 15 GWV with embedded DU fragments	No significant differences in micronuclei frequency in peripheral blood lymphocytes in GWV with high versus low urine U.
Broderick et al., 2011	9 symptomatic GWV, 11 veteran controls	Symptomatic GWV showed mixed Th1/Th2 phenotype, with significantly higher IFN-c and IL-5 production in vitro, significantly higher plasma IL-6 and significantly lower NK cell activity. Symptomatic GWV showed persistent elevations in CD2+/CD26+ and CD8+/CH26+ T cell counts. IL-1α , IL-10 and NPY not observed in symptomatic GWV, possibly indicating immune exhaustion. NPY was a more central figure in symptomatic GWV immune networks. Significantly higher numbers of immune networks were maintained in symptomatic GWV; pattern was enhanced during exercise. Majority of immune markers show significant differences in node extent, a novel metric of immune marker influence over time across GWV groups.
Broderick et al., 2012	26 symptomatic GWV matched to 13 sedentary GWV, 9 CFS	Symptomatic GWV showed higher expression of immune markers IL-6 in plasma and IL-5 and TNF-α and INF-γ in PHA-stimulated culture.
Broderick et al., 2013	20 symptomatic GWV, 22 GWV controls, 7 CFS/ME	19 significant immunological gene expression pathway activation differences found in symptomatic GWV compared to controls and CFS/ME. Indications of decreased apoptotic signaling in GWI, and changes in PRL/NF-κB signaling. GWI symptom severity associated with PRL/ NF-κB, T and NK cells, IL-10 and IL-12 and CD2+ cell abundance.
Johnson et al., 2013	43 ill GWV, 21 healthy GWV controls	Ill GWV and healthy control GWV had similar platelet functioning. However, ill GWV demonstrated elevated platelet counts and higher rates of spontaneous aggregation, as well as elevated responses to thrombin receptor agonist peptide 6 and C-reactive protein.
Phillips et al., 2009	579 GWV seabees	No association found between squalene antibody status and multisymptom illness.
Smylie et al., 2013	30 Ill GWV, 22 subjects with CFS/ME, 30 healthy sedentary GWV	Male GWI participants had higher levels of IL-13 in combination with IL-10 and IL-23 at rest, and elevations in IL-13 in the context of IL-10, IL-23, and IL-1b post-exercise. Male CFS participants had elevations of IL-23 at rest, and IL-2 in context of IL-16, 10, and 15 at peak effort in comparison to healthy males. Female GWI subjects had elevations in IL-8 and IL-5, and decreases of IL-10 were seen at peak effort, and decreases in IL-23 and IL-1a were observed post-exercise. Female CFS/ME subjects had decreased IL-4 and increased IL-1a at peak effort compared to controls. Female GWI subjects were separated almost perfectly from female CFS/ME subjects based on levels of IL-5 and IL-1b at rest.
Whistler et al., 2009	9 symptomatic GWV, 11 nondeployed veterans	Significant differences in NK cell subsets CD3-CD56+, CD3-16+ and CD3-CD16+. CD3-CD56+ subset showed a significant interaction between illness and time relative to exercise task. Hierarchical clustering distinguished between cases and controls based on PRF and KLR complex receptors. Significant differences found between CD4/CD8 ratios between cases and controls. Salivary cortisol decreased in symptomatic GWV in response to exercise.

Abbreviations: GWV = Gulf War veterans, DU = depleted uranium, U = uranium, CFS/ME= chronic fatigue syndrome/myalgic encephalomyelitis; GWI = Gulf War illness, PRL= prolactin, NF-κB = nuclear factor –κB, NK = natural killer, PHA= phytohaemagglutinin, ME = myalgic enchephalomyelitis

E. Conclusions and Recommendations

Research findings

- Neuroimaging and EEG parameters. Consistent with evidence presented in the 2008 Committee report, new neuroimaging and EEG research has assessed veterans with Gulf War illness and veterans with sarin/cyclosarin exposure. Fourteen of fifteen new studies show structural and electrical abnormalities in the central nervous system associated with Gulf War illness and with exposure to the nerve gas agents sarin and cyclosarin.

- Cognitive abilities. Four of six new studies on cognitive function in Gulf War veterans provide further support for the conclusion from the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and for Gulf War veterans who experienced specific exposures in theater. These findings support the evidence from imaging and EEG probes that nervous system dysfunction is a key element in veterans' ill health.

- Neuroendocrine function. Studies continue to support the conclusion from the 2008 report that neuroendocrine dysfunction, as assessed by altered hypothalamic pituitary axis (HPA) functioning in Gulf War veterans, is present and is not consistent with the typical pattern seen in post-traumatic stress disorder.

- Autonomic nervous system. The 2008 RACGWVI report identified a number of scientific publications documenting autonomic nervous system dysregulation in Gulf War veterans. Since 2008, the only published study that looked specifically at autonomic function in Gulf War veterans was by Haley et al. (2013). This study confirmed diminished night-time heart rate variability in all three Haley Syndrome groups.

- Immune system. Six of eight studies conducted on immune system alterations in Gulf War veterans since 2008 showed immune dysregulation. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. Additionally, changes occurring during or following exercise reiterate that immunological (and other) manifestations of Gulf War illness may only become apparent in specific experimental or clinical settings under "challenge" conditions.

Recommendations

- Research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans should continue to focus on the central and autonomic nervous systems and on immunological and neuroendocrine outcomes in order to identify targets for treatment interventions and outcomes that should be improved during such treatments.

    1. Clear, operationalized case definitions are important for this work. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, non-veteran patients with multisymptom illnesses like chronic fatigue syndrome or fibromyalgia may show different patterns of immunological or neurological function than veterans who have Gulf War illness and meet criteria for these disorders.

    2. Similarly, Gulf War theater exposures, age, and other variables likely moderate pathobiological effects and should be carefully addressed in research.

    3. In some studies that have included female Gulf War veterans, it appears that gender differences may play a role in the pathobiological expression of Gulf War illness and its

effects. Gender should be considered whenever possible in mechanistic and treatment research on Gulf War illness.

4. Since the pathobiological mechanisms underlying Gulf War illness are poorly understood, exploratory probes such as genomics, metabolomics, lipidomics and proteomics may yield useful information that can lead to more focused research.

5. Epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative.

6. In order to effectively pursue "omics" and genetic research, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standard protocols for sample collections should be established and followed.

7. Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e., acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness progression. Analysis should be integrative and deployed across these interacting systems whenever possible using methodologies that formally acknowledge regulatory control.

8. Animal models may be appropriate to investigate mechanistic hypotheses and illness or exposure effects.

4| Gulf War Illness Treatment Research

Longitudinal studies described in the 2008 Committee report indicated that few veterans were recovering from symptoms of Gulf War illness at the time of the report release. Most Gulf War veterans showed stability in symptom number and severity over time, while small numbers recovered substantially or became progressively worse. In two studies on U.S. troops, no significant difference was found between the types or number of symptoms reported years after baseline symptom evaluation (Ozakinci et al., 2006; Proctor et al., 1998), indicating that substantial recovery had not occurred. In a similar study of British Gulf War veterans, symptom evaluations done four years apart showed improvements in measures of fatigue and psychological stress but worsening physical functioning (Hotopf et al., 2003). For chronic multisymptom illness (CMI), 90% of those diagnosed with CMI continued to meet the case definition two years later (Wolfe et al., 2002). In another study, veterans with the most severe symptom manifestations at baseline were significantly more likely to report declining health four years later (Hotopf et al., 2004).

As of the Committee's report in 2008, there had been only four published studies of treatments for Gulf War illness. In one study, the antibiotic doxycycline was found to reduce mycoplasma infections in 11 of 14 veterans (Nicolson et al., 1995; Nicolson and Nicolson, 1996). However, a much larger study found no significant positive effects after doxycycline treatment (Donta et al., 2004). The effect of a combination of exercise and cognitive behavioral therapy (CBT) was also tested in Gulf War veterans; CBT was associated with small but statistically significant improvements on the Physical Component Score of the Medical Outcomes Short Form. In another multidisciplinary study with veterans that included nutritional changes, exercise, and education, little improvement was seen (Engel et al., 2000).

Since the 2008 Committee report, the number of treatment studies has dramatically increased, particularly reflecting the work of the Gulf War Illness Research Program (GWIRP) of the DoD Congressionally Directed Medical Research Program (CDMRP), which is specifically focused on treatments. Since its founding in FY2006 through FY2012, the CDMRP program has funded 57 projects, including 18 treatment studies, 11 clinical studies in humans and 7 preclinical studies in animal models. The remaining studies were studies of diagnostic biomarkers and studies of mechanisms underlying the illness to identify targets for treatments.

Early results from these studies, as well as preliminary results of other studies reported to the Committee, provide encouraging signs that the treatment goals identified in the 2010 Institute of Medicine report are achievable: "Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. The committee suggests a path forward to accomplish these goals and we believe that, through a concerted national effort and rigorous scientific input, answers can likely be found" (Institute of Medicine, 2010, p. x).

A. Published studies

In a study on symptomatic Gulf War veterans, Baraniuk (2013) found that administering an amino acid supplement containing L-carnosine reduced irritable bowel syndrome (IBS)-associated diarrhea (Baraniuk et al., 2013). In addition, Gulf War veterans randomized to receive L-carnosine showed a significant improvement in performance on the digit symbol substitution cognitive task. There were no improvements in fatigue, pain, hyperalgesia and activity levels when measured before and after treatment.

Prolonged exposure therapy is an approach that has been used with patients who have experienced a traumatic event. Patients are asked to visualize traumatic memories, revisit trauma-related situation safely and receive psychoeducation regarding alternative stress responses. In veterans with post-traumatic stress disorder (PTSD), prolonged exposure therapy was shown to significantly reduce PTSD symptoms in a population of veterans from the Gulf War, OIF, OEF and OND (Operation New Dawn; Yoder et al., 2012). Interestingly, Gulf War veterans showed a statistically significant reduced treatment effect

compared to other veteran groups and symptom reduction occurred at a slower pace than the other veteran groups.

