DETERMINING TYPES OF HEALTH EFFECTS TO PERSIAN GULF VETERANS DUE TO EXPOSURE TO OCCUPATIONAL HAZARDS

THESIS

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Results indicate there are many current data gaps concerning health effects from exposure to occupational chemicals. There was a statistically significant relationship between the symptom frequencies of CFS and PGVI, but not for solvents or for PB. These results suggest that CFS should be further examined as a possible related diagnosis for PGVI. Further research in this area should probably not be spent looking into solvents, as there was no association with the symptom frequencies of PGVI. PB should be examined as a synergistic agent in combination with other chemicals.

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Master of Science in Engineering and Environmental Management

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The views expressed in this thesis are those of the author and do not reflect the official policy or position of the Department of Defense or the U.S. Government.

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Rebecca A. Nelson

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List of Acronyms

ADD	attention-deficit disorder
AOR	Area of Responsibility
CBW	Chemical and Biological Warfare
CCEP	Comprehensive Clinical Evaluation Program
CFS	Chronic Fatigue Syndrome
CNS	central nervous system
DEET	N,N-diethyl-m-toluamide
DoD	Department of Defense
EHRC	Environmental Hazards Research Center
FDA	Food and Drug Administration
HDL	high-density lipoprotein
IND	investigational new drug
IOM	Institute of Medicine
LOAEL	lowest observed adverse effect level
MCS	Multiple Chemical Sensitivity
NAAQS	National Ambient Air Quality Standards
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
ODS/S	Operations DESERT SHIELD/STORM
PAH	Polycyclic Aromatic Hydrocarbons
PG	Persian Gulf
PGIRCC	Persian Gulf Interagency Research Coordinating Council
PGVI	Persian Gulf Veterans' Illnesses
PGW	Persian Gulf War
PTSD	Post-Traumatic Stress Disorder
TEPP	tetraethyl pyrophosphate
USAEHA	U.S. Army Environmental Health Agency
USAF	United States Air Force
USAMRMC	U. S. Army Medical Research and Materiel Command
USEPA	U.S. Environmental Protection Agency
VA	Department of Veterans' Affairs
VAMC	VA Medical Center

List of Units

atm	atmospheres
atm -m^3/mol	atmospheres-cubic meter per mole
^{o} C	degrees Centigrade
^{o} F	degrees Fahrenheit
g/mL	grams per milliliter
kg/m^3	kilograms per cubic meter
ug/m^3	micrograms per cubic meter
mg/kg	milligrams of dose per kilogram body weight
mg/L	milligrams per liter
mm Hg	millimeters of mercury
K_{ow}	octanol-water partition coefficient
K_{oc}	organic carbon partition coefficient
ppm	parts per million
%	percent

Abstract

Persian Gulf Veterans' Illnesses (PGVI) consists of multiple illnesses with overlapping symptoms and causes. This research examined health effects literature concerning several occupational chemicals, to identify significant adverse health trends and assess research quality, completeness, and relevance. After compiling this knowledge base, the research focus was narrowed to Chronic Fatigue Syndrome (CFS), solvents, and pyridostigmine bromide (PB). The existing data was analyzed and compared to PGVI health data using the nonparametric statistical method of contingency table analysis to prove or disprove a link between the substance and PGVI. The results of the contingency table analysis was used to make inferences concerning the relationship between the substances and PGVI.

Results indicate there are many current data gaps concerning health effects from exposure to occupational chemicals. There was a statistically significant relationship between the symptom frequencies of CFS and PGVI, but not for solvents or for PB. These results suggest that CFS should be further examined as a possible related diagnosis for PGVI. Further research in this area should probably not be spent looking into solvents, as there was no association with the symptom frequencies of PGVI. PB should be examined as a synergistic agent in combination with other chemicals.

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I. Introduction

1.1 Problem Background

Since the end of Operations DESERT SHIELD and DESERT STORM (ODS/S) in February 1991, and the return of U.S. and Allied forces from the Persian Gulf region, military personnel have reported a variety of adverse health effects. Reported symptoms include any combination of fatigue, skin rashes, muscle and joint pain, headaches, memory loss, difficulty breathing, and gastrointestinal and respiratory problems, many of which may not readily fit into a common diagnosis. **[46:1; 24:31]**. Less common complaints include back pain, diarrhea, dyspnea, sleep disturbance, depression, and bleeding gums **[19: table 3]**. Additionally, veterans are reporting similar symptoms in their spouses and also birth defects in their children born after their return from the Persian Gulf **[46:1]**. To date, over 29,000 Gulf War veterans have registered with the Veterans Administration's Persian Gulf War Registry, an additional 9,000 have registered separately with the Pentagon, and more veterans are joining every month. **[8:30]**. This collection of symptoms and illnesses has been given a variety of names in the literature, such as Gulf War Syndrome, Desert Fever, Desert Storm Syndrome, Desert War Syndrome, and Persian Gulf Veterans' Illnesses (PGVI).

Recently the Pentagon released a statement concluding that a single Persian Gulf mystery illness does not exist. After examining over 10,000 veterans and family members

in 1994, the Pentagon concludes that Gulf War Syndrome is in fact "multiple illnesses with overlapping symptoms and causes." **[48]**. This is similar to the conclusion reached by the National Institutes of Health in June 1994 **[46:16]**, and by the Defense Science Board task force formed to study Persian Gulf War health effects **[20:2]**.

Military members who served in the Persian Gulf Area of Responsibility (AOR) were exposed to a large variety of toxic substances, including smoke from oil-well fires, diesel fumes, jet fuels JP-4 and JP-8, toxic paints and solvents, pesticides such as N,N-diethyl-*m*-toluamide (commonly called DEET), depleted uranium used in munitions and armor, and experimental drugs such as pyridostigmine bromide, botulinum toxoid, and anthrax vaccine **[24:31; 46:6-12; 26:94; 33:55; 20:47-53]**. Many veterans, both in the U.S. and from other countries, also report that they were exposed to chemical and biological warfare (CBW) agents, although this information is being disputed. **[17:1560; 25:26; 1:395; 8:30; 33:52-53]**. In addition, veterans had to suffer through intense heat, sand dust, extreme stress, occasional food poisoning, and two types of leishmaniasis caused by sand flies **[46:6-12; 20:47-53]**. Any or all of these causal agents may play a role in PGVI, and a series of studies are currently being conducted to determine these relationships. These research efforts are being coordinated by the Persian Gulf Interagency Research Coordinating Council (PGIRCC) since its formation in 1993 in response to a need to conduct coordinated research efforts across all DoD agencies **[64:10]**.

1.2 Current Research in this Area

The federal government has begun a number of assistance programs and research efforts as a result of the large number of health complaints. The Department of Veterans Affairs (VA) was designated as the lead agency for all federally funded research into the health effects of the Persian Gulf War in 1993 by President Clinton **[64:3]**. Several specific research goals were set, and the steps for reaching the research goals were laid out. The research efforts are divided into four areas: population studies, clinical evaluations, clinical research, and clinically relevant basic research **[64:7-8]**.

Population studies refer to "all activities associated with population studies of Persian Gulf War participants or comparable cohorts" **[64:7]**. One example of a population study is the U.S. Army and Joint Environmental Support Group collecting demographic data with its "Combat Unit Tracking Data Base," which will establish a listing of units deployed to the Persian Gulf and their geographic locations during the war **[64:8]**. Another example is the VA's "Persian Gulf Veterans Health Registry," established by Public Law 102-585 **[62:4975]**.

Clinical evaluations are activities aimed at collecting and evaluating clinical data from the Persian Gulf veterans. These clinical evaluations of Persian Gulf veterans are being conducted through such programs as the VA Persian Gulf Registry Examination, the VA Persian Gulf Referral Centers, and the DoD Comprehensive Clinical Evaluation Program (CCEP) **[64:8]**. The CCEP recently completed a comprehensive medical evaluation of 10,020 veterans. This report summarizes the chief medical complaints of the

veterans, lists the diagnoses made of some of their symptoms, and has much information on birth defects of children born to these veterans **[19]**.

Clinical research are studies devoted to determining "whole human organ system" reactions through exposure to particular agents **[64:8]**. Current clinical research includes a study being done by the VA Medical Center (VAMC) Environmental Hazards Research Center (EHRC) in East Orange, NJ where Persian Gulf veterans who have manifested symptoms indicating multiple chemical sensitivity are exposed to organic solvents through nasal and dermal routes. Dose-response relationships will then be established for symptomatic and neurobehavioral endpoints **[64:8]**.

Clinically relevant basic research is aimed at testing specific research hypotheses in a controlled laboratory setting, using *in vivo* or *in vitro* methods. This basic research spans many disciplines, including physiology, toxicology, immunology, and molecular biology **[64:8]**. The VA established three Environmental Hazards Research Centers (EHRC) to focus on the problems cited by personnel serving in the Persian Gulf. Each center will receive $500,000 annually for up to 5 years, which represents the largest single research commitment to investigate an unexplained illness **[64:16]**. The Boston, MA EHRC will be conducting six Persian Gulf-related research projects to determine the health effects of environmental exposure to hazardous situations. Particular emphasis is being placed on behavioral toxicology, immunology, cancer epidemiology, and behavioral psychopathy **[64:16]**. The data collected will be shared with the Boston VAMC in order to examine multiple hypotheses. At the East Orange NJ EHRC, four projects are planned

to gather information about illnesses and environmental stress factors in Gulf War veterans for development of the most characteristic symptom profiles. The Portland, OR EHRC will conduct four projects to examine health effects associated with exposure to selected environmental chemical and biological hazards related to military service **[64:18]**.

This thesis effort attempts to consolidate all known health effects caused by occupational exposures to a number of toxic substances, and investigate a statistical link between symptoms being manifested in Persian Gulf veterans and symptoms known to be caused by these occupational exposure agents. The results will then be used by the U.S. Army Medical Research and Materiel Command in order to conduct clinically relevant basic research in the areas of concern identified by this report.

1.3 Interim Findings

The Institute of Medicine's (IOM) Committee to Review the Health Consequences of Service During the Persian Gulf War was formed in December 1993 upon requirement of Public Law 102-585 **[62:4979; 33:v]**. The committee performed an assessment of all research activities conducted to date by the VA and the Secretary of Defense connected to PGVI, and made recommendations to improve data collection, ensure that there is a sound scientific basis for studies being conducted, and give "constructive criticism" in these areas **[33:v-vi]**. The IOM report had many recommendations in the area of study design needs, data collection and sharing, and areas of PGVI that are being underinvestigated. This research effort has taken a similar approach, but the scope is much broader: all health

effect studies, past and present, are being examined for pertinent health information, not just recent Persian Gulf-related studies. This health effects information will be assembled into an understandable format that will clearly show relationships between toxic substances and symptoms of PGVI. Nonparametric statistical methods will then be employed to find significant links between these symptoms and PGVI. The results can then be used by the Department of Defense to easily identify areas of research that need further investigation, and also to prioritize research funding based on the information in the matrix, such as areas that have been underinvestigated.

1.4 Goal of Research

The goal of this research is to find a statistically significant link between symptoms reported by Persian Gulf veterans and symptoms identified as being caused by certain toxic substances commonly used in the Persian Gulf, in order to connect the syndrome to the occupational exposures encountered by the soldiers.

1.5 Research Objectives

The following research activities will be conducted to meet this goal:

1. Within both civilian and military scientific arenas, conduct an extensive research of literature relating to human and animal health effects studies pertaining to a number of toxic substances known to have been in use in the Persian Gulf AOR to date, concentrating in the areas of intermediate to chronic health effects versus acute effects.

