Appendix D. Ongoing Research Related to Illnesses Among Gulf War Veterans

Sources:
RWG (Research Working Group). 1998. Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 1997. March, 1998. Persian Gulf Veterans Coordinating Board.

RWG (Research Working Group). 1999. Interagency Gulf War Research Projects Database. January, 1999. Persian Gulf Veterans Coordinating Board.

This Appendix contains short descriptions of ongoing, U.S. Government-funded research projects grouped according to the following topics:
A. Multiple Chemical Sensitivity in Gulf War Veterans
B. Genetic Differences in Susceptibility / Biomarkers of Disease
C. Toxicity of Mixtures of Chemicals and Other Risk Factors
D. Treatment of Gulf War Veterans with Illnesses
E. Toxicity of Low-Level Exposure to Chemical Warfare Agents
F. Toxicity of Pyridostigmine Bromide
G. Assessment / Definition of Gulf War Illnesses
H. Disease Prevalence and Associations between Chemical Exposures and Illnesses in Gulf War Veterans
I. Toxicity from Depleted Uranium.

For each project the sponsoring agency (DoD, DVA, DHHS) and research project number are noted (e.g., DoD-1; DVA-1 or DHHS-1)).

A. Multiple Chemical Sensitivity in Gulf War Veterans

Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. DoD-31. (Also cited in section G.)
Measure and compare physiologic variables (e.g., pain sensitivity, esophageal smooth muscle motility) and biochemical variables (changes in neurohormone levels in response to different stressors, cerebral fluid levels of neurotransmitters) in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome, chemical sensitivities, or fibromyalgia, and in healthy controls.

Veterans' Administration Medical Center, Boston, Massachusetts. R. White, Ph.D. Neuropsychological Functioning in Persian Gulf Era Veterans. DoD-32. (Also cited in section G.)
Compare results from in-depth neuropsychological evaluations in treatment-seeking Gulf War veterans, non-deployed veterans of Gulf War era, and groups of healthy (non-treatment seeking) veterans. Development and administration of a questionnaire to identify multiple chemical sensitivity.

Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe. Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans. DoD-52. (Also cited in section G.)
Identification and description of self-reported Gulf War environmental and psycho-social combat-theater exposures, functional health status, and health perceptions in a cohort of male and female Gulf War veterans. Development of a survey to identify subjects with multiple chemical sensitivity (MCS)-like symptoms and examination of potential correlations between specific risk factors and MCS-like symptoms.

University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School: H. Kipen, M.D., M.P.H. Defining Gulf War Illness. Cooperative Research Agreement with CDC. DHHS-6. (Also cited in section G.)
Evaluate the persistence and stability of self-reported symptoms in two samples of U.S. Gulf War veterans. Compare the appropriateness of standard working definitions for chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity with factor-analysis-derived case definitions to describe unexplained illnesses in Gulf War veterans.

Veterans Administration Medical Center, East Orange, NJ: B. Natelson, M.D. Physiological and Psychological Assessments of Persian Gulf Veterans. DVA-5B. (Also cited in section G.)
Compare physiological, immunological, and neuropsychological variables in healthy veterans, veterans with chronic fatigue syndrom and/or chemical sensitivities, and civilians with chronic fatigue syndrome or chemical sensitivities.

Veterans' Administration Medical Center, East Orange, New Jersey: N. Fiedler, Ph.D. Effects of Exertion and Chemical Stress on Persian Gulf Veterans. DVA-5C. (Also cited in section G.)
Examination of effects of acute exhaustive exercise or acute exposure to 5 ppm diesel fumes on psychophysiologic variables (e.g., heart rate, blood pressure, respiration rate) and performance in a vigilance task in groups of healthy Gulf War veterans and groups of Gulf War veterans previously diagnosed with fatiguing illness (chronic fatigue syndrome and/or chemical sensitivities).

Veterans' Administration Medical Center, Tuscon, Arizona: I.R. Bell, M.D., Ph.D. Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance. DVA-48. (Also cited in section G.)
Comparison of blood pressure, heart rate, and neurobehavioral responses to repeated laboratory exposures to placebo, jet fuel, or perfume in three groups of Gulf War veterans: 1) ill with increased chemical intolerance attributed to military service; 2) ill without increased chemical intolerance; and 3) healthy without chemical intolerance; and a group of healthy Gulf War-era non-deployed veterans. Measure and compare characteristics associated with enhanced vulnerability to sensitization among these groups.

B. Genetic Differences in Susceptibility / Biomarkers of Disease

University of North Carolina, Chapel Hill: D.H. Overstreet, Ph.D. Effects of Pyridostigmine in Flinders line Rats Differing in Cholinergic Sensitivity. DoD-33. (Also cited in section F.)
Examine physiologic and biochemical responses to pyridostigmine in a genetic line of rats with putative supersensitivity to organophosphate nerve agents. Examine if repeated exposure to pyridostigmine protects against short-term body temperature decreases induced by organophosphate cholinergic agents (diisopropylphosphate, chlorpyrifos).