In another non-invasive treatment study, Amin et al. (2011) randomized symptomatic Gulf War veterans with sleep disordered breathing to receive a nasal continuous positive airway pressure (CPAP) mask or a sham nasal CPAP (Amin et al., 2011b). Compared to the sham control group, the veterans receiving therapeutic CPAP treatment showed significant improvements in fatigue scores, cognitive function, sleep quality and measures of physical and mental health.

B. Ongoing studies

Intranasal insulin has been shown to improve cognitive function in adults with amnestic mild cognitive impairment (aMCI) and in adults with mild to moderate Alzheimer's disease (Craft et al., 2012), with specific improvements in delayed memory tasks and in caregiver-related functional assessments. In addition, Aβ-42 protein levels, which are associated with Alzheimer's disease and aMCI, were shown to be reduced in the cerebrospinal fluid of subjects receiving insulin. Other studies have reported that intranasal insulin reduced pro-inflammatory cytokines associated with neuroinflammation and modulated cortisol levels (Bohringer et al., 2008; Fishel et al., 2005). These results motivated a two-site (Bronx, NY and Boston, MA) randomized, double-blind, clinical treatment trial of intranasal insulin in Gulf War illness. This study will be conducted by J. Golier at the Bronx Veterans Medical Research Foundation, M. Krengel at the Boston VA Research Institute and K. Sullivan at the Boston University School of Public Health, who will collectively determine whether intranasal insulin can similarly improve cognitive function and overall health in Gulf War veterans and will explore neuroendocrine responses post-treatment. Gulf War veterans will receive one of two different doses of daily intranasal insulin or placebo administered over eight weeks. They will be assessed to determine whether treatment is associated with improvements in scores on tests of memory and attention, measures of overall physical health and mood, and symptoms characteristic of Gulf War illness such as fatigue, pain, sleep quality and perception of poor cognitive functioning.

Chronic multisymptom illness (CMI) in Gulf War veterans appears to involve dysfunction in neuroendocrine signaling within the hypothalamic-pituitary-adrenal (HPA) axis. J. Golier at the Bronx, NY, VA, is running a randomized controlled crossover trial in Gulf War veterans using mifepristone, a synthetic steroid that blocks the glucocorticoid receptors. Gulf War veterans will receive either placebo or mifepristone for 4 weeks at a time. Changes in cognitive function, HPA axis activity, and measures of fatigue, depression and PTSD will also be evaluated. In another study on chemical receptor antagonists, W. Meggs from East Carolina University is conducting a clinical trial to determine if three-month regimens of low-dose naltrexone and dextromethorphan (which block opioid and NMDA chemical receptors in the brain, respectively) reduce neuroinflammation and reported symptom scores in Gulf War veterans.

Coenzyme Q10 (CoQ10) is a chemical that is produced by the body and has recently received attention as a supplement that may improve immune function, cardiovascular health and blood pressure. B. Golomb and colleagues at University of California at San Diego are currently analyzing data from a cross-over study in which Gulf War veterans received CoQ10 supplements or a placebo for 16 weeks. Assessments included quality of life measures such as poor sleep and other symptoms associated with Gulf War illness. Preliminary analysis showed that 100mg of CoQ10 significantly reduced commonly reported symptoms such as fatigue, dysphoric mood and pain and also improved physical functioning in treated veterans compared to veterans receiving placebo.

Many Gulf War veterans who reported gastrointestinal distress during deployment developed irritable bowel syndrome (IBS) post-deployment (Tuteja, 2011). A. Tuteja at the Western Institute for Biomedical Research at the VA Medical Center in Salt Lake City is currently investigating whether administering a

12-week course of probiotics (or a placebo) to IBS-diagnosed Gulf War veterans alters IBS and non-intestinal symptoms. Blood markers of inflammation will also be assessed.

Studies exploring treatments that do not include medications or supplements that could be applied to Gulf War veterans have also been initiated since the 2008 Committee report. Light emitting diodes (LED) that emit near-infrared (NIR) light have been used for photobiomodulation treatment, which consists of exposure to wavelengths of light in the near infrared region of the spectrum (630-1000 nm). M. Naeser and colleagues at the VA Boston Healthcare System in Boston have recruited Gulf War veterans who reported musculoskeletal pain, fatigue, mood or cognitive symptoms to participate in either LED or sham treatment. Outcomes assessed include attention, memory, executive function, psychomotor function, pain, fatigue, mood and inflammatory markers in blood. Repetitive transcranial magnetic stimulation (rTMS) uses a magnetic field to induce weak electrical activity in the brain, and has been used therapeutically for mood disorders (Bersani et al., 2013a; Bersani et al., 2013b), stroke recovery (Dimyan and Cohen, 2010) and for other neurological disorders. W. Ashford at the VA Palo Alto Health Care System has received federal funding to explore whether rTMS will reduce chronic pain in Gulf War veterans compared to Gulf War veterans randomized to receive a sham treatment. Chronic musculoskeletal pain in Gulf War veterans is also the focus of a study being conducted by D. Cook at WMS Middleton Memorial Veterans Hospital in Wisconsin. Gulf War veterans will be randomized to either resistance exercise training or a control program. Outcomes measured include pain sensitivity and regulation, total physical activity level and changes in white matter signal on brain magnetic resonance imaging (MRI).

In an ongoing study by L. Conboy at the New England School of Acupuncture and the Osher Institute at Harvard School of Public Health, Gulf War veterans have been randomized to receive acupuncture treatment for symptoms associated with Gulf War illness. Treatment response is being assessed along the dimensions of sleep, fatigue, pain, psychosocial variables and inflammatory markers. This study builds on a recently published feasibility study completed by Conboy et al. (2012) that examined recruitment, treatment and data collection procedures in a Gulf War veteran patient group. Preliminary data from the acupuncture treatment study show that veterans reported significant reductions in pain and both primary and secondary health complaints, with results being more positive in the bi-weekly versus weekly treatment group.

Acupuncture in combination with restorative sleep and yoga practice for Gulf War-related chronic multisymptom illness is being explored by M. Reinhard at the War Related Illness and Injury Study Center (WRIISC). Outcomes measured will include physical and cognitive function, pain and sleep. Acupressure for Gulf War illness symptoms is being investigated by V. Lin at the Cleveland Clinic Foundation. Symptomatic Gulf War veterans will be recruited and randomized to receive acupressure treatment or no treatment for 12 sessions over six weeks. Symptoms will be evaluated across both groups, and before and after treatment in the veterans randomized to the acupressure treatment arm.

Nasal irrigation is currently used as a therapy for sinusitis. In this procedure, the sinuses are flooded with either saline or a medicated Xylitol solution to improve functioning of the nasal cavity. Because Gulf War veterans have reported sinus problems, D. Rabago and colleagues at the University of Wisconsin are implementing a 26-week randomized controlled trial using Gulf War veteran subjects, where one-third will receive saline nasal irrigation, one-third will receive Xylitol nasal irrigation and another third will receive routine medical care only. Sinus symptoms, quality of life measures and cytokine quantification will be used as outcomes.

Some physicians and scientists believe that prolonged exposure to complex mixtures of chemicals such as pesticides, nerve gas agents, and smoke from oil fire create ongoing sensitivities to everyday chemicals found in the home environment. Under the supervision of D. Carpenter at State University of New York-Albany, a detoxification study is underway in which Gulf War veterans will participate in a program that

includes exercise, vitamin and mineral supplementation, and low-heat sauna. Measures of fatigue, pain, mental health and cognitive function will be assessed in those that complete the program and in randomly assigned wait listed controls receiving usual care.

Mindfulness interventions and cognitive therapies may be effective in reducing symptoms of chronic disease (Merkes, 2010), sleep disorders (Winbush et al., 2007) and other symptoms in the general population. Mindfulness-Based Stress Reduction (MBSR) is currently being tested as a treatment for Gulf War illness at the VA Puget Sound Health Care System in Seattle, WA, by S. Hunt and D. Kearney. Gulf War veterans will be randomized to eight weeks of MBSR or treatment as usual. Symptom severity and measures of neurocognitive function will be assessed before and after treatment. Mind-body bridging (MBB) is a practice similar to MBSR believed to bring attention to body tension, self-centered dysfunctional thinking and an unhealthy dichotomization of mind and body. Y. Nakamura at the University of Utah is currently conducting a study in which Gulf War veterans will be assigned to either sleep-related MBB or Supportive Education (SED) after clinical evaluation. After 6 hours of treatment over 3 weeks, subjects will complete follow up questionnaires to determine the efficacy of therapy programs. Funding has recently been granted to L. McAndrew at the New Jersey WRIISC to determine whether Problem Solving Cognitive Therapy reduces disability in veterans diagnosed with Gulf War illness.

B. Golomb (University of California at San Diego) has received funding for a treatment study survey of Gulf War veterans to determine which, if any, treatment interventions have been used and found effective. A Ft. Devens survey administered by the VA Boston and Boston University research team will target similar questions.

C. Treatment studies using animal models of Gulf War illness

Animal studies of potential treatments such as antibiotics or other medications offer the opportunity to test the safety and efficacy of medical interventions for Gulf War illness. Since 2008, only one study on antibiotics has been published that may translate into treatment developments for Gulf War veterans. Using the broad-spectrum antibiotic minocycline in a rat model of overactive immune system stimulation, neuroinflammatory cytokine release was significantly inhibited, mRNA immune markers in the cortex and hippocampus were reduced, and illness associated behaviors were also reduced (Henry et al., 2008). J. O'Callaghan from Centers for Disease Control is currently studying minocycline as a potential treatment to reduce neuroinflammation in an animal model of Gulf War illness.