2. Identify the health effects of each substance under investigation in a number of categories, including respiratory effects, neurological effects, and immunological effects, for oral, dermal, and inhalation exposures.

3. Analyze the data for significant trends and identify research quality, completeness, and relevance in these health categories in a visual format.

4. Narrow the field of study to the most significant routes of exposure and symptoms displayed. Use contingency table analysis of data collected in these studies to determine if PGVI and symptoms of exposure of a substance are homogeneous or not, and at what particular significance level. The term homogeneous means that in comparing the 2 populations, the same proportion of the population falls into each category.

5. Recommend further study in areas that appear to be of concern to Persian Gulf veterans.

The specific methods used to achieve these goals and the results of the overall research effort are detailed in Chapters III and IV of this thesis.

II. Literature Review

2.1 Introduction

The purpose of this chapter is to acquaint the reader with the exposure conditions experienced by Persian Gulf personnel and with the properties of the various substances being investigated, including relevant information about exposure routes, current regulatory guidelines, current usage of the substances by the military, and the substances' known effects on human and animal physiology. Some terminology used in this chapter is defined in Appendix A.

2.2 Persian Gulf Exposure Scenario

General environment. Temperatures in the Area of Responsibility (AOR) average 108 degrees Fahrenheit (° F) in July, and 65° F in the winter, with a relative humidity of less than 40 percent, except along coastal areas **[33:44]**. However, air temperature in the summer can reach 115° F. Sand receiving full sun is 30-40 degrees hotter than the air, and can reach over 150° F **[20:5]**. During the rainy season (December through March), the relative humidity increases to over 60 percent, and flash flooding can occur during a rain shower **[33:44]**. The night temperature can be very cold in the winter months, with wind-chills dropping below freezing **[20:5]**. Frequent high winds cause the fine sand in the area to cover every surface and get in the eyes and mouth. The amount of particulate matter in the air often is higher than the National Ambient Air Quality Standards (NAAQS) PM-10

standard of 150 ug/m^3 **[29:55; 46:9]**. Natural dangers to personnel in the desert included venomous snakes, scorpions, spiders, and sand flies that carry disease. Additionally, after the Kuwait oil wells were set on fire, personnel in the region reported that they breathed in an oily residue and found a layer of soot covering the area **[20:5]**. The following sections will discuss each toxic substance in detail.

2.3 Petroleum Vapors and Combustion Products

Exposure to petroleum vapors, combustion products, and solvents was common during the Persian Gulf War. Kerosene and diesel fuel were used in tent heaters during the winter months, and diesel fuels were sprayed on roads as a dust suppressant, which would volatilize **[46:7, Appendix B]**. Diesel exhaust from electric generators and refueling operations would have caused localized petroleum vapor exposure. The oil well fires in Kuwait had wide-spread consequences, causing oily film and particulates to become airborne for hundreds of miles. Exposures to gases and particulate soot from these fires were more frequent and severe as troops were closer in proximity to the wellfields **[46:7-8]**. JP-4 and JP-8 aircraft fuels were also used in the AOR **[App. B]**.

2.3.1 Diesel Fuel

The diesel fuel described in this section will be fuel oil number 2-D, also known as diesel fuel, diesel fuel oil no. 2, diesel oil no. 2, no. 2 diesel, and diesel oil (medium) **[59:68]**, although all types of fuel oils were used in the AOR. All fuel oils have certain

similar properties, as they are all refined from crude petroleum and can be categorized as a distillate fuel or as a residual fuel, depending on their method of production. Diesel 2 is considered to be a distillate fuel. All fuel oils consist of complex mixtures of aliphatic and aromatic hydrocarbons. Diesel fuels contain predominately C_{10} - C_{19} hydrocarbons, which consist of approximately 64% aliphatic hydrocarbons, 1-2% olefinic hydrocarbons, and 35% aromatic hydrocarbons. All fuel oils contain less than 5% polycyclic aromatic hydrocarbons (PAH). PAH has been shown to suppress immune responses, which result in long-lasting reductions in antibody-producing cells **[35:271]**. Some PAH compounds, such as benzo(a)pyrene, have been linked to cancer, especially when in combination with other promoters **[35:107]**.

2.3.1.1 Physical and chemical properties

The physical and chemical properties of diesel fuel 2 can be found in Table 2-1.

Characteristic	Fuel oil no. 2-D (diesel 2)
Molecular weight	No data
Color	Colorless to brown
Physical state	Liquid
Percent sulfur	30%
Melting point	18° C
Boiling point	282 - 338° C
Density at 20° C:	0.8700 - .0.9500 g/mL
Odor	Kerosene-like
Solubility in water at 20° C	Approximately 5 mg/L
Log K_{ow}	3.3 - 7.06
Log K_{oc}	3.0 - 6.7
Vapor pressure @ 21° C	2.12 - 26.4 mm Hg
Henry's Law constant @ 20° C	5.9 x 10^{-5} to 7.4 atm-m^3/mol
Autoignition temperature	254 - 285° C
Flashpoint (closed cup)	52° C
Flammability limits (% volume in air)	1.3 - 6.0%

Table 2-1 Physical and Chemical Properties of Diesel Fuel 2 [59:70; 40:A-17]

2.3.1.2 Health effects from inhalation exposure

There is no data regarding human death due to exposure to diesel fuel vapors; however, there are many animal studies that indicate mortality for acute (one-time) inhalation and after a prolonged exposure period.

Respiratory effects in humans include fluid in the lungs and in the alveolae **[59:16]**. In a study of feral cats exposed to the Kuwait oil fires, mild hyperplasia of the bronchial gland, bronchiolar gland, tracheal gland, and mild laryngeal lesions were observed, as was a coal-dust pigmentation of the lungs **[44:2]**. One of the cats also had collapsed pulmonary alveoli in both lungs.

Cardiovascular effects include hypertension and rapid heartbeat following acute inhalation. Increases in the diameter of blood vessel openings were seen in mice that were acutely exposed. Gastrointestinal effects include nausea, abdominal cramps, vomiting, and diarrhea **[59:16]**. Hematological effects from inhalation were subcutaneous hemorrhage, mild nose bleeds, low platelet counts, and retinal arteriole constriction, occurring four weeks after a prolonged exposure to diesel fuel vapor **[59:17]**. No data exists concerning musculoskeletal, immunological, or hepatic effects of inhalation of diesel fuel.

Acute liver failure occurred in a man who had been exposed to diesel fumes for 10 days while driving a truck **[59:18]**. However, no animal studies have been done concerning renal effects. A burning sensation in the eyes and itching is common. Hyperemic conjunctiva has also been reported after inhalation exposure; however, all symptoms subsided within 4 days **[59:18]**.

No skin lesions are seen to occur from diesel fumes. Systemic effects that have been linked to diesel inhalation include a decreased appetite for food and water, with a corresponding weight loss and dehydration, in mice. Similar effects were induced in rats **[59:19]**. Observed neurological effects in humans include coordination and concentration difficulties, fatigue, headache, apparent intoxication, and anorexia. All effects subsided within 4 days **[59:20]**.

No developmental or reproductive effects were observed in the fetuses of rats; no human data is available. One *in vivo* study exists for genotoxic effects in rats; no adverse effects were observed **[59:21]**. Cancer has not been scientifically linked to inhalation exposure to diesel fuel, either in humans or laboratory animals **[59:21]**.

2.3.1.3 Health effects from oral exposure

Numerous case studies exist that identify death in humans after ingestion of fuel oils. Most of these case studies were children under 5 years old, but in some cases the children were as old as 15 **[59:22]**. Death occurred from fuel-induced respiratory toxicity in the form of lipoidal pneumonia, after aspiration of oil into the lungs upon vomiting **[59:25]**. Death from ingestion of fuel oil has also been observed in laboratory animals.

Respiratory effects in humans include pneumonitis, pulmonary edema, bronchitis, pneumonia, lung infiltrates and effusions, dyspnea, and tachypnea **[59:25]**. Abnormal chest radiographs showing small airway lesions in exposed children persisted for 10 years

after the initial ingestion of oil, suggesting there may be long-term respiratory effects from ingestion of fuel oils **[59:25]**.

Cardiovascular effects include tachycardia, cardiomegaly, and increased cardiac palpitations in humans **[59:26]**. The most common gastrointestinal effect in humans was vomiting, including bloody vomit. Other gastrointestinal effects are abdominal pain and distention, gastroenteritis, and diarrhea. No gastrointestinal effects were observed in laboratory animals **[59:26]**. Hematological effects observed in children consisted of increased leukocyte counts in 37-80% of the study populations; again, no adverse effects have been observed in laboratory animals **[59:26]**. No data is available concerning musculoskeletal, developmental, reproductive, carcinogenic, or immunological effects in humans or animals.

No hepatic effects have been studied in humans; in rats, a slight cellular infiltration and mild vacuolization of the liver were found, and in one study necrosis was found in the hepatocytes of rats. Renal effects were not found in humans after ingestion of fuel oils; in rats, hyaline droplets were found in the kidneys, and a statistically significant increase in creatinine levels was noted **[59:27]**.

Dermal effects in humans from oral ingestion of fuel oil could not be proven. Large blisters, erythema, and peeling skin were found in one case, but these symptoms could also have been from simultaneous dermal exposure in addition to oral exposure to fuel oils **[59:27]**. Fever has also been observed in children following ingestion of fuel oil.

Human neurological effects include lethargy, semicoma and/or coma, unconsciousness, drowsiness, restlessness, convulsions, and irritability. Neurasthenia, impaired attention span and sensorimotor speed were also observed, but no effects on memory function or manual dexterity were found **[59:28]**. Similar neurological effects were noted in animal experiments. No human genotoxic studies exist, but animal studies indicate marked increases in percentage of aberrant bone marrow cells **[59:29]**.

2.3.1.4 Health effects from dermal exposure

No cases of death in humans due to dermal exposure have been documented. In animals, several studies have found that both acute and chronic dermal exposures caused death in mice. Respiratory effects were noted in a man who had washed his hair in diesel fuel; however, it could not be distinguished whether the effects were from dermal or inhalation exposure **[59:30]**. In rats, there were no respiratory effects associated with dermal exposure to fuel oils. Cardiovascular effects in man from dermal exposure were similar to that of oral and inhalation exposure (a significant increase in heart palpitations). Again, no changes were noted in mice.

Gastrointestinal effects in man may include nausea, abdominal cramps, diarrhea, and epigastric pain. Once again, no effects were observed in animal studies **[59:30]**. Hematological effects in man from dermal exposure to fuel oil include decreased hemoglobin concentration and increased erythrocyte sedimentation rate. The same effects were observed in male mice, and also a dose-related decrease in splenic relative weight

[59:30]. No studies of human musculoskeletal and hepatic effects have been done; in animals, no changes were noted. Acute renal failure and oliguria occurred in the case of the man who washed his hair in diesel fuel; again, there is no knowledge of whether this effect was from dermal or inhalation exposure **[59:35]**. Kidney injury was sustained in mice following a 60-day exposure to various fuel oils.

Dermal effects in man include dermatitis, large blisters, peeling skin, and erythema. Human ocular effects observed in man include subconjunctival hemorrhages and eye irritation **[59:36]**. Dermal effects were repeated in laboratory animals, but no ocular effects were noted. Additional systemic effects reported in man include edema, loin pains, thirst, and severe exhaustion **[59:37]**. No immunological effects have been studied in humans after dermal fuel oil exposure; in animals, decreases in the relative weights of the lymph nodes and thymus were noted **[59:37]**.