Hebrew University of Jerusalem, Israel: H. Soreq, Ph.D. Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses. DoD-51.
Examination of the protective value and potential side-effects of transgenic expression of various cholinesterases in mice. Transgenic mice with two copies of the human gene encoding the synaptic form of acetylcholinesterase show elevated activity levels of acetylcholinesterase in central nervous system cholinergic neurons, less sensitivity to organophosphate neurotoxicity, and deficits in cognitive functions such as learning and memory. Other transgenic lines of mice will be developed with different genes encoding acetylcholinesterases with different subcellular and tissue-specific patterns of expression. Sensitivity to organophosphate neurotoxicity and cognitive and neuromotor behavior will be evaluated in these mice. DNA from human subjects who display hypersensitivity to anti-cholinesterase agents, such as pyridostigmine, organophosphate insecticides, and organophosphate warfare nerve agents, will be examined in search of particular gene sequences that may correlate with hypersensitivity.

University of Nebraska Medical Center: O. Lockridge, Ph.D. Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness. DoD-60.
Comparison of blood butyrylcholinesterase activity levels and genotype in healthy and ill Gulf War veterans.

Veterans' Administration Medical Center, Boston, Massachusetts: D. Sherr, Ph.D. The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility. DVA-4C.
Examination of PAH-induced effects on immunological and cell transformation variables in transgenic mice with varying levels of AhR expression in lymphocytes. Results will test hypothesis that levels of AhR in mice correlate with the intensity of immunotoxic and carcinogenic responses to PAHs. Comparison of levels of AhR in peripheral blood lymphocytes in symptomatic and asymptomatic Gulf War veterans will examine possible association between putative PAH sensitivity and Gulf War Illnesses.

Veterans' Administration Medical Center, East Orange, New Jersey: J. Ottenweller, Ph.D. Effects of Genetics and Stress on Neurobehavioral Responses to Pyridostigmine in Rats. DVA-5D. (Also cited in section F.)
Examination of neurobehavioral variables (e.g., startle response and behavioral rhythms) in two strains of rats at varying times after exposure to pyridostigmine bromide for 7 days and a 3-day chronic stress regime.

Veterans' Administration Medical Center, East Orange, New Jersey: R.J. Servatius, Ph.D. Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction. DVA-49. (Also cited in section B.)
Determination of pharmacokinetics of pyridostigmine bromide in two genetic strains of rats that differ in inherent levels of butyrylcholinesterase. Comparison of the effects of pyridostigmine bromide and the cholinesterase inhibitors edrophonium and neostigmine on butyrylcholinesterase activity and startle response. Examine the effects of physically-induced stress and pyridostigmine pretreatment on brain acetylcholinesterase activities.

C. Toxicity of Mixtures of Chemicals and Other Risk Factors

University of Florida: F. van Haaren, Ph.D. Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats. DOD- 37.
Evaluate effects of exposure rats to pyridostigmine bromide, permethrin, and DEET, alone or in combination, on several measures of neurobehavior and immune system function.

Battelle Memorial Institute, Columbus, Ohio: C.T. Olson, Ph.D. Assessment of Subchronic Neurobehavioral and Neuropathic Effects in Rats. DOD-54.
Examination of neurobehavioral and neuropathological measures in rats 30 days after exposure for 4 days to low levels of chemicals, alone or in combination of chemicals, to which Gulf War troops may have been exposed (sarin, pyridostigmine bromide, DEET).

Prinz Maurits Laboratory, Netherlands: H. vanHelden, Ph.D. Low-level Exposure of Guinea Pigs and Marmosets to Sarin Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects. DOD-55. (Also cited in section E.)
Examination of respiration variables, central nervous system variables, and miosis in guinea pigs and marmosets acutely exposed by inhalation to low levels of airborne sarin (with and without pretreatment with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

University of California: B. Wilson, Ph.D. Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine. DoD-56. (Also cited in section E.)
Morphological and biochemical examinations of brain, spinal cord, and peripheral neuromuscular and sensory systems in mice and hens acutely exposed to low levels of airborne sarin (with or without pre- or co-exposure with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

Battelle Memorial Institute, Columbus, Ohio: C.T. Olson, Ph.D. Neurophysiologic and Neuropathologic Effects in Monkeys Exposed to Low Levels of Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid. DOD-61.
Examination of neurophysiological variables, blood biochemical variables (e.g., acetyl cholinesterase and neurotoxic esterase), and histopathology of tissues in groups of monkeys given 14-day exposures to the following substances or mixtures of substances at dose levels that produce cholinesterase inhibition without observable signs of intoxication: saline control; positive control - diisopropyl fluorophosphate; sarin + botulinum toxoid; pyridostigmine + DEET + chlorpyrifos; and (sarin + botulinum toxoid) + (pyridostigmine + DEET + chlorpyrifos). Neurophysiologic variables will be examined immediately after exposure and at 60, 90, and 180 days after exposure.

Southern Illinois University: S.M. Somani, Ph.D. Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice. DoD-62.
Examination of the interactive neurotoxic effects of low-level sarin exposure, physical exercise, and pyridostigmine exposure on neurobehavioral, electrophysiological, and biochemical variables and on microscopic structure of nervous system tissues in mice.

Virginia Polytechnic Institute: S. Holladay, Ph.D. Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid. DHHS -7
Examine immunological variables in mice after dermal exposure to the insecticide permethrin, alone and in combination with cis-urocanic acid.

Lawrence Livermore National Laboratory: J.S. Vogel, Ph.D. Strategy to Identify Non-Additive Response to Chemical Mixtures. DHHS-8.
Measure quantities of an organophosphate insecticide in nerve cell membranes in mice following low-levels of exposure to the insecticide alone and in combination with low-levels of mixtures of other ester compounds.