A number of other ongoing studies are using animal models of Gulf War illness to explore potential treatments in humans. M. Abou-Donia from the Duke University Medical Center has been testing flupirtine in animals exposed to pesticides, which can recreate many symptoms seen in Gulf War veterans. Flupirtine has been shown to improve learning, memory and cognition while diminishing muscular pain. Rats exposed to the pesticides and to subsequent daily doses of flupirtine will undergo sensorimotor and behavioral function tests, as well as be evaluated for signs of oxidative stress, apoptosis and abnormal neuronal morphology in the brain.

Drugs used to treat neurological and psychiatric diseases in human patients are also being explored in animal models of Gulf War illness. Anti-depressants are being investigated as treatments for the central nervous system impairments associated with Gulf War illness by A. Shetty and colleagues at the Texas A&M Health Science Center College of Medicine and the Central Texas Veterans Health Care System. After exposing mice to stress, pyridostigmine bromide and two pesticides, the anti-depressant fluoxetine is being administered in combination with one of two antioxidants, either resveratrol or curcumin, both of which are believed to have anti-inflammatory effects. In separate trials, both the medication and dietary supplements are combined with voluntary exercise. The efficacy of each treatment arm will be assessed using cognitive behavioral tests, neural stem cell proliferation and measures of oxidative stress. Drugs

used to treat Alzheimer's disease are also being explored in a sarin exposure-based animal model by M. Morris at Wright State University.

Drug discovery and development studies are underway to determine if cognitive enhancers that improve memory and treat mood disorders such as depression could be used in symptomatic Gulf War veterans. L. Niu at State University of New York-Albany uses novel RNA-based techniques to identify drugs that potentiate glutamatergic subunits of the alpha-amino-3-hydroxl-5-methyl-4-isoxazole propionate (AMPA) receptor. Drugs that activate particular AMPA receptor subunits may hold the promise of selective targeted therapies with fewer side effects compared to drugs with broader affinities and effects.

Research teams working on the two "consortia" funded by the DoD CDMRP are addressing the full spectrum of treatment development, including identifying underlying mechanisms in mouse models, determining if Gulf War veterans show similar mechanisms, identifying targets to treat those mechanisms, identifying drugs or other treatments that address those targets and conducting pilot studies of those treatments in Gulf War veterans.

In conclusion, comparisons between the 2008 Committee report and the current report reveal a shift in the number and diversity of studies exploring treatments that either directly or indirectly address symptoms documented in Gulf War veterans. Promising approaches that have gone through limited trials to date include dietary supplements and continuous positive airway pressure (CPAP) therapy. It will continue to be important to explore both conventional medical approaches (such as medications or devices) as well as alternative therapies such as meditation, mindfulness training and acupuncture/acupressure. Treatments based on proposed mechanisms of illness presentation and on specific symptoms are under development and must be pursued urgently.

Table 1. Published Studies Assessing Treatments for Gulf War Veterans: 2009-2013

Study	*Groups Studied*	*Parameter(s) Evaluated*	*Key Findings*
Amin et al., 2011	18 symptomatic GWV with SDB randomized into CPAP vs. sham	Pain VAS, FSS, cognition VAS, PQSI, general health short form 36	CPAP group showed significant improvements in pain, sleep, fatigue, cognitive function, and physical and mental health. Sham subjects exhibited significant levels of symptom worsening.
Baraniuk et al., 2013	25 symptomatic GWV randomized to receive L-carnosine or placebo.	Self-report on pain, fatigue, psychosocial variables, gastrointestinal distress, activity level, WAIS-R	Digit symbol substitution scores increased significantly with L-carnosine treatment, indicating cognitive improvement, and a decrease in IBS-associated diarrhea.

Abbreviations: GWV: Gulf War veterans; SDB= sleep disordered breathing, CPAP = continuous positive airway pressure, VAS= visual analog scales, FSS = Fatigue Severity Scale, PSQI= Pittsburgh Sleep Quality Index, WAIS-R = Wechsler Adult Intelligence Scale-Revised, IBS = Irritable Bowel Syndrome, OEF= Operation Enduring Freedom, OIF = Operation Iraqi Freedom, OND = Operation New Dawn, PCL = Post-traumatic stress disorder checklist, CAPS = Clinician Administered PTSD Scale, LEC = Life Events Checklist, BDI = Beck Depression Inventory, PTSD = Post-traumatic stress disorder.

D. Conclusions and recommendations

Research findings

Treatment research has increased significantly since 2008, particularly reflecting the work of the Gulf War Illness Research Program (GWIRP) of the DoD Congressionally Directed Medical Research Program (CDMRP). However, most of these studies are underway, with results pending. Promising

preliminary reports from the limited trials to date indicate possible benefits provided by coenzyme Q10 (a dietary supplement), acupuncture, and use of continuous positive airway pressure (CPAP) during sleep in veterans with sleep disorders.

Early results provide encouraging signs that the treatment goals identified in the 2010 Institute of Medicine report are achievable: "Veterans who continue to suffer from these discouraging symptoms deserve the very best that modern science and medicine can offer . . . to speed the development of effective treatments, cures, and, it is hoped, preventions. The committee suggests a path forward to accomplish these goals and we believe that, through a concerted national effort and rigorous scientific input, answers can likely be found" (Institute of Medicine, 2010, p. x).

It will continue to be important to explore both conventional medical approaches (such as medications or devices) as well as alternative therapies. Treatments based on proposed mechanisms of illness presentation and on specific symptoms are currently under development through two CDMRP-funded collaborative consortia and through other trials by individual investigators. These projects have the potential to identify treatments that address the fundamental physiological alterations underlying the illness, rather than simply the symptoms.

Recommendations

The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures.

This research should include a number of critical elements.

1. Clear, operationalized case definitions for Gulf War illness and other diagnostic subgroups for whom treatments are designed are essential.

2. Clear, operationalized definitions of the clinical targets for treatment must be included in the research plan.

3. Treatment outcomes must be clearly defined so that it is possible to quantify improvements associated with interventions.

4. Where possible, treatment outcomes should include improvement in measures associated with expressions of underlying pathology (abnormal laboratory and functional assays).

Treatment approaches based on known mechanistic pathways of Gulf War illness should be pursued. Effective treatments of Gulf War illness could also lead to significant breakthroughs in the treatment of other exposure-related occupational and environmental health problems. Funding agencies should support intervention development at the proof-of-concept level as well as large-scale clinical trials as they become appropriate. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

Although the perfect animal model of Gulf War illness has not yet been developed, preclinical animal models can and should be used to develop and test new treatments focused on pathobiological mechanisms of Gulf War illness and the effects of Gulf War theater exposures. Highly promising avenues for preclinical animal research are identified in a draft VA research strategic plan (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf Section 5.6).

Center- and consortium based treatment research efforts can capitalize on multi-disciplinary expertise and multi-pronged approaches to treatment targets and pre-clinical trials. The CDMRP treatment consortia are an important step in developing integrated treatments for ill Gulf War veterans as an initial assessment of treatment safety and efficacy in Phase I/II trials. Since CDMRP has limited capacity to fund larger clinical trials, validation studies through the VA Cooperative Studies Program (CSP) or similar large, multi-site, government sponsored programs are necessary to provide final confirmation validation of initial safety and efficacy from Phase I/II trials. When a pilot treatment study funded by VA or CDMRP shows promising results and is judged to have scientific merit (such as the CPAP intervention in Gulf War veterans with sleep apnea), VA should follow up with a larger trial or other systematic assessment of the treatment's potential benefits.

Data on effective treatments from VA's 2005 longitudinal survey should be published. Information from veterans with Gulf War illness and their treating physicians on effective treatments should be collected and published. This should include reconducting the IOM review of treatments by Gulf War veterans' medical practitioners ordered by Congress in 2010 (Public Law 111-275, 2010, Section 805). This study was transformed into a literature review of treatments for mainly mental health problems by a group with no experience in treating Gulf War illness.

VA Annual Reports to Congress on Gulf War illness research funded by VA should include only studies and treatment trials in which the health of Gulf War veterans is the central focus and in which the study participants are primarily Gulf War veterans.

Congress should maintain its funding to support the effective treatment-oriented Gulf War Illness Research Program at the DoD Office of Congressionally Directed Medical Research Programs, for openly competed, peer-reviewed studies to identify:

1. Effective treatments for Gulf War illness,

2. Objective measures that distinguish veterans with Gulf War illness from healthy veterans, and

3. Underlying biological mechanisms potentially amenable to treatment.

Research Priorities and Recommendations

Epidemiologic research on Gulf War illness, ill health, medical disorders, disability and mortality in Gulf War veterans

Based on current knowledge about ill health in Gulf War veterans and given the limitations of epidemiologic research conducted to date in this population, the committee offers the following research recommendations.

Case definition of Gulf War illness. In the absence of a consensus case definition of Gulf War illness 23 years after the appearance of this condition, it remains difficult to assess and compare research findings in epidemiological, pathobiological or treatment research on the disorder. The Committee recommends the following approaches to the development of such a definition.

1. An evidence-based, expert consensus-driven case definition for Gulf War illness should be developed. This process should include 1) a review of the existing literature relevant to case definitions for Gulf War illness, 2) in-depth statistical and epidemiologic assessment of the strengths and weaknesses of different case definition approaches using datasets that provide representative data on symptoms and medical conditions affecting 1990-1991 Gulf War era veterans and 3) final case definition parameters and guidelines developed by an expert consensus panel that includes scientists experienced in Gulf War illness research and symptom-based case definitions and veterans affected by Gulf War illness (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf). The recent IOM panel on case definitions of Gulf War illness also commented that a data based case definition of the disorder could be derived (Institute of Medicine, 2014). This effort should involve representatives from VA, a broad spectrum of scientists conducting research in Gulf War veterans, clinicians knowledgeable about the problem, and Gulf War veterans. It could be organized through the Gulf War Illness Research Program of the Department of Defense Congressionally Directed Medical Research Program (CDMRP) through its competitive grant proposal process with scientific review.

2. VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War. This recommendation is also supported by the 2014 Institute of Medicine report on case definitions of the illness (Institute of Medicine, 2014).

Improved methodology in Gulf War epidemiologic research. It is important that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.

2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.

3. Consideration of subpopulations with multiple health outcomes.

4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that control as fully as possible for confounding effects of multiple exposures and etiologic factors that may be associated both with the exposures and outcomes of interest. Consideration of the effects of mixed exposures is also key.

Monitoring the health of Gulf War veterans

Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this veteran group ages. A plan for such monitoring was included in the plan proposed by a VA Strategic Planning group composed of representatives from RACGWVI, the VA National Research Advisory Council and VA staff (see http://www.va.gov/RAC-GWVI/VA_draft_strategic_plan.pdf Section 5.2). Such surveillance should include outcomes described in this document, including Gulf War illness; neurological disorders, including Parkinson's disease; autoimmune conditions such as multiple sclerosis; brain, lung and other cancers; cardiovascular disorders and dysfunction; sleep dysfunction; adverse reproductive outcomes and birth defects; general ill health and disability; mortality, and other disorders and outcomes that emerge as important during the surveillance process. This effort should include the following elements.

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans is critical. VA's longitudinal survey currently in process should be extended to add a symptom inventory adequate to define the illness according to existing commonly-used case definitions, as previously recommended by the Committee: "[The current survey instrument] cannot determine the prevalence, progression, or correlates of this illness. . . [I]t is unthinkable that the largest national study of Gulf War veterans would not provide the data required to evaluate the signature problem of the 1991 Gulf War" (Research Advisory Committee on Gulf War Veterans' Illnesses, 2012).

2. VA's longitudinal survey can be effectively used to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans. Survey data should be used to flag conditions of possible importance and followed up with detailed investigation, including the clinical evaluations that are required to determine specific medical diagnoses affecting Gulf War veterans at excess rates.

3. A study on the prevalence of "multiple sclerosis, Parkinson's disease, and brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose" in Gulf War and recent Iraq/Afghanistan war veterans was required by Congress in 2008 (Public Law 110-389, 2008, Section 804) and should be carried out. These assessments should be repeated and published at a minimum of 5-year intervals.

4. Systematic assessment of overall and disease-specific mortality in all Gulf War veterans and in specific subgroups of interest is essential. The results of these assessments should also be published at 5-year intervals.

5. VA's longitudinal survey should be used to assess rates of medical conditions, including neurological and behavioral disorders and birth defects, in children of Gulf War era veterans. Survey data can be used to flag conditions of possible concern and followed up. It is also important that VA publish results from studies of veterans' children that were conducted over 10 years ago.

6. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance is critical as some health outcomes are related to specific exposures and experiences in theater. These subgroups can be defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater, or other predictors.

Research into the causes of Gulf War illness, ill health and disability in Gulf War veterans: Human studies

Exposure studies in Gulf War veterans to identify the etiologic agents that may have been causative in Gulf War illness remain important because they clarify the physiological basis of the disorder and may help to determine treatment targets for Gulf War illness and other health problems in Gulf War veterans. Research in this area should include the following elements.

1. Objective markers of exposure should be utilized whenever possible. These include environmental sampling and modeling of conditions in theater.

2. Identification of biomarkers of exposure and downstream effects of exposures since the war that are present years after the exposure occurred have strong potential for understanding the physiological effects of Gulf War theater exposures and the relationship of these exposures to Gulf War illness. Applicable methods might include genomic, genetic, epigenetic, proteomic, lipidomic and metabolomic assays to explore suspected physiological effects and to identify novel, unsuspected pathways of illness.

3. Research and statistical methods that consider the mixed exposure scenario experienced by Gulf War veterans in theater are essential. These should focus on assessing effects of individual exposures as well as various exposure combinations and mixtures. Mixed exposures include not only mixtures of chemicals but also chemicals combined with heat, dehydration, infection, and other environmental stressors.

Research into the causes of Gulf War illness, ill health and disability in Gulf War veterans: Animal models

Studies that utilize animal models (multiple types of species and genetically altered rodents) 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, as well as low-level sarin or sarin surrogate, and environmental stressors such as heat and dehydration, all have been informative to date. Research using animal models in Gulf War illness should continue to examine the immediate, delayed, and persistent effects of acute exposures to chemicals and chemical mixtures. Future animal model research should focus on:

1. Studies that characterize persistent effects of Gulf War-related exposures, alone and in combination, on proinflammatory processes in the central nervous system, autonomic nervous system and peripheral target organs, including those that encompass mitochondrial dysfunction and accumulation of reactive oxygen species.

2. Studies that evaluate systemic immune parameters in animal models, with an emphasis on those parameters that sensitize ill veterans to Gulf War illness, will also be informative.

3 Animal research to identify biomarkers indicative of past exposures to Gulf War-related toxic compounds that can be applied to Gulf War veterans is important. This includes studies that identify persistent or "downstream" changes in biochemical processes in relation to past neurotoxicant exposure(s) and that identify persistent changes in the central nervous system and in autonomic function associated with Gulf War-related exposures and conditions. Exploratory biomarker research in animal models that assesses genomic, genetic, epigenetic, proteomic, metabolomic and lipidomic pathways of exposure effect may also be informative.

4. Animal models of Gulf War illness are recommended for rapid screening of potential therapies.

Pathobiology of Gulf War illness, ill health and disability in Gulf War veterans

Research on the pathobiological underpinnings of Gulf War illness and ill health in Gulf War veterans should continue to focus on the central and autonomic nervous systems and on immunological and neuroendocrine outcomes in order to identify targets for treatment interventions and outcomes that should be improved during such treatments.

1. Clear, operationalized case definitions are important for this work. Findings may differ in differing patient populations, either defined with different Gulf War illness criteria or experiencing different health problems. For example, non-veteran patients with multisymptom illnesses like chronic fatigue syndrome or fibromyalgia may show different patterns of immunological or neurological function than veterans who have Gulf War illness and meet criteria for these disorders.

2. Similarly, Gulf War theater exposures, age, and other variables likely moderate pathobiological effects and should be carefully addressed in research.

3. In some studies that have included female Gulf War veterans, it appears that gender differences may play a role in the pathobiological expression of Gulf War illness and its effects. Gender should be considered whenever possible in mechanistic and treatment research on Gulf War illness.

4. Since the pathobiological mechanisms underlying Gulf War illness are poorly understood, exploratory probes such as genomics, metabolomics, lipidomics, and proteomics may yield useful information that can lead to more focused research.

5. Epigenetic and genetic approaches to research on Gulf War illness pathobiology are likely also to be informative.

6. In order to effectively pursue "omics" and genetic research, standardized sample collections in research that uses biological specimens can expedite exploratory and hypothesis-driven research. Standard protocols for sample collections should be established and followed.

7. Increased emphasis should be placed on the study of alterations in regulatory dynamics both within and across the principal regulatory axes, including the endocrine, immune and nervous systems. These should include response to standardized challenges at different time scales, i.e., acute response to exercise, circadian rhythm, and monthly cycles as well as long-term illness progression. Analysis should be integrative and deployed across these interacting systems whenever possible using methodologies that formally acknowledge regulatory control.

8. Animal models may be appropriate to investigate mechanistic hypotheses and illness or exposure effects.

Treatment research and clinical trials

The Committee believes that the first priority of federal Gulf War illness research must be the identification of effective treatments to improve the health of Gulf War veterans and to protect the health of current and future American servicemen and women at risk of similar exposures.

This research should include a number of critical elements.

1. Clear, operationalized case definitions for Gulf War illness and other diagnostic subgroups for whom treatments are designed are essential.

2. Clear, operationalized definitions of the clinical targets for treatment must be included in the research plan.

3. Treatment outcomes must be clearly defined so that it is possible to quantify quantified improvements associated with interventions.

4. Where possible, treatment outcomes should include improvement in measures associated with expressions of underlying pathology (abnormal laboratory and functional assays).

Treatment approaches based on known mechanistic pathways of Gulf War illness should be pursued. Effective treatments of Gulf War illness could also lead to significant breakthroughs in the treatment of other exposure-related occupational health problems. Funding agencies should support intervention development at the proof-of-concept level as well as large-scale clinical trials as they become appropriate. It may be possible to leverage support from other federal health agencies interested in exposure-related diseases and disorders for this effort.

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Acknowledgements

We thank the scientists and government officials listed below who have provided presentations at Committee meetings since 2008. 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.

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November 17, 2008 (Washington, D.C.)