Neurological effects observed in man include anorexia, neurasthenia, and impaired attention and sensorimotor speed. No similar effects were noted in mice **[59:38]**. No developmental, genotoxic, effects in humans or animals have been studied. No reproductive studies have been done on humans; in animals, no histological changes were noted.

No cancer studies have been performed on humans; studies in animals indicate skin tumors formed in mice, but as the tumors were not dose-related, and they did not occur in other mice strains, it is suspected that these tumors might be characteristic of that

particular strain of mice **[59:39]**. No other carcinogenic effects have been found in animal studies of dermal fuel oil exposure.

2.3.2 Kerosene

Kerosene tent heaters were in use during the winter months in the AOR. Kerosene is also used in cooking, illumination, and in space heaters **[50:31]**. Kerosene is also known as fuel oil no. 1, JP-5, coal oil, kerosine, deodorized kerosene, straight-run kerosene, range oil, and by the trade name Deobase **[59:1]**. Kerosene heaters are significant sources of inorganic combustion gases NO, NO_2, SO_2, and CO, and particulates, as well as PAH (known to be a carcinogen) **[45:152]**. One study on emissions of kerosene heaters measured a particulate concentration of 3.5 mg/m^3 of soot **[45:154]**, which is lower than OSHA standards **[52]**. However, the particles emitted from the heaters were mostly mutagenic in nature.

Sources of exposure to kerosene in the Persian Gulf include inhalation of aerosol and combustion products, dermal exposure of occupational workers, and possibly oral exposure (although unlikely). The following sections discuss the risks of exposure to kerosene through these routes.

2.3.2.1 Physical and chemical properties

The physical and chemical properties of kerosene are shown in Table 2-2.

Characteristic	Fuel oil no. 1 (kerosene)
Molecular weight	No data
Color	Pale yellow, colorless, brown
Physical state	Liquid
Melting point	-45.6 ° C
Boiling point	175 - 325° C
Density at 20° C:	0.80 g/mL
Odor	Kerosene-like
Solubility in water at 20° C	Approximately 5 mg/L
Partition coefficients:	
Log K_{ow}	3.3 - 7.06
Log K_{oc}	3.0 - 6.7
Vapor pressure @ 21° C	2.12 - 26.4 mm Hg
Henry's Law constant @ 20° C	5.9 x 10^{-5} to 7.4 atm-m^3/mol
Autoignition temperature	229° C
Flashpoint (closed cup)	38° C
Flammability limits (% volume in air)	0.7 - 5 %

Table 2-2: Physical and Chemical Properties of Kerosene [59:70]

2.3.2.2 Health effects from inhalation exposure

No deaths occurred in rats acutely exposed to 5,000 mg/m^3 of kerosene; this was the only concentration tested **[59:8]**. No throat irritation was found in humans after acute exposure to kerosene fumes **[59:9]**, chronic exposures to kerosene aerosols or combustion products did not induce asthmatic effects either. In animals, reductions in tidal volume and dynamic lung compliance, bronchoconstriction, and an increase in pulmonary resistance were observed in acute studies **[59:9; 14:2]**. Chronic studies showed no animal respiratory effects.

Cardiovascular effects have not been studied in humans after exposure to kerosene. Chronic animal studies induced aortic plaques in guinea pigs that resemble those seen in atherosclerosis **[50:35]**. Also in this study were observed lowered total blood cholesterol and HDL levels. Effects were similar with both smoke and aerosol exposures. A subchronic animal study showed no gastrointestinal effects in rats or dogs **[59:17]**. No hematological or musculoskeletal effects were observed in this same study, and no other studies were found that pertained to these areas.

Hepatic effects in animals after an intermediate exposure to kerosene vapors include decreases in blood glucose levels, increases in blood lactate and pyruvate levels **[59:17]**. No studies have been performed relating to renal effects in humans after inhalation exposure to kerosene. One intermediate animal study showed no histopathological changes in the renal systems of rats or dogs **[59:18]**. An acute exposure to kerosene vapors did not induce eye irritation in human volunteers. No studies exist that show any dermal effects in humans or animals after kerosene vapor exposure **[59:19]**.

No studies have been performed in the areas of immunological effects from inhalation of kerosene. Acute kerosene exposure induced olfactory fatigue and taste sensation in volunteers **[59:20]**. No developmental, reproductive, or genotoxic studies have been done for humans or animals concerning kerosene inhalation exposures **[59:20-21]**.

One study looked at carcinogenicity in humans after chronic inhalation exposure to kerosene; it concluded there was no association between use of kerosene and bronchial

cancer **[59:21]**. Another study examined the mutagenicity of particles emitted from kerosene heaters; mutagenic effects were seen, most likely resulting from the presence PAH in the particulates emitted **[45:156]**.

2.3.2.3 Health effects from oral exposure

Most cases of death resulting from oral intake of kerosene are in children under 5 years old. Cause of death was primarily due to kerosene-induced respiratory toxicity in the form of lipoidal pneumonia **[59:22]**. Other respiratory effects associated with death from kerosene ingestion include, pneumothorax, emphysema, and pneumonitis.

Respiratory effects in humans associated with non-fatal ingestion of kerosene include pneumonitis, pulmonary edema, bronchopneumonia, bronchitis, lung infiltrates and effusions, cough, dyspnea, tachypnea, and pneumonia **[59:25]**. It is believed that respiratory effects are caused by aspiration of kerosene into the lungs during vomiting.

Cardiovascular effects noted in children who had accidentally ingested kerosene include tachycardia and cardiomegaly **[59:26]**. Acute studies in animals showed decreased heart rate and blood pressure. No intermediate length studies have been performed on animals.

The most common gastrointestinal effect seen in children after kerosene ingestion is vomiting, including bloody vomit. Other effects include abdominal pain and distention, gastroenteritis, and diarrhea **[59:26]**.

Hematological effects seen in children following kerosene ingestion are increased leukocyte counts **[59:26]**. An acute animal study showed increased hematocrit, decreased white blood cell counts, and increased erythrocyte counts in rats.

No studies were found for humans or animals concerning musculoskeletal effects. No human studies exist concerning hepatic effects; in animals, slight cellular infiltration and mild vacuolization of the liver were found after an acute dosage of kerosene **[59:26]**. Renal effects in children were slight, only occasionally was albuminuria observed **[59:27]**. Animal studies showed slight cellular infiltration and mild vacuolization of the kidneys. Dermal effects noted in human oral exposure to kerosene are suspect, due to kerosene also being found on the skin **[59:27]**.

Children ingesting kerosene also have been reported to have fevers, some with pulmonary complications. No other systemic effects were observed in animal tests **[59:27]**.

No studies have been found pertaining to immunological, developmental, reproductive, or carcinogenic effects in humans or in animals **[59:27-28]**. Neurological effects found in children who had accidentally ingested kerosene include lethargy, coma, and semicoma, and complications of the central nervous system **[59:28]**. Other effects noted were convulsions, unconsciousness, restlessness, and irritability. Animal studies showed similar effects. Genotoxic effects have not been studied in humans; in animals, one study inconclusively showed marked, but not dose-related increases in aberrant cells in bone marrow **[59:29]**.

2.3.2.4 Health effects from dermal exposure

Kerosene has not induced death in humans **[59:29]**. Animal studies also have not been shown to induce death from dermal exposure to kerosene **[59:29]**. Respiratory effects were not seen in a study involving mice **[59:29]**. No studies have been conducted regarding cardiovascular, gastrointestinal, or musculoskeletal effects in humans or animals **[59:30]**.

Hematological effects seen in an acute animal study include a decrease in the relative splenic weight of male mice **[59:30]**.

Hepatic effects were not observed in male mice in an acute study **[59:35]**. Renal effects were not noted in this same study. No studies exist concerning renal or hepatic effects in humans.

Dermal effects of exposure to kerosene seen in humans include dermatitis, dermatosis, hyperemia, cellular damage of the epidermis, edema, cytolysis, and other histological changes in skin cells **[59:36]**. All dermal effects subsided within 3 days. Another study reported erythema, bullae, burning, and itching **[59:36]**, and another observed blisters, reddening, pustules, soreness, and burning **[59:36]**. Animal studies showed rough skin, edema, and inflammation **[59:36]**. Another study reported skin thickening, temporary hair loss, folliculitis, hyperplasia, spongiosis, intracellular vacuolization, and epidermal necrosis in male mice **[32:249-251]**. Ocular effects were not studied in animals or humans.

Immunological effects seen in male mice include decreases in the relative weights of the lymph nodes and thymus, as well as a number of histopathological changes, in one acute study **[59:37]**. Neurological effects observed in this same study included increased responses to tactile stimuli and hyperactivity **[59:38]**.

Developmental, reproductive, genotoxic, and carcinogenic effects of dermal exposure to kerosene have not been studied in animals or humans.

2.3.3 JP-4 Jet Fuel

Jet propellant-4 (JP-4) is a liquid aviation turbine fuel used by the U.S. Air Force (USAF). JP-4 is refined from either crude petroleum or shale oil. A chemical additive package is then blended with the oil, as specified by the USAF **[60:1]**. JP-4 is a wide-cut fuel, meaning that it is distilled from crude oil or shale oil using a broad temperature range, and consists of a range of hydrocarbon chain lengths (C_4 - C_{16}) **[9:194]**. JP-4 is a complex blend of up to 300 different hydrocarbon compounds **[41:388]**. All jet fuels consist of a blend of various hydrocarbons, such as alkanes, cyclohexanes, aromatics, olefins, and also small amounts of benzene, n -hexane, and PAH **[60:5-6]**. Since JP-4 is specifically used for aircraft, the most likely exposed population would be military and civilian personnel working in the aircraft maintenance or flightline areas, flight crews and pilots, and personnel involved in the manufacture and transportation of JP-4. Contaminated soil or water from a JP-4 spill is another way for individuals to come into contact with the fuel.

2.3.3.1 Physical and chemical properties

The physical and chemical properties of JP-4 are shown in Table 2-3.

Characteristic	JP-4
Molecular weight	Not applicable
Color	Colorless to straw-colored
Physical state	Liquid
Melting point	-40 to 72 ° C
Boiling point (1 atm)	45 to 300° C
Density at 15° C:	751 - 802 kg/m^3
Odor	Similar to gasoline or kerosene
Odor threshold in air	1 ppm
Solubility in water at 20° C	Insoluble
Partition coefficients:	
Log K_{ow}	3 - 4.5
Log K_{oc}	No data
Vapor pressure @ 20° C	91 mm Hg
Henry's Law constant @ 20° C	1.00 x 10^{-4} to 1.00 x 10^{+1} atm-m^3/mol
Autoignition temperature	246 ° C
Flashpoint (closed cup)	-23 to 1° C
Flammability limits (% volume in air)	1.3% lower, 8.0% upper

Table 2-3 Physical and Chemical Properties of JP-4 [60:42]

2.3.3.2 Health effects from inhalation exposure

There are no reports of human death from JP-4 exposure. Several intermediate length animal studies did not show any mortality from exposure to 5000 mg/m^3 concentration of JP-4 **[60:6]**.