Duke University Medical Center: M. Abou Donia, Ph.D. Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals. DoD-72.
Examination of neurobehavioral variables, permeability of the blood-brain barrier, and electrophysiological variables in rats exposed subchronically to low levels of sarin alone and in combinations with stress, heat, or pyridostigmine. Other exposure regimes will examine variables in response to: low-level sarin plus heat and pyridostigmine; sarin plus stress and pyridostigmine; and sarin plus stress, heat, pyridostigmine, DEET, and permethrin.

Duke University Medical Center: M. Abou Donia, Ph.D. Toxic Interactions of Prophylactic Drugs and Pesticides. DoD-75.
Examination of neurobehavioral variables, cholinesterase activities in blood, brain, and liver, and permeability of the blood-brain barrier in rats exposed for 60 days to pyridostigmine bromide, DEET, and permethrin, alone, in binary and tertiary combinations, and at various dose levels.

Medical University of South Carolina: D.E. Keil, Ph.D. Evaluation of Immunotoxicity Due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel. DoD-76
Examine immunological variables (e.g., natural killer cell activity, macrophage function, disease resistence) in animals (species not specified) exposed to sub-chronic, low levels of DEET, pyridostigmine bromide and JP-8 jet fuel. Hypothesis to test is that exposure to these 3 agents acting together leads to immune system dysfunction.

North Carolina State University: J. Riviere, Ph.D. Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War. DoD-77.
Examine dermal absorption and skin toxicity of pydridostigmine bromide, permethrin, and DEET, alone and together, using a flow through diffusion technique with porcine skin or an isolated perfused porcine skin flap technique.

New York University Medical Center: H.L.. Evans. Experimental Models of Gulf War Syndrome. DoD-78.
Measurement of cognitive function variables, sensory evoked potential variables, diurnal rhythms in locomotion, and pulmonary function variables in rats and macaques before and after low-level exposures to (alone and in combination): inhaled sarin or soman; orally administered pyridostigmine; and psychological stress from exposure to novel stimuli.

D. Treatment of Gulf War Veterans with Illnesses

Louisiana Medical Foundation: E. Hyman, M.D. Antibacterial Treatment Method Based on the Excretion of Dead and Decaying Spherical Bacteria. DoD-67.
Clinical evaluation for bacteriuria in Gulf War veterans with "Desert Storm Syndrome" and effectiveness of antibiotic treatment or placebo in relieving symptoms of fatigue, cognitive dysfunction, joint and somatic pain, headache, dermatitis, and gastrointestinal dysfunction.

Multiple VA Medical Centers: S. Donta, M.D. DVA/DoD Multi-site Treatment Trial for Chronic Fatigue Syndrome and Fibromyalgia in Gulf War Veterans. VA/DoD-1D & 1V.
A 2-year, multiple-site, randomized control trial (starting in 1999 and ending in 2001) to compare treatment methods for U.S. Gulf War veterans who have unexplained chronic symptoms of pain, fatigue, and/or cognitive difficulties. Patients will be Gulf War veterans who are chronically experiencing at least two of the following self-reported symptoms: 1) fatigue that limits work, recreational, or social activity; 2) musculoskeletal pain in two or more body regions; and 3) difficulties in memory, concentration, or attention. The program will evaluate 339 randomly assigned patients in each of four treatment groups: 1) "usual and customary care" (the control group); 2) cognitive behavioral therapy plus usual and customary care; 3) aerobic exercise plus usual and customary care; and 4) cognitive behavioral therapy, plus aerobic exercise, and usual and customary care. Treatment will be in a group format and will last for 3 months (one hourly session per week for 12 weeks).

Walter Reed Army Institute of Research: *J. Meyerhoff. Combat Stress Pharmacotherapy. DoD 6A.*
Testing of behaviorally-active clinically-available drugs (e.g., valium, beta blockers, antidepressants) to reverse or prevent conditioned-defeat behavior in mice. The investigators are using the conditioned-defeat behavior in mice as a model of combat stress reaction and post-traumatic stress disorder.

Veterans' Administration Medical Center, Perry Point & Multiple Sites: S. Donta, M.D. Antibiotic Treatment of Gulf War Veterans' Illnesses. DVA-55
This is a 30-month, prospective, randomized, double-blind, placebo-controlled clinical trial. The trial will identify 450 Gulf War veterans who are experiencing at least two of three chronic symptoms (fatigue, musculoskeletal pain, and neurocognitive dysfunction) and who are mycoplasma-positive. Subjects will be randomly assigned to 12-month treatments with either 300 mg doxycycline per day or placebo. Patients will be seen monthly during the medication phase and at 18 months. Physical function will be evaluated before treatment starts, and at 3, 6, 9, 12 and 18 months. Patients will also complete questionnaires designed to provide measures of pain, fatigue, and neurocognitive dysfunction.

E. Toxicity of Low-Level Exposure to Chemical Warfare Agents

TNO Prinz Maruits Laboratory, Rijswijk, Netherlands: H.P. Benschop, Ph.D. Toxicokinetics of VX in Rats, Hairless Guinea Pigs and Marmosets. DoD-50.
Develop methodology for and clarify the toxicokinetics of VX stereoisomers in laboratory animals.

Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico: R. Henderson, Ph.D. Long-term Effects of Subclinical Exposures to Sarin in Rats.. DoD-53.
Examination of toxicokinetics of sarin in nervous tissue of rats exposed, once or repeatedly, by inhalation to low and high airborne concentrations. Examine brain biochemical markers of effect (e.g., muscarinic and nicotinic

receptor densities, acetylcholinesterase activities) immediately following exposure and one month after exposure, to examine persistence of effects.