Secretary James Peake	U.S. Department of Veterans Affairs
Dr. William Goldberg	VA Office of Research and Development
Dr. Maxine Krengel	VA Boston Healthcare System
Lord Alfred Morris	British House of Lords
Dr. Robert Haley	University of Texas Southwestern

February 23-24, 2009 (Dallas, TX)

Dr. William Goldberg	VA Office of Research and Development
Dr. Ronald Killiany	Boston University
Dr. Christopher Filley	University of Colorado Denver VAMC
Dr. Carla Bann	University of Texas Southwestern
Dr. Richard Briggs	University of Texas Southwestern
Dr. Sergey Cheskov	University of Texas Southwestern
Dr. Munro Cullum	University of Texas Southwestern
Dr. Thomas Ferree	University of Texas Southwestern
Dr. Kaundinya Gopinath	University of Texas Southwestern
Dr. Robert Haley	University of Texas Southwestern
Dr. John Hart	University of Texas Southwestern
Mr. Vincent Iannacchione	University of Texas Southwestern
Dr. Michael Kraut	University of Texas Southwestern
Dr. Hanzhang Lu	University of Texas Southwestern
Dr. Roderick McColl	University of Texas Southwestern
Dr. Timothy Odegard	University of Texas Southwestern
Dr. Mette Posamentier	University of Texas Southwestern
Dr. Wendy Ringe	University of Texas Southwestern
Dr. Bart Rypma	University of Texas Southwestern
Dr. Jeffrey Spence	University of Texas Southwestern
Dr. Dixie Woolston	University of Texas Southwestern

June 29-30, 2009 (Boston, MA)

Dr. William Goldberg	VA Office of Research and Development
Dr. Ronald Bach	Minneapolis VA Medical Center
Dr. Gordon Broderick	University of Alberta
Dr. Philip De Fina	International Brain Research Foundation, Kessler Institute for Rehabilitation
Dr. Douglas Dockery	Harvard University School of Public Health

Dr. Keith Kelley	University of Illinois at Urbana-Champaign
Dr. Nancy Klimas	Miami VA Medical Center
Dr. Margaret Naeser	VA Boston Healthcare System
Dr. Meryl Nass	Mt. Desert Island Hospital

<u>November 2-3, 2009</u> (Washington, DC)

Dr. William Goldberg	VA Office of Research and Development
Mr. John Gingrich	VA Chief of Staff
Dr. Joel Kupersmith	VA Chief Research and Development Officer
Dr. Timothy O'Leary	Dir. of Clinical Science R & D, Veterans' Health Administration
Dr. Mohammad Amin	Northport VAMC
Dr. Peter Dorsher	Mayo Clinic Jacksonville
Dr. Clement Furlong	University of Washington
Dr. Robert Haley	University of Texas Southwestern
Dr. Freya Kamel	National Institute of Environmental Health Studies (NIEHS)
Dr. Oksana Lockridge	University of Nebraska
Dr. Rosemary Toomey	Boston University

<u>March 1-2, 2010</u> (Washington, DC)

Dr. William Goldberg	VA Office of Research and Development
Mr. John Gingrich	VA Chief of Staff
Dr. Joel Kupersmith	VA Chief Research and Development Officer
Ms. Lois Mittelstaedt	Chief of Staff, VBA Office of the Under Secretary for Benefits
Dr. Peter Baas	Drexel University
Dr. Douglas Fields	National Institutes of Health (NIH)
Dr. Robert Haley	University of Texas Southwestern
Dr. Nancy Klimas	Miami VAMC
Dr. Bjorn Knudtzen	Norwegian Armed Forces Medical Services
Dr. Gudrun Lange	DVA New Jersey Healthcare System
Dr. Vidar Lehmann	Norwegian Armed Forces Medical Services
Dr. Mariana Morris	Wright State University
Dr. Linda Watkins	University of Colorado

<u>June 28-29, 2010</u> (Washington, DC)

Dr. William Goldberg	VA Office of Research and Development
Mr. John Gingrich	VA Chief of Staff
Dr. Joel Kupersmith	VA Chief Research and Development Officer
Dr. Fiona Crawford	Tampa VA Medical Center
Dr. Apostolos Georgopoulos	Minneapolis VA Medical Center
Dr. Ronnie Horner	University of Cincinnati
Dr. Michael Mullan	Roskamp Institute
Col. Jonathan Newmark	Chemical/Biological Defense DoD
Dr. Ashok Shetty	Durham VA Medical Center
Dr. Alvin Terry	Medical College of Georgia
Dr. Michael Weiner	San Francisco VA Medical Center
Capt. Melissa Kaime	Congressionally Directed Medical Research Program

November 1-2, 2010 (Boston, MA)

Dr. William Goldberg	VA Office of Research and Development
Dr. Dane Cook	William S. Middleton Mem Veterans Hospital
Dr. Jeffrey Mogil	McGill University
Dr. Kenneth Jeffrey Myers	Malcolm Randall VA Medical Center
Dr. Richard Clapp	Boston University School of Public Health
Dr. Carl Hauser	Beth Israel Deaconess Medical Center
Dr. Lea Beaulieu	Boston University School of Medicine
Dr. Jean van Seventer	Boston University School of Public Health
Dr. Christopher Brady	VA Boston Healthcare System
Dr. Neil Kowall	VA Boston Healthcare System
Dr. Steven Perrin	ALS Therapy Development Institute
Dr. Lisa Conboy	The New England School of Acupuncture
Dr. Ann Louise Oaklander	Massachusetts General Hospital
Dr. Maximillian Klein	Massachusetts General Hospital

February 28 – March 1, 2011 (Washington, DC)

Dr. William Goldberg	VA Office of Research and Development
Dr. Joel Kupersmith	VA Office of Research and Development
Dr. Jeanette Akhter	VA Washington, DC
Dr. Wesson Ashford	Palo Alto VAMC
Dr. Christopher Brady	VA Boston Healthcare System
Col. Melissa Forsythe	DoD Congressionally Directed Medical Research Program
Dr. John Gallin	NIH Clinical Center
Dr. Brenda Jasper	VA Washington, DC
Dr. Maxine Krengel	VA Boston Healthcare System
Dr. Gudrun Lange	DVA New Jersey Healthcare System
Dr. Mian Li	VA Washington, DC
Dr. Kelly McCoy	VA Washington, DC
Dr. Louise Mahoney	Palo Alto VAMC
Dr. Dawn Provenzale	VA Office of Research and Development
Dr. Anna Rusiewicz	DVA New Jersey Healthcare System
Dr. Aaron Schneiderman	VA Office of Environmental Agents
Ms. Karen Soltes	VA Washington, DC

June 27-28, 2011 (Washington, DC)

Dr. William Goldberg	VA Office of Research and Development
Dr. Gordon Broderick	University of Alberta
Dr. Maximilian Buja	Gulf War Steering Committee
Dr. Nancy Klimas	Miami VA Medical Center
Dr. Polly Matzinger	National Institutes of Health, NIAID
Dr. Scott Panter	San Diego VA Medical Center
Mr. Joseph Salvatore	VA Office of Policy and Planning

January 31-February 1, 2012 (Washington, DC)

Dr. Ann C. Bonham	National Research Advisory Council

Dr. John P. Donoghue	National Research Advisory Council
Dr. David Korn	National Research Advisory Council
Dr. Christine Laine	National Research Advisory Council
Dr. Maximillian Buja	Gulf War Steering Committee
Dr. Tilo Grosser	Gulf War Steering Committee
Dr. Loren Koller	Gulf War Steering Committee
Dr. William Goldberg	VA Office of Research and Development
Dr. James Baraniuk	Georgetown University
Dr. Mian Li	VA Washington, DC
Dr. Julia Golier	James J. Peters Bronx VAMC
Dr. Robert Jaeger	VA Office of Research and Development
Dr. Victor Kalasinsky	VA Office of Research and Development
Dr. Joel Kupersmith	VA Office of Research and Development

June 18-19, 2012 (Boston, MA)

Dr. Robert Jaeger	VA Office of Research and Development
Dr. Victor Kalasinsky	VA Office of Research and Development
Dr. Dane Cook	William S. Middleton Mem Veterans Hospital
Dr. Robert Haley	University of Texas Southwestern
Dr. Apostolos Georgopoulos	Minneapolis VA Medical Center
Dr. Alvin Terry	Georgia Health Sciences University
Dr. Diane Rohlman	Oregon Health Sciences University
Dr. Christopher Brady	VA Boston Healthcare System
Dr. Rodney Johnson	University of Illinois, Urbana
Dr. Lisa Conboy	The New England School of Acupuncture
Dr. Britta Holzel	Massachusetts General Hospital/Harvard Medical School
Dr. Chenchen Wang	Tufts University School of Medicine

February 4, 2013 (Teleconference)

Dr. Victor Kalasinsky	VA Office of Research and Development

June 17-18, 2013 (Washington, DC)

Gen. Jose Riojas	VA Chief of staff
Dr. Henry Heng	Wayne State University
Dr. Dawn Provenzale	Durham VA Medical Center
Dr. Fiona Crawford	Tampa VA Medical Center
Mr. Rakib Rayhan	Georgetown University
Dr. Julia Golier	Bronx VA Medical Center
Dr. Victor Kalasinsky	VA Office of Research and Development
Dr. Robert Jaeger	VA Office of Research and Development
Dr. Timothy O'Leary	VA Office of Research and Development
Dr. Victoria Davey	VA Office of Public Health
Dr. Robert Jesse	VA Principal Deputy Under Secretary for Health
Mr. Jonathan Gurland	VA Office of General Counsel

<u>January 7-8, 2014</u> (Washington, DC)

Dr. Gordon Broderick	Nova Southeastern University
Col. Melissa Forsythe	Congressionally Directed Medical Research Program
Dr. Victor Kalasinsky	VA Office of Research and Development
Dr. Robert Jaeger	VA Office of Research and Development
Mr. Jonathan Gurland	VA Office of General Counsel
Ms. Jessica Tanner	VA Office of General Counsel

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APPENDICES

APPENDIX A: Committee members

James H. Binns (Committee Chair)
Mr. Binns is a 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 ADR Ultrasound, two medical imaging manufacturing companies that he led from startup to merger with General Electric and Squibb, respectively. He is a graduate of Stanford University and Harvard Law School.

James A. Bunker
James A. Bunker is the Executive Director of the National Gulf War Resource Center (NGWRC) has been on the Board of Directors since 2002. During Operation Desert Shield / Desert Storm, Jim was assigned to the Tactical Operations Center of the 4th Battalion, 5th Field Artillery, commanded by LTC John R. Gingrich. He was EVAC out and later medically discharged due to injuries from his service. Since his discharge, he has worked with grassroots organizations to provide information to veterans and their supporters regarding health care and claims. He is an advocate for changes in VA policy and legislation to improve quality of life for veterans. Jim successfully lobbied the Kansas Legislature to create the *Kansas Persian Gulf War Veterans Health Initiative*. Jim then served as chair of the advisory board. This group sponsored groundbreaking research by Lea Steele, PhD, commonly known as the *Kansas Study* after its publication, which showed a connection between deployment in the Southwest Asia Theater and Gulf War Illness. Jim received special recognition from both chambers of the Kansas Legislature for his advocacy work on behalf of Kansas Veterans.