Respiratory effects in humans are minimal; one pilot who had been acutely exposed to JP-4 fumes experienced a feeling of intoxication, but pulmonary functions were normal upon examination. Another group of individuals experienced feelings of suffocation and pain upon inhalation, but again, no health effects were found **[60:11]**. Intermediate and chronic animal tests indicate no adverse respiratory effects.

Hematological effects were not found in one case of acute JP-4 exposure. In intermediate and chronic animal testing several effects were noted; specifically, decreased white and red blood cell counts and bone marrow cytopenia, although effects did reverse themselves **[60:11]**.

Hepatic studies have not been done for humans; in animals, hepatocellular fatty change occurred in 88-89% of mice after a 90-day continuous exposure to JP-4 vapors **[60:12]**. This change was regarded as a reversible degenerative process. Other intermediate animal studies did not show any histopathic changes in the liver. One year after exposure to JP-4, an increased incidence of hepatic inflammation occurred in mice **[60:12]**.

Renal effects have not been studied in humans. In an intermediate animal study, blood urea nitrogen was elevated in rats exposed to JP-4 for 90 days. However, in a similar study, blood urea nitrogen was decreased, indicating that there is no consistent effect on the kidneys **[60:12]**. Renal function was affected in these rats also; a 50-70% decrease in osmolality was seen in two studies conducted by the USAF **[60:12-13]**. Blood urea nitrogen and creatinine were significantly increased in all animals as well. Absolute kidney weight was increased in all strains of rat involved in this study. The kidneys also had a discoloration, and hyaline droplets were found in tubular epithelium at a corresponding severity with higher dosage **[41:389; 60:13]**. Also found were intratubular casts of necrotic debris in the outer renal medulla. All these histopathological changes in the kidneys of rats indicate a kidney disease syndrome that is unique in male rats, and

cannot be induced in female rats **[60:13]**. Other systemic effects of inhalation of JP-4 include a decrease in body weight, the severity again related to exposure period and inhalation concentration **[41:389; 60:13]**.

No studies exist that examine immunological effects of JP-4 inhalation. Neurological effects found in humans include grogginess, intoxication, muscular weakness, decreased sensitivity to pain, headache, anxiety, sleep disturbances, memory impairment, irritability, and nausea **[60:14]**. Several studies also documented audiological and opto-vestibular changes, symptoms of polyneuropathy (such as muscle cramps, numbness, and restless legs), and decreased motor function **[60:14]**. Similar results are reported in animal studies.

No studies exist documenting any developmental, reproductive, or genotoxic effects of inhalation of JP-4, either in humans or animals. Carcinogenic effects have not been studied in humans, but chronic animal studies show an increase in hepatocellular adenomas, alveolar, bronchial, and pulmonary tumors, and C-cell and kidney adenomas **[60:15-16]**. Another study found renal carcinomas in male rats after a one-year exposure to JP-4 **[41:389]**.

2.3.3.3 Health effects from oral exposure

Oral exposure to JP-4 is an unlikely event, since it is controlled by the military for the most part, and it is unlikely that anyone would accidentally ingest JP-4. There are no reported cases of death in humans due to oral exposure to JP-4; however, several animal

studies have shown mortality with acute dosing of JP-4 **[60:16]**. Not much research has been done in the area of oral JP-4 exposure. No human or animal data exists in the areas of respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, immunological, neurological, developmental, reproductive, and carcinogenic effects. One genotoxic study with rats indicated a slight dose-related increase in preimplantation loss of embryos but the study's sample size was considered too small for conclusive results **[60:17]**.

2.3.3.4 Health effects from dermal exposure

No studies have been found relating to death in humans after dermal exposure to JP-4. Several chronic animal studies show mortality to animals after skin applications of JP-4 **[60:17]**. These studies also indicate that shale-derived JP-4 is more toxic than petroleum-derived JP-4. No studies were found pertaining to respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects in animals or humans.

Only one study on acute hepatic effects in animals was found, it indicated no hepatic lesions after a 14-day postexposure period. The same study showed no renal effects from dermal application of JP-4 **[60:20]**.

Dermal and ocular effects include mild to moderate skin irritation in animals, edema and erythema, progressing to skin necrosis. Minimal eye irritation was found in rabbits **[60:20]**.

Immunological effects in animals from shale-derived JP-4 include a mild-to-moderate sensitization potential **[60:20]**. No studies exist for humans or animals in the areas of neurological, developmental, reproductive, or genotoxic effects. Carcinogenic effects found in animal studies include neoplastic lesions at the site of application, squamous cell carcinoma, and fibrosarcoma **[60:21]**. Again, shale-derived JP-4 seemed to be more carcinogenic than petroleum-derived JP-4.

2.4 Solvents (Toluene)

Solvents were used during the Persian Gulf war in painting applications. Toluene is a common solvent and has been studied extensively, therefore it has been chosen as the solvent of concern. Toluene is an industrial solvent, used in manufacturing paint, paint thinner, lacquers, and adhesives **[61:2-3]**. It is also a component of gasolines and kerosene. Toluene is commonly used in consumer products such as nail polish, cosmetics, rubber cement, dyes, and inks **[61:3]**. It is also found in cigarette smoke.

Toluene is produced in the process of making fuels from crude oil, and in making coke from coal, and as a by-product of manufacturing styrene **[61:1]**. Toluene is also known as methylbenzene, phenylmethane, benzene, and under the trade names methacide, methylbenzol, and toluol. Its chemical formula is $C_6H_5CH_3$.

Toluene is often abused as a drug, commonly known as "paint sniffing" or "glue sniffing". It is speculated that Persian Gulf personnel may have abused solvents due to the lack of alcohol in the AOR, although no formal studies have been done to date **[20:49]**.

2.4.1 Physical and chemical properties

The physical and chemical properties of toluene are found in Table 2-4 below.

Characteristic	Toluene
Molecular weight	92.15
Color	Colorless
Physical state	Liquid
Melting point	-95° C
Boiling point	110.6° C
Density at 20° C:	0.8699 g/mL
Odor	Sweet, pungent
Solubility in water at 25° C	534.8 mg/L
Partition coefficients:	
Log K_{ow}	2.69
Log K_{oc}	1.57 - 2.25
Vapor pressure @ 25° C	28.4 mm Hg
Henry's Law constant @ 20° C	5.94 x 10^{-3} atm-m^3/mol
Autoignition temperature	480° C
Flashpoint (closed cup)	4
Flammability limits	1.2 - 7.1

Table 2-4: The Physical and Chemical Properties of Toluene [61:11]

2.4.2 Health effects from inhalation exposure

In Great Britain, about 80 deaths per year are attributed to solvent abuse **[61:12]**. Leading causes of death are cardiac arrhythmias, central nervous system depression, asphyxia, and hepatic and renal failure.

The only respiratory effect noted in occupational human studies is respiratory tract irritation. Intermediate animal studies show irritation, pulmonary lesions, and significantly increased relative lung weight, all of which appear to be dose-related **[61:30]**. Chronic animal studies show inflammation and degeneration of the nasal and respiratory epithelium at moderate concentrations **[61:30]**.

Cardiovascular effects seen in solvent abusers include fatal cardiac arrhythmias, the leading cause of death associated with solvent abuse **[61:31]**. Animal studies show no cardiovascular system lesions, and it appears that toluene is not directly toxic to the cardiovascular system. A study involving dogs showed direct effects on the septal and ventricular muscles of the heart, leading to fatal cardiac arrhythmias **[61:31]**.

No studies have been done in humans regarding gastrointestinal effects. In a chronic animal study, there was a marginal increase in ulcers in the forestomach **[61:32]**. Hematological effects seen in chronic human occupational studies include decreased (reversible) blood leukocyte counts **[61:33]**. Animal studies also showed reversible decreased blood leukocyte counts. No musculoskeletal studies have been done in humans, and all animal studies show no musculoskeletal effects as a result of inhalation of toluene **[61:33]**.

No hepatic effects have been seen in occupationally-exposed workers, even though toluene is extensively metabolized by the liver **[61:34-35]**. Animal studies have shown increases and decreases in liver weight and minor ultrastructural changes.

Renal effects seen in occupationally-exposed workers is a greater secretion of albumin. Solvent abusers have shown much more serious effects, such as severe tubular interstitial nephritis, focal tubular necrosis, hematuria, oliguria, proteinuria, and urinary calculi **[61:36-37]**. Chronic animal studies show no renal effects. Ocular effects seen in humans is mainly eye irritation. No animal studies have been done in the areas of dermal

or ocular effects of toluene inhalation **[61:38]**. Intermediate animal studies also indicate a decrease in body weight **[61:38]**.

Immunological effects in humans include allergic blood disorders and decreased total lymphocytes **[61:38-39]**. Intermediate animal studies showed decreased bactericidal activity in the lungs, with a corresponding increase in respiratory infections **[61:39]**.

Chronic occupational worker studies show that neurological effects include impaired cognitive, auditory, and neuromuscular functions. Solvent abusers exhibit severe CNS dysfunction and narcosis **[61:39-47]**. Animal study results indicate behavioral effects, ototoxicity, alterations in brain neurochemistry, and electrophysiological effects **[61:39-47]**.

Reproductive studies on occupationally-exposed women showed an increased incidence of spontaneous abortions, and in men, changes in gonadotropic hormone levels **[61:47-48]**. The studies concluded that these effects are secondary to central nervous system effects. No adverse reproductive effects were seen in intermediate studies **[61:48]**. Studies of the children of occupationally-exposed workers have shown the following abnormalities: central nervous system (CNS) anomalies, defects of neural tube closures, microcephaly, CNS dysfunction, attention-deficit disorder (ADD), minor craniofacial and limb anomalies, developmental delay, and variable growth **[61:48-49]**. Children of solvent abusers also showed dysmorphism, growth retardation, and renal tubular acidosis **[61:49]**. Genotoxic effects seen in humans are limited to an increase in sister chromatid exchange

frequencies seen in toluene-exposed printers, but animal studies show no genotoxic effects in male mice **[61:50-51]**.

No carcinogenic effects have been seen in men occupationally exposed to toluene vapors; in fact, one study showed lower cancer rates than the general population, a phenomenon known as "healthy worker effect" **[61:51]**. No carcinogenic effects have been detected in animal studies to date.

2.4.3 Health effects from oral exposure

Only one reported death by ingestion of toluene is known; a male mental patient died within 30 minutes of ingesting 60 mL of toluene **[61:52]**. Autopsy results showed constriction and necrosis of the myocardial fibers, a significantly swollen liver, congestion and hemorrhage of the lungs, and acute tubular kidney necrosis. The cause of death was determined to be severe CNS depression **[61:52]**. Animal studies indicate the lethal oral dose of toluene to be age-related; young rats had a much lower LD_{50} than adults **[61:53]**.

Few respiratory effects occur from oral exposure of toluene; lung congestion and hemorrhage occurred in the one fatality as a secondary effect to the cause of death, and subchronic animal studies show no respiratory effects **[61:53]**.

The one human case shows cardiovascular effects in the form of necrosis of myocardial fibers; subchronic animal studies reveal increased relative heart weights, myocardial degeneration, and elevated plasma free fatty acids and triglicerides **[61:53]**.

No gastrointestinal effects were found in the one fatality involving toluene; no gastrointestinal effects were seen in mice or rats in subchronic studies **[61:59]**.

No human data exists concerning hematological effects. Subchronic animal data indicates a slight decrease in the concentrations of leukocytes, lymphocytes, and neutrophils **[61:59]**.

No musculoskeletal data exists regarding human exposure to toluene; a subchronic animal study showed no musculoskeletal effects **[61:59]**.