Prinz Maurits Laboratory, Netherlands: H. vanHelden, Ph.D. Low-level Exposure of Guinea Pigs and Marmosets to Sarin Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects. DoD-55. (Also cited in section C.)
Examination of respiration variables, central nervous system variables, and miosis in guinea pigs and marmosets acutely exposed by inhalation to low levels of airborne sarin (with and without pretreatment with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

University of California: B. Wilson, Ph.D. Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine. DoD-56. (Also cited in section C.)
Morphological and biochemical examinations of brain, spinal cord, and peripheral neuromuscular and sensory systems in mice and hens acutely exposed to low levels of airborne sarin (with or without pre- or co-exposure with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

University of Oregon Health Sciences: P. Spencer, Ph.D. Persian Gulf Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity. DoD-63. (Also cited in section H.)
Health survey and clinical examination of neuropsychological and neurophysiological variables in a sample of the 20,000 U.S. troops who were located within a 50-km radius of Khamisiyah during the first two weeks of March 1991. Comparison groups will include subjects from other Desert Storm troops, subjects from other Desert Shield troops, subjects from other U.S. military groups that served during, but not in, the Persian Gulf, and civilians with a documented history of exposure to organophosphate insecticides that produced non-convulsive health symptoms.

Institute of Medicine/ Medical Follow-up Agency: P. Renzullo. Five-year Follow-up of Army Personnel Exposed to Chemical Warfare Agents. DoD-69. (Also cited in section H.)
Compare hospitalization rates and mortality rates during a 5-year, post-Gulf War period among the following groups: 1) subjects from 2 U.S. Army engineer battalions involved with the March 1991 destruction of the Khamisiyah munitions site; 2) subjects from 2 battalions located within a 50-km radius of the Khamisiyah site during early March 1991; 3) subjects from Persian Gulf battalions never located within a 50-km radius of the Khamisiyah site; and 4) subjects from battalions not deployed to the Persian Gulf.

Aberdeen Proving Ground, Maryland: Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground. DVA/DoD-2VA; DVA/DoD-2DA.
During 1955-1975, 6,720 U.S. army soldiers participated in an experimental chemical warfare exposure program. To determine the long-term neurological and neuropsychological effects of exposure, a current telephone survey with follow-up clinical examination will be conducted.

Veterans' Administration Medical Center, Portland, Oregon: G. Kisby, Ph.D. DNA Damage from Chemical Agents and Its Repair. DVA-6D.
Determine the acute and chronic effects of nitrogen mustard on DNA adducts of human skin tissue and mouse cerebral cortex mixtures.

F. Toxicity of Pyridostigmine Bromide.

University of North Carolina, Chapel Hill: D.H. Overstreet, Ph.D. Effects of Pyridostigmine in Flinders line Rats Differing in Cholinergic Sensitivity. DoD-33. (Also cited in section B.)
Examine physiologic and biochemical responses to pyridostigmine in a genetic line of rats with putative supersensitivity to organophosphate nerve agents. Examine if repeated exposure to pyridostigmine protects against short-term body temperature decreases induced by organophosphate cholinergic agents (diisopropylphosphate, chlorpyrifos).

Purdue Research Foundation: G.E. Isom, Ph.D. Pyridostigmine-induced Neurodegeneration in Rats: Role of Neuronal Apoptosis. DoD-59.
Description of dose-response relationships for apoptotic cell death in brain regions of rats exposed orally to pyridostigmine. Examination of biochemical and molecular variables in apoptotic cultured cerebellar granule cells exposed to pyridostigmine. Examination of potential linkage between apoptosis and pyridostigmine-induced generation of intracellular reactive oxygen species.

Midwest Research Institute: M.R. Cook, Ph.D. Individual Differences in Neurobehavioral Effects of Pyridostigmine. DoD- 64.
Examination of physiological (including blood cholinesterase activities), sensorimotor, and cognitive variables in groups of male and female healthy human volunteers during 2 days immediately after exposure to 13 oral doses of pyridostigmine (either 30 or 60 mg/dose, administered at 8-hour intervals) or placebo. A second study will be conducted under conditions of high ambient temperatures.

Veterans' Administration Medical Center, East Orange, New Jersey: J. Ottenweller, Ph.D. Effects of Genetics and Stress on Neurobehavioral Responses to Pyridostigmine in Rats. DVA-5D. (Also cited in section F.)
Examination of neurobehavioral variables (e.g., startle response and behavioral rhythms) in two strains of rats at varying times after exposure to pyridostigmine bromide for 7 days and a 3-day chronic stress regime.

Veterans' Administration Medical Center, Portland, Oregon: R. Drake-Baumann, Ph.D. Neurotoxicology of Environmental Pollutants and Warfare Agents. DVA-6C.
Examination of the effects of acute and chronic exposure of pyridostigmine bromide on cholinergic function of spinal cord-dorsal root ganglia-muscle cultures of fetal mice. Examination of the neurological activity of cerebellar explant cultures of newborn mice after two week exposure to sodium bromide.

Veterans' Administration Medical Center, East Orange, New Jersey: R.J. Servatius, Ph.D. Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction. DVA-49. (Also cited in section B.)
Determination of pharmacokinetics of pyridostigmine bromide in two genetic strains of rats that differ in inherent levels of butyrylcholinesterase. Comparison of the effects of pyridostigmine bromide and the cholinesterase inhibitors edrophonium and neostigmine on BuChE activity and startle response. Examine the effects of physically-induced stress and pyridostigmine pretreatment on brain acetylcholinesterase activities.