Floyd E. Bloom, MD
Dr. Bloom is Professor Emeritus in the Molecular and Integrative Neuroscience Department at The Scripps Research Institute, and was the Founding CEO and Board Chairman of Neurome, Inc. 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 coauthored over 700 scientific articles and is the immediate past Editor-in-Chief of Science Magazine.

Fiona Crawford, PhD
Dr. Crawford is a neuroscientist, the President of the Roskamp Institute, an independent research institute in Sarasota, Florida, and a VA researcher. Her early Alzheimer's Disease (AD) research identified disease-causing mutations which enabled the development of cell and animal models of the disease. Through extensive preclinical and clinical research, the Institute's drug discovery program has advanced a novel drug into a Phase III AD clinical trial. In addition to AD, her neuroscience research is focused on military and veterans' issues, primarily Gulf War Illness (GWI), Traumatic Brain Injury (TBI) and post-traumatic stress disorder (PTSD). She is developing and utilizing novel, clinically relevant, laboratory models coupled with state-of-the-art "omic" technology to identify therapeutic targets and blood biomarkers in these complex conditions. She publishes extensively in peer-reviewed journals on her work, and is funded by the Veterans Administration, the National Institutes of Health and the Department of Defense.

Beatrice A. Golomb, MD, PhD
Dr. Golomb is Professor of Medicine and of Family and Preventive Medicine at the University of California at San Diego with 22 years' experience caring for veteran patients. Her research focuses on the relation of oxidative stress and cell energetics to exposures, medications, diet, health, aging and disease; on research methodology; and on Gulf War illness. Working for RAND, 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.

Joel C. Graves, DMin
Rev. Dr. Graves is an Anglican priest 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 Gulf War he served as battalion adjutant, responsible for medical and maintenance recovery assets for the 1st Battalion, 67th Armored Regiment of the 1st "Tiger" Brigade Independent Task Force. His unit served on the left flank of the 2nd Marine Division and took the northern part of Kuwait City. He has Gulf War illness.

Nancy Klimas, MD
Nancy Klimas, MD, is Director of Clinical Immunology Research at the Miami VAMC and directs the GWI and ME/CFS clinical and research program at the Miami VA. She is Director of the Nova Southeastern University Institute for Neuro-Immune Medicine; Professor of Medicine and Chair of the Department of Clinical Immunology at Nova Southeastern University College of Osteopathic Medicine; and Professor Emerita, University of Miami School of Medicine. She is a member of the VA Research Advisory Committee for GWI, the NIH P2P CFS/ME committee, the Institute of Medicine ME/CFS review panel and has advised three Secretaries of Health and Human Services during her repeated service on the HHS CFS Advisory Committee. She is currently funded by the VA, DoD and NIH to study these complex disorders using a systems biology approach with a strong focus on illness models that lead to therapeutic targets and clinical trials.

James P. O'Callaghan, PhD
Dr. O'Callaghan serves as CDC Distinguished Consultant, Centers for Disease Control and Prevention-NIOSH, and Head of the Molecular Neurotoxicology Laboratory in the Toxicology and Molecular Biology Branch of the Health Effects Laboratory Division at the Centers for Disease Control and Prevention, NIOSH, Morgantown, WV. His research group investigates the molecular and cellular basis of gliosis, a dominant response of the central nervous system to chemical- and disease-induced injury. Prior to joining CDC-NIOSH, Dr. O'Callaghan served as the Senior Science Advisor to the Neurotoxicology Division of the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency (EPA). At the EPA and CDC-NIOSH, Dr. O'Callaghan has conducted extensive research on the neurotoxicity profiles of many types of chemicals. He also has examined the neurotoxic effects of drugs of abuse, nerve agents, and pesticides under external sponsorship (NIDA, DoD, CDC Foundation). Dr. O'Callaghan has co-authored over 175 scientific papers in the area of neurotoxicology and his research findings have been presented by invitation at numerous national and international conferences. In 1992 he was awarded the EPA's and the Society of Toxicology's Science Achievement Award for his work in developing and validating a bioassay for neurotoxicity. Because of Dr. O'Callaghan's expertise in the area of neurotoxicity, he has worked as a consultant for a number of public and private institutions, including the U.S. FDA, the U.S. Army, the VA and the NIH.

Stephen Ondra, MD
Dr. Stephen Ondra was named senior vice president and enterprise chief medical officer at Health Care Service Corporation in February 2013. Previously, he served as senior vice president and chief medical

officer at Northwestern Memorial Hospital. In his new role, Dr. Ondra will report directly to the HCSC president and CEO and will be involved in a wide range of corporate activities and strategic policy planning. Dr. Ondra served in government as an advisor in the Obama Administration from 2009 to 2012. In 2009, he was appointed by President Obama as the senior advisor for Health Affairs to Secretary Shinseki at the Department of Veterans Affairs. In 2010, he was moved to the Executive Office of the President and served in the Office of Science and Technology Policy. In addition to other duties at the White House, he served as a co-chair of the National Science and Technology Council for Health Information Technology, on the Deputy group for the implementation of the Affordable Care Act and on the Federal Health Information Technology Policy and Standards Committees.

Martin A. Philbert, PhD
Dr. Philbert is the Dean of the University of Michigan School of Public Health. His research focuses on the development of flexible polymer nanoplatforms for optical sensing in tissues and the early detection and treatment of brain tumors. He has authored of more than 200 peer-reviewed scholarly manuscripts, abstracts and book chapters. He is an elected member of the Institute of Medicine of the National Academies of Science (USA), a Fellow of the Royal Society of Chemistry (U.K.) and a Fellow of the Academy of Toxicological Sciences (USA). He is the Chair of the newly formed U.S.-EPA Chemical Assessment Advisory Committee that provides peer review of IRIS assessments. Dr. Philbert has served as the Chair of the US-FDA Science Advisory Board, and Co-Chair of the US-EPA Board of Scientific Counselors.

Lea Steele, PhD
Dr. Lea Steele is Research Professor of Biomedical Studies at Baylor University where she directs the Veterans Heath Research Program, a multidisciplinary program that conducts clinical and epidemiologic studies focused on complex health conditions affecting war veterans. She is an epidemiologist and human ecologist whose research, since 1998, has focused on the health consequences of military service in the 1991 Gulf War. Dr. Steele is Past Scientific Director of the Research Advisory Committee on Gulf War Veterans' Illnesses. She previously directed the Kansas Persian Gulf War Veterans Health Initiative, a research and service program sponsored by the State of Kansas, and was principal investigator of the Kansas Gulf Veterans Health Study.

Kimberly Sullivan, PhD (Associate Scientific Director)
Dr. Sullivan is a Research Assistant Professor at the Boston University School of Public Health department of Environmental Health. Dr. Sullivan has worked in the field of behavioral neurotoxicology since 1995. She has coordinated field studies in neurotoxicology (i.e., pesticides, methylmercury), neurobehavioral outcomes and the effects of stressors and genetic predisposition to disease on cognitive functioning. She was the Principal Investigator (PI) on a study of cognition and structural MRI in pesticide-exposed Gulf War veterans and most recently is the PI on a multi-site consortium study of the pathobiology of Gulf War Illness.

Roberta F. White, PhD (Scientific Director)
Dr. White is Professor and Chair of the Department of Environmental Health at Boston University School of Public Health, where she is also the Associate Dean for Research. 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, modeling the effects of exposures to toxicant mixtures and exposures in the context of other environmental stressors, and the effects of exposures in vulnerable populations.

APPENDIX B: Committee Charter

DEPARTMENT OF VETERANS AFFAIRS
CHARTER OF THE
RESEARCH ADVISORY COMMITTEE ON
GULF WAR VETERANS' ILLNESSES

1. OFFICIAL DESIGNATION: Research Advisory Committee on Gulf War Veterans' Illnesses.

2. AUTHORITY: The Committee is authorized by Public Law 105-368, § 104, and operates under the provisions of the Federal Advisory Committee Act, as amended, 5 U.S.C. App. 2.

3. OBJECTIVES AND SCOPE OF ACTIVITY: The Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses provides advice and makes recommendations to the Secretary of Veterans Affairs on proposed research studies, 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 Committee shall meet in public session to review and advise the Secretary about VA-funded research relevant to understanding and treating the health consequences of military service during the 1990-1991 Gulf War; the processes conducted to solicit, review, and select such VA-funded research; and the methods, results, and implications of the research. The Committee may also review publically available research plans, initiatives, strategies, and activities from other agencies supporting research about the health consequences of military service in the Southwest Asia theater of operations during the 1990-1991 Gulf War. The Committee may advise the Secretary about the relationship between VA-funded research and research supported by other agencies. The Committee shall have access, to the extent provided by law, to VA documents and other information relevant to such reviews.

4. DESCRIPTION OF DUTIES: 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 may develop additional reports and recommendations regarding relevant research. All reports and recommendations must be approved by the Committee, in open public session, prior to submission to the Secretary or to other appropriate officials, as directed by the Secretary.

5. OFFICIAL TO WHOM THE COMMITTEE REPORTS: The Committee reports to the Secretary of Veterans Affairs.

6. OFFICE RESPONSIBLE FOR PROVIDING THE NECESSARY SUPPORT TO THE COMMITTEE: Support for the Committee will be provided by the Veterans Health Administration Office of Research and Development.

7. ESTIMATED ANNUAL OPERATING COSTS IN DOLLARS AND STAFF-YEARS: The annual cost for operating the Committee may not exceed $400,000 per year. This operating cost includes approximately four full-time equivalent staff members who will support the Committee. All Committee 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 duties as members of the Committee.

8. DESIGNATED FEDERAL OFFICER: 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.

9. ESTIMATED NUMBER AND FREQUENCY OF MEETINGS: The Committee is expected to meet at least once and up to three times annually.