Hepatic effects seen in the suicide case was an enlarged liver. Subchronic animal studies corroborate this finding; liver weights increased in mice and rats. One 6-month animal study at a low dosage showed no liver weight increase **[61:59]**.

Renal effects in the suicide case consisted of acute tubular necrosis. The only significant animal findings include a decrease in the absolute kidney weight in mice for a subchronic study (but no change in the relative kidney weight), and lethal rat studies found hemorrhages of the urinary bladder **[61:59-60]**.

No studies exist concerning dermal or ocular effects of toluene ingestion. No changes in spleen weight or body weight occurred in a subchronic animal study **[61:60]**.

Immunological effects in subchronic animal studies include decreases in thymus weights, mixed lymphocyte culture responses, and antibody plaque-forming cell responses, as well as depressed mitogen-stimulated lymphocyte proliferation and interleuken-2 immunity **[61:60]**.

Neurological effects observed in animals include decreased open-field activity, impaired motor coordination, increased relative brain weights, and vision effects **[61:60-61]**. There were also changes in neurotransmitter levels in six areas of the brain in mice. The neurotransmitters in question affect mood, emotional state, and aggressive behavior **[61:61]**.

No human reproductive, developmental, or genotoxic studies have been done; no reproductive effects were noted in a study involving mice **[61:62]**. Developmental studies on animals revealed adverse effects on neurological function and open-field activity **[61:62]**. No genotoxic animal studies have been done. No carcinogenic data exists for orally administered toluene in humans or animals **[61:61]**.

2.4.4 Health effects from dermal exposure

Not many studies have been performed concerning dermal effects of toluene. No data exists in the areas of lethality, respiratory, cardiovascular, gastrointestinal, hematological, or musculoskeletal effects **[61:64]**. No hepatic effects or changes in the liver morphology was seen in one animal study **[61:64]**. No renal effects were found in that same animal study.

Dermal effects in occupationally exposed workers include skin irritation, due to the fact that toluene removes skin oils **[61:64]**. Eye irritation has also been reported by occupationally exposed workers. Animal studies of dermal exposure to toluene found karyopyknosis, karyolysis, spongiosis, and cellular infiltration of the dermis **[61:65]**.

Rabbits sustained a slight irritation of the conjunctival membranes, but no permanent corneal injury, following toluene applications **[61:65]**.

No studies have been done in the areas of immunological, neurological, developmental, or reproductive effects in humans or animals as a result of dermal toluene exposure. Genotoxic *in vitro* studies generally indicate that toluene is nonmutagenic and nongenotoxic **[61:90]**.

No human carcinogenic studies have been done; in animals, toluene markedly inhibits the formation of tumors on the skin, but the pattern of inhibition indicated that the observed effect was not likely to be due to a direct chemical effect on the promoter **[61:65]**.

2.5 N, N -diethyl-*m*-toluamide (DEET)

DEET (chemical composition $C_6H_4CH_3CON(C_2H_5)_2$) is the most commonly used insect repellent today, and the insect repellent of choice for the U.S. military **[58:1509]**. It has been on the commercial market since 1957. DEET is formulated as a liquid and a gel, in pressurized or pump containers, as a stick, and in impregnated towelettes **[6:610]**. The concentration of DEET in a product affects its protection duration and the range of insects it will repel. Therefore, lower concentrations of DEET need to be applied more often to be as effective. Formulations prepared for the U.S. Army include a 75% liquid solution of DEET in ethanol, a 33% DEET extended duration formulation, and a 19% DEET stick **[43:4]**. Several common commercial products containing DEET include Deep Woods Off

and Cutter Insect Repellent. Trade names for DEET include Metadelphene, OFF, and MGK Diethyltoluamide **[63:26]**. Products containing as high as 100% DEET have been manufactured and distributed to the public, even though U.S. and British forces have found that 75% DEET products are sufficient for protection against mosquitoes **[6:611]**. Preparations containing less than 50% DEET are almost free of side effects in adults; children are more susceptible to DEET, and serious side effects have been seen in children using only 20% DEET solutions **[503:611]**.

At the Senate Veterans' Affairs Committee hearing on May 6, 1994, Dr. James Moss presented his research findings that when used in combination with pyridostigmine bromide (PB), DEET became ten times as toxic to roaches than when used alone **[18:478]**. This significant finding could have serious ramifications for military personnel who used DEET while taking PB pills. A preliminary toxicity study has been recently completed concerning lethal oral doses of DEET, permethrin (an insecticide used to impregnate military battle dress uniforms), and PB; results indicate that DEET, permethrin, and PB combined have more than an additive lethal effect on rats **[43:11]**. Additional research in this area is being planned by DoD.

2.5.1 Physical and chemical properties

The physical and chemical properties of technical DEET (at least 95% DEET, used to manufacture insecticides) are contained in Table 2-5.

Characteristic	DEET (technical grade)
Molecular weight	191.26
Color	Amber, clear
Physical state	Liquid
Specific gravity @ 25°C	0.990 - 1.000
Boiling point @ 1 mm Hg	111° C
Odor	None to a characteristic pyridine-like
Solubility in water at 20° C	Practically insoluble
Log K_{ow}	None reported
Vapor pressure @ 25° C	1.67 x 10^{-3} mm Hg
Flashpoint (open cup)	150 - 155° C

Table 2-5: Physical and Chemical Properties of DEET [2:98; 43:6; 63:24-29]

DEET is quickly absorbed through the skin and enters the bloodstream, where it is metabolized. One study observed that almost 48% of applied DEET was absorbed into the skin within 6 hours **[55:422]**. Most of the absorbed DEET is excreted from the body through the urine within 24 hours, although traces of DEET can be found in the blood for 2 to 3 days and in the skin and fatty tissues for up to 3 months **[55:422; 56:510]**. DEET is metabolized through the liver, kidneys, to the intestines, and is not bioaccumulated in the body **[63:37]**. In one study using mice, researchers found high levels of DEET in the brain, lungs, and adrenals **[56:511]**. If this is indeed true, the chances of DEET interacting with pyridostigmine bromide in the brain are high.

2.5.2 Health effects from inhalation exposure

Very little human data exists on the inhalation effects of DEET, although many animal studies have been conducted. No deaths occurred in rats who were exposed to

saturated DEET vapors for 7 weeks **[63:52]**. Respiratory effects in the form of tracheitis were seen in rats exposed for 30 days **[56:515]**. Cardiovascular effects were observed in this same study; the rats developed pulmonary edema.

Gastrointestinal effects observed in dogs that were subchronically exposed to DEET vapors included periodic nausea and vomiting **[56:515]**.

Hematological effects observed in one subchronic inhalation study included slight nosebleeds in rats **[56:515]**, and hyperemia was observed in the ears, feet, and tails of rats in another subchronic study, as well as slight nosebleeds **[2:105]**. No studies were found concerning dermal, musculoskeletal, hepatic, renal, immunological, or carcinogenic effects from inhalation of DEET.

Ocular effects found in one subchronic study were an exudate from the eyes, and also from the nose, in rats **[56:515]**. Neurological effects seen after behavioral tests to animals subchronically exposed to high doses of DEET include shaking, prostration, and loss of balance **[56:519]**. Abnormal sperm morphology was seen in rats when exposed to DEET vapors **[63:36]**. Overall, DEET appears to induce few serious side effects when used properly, although more studies need to be conducted in this area.

2.5.3 Health effects from oral exposure

Much more research has been done in the area of oral exposure to DEET, and there is human data concerning oral DEET effects. One Russian case of DEET ingestion started with a comatose state accompanied by severely lowered blood pressure and heart

rate. The second day after ingestion, the patient died from a massive generalized bowel infarction **[58:1510]**. In animals, this hypotensive effect was also seen. Rabbits given acute lethal doses of DEET displayed signs of hyperemia of the ears, lacrimation, chromodacryorrhea, depression, prostration, epileptic tremors, and asphyxial convulsions. Respiratory failure preceded cardiovascular failure **[39:217; 2:100]**. Autopsy of the rabbits showed hyperemia of the respiratory tract.

Respiratory effects seen in non-fatal cases include hemorrhages of the lungs found post-mortem after a subchronic feeding study of rats **[2:110]**. Respiratory depression developing into toxic hepatitis preceded death in one human case study **[58:1510]**. Ingestion of DEET by a child revealed slowed respiration (among many other symptoms) **[58:1509]**.

Cardiovascular effects from DEET include significant decreases in serum calcium, and increases in serum trigliceride and cholesterol, seen in subchronic feeding studies with rabbits **[56:515]**. Human effects include a slowed pulse rate and low blood pressure, as well as hypotension and tachycardia **[39:220; 58:1509]**.

Gastrointestinal effects seen in humans include hyperemia of the gastrointestinal tract **[2:100]**, vomiting with a strong odor of DEET **[58:1509]**, and abdominal pain and diarrhea **[55:422]**.

Hematological effects were not found in any of the animal tests **[63:50]**, although the blood stream is the primary means of metabolism of DEET in the body. DEET remains in the blood for up to 3 days **[56:510]**.

Musculoskeletal effects seen in one human case study include lack of deep-tendon reflexes while in a comatose state **[58:1510]**. An animal study showed decreased muscle tone and foot splay **[57:64]**.

Hepatic effects seen in subchronic oral animal studies showed significant increase in relative liver weight in rats **[2:110; 57:64]**.

Renal effects seen in subchronic animal studies show increased relative kidney weight **[2:110]**. An animal study showed staining of the urine **[57:64]**.

Ocular effects seen in one human case study revealed a lack of corneal and blink reflexes while in a comatose state **[58:1510]**.

Other systemic effects include a progressive weight loss in animals fed sublethal doses of DEET **[63:50; 56:515; 2:108; 57:64,66]**.

Immunological effects have not been studied in humans or animals. Neurological effects are extensive in humans following accidental ingestion of DEET. Several case studies show pupils fixed and dilated, clonic spells, seizures, stiffening, CNS depression, prostration, hypertonic activity, and convulsions **[58:1509-1510]**. The types of symptoms and their severity are dependent on dose ingested and also the time lapse before medical attention is received. An animal study showed hypoactivity and ataxia in rats after oral intake of DEET **[57:64]**.

Developmental effects were studied in rats and rabbits, but no statistically significant signs of fetal toxicity were found **[57:64,66]**. There was an indication of some low birth weights in the offspring of dosed rats, however.

Reproductive effects seen in oral DEET administration to male rats were increased relative testes weight **[63:50]**, and significant testicular hypertrophy **[56:516; 2:110]**.

Genotoxic effects seen in animal studies include a reduction in implants of fetuses in pregnant females **[63:53, 55]**, although several studies show that the fetus does not bioaccumulate DEET and no adverse effects are seen in offspring **[56:517]**.

Carcinogenic effects of DEET ingestion have not been studied adequately in animals or humans **[63:50]**.

2.5.4 Health effects from dermal exposure

Death has been induced in animals from acute dermal application of DEET **[63:43; 2:99]** and death also has occurred in humans. The human cases are considered to be caused by severe hypersensitivity to DEET and its metabolites, and all of the cases were children **[56:520; 55:422]**. Children seem to be especially sensitive to DEET, as are adults who use repeated applications of DEET over long periods of time **[30:16]**. DEET can build up in fatty tissues and the skin.

Respiratory effects reported in humans include asthma in a hypersensitive woman **[56:520]**. No studies were located concerning cardiovascular, gastrointestinal, or musculoskeletal effects of dermally-applied DEET. Hematological effects seen in humans include angioedema **[56:520]**.