G. Assessment/Definition of Gulf War Illnesses

Walter Reed Army Institute of Research: Meyerhoff. Combat Stress Diagnosis, PTSD Prevention. DoD-6B.
Develop methods for early diagnosis of soldiers at risk for combat stress reaction and post-traumatic stress disorder. Measure effect of stress on levels of several hormones (e.g., cortisol, testosterone) in plasma and saliva, and on voice frequency modulation.. Conduct a prospective study of changes in acoustic startle responses and saliva levels of hormones in soldiers subjected to stressful deployments.

Air Force Institute of Pathology, Washington, DC: LTC D. Dunn. Effects of Gulf War Service on Military Working Dogs. DoD-13.
Comparison of clinical and pathological assessments of 112 Gulf War-deployed military working dogs and 472 non-deployed military working dogs matched for age, sex, and breed. After military service is completed, dogs will receive complete physical examinations, a neurological examination, a behavioral assessment, a necropsy, and histopathological examinations of samples from leg muscles, nervous tissues, liver, kidney, lung, brain, and fat.

Walter Reed Army Institute of Research: MAJ J. Stuart. Acute and Long-term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families. DoD-23.
Assess psychological well-being of Army Reserve and National Guard units and their families.

Klemm Analyses Group: R.J. Klemm, Ph.D. Epidemiological Studies Persian Gulf Illnesses, Persian Gulf Women's Health Linkage Study. DoD-30.
Survey of health symptoms in sample of Gulf-deployed and non-deployed female veterans.

Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. DoD-31. (Also cited in section A.)
Measure and compare physiologic and biochemical variables in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome or fibromyalgia, and in healthy controls.

Veterans' Administration Medical Center, Boston, Massachusetts. R. White, Ph.D. Neuropsychological Functioning in Persian Gulf Era Veterans. DoD-32. (Also cited in section A.)
Compare results from in-depth neuropsychological evaluations in treatment-seeking Gulf War veterans, non-deployed veterans of Gulf War era, and healthy (non-treatment seeking) veterans. Development and administration of a questionnaire to identify multiple chemical sensitivity.

University of Texas, SW: R.G. Haller, M.D. Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms. DoD-36.
Compare physiologic and biochemical variables of muscle function (e.g. oxygen transport and utilization, and enzyme levels) in symptomatic Gulf War veterans with chronic fatigue and asymptomatic "controls".

VA Medical Center, West Haven CT: S. Southwick, M.D. Psychological and Neurobiological Consequences of the Gulf War Experience. DoD-40.
Compare memory function over time and magnetic resonance brain images in 20 Gulf War-deployed veterans with PTSD, 20 Gulf War-deployed veterans without PTSD, and 20 non-deployed veterans of the Gulf War era without PTSD.

University of Pennsylvania: K. Vandenborne, Ph.D. Evaluation of Muscle Function in Persian Gulf Veterans. DoD-41.
Various measures of skeletal muscle function will be evaluated in Gulf War veterans with unexplained illnesses compared with a control group.

VA Medical Center, Birmingham, AL: W. Blackburn, Jr., M.D. An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment. DoD-42.
Case-control evaluation of immunologic and neuropsychological variables and self-reported risk factors in Gulf War veterans with chronic unexplained illness compared with asymptomatic Gulf War veterans.

University of Cincinnati Medical Science Center: J. Bernstein, M.D. Investigation of Seminal Plasma Hypersensitivity Reactions. DoD-44.
Examination of blood, semen, and immunological variables in Gulf War veterans and their sexual partners who are experiencing a burning sensation after contact with semen.

Naval Post-Graduate School, Monterey, CA: H. Bhargava. Exploratory Data Analysis with the CCEP Database. DoD-46.
Develop a generic computer program to statistically analyze the DoD CCEP database.

Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe. Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans. DoD-52. (Also cited in section A.)
Identification and description of self-reported Gulf War environmental and psycho-social combat-theater exposures, functional health status, and health perceptions in a cohort of male and female Gulf War veterans. Development of a survey to identify subjects with multiple chemical sensitivity (MCS)-like symptoms and examination of potential correlations between specific risk factors and MCS-like symptoms.

Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. Physiologic Effects of Stress in Gulf War Veterans. DoD-57.
Clinically examine, psychologically evaluate and measure several physiological variables in symptomatic and asymptomatic Gulf War-deployed veterans; evaluate performance in dolorimeter tests and tilt table tests.

University of Iowa: B. Doebbeling, M.D. Illness Among Persian Gulf War Veterans: Case Validation Studies. DoD-58.
Administer personal interviews, physical examinations, risk factor assessment, and assessment of neuropsychological, neurophysiological, and psychiatric variables in deployed and non-deployed Gulf War-era veterans. Conduct nested case-control studies of risk factors for various illness classifications.

University of Texas Southwestern Medical Center, Dallas, Texas: R.W. Haley, M.D. Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Syndromes. DoD-65. (Also cited in section H.)
Ask survey questions regarding personality assessments, health symptoms, and wartime exposures to members of a naval battalion that served in the Gulf War. Use two-step factor analysis to identify possible syndromes. Develop a battery of clinical and laboratory tests to assess neurotoxicity (brain or nerve damage) and compare aggregate performance in groups of symptomatic and asymptomatic subjects. Analyze self-reported wartime exposure data and symptom data for statistically significant associations. Develop a plan for conducting a similar survey and clinical examination of a sample of subjects that is based on the entire population of Gulf War veterans.