10. DURATION: There is a continuing need for the Committee to assist the Secretary in carrying out the responsibilities described in Public Law 105-368, § 104.

11. COMMITTEE TERMINATION DATE: None.

12. MEMBERSHIP AND DESIGNATION: The Committee will be composed of approximately 12 members. Several members may be regular Government employees, but the majority of the Committee's membership will be special Government employees. The Committee membership will include, but is not limited to, Gulf War Veterans, representatives of such Veterans, and members of the medical and scientific communities representing appropriate disciplines such as, but not limited to, epidemiology, immunology, environmental health, neurology, and toxicology.

The Secretary will appoint Committee members for either a 2 or 3-year term of service. The Secretary may reappoint Committee members for additional 1 or 2-year terms. The Secretary will appoint the Chair of the Committee for an initial 2-year term. The Secretary may reappoint the Chair for an additional 1 or 2-year term.

The Secretary may appoint 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 individual advice and consultation, and may advise the Committee on factual or technical aspects research at the request of the Committee chair, but they shall not be members of the Committee. Panelists will be nominated by the Committee chair and appointed by the Secretary.

13. SUBCOMMITTEES: The Committee is authorized to establish subcommittees, with DFO approval, to perform specific projects or assignments as necessary and consistent with its mission. The Committee chair shall notify the Secretary, through the DFO, of the establishment of any subcommittee, including its function, membership, and estimated duration. Subcommittees will report back to the Committee.

14. RECORDKEEPING: Records of the Committee shall be handled in accordance with General Records Schedule 26 or other approved agency records disposition schedules. Those records shall be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. § 552.

15. DATE CHARTER IS FILED:

APPROVED: _____ Date: 5/17/2013
Eric K. Shinseki
Secretary of Veterans Affairs

APPENDIX C: Effects of Pesticide Exposure in Non-Gulf War Cohorts

Exposures to pesticides were prominent in the Gulf War and were identified in the 2008 report as a key etiologic factor in the ill health of Gulf War veterans. Since 2008, multiple studies have examined the effects of pesticides that were present in the Gulf War in other occupational cohorts, including agricultural workers, pesticide applicators, and sheep farmers. These studies are relevant because of the importance of pesticide exposures in the Gulf War and because the health effects seen in these occupational groups closely parallel the symptoms of Gulf War illness. Therefore, we review them briefly here with regard to the role of the PON1 genotype (an enzyme that metabolizes organophosphatess) in pesticide effects and to the relationship between occupational pesticide exposures and neurocognitive outcomes. The papers reviewed are summarized in Table 1.

1) PON1

Lacasana et al. (2010a, 2010b) evaluated the relationship between organophosphate exposures, paraoxonase 1 (PON1) genotyping, and thyroid functioning in a sample of floricultural workers (Lacasana et al., 2010a; Lacasana et al., 2010b). Enzyme activity and thyroid functioning increased as exposure increased during the rainy season. Increases in all dimethylphosphates and all diethylphosphates were associated with dose-response increases in thyrotropin. Total thryoxine increased in a dose-response manner, with increases in all dimethylphosphates and in diethylphosphate(Lacasana et al., 2010a). Genotyping revealed an interaction between the $PON1_{192}$ polymorphism, total dialkylphosphates, total dimethylphosphates, thyrotopin, and total thyroxine (Lacasana et al., 2010b). Manthripragada et al. (2010) investigated the relationship between exposures, PON1 genotyping and Parkinson's disease (PD) (Manthripragada et al., 2010). All participants had similar levels of occupational exposures to organophosphates, but participants with Parkinson's disease had higher rates of residential exposures. Participants with polymorphism $PON1_{155}$ had twice the risk of developing Parkinson's disease when exposed to diazinon and three times the risk when exposed to chlorpyrifos.

2) Cognition

Rohlman et al. (2011) reviewed 19 studies correlating cognition and biomarkers of organophosphate (OP) exposure (Rohlman et al., 2011). They concluded that higher exposures were associated with poorer performance on tasks assessing motor speed and coordination, information processing speed, executive functioning, verbal abstraction, sustained attention, memory, and perception. Multiple studies summarized in this review reported lower cholinesterase (ChE) levels in OP exposed subjects. However, only one found a correlation between cholinesterase levels and test performance: this was seen in Egyptian adolescents with high exposures (Abdel Rasoul et al., 2008). Another study summarized by Rohlman et al. found a correlation between organophosphate metabolites in urine and performance on tests assessing attention and fine motor speed (Rothlein et al., 2006).

A meta-analysis by Rohlman and colleagues of research outcomes in 17 studies evaluating cognition in agricultural workers and pesticide applicators (Ismail et al., 2012) found poorer performance on measures of memory, attention, motor speed and coordination, visual motor processing, verbal abilities, and perception in exposed cohorts. Agricultural workers performed worse on Digit Span and Trail-making Test part A compared to pesticide applicators. Overall, Wechsler Intelligence Block Design performance decreased as time of exposure in years increased (Ismail et al., 2012). Another meta-analysis of 16 research studies found that most studies demonstrated exposure-associated declines in performance on tasks assessing reaction time, fine motor control, memory, attention, visuospatial functioning and mood (Ross et al., 2013).

Mackenzie-Ross et al. (2010) examined sheep farmers with exposure to organophosphates, finding poorer performance on measures of memory, response speed, fine motor control, mental flexibility, and strategy making, as well as higher rates of anxiety and depression (Mackenzie Ross et al., 2010). Differences in

performance between farmers and controls remained after controlling for mood. As exposure duration increased, performance on measures of memory, verbal ability, fine motor control, and executive functioning became worse.

Pesticide exposure in a number of occupational environments has been associated with poorer cognitive function. A study of pesticide applicators found that use of pesticides was negatively associated with performance on computerized tasks from the Neurobehavioral Evaluation System-3 such as learning tasks, sequences A and digit-symbol. However, some positive associations between exposures and cognitive performance were found in which higher exposure was associated with better test scores (Starks et al., 2012). Blanc-Lapierre et al. (2013) found an increased risk of poorer performance on most cognitive tasks in vine workers exposed to pesticides compared to non-exposed controls (Blanc-Lapierre et al., 2013). There was an increased risk of performance being worse at follow-up compared to baseline for almost all measures of cognition in exposed workers.

3) Conclusions

Taken together, these studies on a diverse group of pesticide-exposed occupational groups reveal adverse changes in cognitive function that parallel those seen in Gulf War veterans, including associations between self-reported exposures during the Gulf War and reduced mood functioning and poorer performance on tasks of memory, attention and motor functioning (Toomey et al., 2009; White et al., 2001).

These findings provide additional support to the already-compelling evidence in studies of Gulf War veterans that pesticide use is causally associated with the development of Gulf War illness. Further research in both Gulf War and occupational pesticide groups may yield results with broad mechanistic and therapeutic applications.

Table 1. Studies of Pesticide Exposures in Non-Gulf War Cohorts

Study	***Groups Studied***	***Parameter(s) Evaluated***	***Key Findings***
PON1			
Lacasana 2010a	136 Mexican floriculture workers during rainy season (84 participated again during dry season)	Urine samples were assessed for pesticide metabolites. Serum samples were assessed for PON1 enzyme activities, TSH and thyroid hormone levels, and *p,p*'-DDE levels	Serum POase, DZOase, TSH, and T_4 activity levels were significantly higher during the rainy season. An increase in total DMP and DEP levels correlated with a significant increase in TSH levels in a dose response relationship. An increase in total DMP induced an increase in total T_4 levels in a dose response relationship. Only an increase in DEP was significantly associated with an increase in T_4.
Lacasana 2010b	136 Mexican floriculture workers during rainy season (84 participated again during dry season)	Urine samples were assessed for pesticide metabolites. Serum samples were assessed for PON1 polymorphisms and PON1 enzyme activities, TSH and thyroid hormone levels, and *p,p*'-DDE levels.	An interaction was found between $PON1_{192}$ polymorphism and total DAP and DMP on TSH and T_4 levels. An increase in DZOase activity caused a decrease in TSH variation due to DAP or DMP levels. Increases in serum base POase activity caused higher serum levels of DMP to affect TSH level variation less.

Study	*Groups Studied*	*Parameter(s) Evaluated*	*Key Findings*
Cognition Meta-Analyses and Reviews			
Ismail 2012	Agricultural workers and pesticide applicators	Meta-analysis of neurobehavioral performance in 22 cohorts drawn from 17 studies	Exposed cohorts had poorer performance in measure(s) of memory, attention, sustained attention, motor speed and coordination, visual motor processing, verbal abilities, and perception. Performances were similar for job type, with the exception of agricultural workers performing worse on Digit Symbol and Trail-making A compared to pesticide applicators. Block design performance decreased as duration of exposure increased.
Rohlman 2011	Adult and adolescents with chronic occupational OP exposure	Review of correlation between neurobehavioral performance and biomarkers of OP exposure in 19 studies	Across 19 studies deficits were seen in motor speed and coordination, information processing speeds and executive functioning, verbal abstraction, sustained attention, attention and short-term memory, memory, and perception. 7 studies reported lower ChE activity in those exposed, but only 1 study found a correlation between neurobehavioral performance and ChE activity. 4 studies reported OP metabolites in urine, but only one found a correlation between metabolites and neurobehavioral performance.
MacKenzie -Ross 2013	Adults with long-term, low level occupational exposures to OPs	Meta-analysis of neurobehavioral performance in 16 studies	13 of 16 studies found evidence of neurobehavioral impairment ranging from subtle deficits to major impairments in multiple domains such as reaction time, fine motor control, memory, attention, and visuospatial deficits. The three studies not reporting differences were found to be methodologically flawed. Emotional difficulties were also reported by a majority of studies.
Cognition Primary Papers			
Blanc-Lapierre 2013	614 vine workers from the Bordeaux area of France (443 exposed; 171 non-exposed controls)	Cognitive functioning (the Mini-Mental Status Exam, the Benton Visual Retention Test, the Stroop Test, Trail-making Test Part A, the Wechsler Paired-Associates Test)	Exposure resulted in a higher risk of performing poorly for all tests except the Wechsler Paired-Associates Test for chlorpyrifos and quinalphos, and for Trail-making Test A with methidathion. The risk of worsening from baseline to follow up increased with exposure for all measures except Trail-making Test Part A with chlorpyrifos, methidathion, and phosalone.
Mackenzie-Ross 2010	127 sheep farmers (67 working, 60 retired), 78 controls (38 working, 40 retired)	Cognitive functioning (Wechsler Adult Intelligence Scale-III, Wechsler Memory Scale-III, Trail-making A & B, the Graded Naming Test, the Grooved Pegboard test, the California Computerized Assessment Package, the Medical Symptom Validity Test), Mood (Hospital Anxiety and Depression Scale), PON1	Farmers were significantly impaired on measures of memory, response speed, fine motor control, mental flexibility, and strategy making; and demonstrated higher rates of anxiety and depression. Differences remained when mood was controlled and when compared to normative data instead of the control group. Significant negative correlations were found between exposure duration and auditory memory, visual memory, verbal ability, and strategy making; and a positive correlation with fine motor control. PON1 status did not affect outcome.