Hepatic effects seen in rabbits subchronically exposed to dermal doses of DEET include increased kidney weights and marked histopathological changes **[63:52]**. Renal

effects seen in occupational users of DEET include difficulty in stopping or starting the urinary stream **[56:520]**.

The skin is the primary means of introduction of DEET into the body. Almost 48% of applied DEET is absorbed into the skin within 6 hours **[55:422]**. Dermal effects reported in extremely sensitive individuals include contact urticaria and anaphylaxis, although the EPA has determined that DEET is not a skin sensitizer **[63:59; 6:611]**. Other dermal effects noted in humans include desquamation around the nose, necrosis, skin rash, blisters, and scarring after a chronic application of DEET **[63:59; 56:520; 2:103]**. Human subjects also complained of tingling sensations at application sites **[2:103]**. Additionally, acute animal studies reveal mild erythema, desquamation, and skin dryness **[2:102; 56:516]**. Users of DEET in the Vietnam War reported developing scarring bullous dermatitis in the inner elbow region **[56:521]**.

Ocular effects of dermally applied DEET include marked transitory irritation, edema, erythema, lacrimation, conjunctivitis, pus, and opacity in rabbit eyes **[2:104; 63:36,45]**. Workers who use DEET regularly have reported conjunctivitis and burning eyes **[63:60]**. Animal studies show irritation of the conjunctival epithelium and corneal opacification **[56:515]**.

Immunological effects are not associated with DEET. Despite the occasional skin reaction to users of DEET, it has been declared to not be a skin sensitizer by the USEPA **[63:59]**.

Neurological effects reported in children after application of DEET include encephalopathies, with convulsions and ataxia **[56:520]**. Three children of the six died from the application of DEET. Physicians felt the deaths and reactions were due to hypersensitivity to DEET and its metabolites **[56:520]**. Occupational users of DEET report occasional periods of confusion and an "abnormal sensation of decreased sweating" after using DEET **[56:520]**. Other reported symptoms include muscle cramps, insomnia, irritability, and depression **[56:520]**.

Developmental effects were not found in extensive animal tests **[63:53]**. No changes were found in fetal weight, fetal length, or placental weights, and no soft tissue or skeletal anomalies were observed, when compared to untreated rabbits **[56:516]**.

Reproductive effects suggested by preliminary subchronic testing include spermhead abnormalities **[63:53; 56:516]** and altered sperm motility in rats **[56:516]**. Genotoxic effects have not been studied in humans or animals from dermal exposure of the mother.

One study examined the carcinogenic effects of DEET in mice and rabbits. The results showed an absence of tumor formation in all of the test animals over the animals'' lifetime **[56:518]**, despite daily dermal applications. *In vitro* studies done for the US Army showed no mutagenicity **[56:518]**.

2.6 Pyridostigmine Bromide (PB)

Pyridostigmine bromide was given to the military troops as a pretreatment for nerve agent poisoning. Personnel were provided with pyridostigmine bromide at doses of 30 milligrams in blister packs of 21 tablets each **[46:9]**. The military members were instructed to start taking the drug on their commanding officer's orders, in anticipation of a chemical attack. The personnel were to take the drug once every 8 hours for 7 days, or until the order was given to discontinue the treatments.

Pyridostigmine is one of a class of drugs called anticholinesterase agents, which function by binding *reversibly* with acetylcholinesterase. This allows the temporary buildup of acetylcholine, which may allow continuous stimulation of cholinergic receptors throughout the central and peripheral nervous system, resulting in denying access of nerve agents to these receptors **[806:56; 3:222]**. This effect has been taken advantage of in protecting military personnel from nerve agents, which bind *irreversibly* with acetylcholinesterase. PB bonds spontaneously dissociate, returning to normal synaptic function **[16:250]**. Treatment of soldiers with PB was observed to cause short-term adverse effects, such as nausea, vomiting, headache, dizziness, and cramping **[46:10]**. Pyridostigmine is generally considered safe by physicians, and it has been used for decades to treat patients with myasthenia gravis in doses up to 6,000 mg/day for life. No long-term adverse effects have been noted in these patients **[46:10]**, although the side effects of PB are almost identical to the actual manifestation of myasthenia gravis, and therefore they may be indistinguishable **[54:1084]**. There is a possibility that exposure to pesticides

might enhance the acute effects of pyridostigmine. Since PB was administered orally in tablet form, the inhalation and dermal routes of exposure are not being considered.

2.6.1 Health effects from oral exposure

Death was observed in animal studies at doses greater than 2 mg/kg **[3:228]**. Respiratory effects reported by soldiers taking PB include a worsening of bronchitis and asthma in individuals already having those symptoms **[34:694]**, and dyspnea, coughing, and sputum in human tests **[16:253]**. Another human study reported complaints of shortness of breath **[5:212]** which the authors attribute to effects of acetylcholine inhibition on bronchial smooth muscle.

Cardiovascular effects seen in troops taking PB include a decrease in heart rate of about 5 beats per minute **[34:693]**. A study conducted to determine effects of PB and heat stress on the human body determined that PB slowed the heart rate at higher ambient temperatures **[36:221]**.

Gastrointestinal effects reported by Persian Gulf personnel after administration of PB include nausea, vomiting, flatus, diarrhea, and abdominal cramping **[34:693; 16:253; 46:10]**. These symptoms all appeared in two women of low weight (45 to 50 kg) **[34:694]**.

Hematological effects observed in some soldiers included nosebleeds, acute elevations in blood pressure, and hypertension **[34:694]**. One study revealed that PB

decreases skin blood flow at rest and during exercise, which affects heat exchange in the body **[36:222]**.

Musculoskeletal effects were seen in several animal studies. Rats that were administered PB showed a dose-dependent decrease in tetanic contracture of skeletal muscle, indicating muscle wasting **[3:224-227]**. Other animal studies showed significantly reduced endurance capacity in rats given PB versus control animals **[27:894; 42:1930]**.

No hepatic, ocular, immunological, developmental, reproductive, genotoxic, or carcinogenic effects have been investigated.

Renal effects reported by U.S. soldiers upon oral administration of PB include urinary urgency and frequency **[34:694]**. Pyridostigmine is rapidly excreted from the body; more than half of a given dose is excreted within one hour **[4:423]**. Dermal effects reported by Persian Gulf personnel include rashes **[34:694]**.

Other systemic effects seen in animal tests were a significant body weight loss experienced during the beginning of the test **[3:223]** which gradually reversed itself.

Neurological effects reported by Persian Gulf troops after PB administration include headaches, rhinorrhea, dizziness, and tingling of the extremities **[46:10; 16:252]**. Also documented were cases of vivid daydreams, vertigo, and profuse sweating **[34:693-694]**. Severe neurological symptoms appeared in two women of approximately 45 to 50 kg; it is speculated that the dose of 30 mg per tablet was too high for their body size, but no investigation has been done to date concerning dose and body size **[34:694]**. An interesting study on effects of PB on subjective measures of performance actually found

that personnel taking PB scored higher on a mathematics test than controls **[5:211]**; however, reaction times of the personnel administered PB was also higher than controls. Animal studies also show neurological symptoms, including pupil constriction **[10:314]**

2.7 Nerve Agents Soman (GD), Sarin (GB), and Tabun (GA)

Sarin, soman, and tabun are nerve agents that bind irreversibly to acetocholine receptors, and cause neurotoxicity. Sarin is properly known as isopropyl methylphosphonofluoridate, and tabun is known also as ethyl *N*-dimethyl phosphoroamidocyanidate **[35:527]**. These two substances were originally developed by the German government, and kept secret by them as potential chemical warfare agents. These nerve agents are related to organophosphate insecticides such as TEPP, malathion, and parathion, but are much more toxic to humans and mammals **[35:527]**. The main expected route of exposure to chemical nerve agents is through inhalation of the gas after a chemical weapon is detonated, although oral and dermal exposure to the aerosol also occurs. Symptoms of organophosphate poisoning are similar in all scenarios, although symptoms may appear in different orders.

2.7.1 Health effects from exposure

As these nerve agents are considered potent chemical warfare agents, death is their primary goal. Death is usually caused by asphyxia resulting from respiratory failure, with

contributing factors of bronchoconstriction and increased bronchial secretions, paralysis of respiratory muscles, and CNS depression and paralysis **[35:528]**.

Death occurred in one animal study involving primates; 14 of 36 animals died during the exposure period; 7 died within 1.5 hours of dosing **[7:173]**.

Respiratory effects from organophosphate compounds include tightness in the chest, wheezing due to bronchoconstriction, increased salivation, and lacrimation **[35:528]**. Respiratory failure caused by muscular weakness leads to dyspnea and cyanosis **[35:528]**. Death results from paralysis of the respiratory system **[35:528]**.

Cardiovascular effects from organophosphate compounds include bradycardia that can lead to heart block, and tachycardia, as well as elevated blood pressure and hyperglycemia **[35:528]**.

Gastrointestinal effects from organophosphate compounds include nausea, vomiting, abdominal cramps, diarrhea, tenesmus, and involuntary defecation **[35:528]**.

Hematological effects found in a primate study include perivascular cuffing, vasculitis, and hemorrhage **[7:173]**.

Musculoskeletal effects of organophosphate compounds include muscular weakness, easy fatigue, followed by twitching, muscle contractions and cramps **[35:528]**.

No evidence of hepatic, dermal, or immunological effects are reported for the organophosphates. Renal effects of some organophosphorous compounds include frequent and involuntary urination due to constriction of the smooth muscle of the bladder **[35:528]**. Ocular effects of organophosphorous compounds include miosis **[35:528]**.

Neurological effects of organophosphate compounds include tension, anxiety, restlessness, insomnia, headache, emotional instability, excessive dreaming and nightmares, neuroses, apathy, confusion, slurred speech, tremor, generalized weakness, ataxia, convulsions, CNS depression of the respiratory center, and coma, seen in people poisoned by organophosphates **[35:528]**. Effects of sarin seen in one animal study include muscular weakness of the limbs, muscle twitching, spinal cord lesions, and slight ataxis 10 days after exposure to sarin aerosol **[31:144]**. Also seen in this study was that neurotoxic esterase activity was significantly inhibited in the brain, spinal cord, and platelets. Neurotoxic effects reported in a primate study using soman include convulsions, muscle tremors, neural degeneration and necrosis, and acute encephalitis **[7:173-174]**. Another soman study in primates showed symptoms of muscle contractions, heavy salivation, constricted pupils, and prostration **[10:314]**. Smaller doses of soman were then given to these primates, which resulted in performance decrement.

No studies have been located concerning developmental, reproductive, genotoxic, or carcinogenic effects from exposure to organophosphate compounds.

2.8 Profile of Chronic Fatigue Syndrome (CFS)

The recently defined illness Chronic Fatigue Syndrome is characterized by unexplained, disabling fatigue (of at least 6 months' duration) that is significantly worsened with minimal physical activity **[28:953; 13:292; 53:7; 11:2049]**. Also

associated with CFS are a myriad of other, nonspecific symptoms, such as myalgias, arthralgias, muscle weakness, low-grade fever, painful lymph nodes, headache, pharyngitis, sleep disturbances, confusion, difficulty concentrating, memory problems, depression, and anxiety **[53:7; 11:2049; 37:S9; 28:953]**. CFS occurs more often in women than in men **[11:2049]**. Many investigators feel that CFS is closely related to Epstein-Barr syndrome, mononucleosis, postviral fatigue syndrome, and myalgic encephalomyelitis **[13:292]** due to all of these illnesses having similar symptomologies. CFS cases begin with an acute viral or flu-like infection episode **[13:292; 11:2049]**, characterized by a fever, sore throat, cough, myalgias, and fatigue **[37:S9]**. Other CFS patients have reported that their initial illness was gastrointestinal, and a small percentage claim to have had mononucleosis initially **[37:S9]**. However the illness begins, it becomes chronic in nature, with patients experiencing "good days" and "bad days". Some patients report having good health for several months at a time followed by a relapse, and others claim to never feel good **[37:S9]**.