Walter Reed Army Institute of Research and Medical Center: C. Engel, Jr., M.D. Replicability of Three Tests for Mycoplasmal Infection of Blood Cells from Symptomatic Gulf War Veterans. DoD-66.
Compare results from three procedures to detect mycoplasmal infection of blood cells drawn from 60 symptomatic Gulf War veterans: polymerase chain reaction procedure; optimized chelex chain reaction procedure; and nucleoprotein gene tracking procedure.

Center for Disease Control and States of Pennsylvania and Florida: W.C. Reeves, M.D. Disease Cluster in a Pennsylvania Air National Guard Unit. DHHS-2.
Determination of a cluster of illnesses among members of the unit. Determination if the cluster was unique to the unit, related to residence in Pennsylvania, or related to Gulf War service. Analysis of survey-collected data on wartime exposures to stressors and multisymptom illnesses to ascertain possible associations. Collection of serum specimens to investigate the presence of possibly unique infectious agents and effects on immune system variables and cholinesterases.

Boston University School of Public Health: D. Ozonoff, M.D. M.P.H. Cognitive Function and Symptom Patterns in Gulf War Veterans. Cooperative Research Agreement with CDC. DHHS-5.
Brain activation patterns (from magnetic resonance images) will be analyzed in 40 symptomatic Gulf-deployed veterans, 40 non-symptomatic Gulf-deployed veterans, 40 Germany-deployed veterans of Gulf War era, and 30 treatment-seeking non-deployed veterans. Evaluation of relationships between MRI patterns and levels of cognitive functioning (finger tapping tasks & tests of visual working memory). Mathematical analysis of previously collected symptom data from Gulf War and Germany-deployed veterans to discern if a set of complaints exists that will be useful for determining cause or developing a case definition. Comparison of neuropsychological test performance and symptom prevalence measures in Gulf War-deployed and non-deployed Danish veterans.

University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School: H. Kipen, M.D., M.P.H. Defining Gulf War Illness. Cooperative Research Agreement with CDC. DHHS-6. (Also cited in section A.)
Evaluate the persistence and stability of self-reported symptoms in two samples of U.S. Gulf War veterans. Compare the appropriateness of standard working definitions for chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity with factor-analysis-derived case definitions to describe unexplained illnesses in Gulf War veterans.

Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe, Ph.D.; L. Pepper, M.D. Evaluation of Cognitive, Neurological and Respiratory Functioning of Persian Gulf Veterans. DVA-4A,4B,4D.
Administration of a health survey questionnaire, an interview about wartime experiences and exposures, a psychological interview, neuropsychological tests examining memory, attention, and learning abilities in a group of 220 Gulf War veterans from Massachusetts, 73 Gulf War veterans from New Orleans, and 50 U.S. veterans deployed to Germany during the Gulf War. Patterns in functional magnetic resonance images of neural tissue will be correlated with performance in tests of motor function and attention in a subgroup of subjects. Possible exposure information for each subject to be evaluated for respiratory function (physical examinations and pulmonary function testing) will be collected from the Army geographical information system and from surveys of occupational history; analysis of the exposure and respiratory function data will search for significant associations.

Veterans Administration Medical Center, East Orange, NJ: B. Natelson, M.D. Physiological and Psychological Assessments of Persian Gulf Veterans. DVA-5B. (Also cited in section A.)
Compare physiological, immunological, and neuropsychological variables in healthy veterans, veterans with chronic fatigue syndrom and/or chemical sensitivities, and civilians with chronic fatigue syndrome or chemical sensitivities.

Veterans' Administration Medical Center, East Orange, New Jersey: N. Fiedler, Ph.D. Effects of Exertion and Chemical Stress on Persian Gulf Veterans. DVA-5C. (Also cited in section A.)
Examination of effects of acute exhaustive exercise or acute exposure to 5 ppm diesel fumes on psychophysiologic variables (e.g., heart rate, blood pressure, respiration rate) and performance in a vigilance task in groups of healthy Gulf War veterans and groups of Gulf War veterans previously diagnosed with fatiguing illness (chronic fatigue syndrome and/or chemical sensitivities).

Veterans' Administration Medical Center, Portland, Oregon: K. Anger, Ph.D. Psychosocial, Neuropsychological, and Neurobehavioral Assessment of Gulf War Veterans with Unexplained Illnesses. DVA-6A.
Comparison of performance in a battery of psychosocial, neuropsychological, and neurobehavioral tests by groups of self-reported healthy and ill (with unexplained symptoms) Gulf War veterans.

Veterans' Administration Medical Center, Portland, Oregon: R. Bennett, M.D. Clinical and Neuroendocrine Aspects of Fibromyalgia. DVA-6B. (Also cited in section H.)
Evaluate by questionnaire and physical examination the presence of Gulf War veterans with fibromyalgia; using a case-control design, examine relationships between self-reported exposures or risk factors and fibromyalgia; examine neuroendocrine variables in cases and controls.

Veterans' Administration Medical Center, New Orleans, LA: J. Vasterling, Ph.D. Memory and Attention in PTSD. DVA-10.
Neuropsychological functions were evaluated in a group of veterans with PTSD, a group of veterans with diagnosed depression, and a group of veterans free of psychopathology. Cognitive functions are to be assessed longitudinally.