Study	*Groups Studied*	*Parameter(s) Evaluated*	*Key Findings*
Manthripragada 2010	351 participants with Parkinson's disease; 363 controls	OP exposure assessed through interview and residential history. Blood samples assessed genotyping for $PON1_{55}$.	Cases and controls had similar levels of occupational exposure, but cases had higher rates of residential exposures. Those exposed to diazinon with the $PON1_{55}$ genotype had a 2 fold increase risk for PD. The risk for developing PD was almost 3 times for $PON1_{55}$ genotype and exposure to chlorpyrifos.
Starks 2012	701 male private pesticide applicators	Cognitive functioning (continuous performance, digit-symbol, finger tapping, grooved pegboard, auditory verbal learning, sequences A and B)	Ever use of ethoprop was negatively associated with digit-symbol, auditory verbal learning total, and sequences A. Ever use of disulfoton and terbufos was also negatively related to sequences A. Cumulative lifetime use of malathion was negatively associated with digit-symbol performance and ethoprop with sequences A. The auditory verbal learning task was positively associated with ever use of coumaphos, tetrachlorvinphos, aldicarb, and carbaryl, and cumulative lifetime use of chlorpyrifos, coumaphos, parathion, phorate, tetrachlorvinphos, aldicarb, benomyl, and carbaryl. Sequences A was positively associated with cumulative lifetime use of benomyl, and Sequences B was positively associated with cumulative lifetime use of coumaphos. Cumulative lifetime use of parathion was positively associated with CPT performance, and ever use of chlorpyrifos was positively associated with grooved pegboard. However, some carbamates and organophosphates were positively associated with cognitive function.

Abbreviations: DMP = dimethylphosphate, DEP = diethylphosphate, POase = paraoxon activity, DZOase = diazoxon activity, TSH = thyrotropin, T_4 = total thyroxine, DAP = dialkylphosphate, PD = Parkinson's disease, ChE = cholinesterase

Abbreviations and Acronyms

aMCI – amnestic mild cognitive impairment
ACh – acetylchlorine
AChE – acetylcholinesterase
ACTH – adrenocorticotropic hormone
ALS – amyotrophic lateral sclerosis
AMPA - alpha-amino-3-hydroxl-5-methyl-4-isoxazole propionate
ANS – autonomic nervous system
APF – acylpeptide hydrolase
ASL – arterial spin labeling
ASP – autonomic symptom profile
ATP- adenosine triphosphate
AUC – area under the curve
BDI – Beck Depression Inventory
BMI – body mass index
BV – Bosnian War veterans
CBT – cognitive behavioral therapy
CAPS – Clinician Administered PTSD scale
CARC – chemical agent resistant coating
CAS – composite autonomic severity
CBF – cerebral blood flow
CD2+ – cluster of differentiation 2
CD8+ – cluster of differentiation 8
CD26+ – cluster of differentiation 26
CDC – U.S. Centers for Disease Control and Prevention
CDMRP – Congressionally Directed Medical Research Programs
CFS – chronic fatigue syndrome
CFTA – cooperative clinical trial award
ChE – cholinesterase
CIA – Central Intelligence Agency
CMI – chronic multisystem illness
CNS – central nervous system
CoQ10 – coenzyme Q10
CPAP – Continuous Positive Airway Pressure
CPF – chlorpyrifos
CPO – chlorypyrifos oxon
CPT- Continuous Performance Test
CRF – corticotropin releasing factor
CSF – cerebrospinal fluid
CSP – Cooperative Studies Program
CT – computerized tomography
DEET – N,N-Diethyl-meta-toluamide, an insect repellent
DEX – dexamethasone
DFP - diisopropylphosphorofluoridate
DHEA - dehydroepiandrosterone
DLWE – difficult living and working environment
DMPFC – dorsomedial prefrontal cortex
DoD – Department of Defense
DRRI – Deployment Risk and Resilience Inventory

DSS – depressive symptom severity
DST – dexamethasone suppression test
DTI – diffusion tensor imaging
DU – depleted uranium
ECG - echocardiogram
EEG – electroencephalography
ERP – event related potential
FM - fibromyalgia
fMRI – functional magnetic resonance imaging
FP-biotin - 10-fluoroethoxyphosphinyl-*N*-biotinamidopentyldecanamide
FSS – Fatigue severity Scale
GAO – U.S. Government Accountability Office
GHP – general health perception
GHQ-12 – General Health Questionnaire
GW – Gulf War
GWI – Gulf War illness
GWV – Gulf War veterans
H-MRS – proton magnetic resonance spectroscopy
HPA – hypothalamic-pituitary-adrenal axis
HRV – heart rate variability
HSC – Hopkins Symptom Checklist
IBS – irritable bowel syndrome
ICP-MS – inductively coupled plasma mass spectrometry
ICP-DRC-MS – inductively coupled plasma-dynamic reaction cell-mass spectrometry
IFOF – inferior fronto-occipital fasciculus
IG - immunoglobulin
IL-1α – interleukin-1 alpha
IL-1β – interleukin-1 beta
IL-2 – interleukin-2
IL-4 – interleukin-4
IL-5 – interleukin-5
IL-6 – interleukin-6
IL-10 – interleukin-10
IL-12 – interleukin-12
IL-13 – interleukin-13
IL-16 – interleukin-16
IL-23 – interleukin-23
IOM – Institute of Medicine, National Academy of Sciences
IPL – inferior parietal lobule
IWV – Iraqi War veterans
KPA – kinetic phosphorescence analysis
LES – Life Events Checklist
LED – light emitting diodes
LV – left ventricular
MBB – mind-body bridging
MBSR – mindfulness-based stress reduction
MCS – multiple chemical sensitivity
MCS – Mental Component Summary
MDD – major depressive disorder
ME – myalgic encephalomyelitis
MF – mental functioning

MOS – U.K. Ministry of Defense
MRI – magnetic resonance imaging
MRS – magnetic resonance spectroscopy
mRNA – messenger ribonucleic acid
MRS – magnetic resonance spectroscopy
MS – multiple sclerosis
MSI – multisymptom illness
NAA – N-acetyl aspartate
NDV – nondeployed Gulf War era veterans
NF-κB– nuclear factor –κB
NG/R – National Guard/Reserve
NIR – near-infrared
NK – natural killer, immune cells
noCBF – normalized regional cerebral blood flow
NMDA - N-methyl-D-aspartate
NPY – Neuropeptide Y
NREM – Non-rapid eye movement
OFC – orbital frontal cortex
OIF/OEF – Operation Iraqi Freedom/ Operation Enduring Freedom
OND – Operation New Dawn
OP – organophosphate
PB – pyridostigmine bromide
PC – phosphatidylcholine
PCL – Post-traumatic Stress Disorder Checklist
PCS – Physical Component Survey
PD- Parkinson's disease
PER – permethrin
PET – positron emission tomography
PET-CT – positron emission tomography-computed tomography
PF – physical functioning
PHA – phytohaemagglutinin
PHG – parahippocampal gyrus
PHS – physical health symptoms
PO – pars orbitalis
PON1 - paraoxonase 1
PPC – posterior parietal cortex
PRL – prolactin
PSL – Psychopathy Checklist
PSQI – Pittsburgh Sleep Quality Index
PSS – Posttraumatic Stress Disorder symptom severity
PT – perceived threat
PTH – parathyroid hormone
PTSD – post-traumatic stress disorder
PTSS – Post-traumatic stress symptomatology
RAC-GWVI – Research Advisory Committee on Gulf War Veterans' Illnesses
rCBF – Regional Cerebral Blood Flow
RNA – Ribonucleic acid
ROS – reactive oxygen species
rTMS – regional transcranial magnetic stimulation
S1 – primary somatosensory cortex

S2 – secondary somatosensory cortex
SF-12 – Medical Outcomes Study Short-Form health Survey, 12 item
SF-36 – Medical Outcomes Study Short Form Survey, 36 items
SD – standard deviation
SDB – sleep disordered breathing
SED – supportive education
SM – sphingomyelin
SMA – supplementary motor area
SORT – Semantic Object Retrieval Test
SPECT – single-photon emission computer tomography
STC – superior temporal cortex
Th – T-helper, immune cells
TH – tyrosine hydroxylase
TSH – thyroid stimulating hormone
U - uranium
UTSW – University of Texas Southwestern
VA – U.S. Department of Veterans Affairs
VAS – visual analog scales
VV – Vietnam veterans
WAIS-R – Wechsler Adult Intelligence Scale - Revised
WRIISC – War-related Injury and Illness Study Center, U.S. Department of Veterans Affairs