A list of the most common symptoms of CFS and their frequency in patients is shown below.

Symptoms	Frequency (%)
fatigue	100
low-grade fever	60 - 95
myalgias	20 - 95
sleep disorder	15 - 90
impaired cognition	50 - 85
depression	70 - 85
headaches	35 - 85
pharyngitis	50 - 75
anxiety	50 - 70
muscle weakness	40 - 70
postexertional malaise	50 - 60
worsening of premenstrual symptoms	50 - 60
stiffness ("gelling")	50 - 60
visual blurring	50 - 60
nocturia	50 - 60
nausea	50 - 60
dizziness	30 - 50
arthralgias	40 - 50
tachycardia	40 -50
paresthesias	30 - 50
dry eyes	30 - 40
dry mouth	30 - 40
diarrhea	30 - 40
anorexia	30 - 40
cough	30 - 40
finger swelling	30 - 40
night sweats	30 - 40
painful lymph nodes	30 - 40
rash	30 - 40

Table 2 - 6: Frequency of Symptoms in Patients with CFS [37:S9]

The symptoms shown in Table 2-6 are not just occasionally experienced; they are present to some degree virtually all of the time in most CFS patients **[37:S9]**. Many of these symptoms are severe enough to impair normal functioning. And, most CFS patients report that they did not have a recurring problem with any of these symptoms before the

acute initial illness began **[37:S9]**. Several different authors have concluded that Chronic Fatigue Syndrome is indeed a distinct illness **[37:S11]**.

Figure 2-1 below is another way to visualize how CFS fits into the realm of illnesses associated with fatigue.

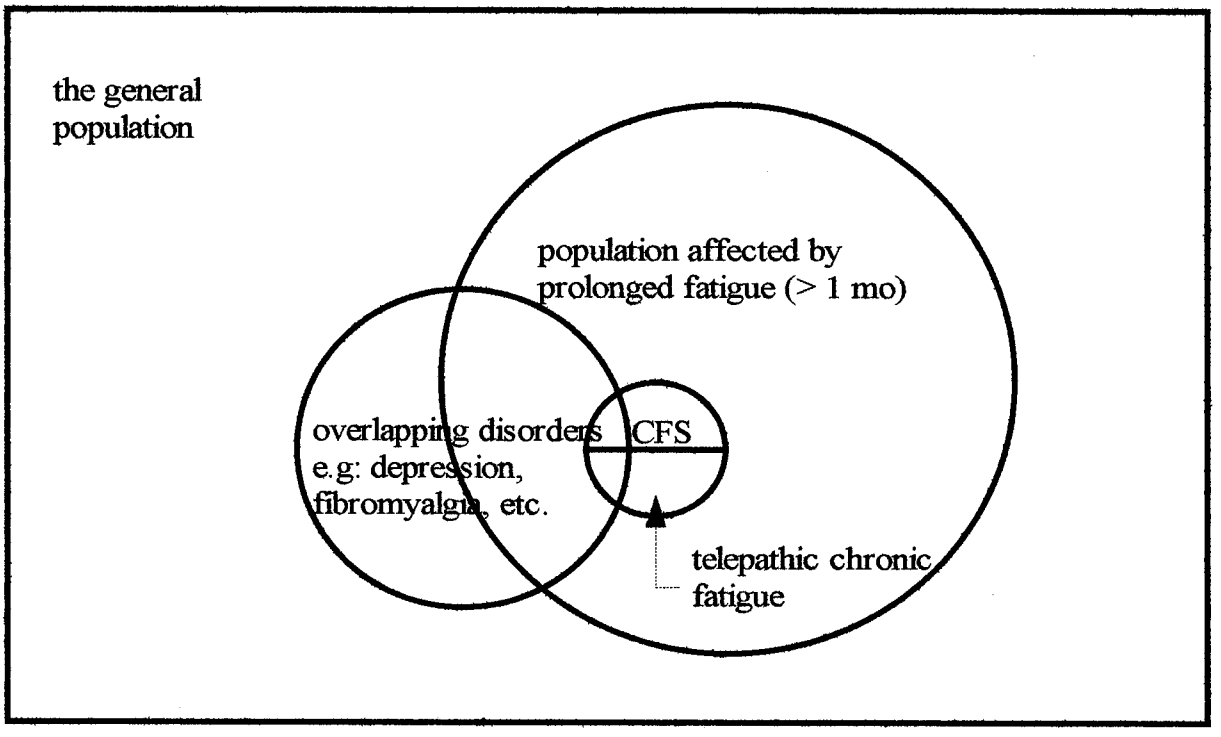

Figure 2 - 1: A conceptual framework of abnormally fatigued populations, including those with the chronic fatigue syndrome (CFS) and overlapping disorders [28:954]

2.9 Profile of Persian Gulf Veterans' Illnesses (PGVI)

As was previously discussed, PGVI is not considered a "single" disease; it is being classified as "multiple illnesses with overlapping symptoms and causes" **[48]**. Although PGVI is still under investigation, the DoD has recently released an initial report that

covers the findings of 10,020 veterans that have completed medical evaluations out of the 22,988 registered with the Comprehensive Clinical Evaluation Program (CCEP). A listing of reported symptoms and their frequency of occurrence in the CCEP participants is shown below.

Symptoms	Frequency (%)
fatigue	47
joint pain	47
headache	39
rash/dermatitis	29
memory loss	33
abdominal pain/gastrointestinal	16
back pain	2
diarrhea	18
dyspnea	16
sleep disturbance	32
chest complaints	1
cough	1
depression	23
muscle pain	22
sinus problems	1
bleeding gums	8
difficulty concentrating	27
hair loss	11
weight loss	7

Table 2-7: Symptom Frequency for CCEP Participants (N=10,020) [19:11]

Many of the symptoms reported by Persian Gulf soldiers participating in the CCEP study are similar to the symptoms of CFS in the previous section, although the CCEP report states that "patients meeting the Chronic Fatigue Syndrome case definition are relatively rare" **[19:25]**.

Another aspect of PGVI that is of great concern to veterans is the indication that PGVI is being passed on to spouses and children born after the veterans' return to the

United States following the Gulf War. Of the 10,020 people examined to date by the CCEP, 9,803 are military service members, 136 are spouses of these members, and 81 are children. Of the 136 spouses that have been examined as of this CCEP report, only 20 are classified as "healthy", and of the remaining 116, most of their symptoms parallel that of the symptom frequencies reported by the military members (Table 2-8) **[19:12]**. Of the 81 children, only 17 are classified as "healthy"; the remaining 64 have a wide range of congenital and psychological disorders, and even cancer has been detected **[19:15]**.

The CCEP report's conclusions parallel that of the National Institutes of Health and the Defense Science Board **[46:16; 20:2]**, but research into PGVI is continuing in the hopes of finding a common causal agent and formulating a case definition for PGVI. The Defense Science Board also recommended that the DoD research into PGVI be coordinated with ongoing research into CFS, due to their similar symptoms **[20:2]**.

2.10 Analysis and Summary

From this literature review, it is clear that Persian Gulf soldiers were exposed to a number of hazardous substances with serious health effects. Some routes of exposure to humans have not been adequately studied to determine a substance's potential health hazards. Also, some areas of health effects have not been addressed in studies previously performed. These data gaps need to be addressed in order to adequately determine human health effects for these toxic substances. Additionally, Persian Gulf Veterans' Illnesses (PGVI) needs to be studied further in order to formulate a case definition and determine

the causes of PGVI, if there is one (or more). Since PGVI was "discovered" only approximately 5 years ago, it remains to be seen if there are long-term health effects, such as cancer.

The data analysis and conclusions can be found in Chapters III, IV, and V.

III. Methodology

3.1 Overview

The focus of this thesis is to find a statistically significant link between demonstrated symptoms of Persian Gulf veterans and symptoms caused by certain toxic substances used in the Persian Gulf AOR. This research into the health effects of occupational substances has shown that the information is not available in many cases, indicating a need for research in these areas. Other areas of health effects have been adequately researched and much data is available for analysis, but that data is not from the same population; for example, one study has human health data and another study has animal data. Since this data cannot be combined or even easily compared, a health effects matrix was then constructed using subjective classifications. These classifications are detailed in the next section.

3.2 Survey of Air Force Civil Engineers

An informal survey was conducted of Air Force site engineers that were stationed in various locations throughout the Persian Gulf AOR. This survey was conducted in order to obtain preliminary information about dust suppression operations, use of insecticides, and to determine if JP-4 or JP-8 were in use during Operation Desert Shield/Storm. The complete survey and replies are in Appendix B.

3.3 Health Effects Matrix

The categories of health effects were divided into seven subjective categories, as seen in Figure 3-1.

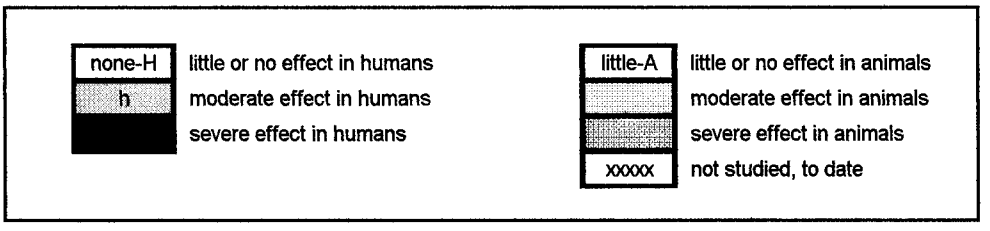

Figure 3-1: Classifications of Health Effects for Matrix

The subjective category "little or no effect" translates to just that; the substance in question does not have any effects, or if it does, the effect is reversible within 24 hours. "Moderate effect" means that there is a more significant health effect that is reversible, but the effect persists for more than one day. "Severe effect" means that the health effect is irreversible, such as death or permanent injury to organs. The category "not studied to date" is interpreted to mean that as far as my research efforts have taken me, I found no information concerning that particular health effect as of the date of this thesis.

Also of note in the health effects matrix is that when at all possible, known human health effects override animal health effects as far as being presented in the matrix. This means that any human effect seen or not seen due to a substance is more informative than an effect also seen in animals. This is because the primary concern in this study is human health effects, and where there is human data, it will be utilized. Animal data may corroborate the human data, but human data is preferred. For example, if a substance

causes no health effects in humans, but has moderate health effects in rats, the matrix will show only the human data. However, both types of health effects will be available to study in Chapter II.

The health effects matrix and its analysis can be found in Chapter IV.

3.4 Analysis of Data

The purpose of the analysis of data in this thesis is to find a statistically significant link between the symptoms reported by Persian Gulf veterans (Table 2-7) and symptoms that are caused by exposure to a toxic substance (substances encountered by Persian Gulf personnel during the Gulf War).