Veterans' Administration Medical Center, Long Beach, California: P.E. Prete, M.D., FACP. Musculoskeletal Symptoms in Gulf War Syndrome. DVA-40.
Survey with or without physician interview to determine differences in musculoskeletal complaints of peace-time versus Gulf War-deployed veterans.

Veterans' Administration Medical Center, Tuscon, Arizona: I.R. Bell, M.D., Ph.D. Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance. DVA-48. (Also cited in section A.)
Comparison of blood pressure, heart rate, and neurobehavioral responses to repeated laboratory exposures to placebo, jet fuel, or perfume in three groups of Gulf War veterans: 1) ill with increased chemical intolerance attributed to military service; 2) ill without increased chemical intolerance; and 3) healthy without chemical

intolerance; and a group of healthy Gulf War-era non-deployed veterans. Measure and compare characteristics associated with enhanced vulnerability to sensitization among these groups.

Veterans' Administration Medical Center, Cincinnati, Ohio: D. Baker, M.D. Psychobiological Assessment of Desert Storm Veterans. DVA-51.
Comparison of a series of questionnaires given to 188 treatment and non-treatment seeking Gulf War veterans. Veterans with post-traumatic stress disorder reported greater combat exposure and a higher incidence of physical symptoms.

Royal Defence Medical College, London: Lt.Col. I.P. Palmer. War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes. DoD-70.
Examine primary source data from hospital and pension records to compare health symptoms characterized as "War Syndromes" in U.K. and U.S. military units from 1900 to present and determine if a common syndrome can be established using blinded statistical (factor) analysis. Associations between such a common syndrome and risk factors, morbidity, and mortality will be sought using: a case-control analysis using a control group of soldiers receiving a pension for loss of a single limb; an historical narrative analysis of morbidity; and a retrospective cohort analysis of mortality data.

Social Sectors Development Strategies, Inc., Natick, Massachusetts: Nicole Bell, Sc.D., M.P.H. Post-Deployment Morbid Stress, Behavior and Health; Developing a Model for Predicting Morbidity, Mortality, and Other Adverse Outcomes. DoD-73.
Using information from the Defense Manpower Data Center Total Army Injury and Health Outcomes Database including Health Risk Appraisals: morbidity of several health outcomes (e.g., hospitalizations for "Gulf War syndrome", CCEP registration, injuries) and mortality will be described for U.S. Army Gulf War veterans. An analysis will be conducted to identify associations between health outcomes and key demographic, behavioral, and stress-related factors. A model will be developed to attempt to predict health outcomes considering predeployment stress variables, predeployment health behaviors, deployment stress variables, and post-deployment variables.

H. Disease Prevalence and Associations Between Chemical Exposure and Illnesses in Gulf War Veterans

Naval Health Research Center Epidemiology Studies: CDR G. Gray, MC, USN. Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors. DoD 1D-1H.
Comparison of reproductive outcomes (e.g., infertility and miscarriages from questionnaire survey) in randomly selected national samples of Gulf War-deployed and non-deployed U.S. veterans (1D). Historical prospective health survey study of symptoms and illnesses in Gulf-deployed and non-deployed Seabees active between August 1990 & June 1991(1E). Comparison of federal and nonfederal hospitalization rates among veterans who have separated from active service (1F). Comparison of prevalence of congenital anomalies among infants born to Gulf War-deployed veterans, non-deployed veterans, and the non-military population (1G). Establish a DoD birth defects health registry (1H).

U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen MD: M.J. Kirkpatrick and J.M. Heller. Development of a Troop Exposure Assessment Model (TEAM)/Health Tracking System. DoD-18; DoD-19.
Establishment of a geographical information system to establish the geographical location for each Gulf War unit during the time period between January 15, 1991 and date of departure. Expected to be used in assessing site-specific exposure and potential health risks associated with oil fires and other potential chemical exposures.

March of Dimes, Sacramento, CA.: J.A. Harris, M.D. Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War. DoD-35.
Compare accuracy of DOD hospital records and California Birth Defects Monitoring Program, and determine availability of data for Gulf War-deployed military reserve personnel in the California Birth Defects Monitoring Program.

King's College, U.K.: S. Wessely, M.D. A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces. DoD-39.
Assess prevalence of symptoms and unexplained illnesses in Gulf War-deployed U.K. veterans, in non-deployed U.K. veterans of Gulf War era, and in Bosnia-deployed veterans. Administer neuropsychological evaluations to randomly-selected cases with unexplained illness and healthy controls.

University of Michigan, Ann Arbor: P.F. Pierce, Ph.D., R.N. Physical and Emotional Health of Gulf War Veterans Women. DoD-45.
Compare the prevalence of general and gender-specific health symptoms in 900 U.S. Air Force Gulf-deployed women and 900 non-deployed U.S. Air Force women.

University of Oregon Health Sciences: P. Spencer, Ph.D. Persian Gulf Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity. DoD-63. (Also cited in section E.)
Health survey and clinical examination of neuropsychological and neurophysiological variables in a sample of the 20,000 U.S. troops who were located within a 50-km radius of Khamisiyah during the first two weeks of March 1991. Comparison groups will include subjects from other Desert Storm troops, subjects from other Desert Shield troops, subjects from other U.S. military groups that served during, but not in, the Persian Gulf, and civilians with a documented history of exposure to organophosphate insecticides that produced non-convulsive health symptoms.

University of Texas Southwestern Medical Center, Dallas, Texas: R.W. Haley, M.D. Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Syndromes. DoD-65. (Also cited in section G.)
Ask survey questions regarding personality assessments, health symptoms, and wartime exposures to members of a naval battalion that served in the Gulf War. Use two-factor analysis to identify possible syndromes. Develop a battery of clinical and laboratory tests to assess neurotoxicity (brain or nerve damage) and compare aggregate performance in groups of symptomatic and asymptomatic subjects. Analyze self-reported wartime exposure data and symptom data for statistically significant associations. Develop a plan for a similar survey and clinical examination of a sample of subjects that is based on the entire population of Gulf War veterans.

Institute of Medicine/ Medical Follow-up Agency: P. Renzullo. Five-year Follow-up of Army Personnel Exposed to Chemical Warfare Agents. DoD-69. (Also cited in section E.)
Compare hospitalization rates and mortality rates during a 5-year, post-Gulf War period among the following groups: 1) subjects from 2 U.S. Army engineer battalions involved with the March 1991 destruction of the Khamisiyah munitions site; 2) subjects from 2 battalions located within a 50-km radius of the Khamisiyah site during early March 1991; 3) subjects from Persian Gulf battalions never located within a 50-km radius of the Khamisiyah site; and 4) subjects from battalions not deployed to the Persian Gulf.

Center for Disease Control and State of Iowa: D. Schwartz, M.D., M.P.H. Health Assessment of Gulf War Veterans from Iowa. DHHS-1.
Telephone-survey assessment of prevalence of self-reported symptoms and illnesses in random samples of Gulf War veterans and non-deployed veterans of the same era who listed Iowa as their home. Initial reports found statistically significant higher prevalence of symptoms of depression, Post-traumatic Stress Syndrome, chronic fatigue, cognitive dysfunction, bronchitis, asthma, fibromyalgia, alcohol abuse, anxiety, sexual discomfort, and health-related quality of life in the deployed group compared with the non-deployed group. To validate self report of asthma, a subset of the telephone-survey subjects will be physically examined.

Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. Retrospective Cohort Mortality Study of Persian Gulf Veterans. DVA-1.
Retrospective follow-up mortality study of 697,000 U.S. Gulf War veterans and a reference group of 803,526 U.S. service members of the same era who were not deployed to the Gulf War theater. Analysis of data up to December 1995 indicated that excess mortality rates in deployed veterans was due to death from external causes (e.g., accident, suicide, homicide). Periodic analysis of updated mortality data will occur.

Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. VA National Survey of Persian Gulf Veterans. DVA-2.
Health survey questionnaire mailed to 15,000 Gulf War and 15,000 non-Gulf War U.S. veterans. Telephone contact and interview of 8,000 randomly selected non-respondents to supplement the postal survey and to assess non-respondent bias. Comprehensive physical examination of 2,000 respondents and family members from each group.

Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. Use of Roster of Veterans Who Served in Persian Gulf Area. DVA-3.
For possible exposure assessment purposes, create a database of troop assignments for all U.S. personnel assigned to the Gulf War and of troop locations and movement during deployment.

Veterans' Administration Medical Center, East Orange, New Jersey: H. Kipen, M.D., M.P.H. Health and Exposure Survey of Persian Gulf Veterans. DVA-5A.
Postal survey of 2800 Gulf War veterans for self-reported exposure factors and health symptoms. Analysis of the survey data to develop case definitions and conduct case-control analysis to identify possible associations between exposure factors and symptoms.

Veterans' Administration Medical Center, Portland, Oregon: R. Bennett, M.D. Clinical and Neuroendocrine Aspects of Fibromyalgia. DVA-6B. (Also cited in section G.)
Evaluate by questionnaire and physical examination the presence of Gulf War veterans with fibromyalgia; using a case-control design examine relationships between self-reported exposures or risk factors and fibromyalgia; examine neuroendocrine variables in cases and controls.
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Veterans' Administration Medical Center, Portland, Oregon: M. Riscoe, Ph.D. Clinical and Epidemiological Leishmania Research. DVA-6E.
Serological testing for the prevalence of leishmania in a random sample Gulf War veterans and controls.

Naval Health Research Center, San Diego, California: C.G. Blood. A Comparison of Post Deployment Hospitalization Incidence Between Vietnam and Gulf War Veterans. DoD-71.
Comparison of post-deployment hospitalization rates in Gulf War veterans and Vietnam veterans. Data will be gathered from medical history and physical examination board databases of the Defense Manpower Data Center.

Duke University Medical Center: J.A. Fairbank. Relationships of Stress Exposures to Health in Gulf War Veterans. DoD-74.
National samples of Gulf-deployed and non-deployed U.S. veterans will be surveyed for information on demographics, health conditions, psychological functioning, and illnesses. Subjects will be classified as cases with multiple symptoms or non-cases, and a subsample of Gulf-deployed and non-deployed cases and non-cases will be interviewed to obtain information about military experiences, pre-military and pre-deployment activities, risk factors, and protective factors. Statistical analysis will look for associations between Gulf War illnesses and various potential health risk factors related to stress.

I. Toxicology of Depleted Uranium

Inhalation Toxicology Laboratory, Albuquerque New Mexico: F. Hahn, Ph.D. Carcinogenicity of Implanted Depleted Uranium Fragments in Rats. DoD-7B.
Evaluation of the presence of tumors in muscles of rats with 2-year exposure to muscle-implanted depleted uranium fragments.