Since the data to be examined are frequency counts from several different populations, and the comparisons to be made are in many different categories, contingency table analysis is the method of data analysis chosen.

3.5 Theories Behind Contingency Table Analysis

A contingency table is an array of natural numbers in matrix form where those numbers represent frequencies **[15:143]**.

Categorical data consist of 2 types of measurement:

1) *nominal measurements*: simple counts, labels, and names
2) *ordinal measurements*: counts, labels, and names that exhibit a qualitative relationship or a rank order **[51:1]**

In cross-classifying these types of data, three types of contingency tables may be created:

1) fully nominal tables, using 2 or more nominal variables
2) mixed tables, created by cross-classifying nominal and ordinal variables
3) fully ordinal tables, using 2 or more ordinal variables **[51:1]**

Traditional techniques available to analyze contingency tables fall into 2 categories:

1) test of independence
2) test of association (or interaction) and agreement **[51:2]**

The contingency table arranges the data into discrete divisions, or ranges, upon which statistical inferences can then be drawn. Due to the subjective nature of the inferences, the results are usually reported in terms of probability statements, with a corresponding degree of confidence. The reader can then make his or her own subjective interpretation of the results.

3.5.1 Hypothesis testing

Hypothesis testing is the process of statistically inferring from random sample data whether or not to accept a certain statement about the populations from which the data sample was obtained. The hypothesis to be tested (the null hypothesis) is evaluated on the basis of the evidence contained in the sample data. The null hypothesis is either accepted or rejected by the test applied to the sample data. Rejection of the null hypothesis implies

to the reader that the sample evidence shows enough doubt about the null hypothesis to say, with some degree of confidence, that the hypothesis is false **[15:76]**.

The degree of confidence is usually translated into a quantity called "level of significance". This level is the maximum probability of rejecting a true null hypothesis.

3.5.2 The Chi-Square Approximation

In applications of contingency table patterns using the chi-square approximation, the asymptotic distribution of the test statistic (T) is the chi-square distribution with (r-1)*(c-1) degrees of freedom, where r is the number of rows, and c is the number of columns of the sample. This distribution is well tabled, and the test statistic is readily computed.

The chi-square analysis not only uses the observed frequencies in each cell, there is also associated with each cell an expected frequency. This expected frequency (E_{ij}) is computed by multiplying the ith row total by the jth column total, and dividing this product by the total number of observations (N) **[21:585]**.

The type of contingency table analysis that will be utilized in this report is a test of association between two different samples (r = 2) using ordinal data, where the two populations are the diseases or substances of concern (example: PGVI versus DEET) and the categories are the symptoms found in humans. The symptoms will have a frequency count associated with one population.

3.6 Data

There are **r** populations in all, and one random sample is drawn from each population. Let n_i represent the number of observations in the *i*th sample (from the *i*th population) for $1 \leq i \leq r$. Each observation in the sample maybe classified into one of **c** categories. Let O_{ij} be the number of observations from the *i*th sample that fall into category *j*, so that:

$$n_{ij} = O_{i1} + O_{i2} + O_{i3}....+ O_{ic} \text{ for all } i$$

The data are then arranged into an r x c contingency table, where the row totals are n_i and the sum of all the row totals (being the total number of observations from all samples) is *N*.

3.7 Assumptions

The following assumptions must be made in order for contingency table analysis to be utilized:

1) each sample is a random sample.

2) the outcomes of the various samples are all mutually independent (particularly among samples, because independence within samples is part of assumption 1)

3) each observation may be categorized into exactly *one* of the *c* categories.

4) the row totals are given, not random.

3.8 Hypotheses

The focus question to be answered in each case is one of heterogeneity: are the symptoms reported in each cell able to be classified into one of the two populations, or are the two populations sufficiently homogeneous so that no difference is detected? In other words, is the distribution of symptoms equal in each population.

Let the probability of a randomly selected value from the *i*th population being classified in the *j*th class be denoted by p_{ij}, for $i = 1...r$ and $j = 1...c$.

Null hypothesis: all of the probabilities in the same category are equal to each other, or, stated mathematically:

$$H_o: \ p_{1j} = p_{2j} \ \text{ for all of } j \ (r = 2)$$

Alternate hypothesis: at least 2 of the probabilities are not equal to each other, also stated as:

$$H_a: \ p_{1j} \neq p_{2j} \ \text{ for some } j$$

3.9 Test Statistic

The test statistic is T, which should have an approximately X^2 distribution with (r-1)*(c-1) degrees of freedom. T will be computed using the following formula:

$$T = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{\left(n_{ij} - e_{ij}\right)^2}{e_{ij}}$$

Figure 3-2: Test Statistic for Contingency Table Analysis [15:155]

where: **T** is the test statistic for the chi-square
$\mathbf{n_{ij}}$ are observed cell counts (or frequencies)
$\mathbf{e_{ij}}$ are estimated expected cell counts
r is the number of samples (2 in all cases)
c is the number of categories of symptoms

3.10 Decision Rule

The critical region of approximate size α corresponds to values of T larger than $X^2_{1-\alpha}$, the **1-**α quantile of a chi-square random variable with (r-1)(c-1) degrees of freedom. Reject H_o if T exceeds $X^2_{1-\alpha}$, otherwise accept H_o **[15:156]**. The approximate value for α is a good approximation to the true value of α if the expected number of cell observations are greater than 5 **[21:586]**. The number 5 is a conservative value; another text says that values as low as 1.0 are still acceptable **[15:156]**. In this data analysis, an α of 0.05 will be used.

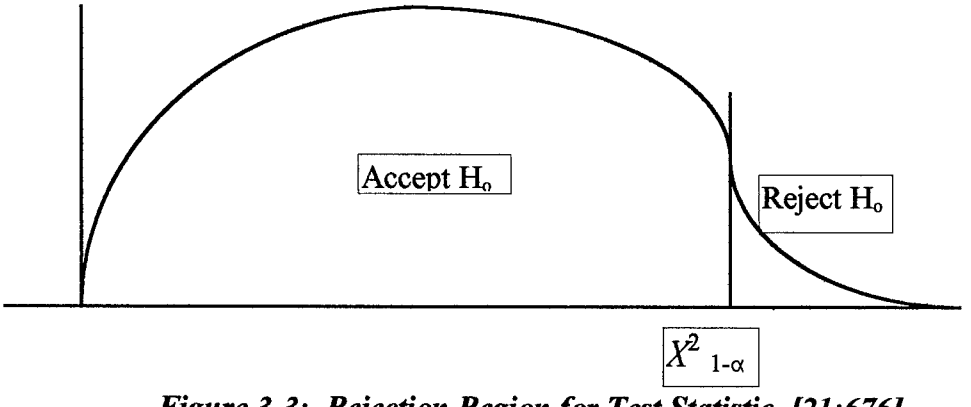

Figure 3-3: Rejection Region for Test Statistic [21:676]

3.11 Limitations

An obvious limitation to this type of data analysis is the fact that I must rely on the data quality of a wide variety of studies. In all cases, the data has been peer-reviewed, so this should not be a major limitation. Another related assumption is that each data set is a random sample of the population represented by the sample.

Another limitation is unavailability of certain data, due to classification of the reports, and the needed data not being provided in the reports. This required some manipulation of the data I do have to fit every analysis to be done. For example, several categories of reported symptoms may all be added together to mean "sleep disturbances".

The results of the contingency table analyses can be found in Chapter IV.

IV. Findings and Analysis

4.1 Results from Health Effects Matrix

Table 4-1 shows health effects by route of exposure (oral, inhalation, dermal) across a wide range of body systems (respiratory, cardiovascular, etc.). The substances shown in the table were selected because of their prevalence of use in the Persian Gulf AOR, except for soman, sarin, and tabun. These three nerve agents were included in this matrix to examine any possible relationship with PGVI, and perhaps to rule out the possibility that they are a contributing factor in PGVI.

As is readily apparent upon examining the matrix, there are a number of substances that have not been thoroughly tested in all exposure scenarios. One example of this is JP-4 aircraft fuel. Almost no study has been done in the area of oral exposure, and very little has been studied in the dermal exposure scenario. Additionally, very little human study has been done with regard to health effects from JP-4 exposure.

Across body systems, the substances that appear to have the most serious health effects on the human body overall are toluene, kerosene, DEET, soman, sarin, and tabun. Pyridostigmine bromide (PB) has a number of potential moderate health effects; however, most of these harmful side effects are associated with overdose, so this should not be a concern for veterans **[54:1084]**.

Compared to Persian Gulf Veterans' Illnesses, the substances that appear to have similarly severe symptoms are DEET, soman, sarin, tabun, PB, kerosene, toluene, and, to

Table 4-1: Matrix of Health Effects by Substance

substance, intermediate to chronic exposure to:

symptoms		JP-4 aircraft fuel	diesel 2		kerosene		toluene	CFS 21	PGVI 21
	death		xxxxxxxxxxxxx					none	none
systemic:	respiratory	xxxxxxxxxxxxx	xxxxxxxxxxxxx					h	
	cardiovascular	xxxxxxxxxxxxx	xxxxxxxxxxxxx		h			xxxxxxxx	h
	gastrointestinal	xxxxxxxxxxxxx	xxxxxxxxxxxxx		h		none-H	xxxxxxxx	h
oral	hematological	xxxxxxxxxxxxx	xxxxxxxxxxxxx		h		little-A	xxxxxxxx	none
dosing:	musculoskeletal	xxxxxxxxxxxxx	xxxxxxxxxxxxx		xxxxxxxxxxxxxxx		none-H	h	h
	hepatic	xxxxxxxxxxxxx	xxxxxxxxxxxxx				h	xxxxxxxx	none
	renal	xxxxxxxxxxxxx	xxxxxxxxxxxxx		little in humans			xxxxxxxx	none
	dermal/ocular	xxxxxxxxxxxxx	xxxxxxxxxxxxx				xxxxxxxx	h 7	
	other	xxxxxxxxxxxxx	xxxxxxxxxxxxx		h		none-H		h 9
	immunological	xxxxxxxxxxxxx	xxxxxxxxxxxxx		xxxxxxxxxxxxxxx			h	h
	neurological	xxxxxxxxxxxxx	xxxxxxxxxxxxx				little-H	xxxxxxxx	
	developmental	xxxxxxxxxxxxx	xxxxxxxxxxxxx		xxxxxxxxxxxxxxx			xxxxxxxx	
	reproductive	xxxxxxxxxxxxx			xxxxxxxxxxxxxxx		none-A	xxxxxxxx	
	genotoxic	none in animals	xxxxxxxxxxxxx				xxxxxxxx	xxxxxxxx	none
	carcinogenic	xxxxxxxxxxxxx	xxxxxxxxxxxxx		xxxxxxxxxxxxxxx		xxxxxxxx	xxxxxxxx	24
		vapors	***smoke***	***vapors***	***smoke***	***vapors***	***vapors***	***CFS***	***PGVI***
	death	none in animals	xxxxxx	1	none-A 3	none-H		none	none
systemic:	respiratory	h			none-H	3	h	h	
	cardiovascular	xxxxxxxxxxxxx	xxxxxx	none-A		h		xxxxxxxx	h
inhalation	gastrointestinal	xxxxxxxxxxxxx	xxxxxx	little - H	xxxxxx	h	little-A	xxxxxxxx	h
dosing:	hematological		xxxxxx	h	xxxxxx	none-A	h	xxxxxxxx	none
	musculoskeletal	xxxxxxxxxxxxx	xxxxxx	xxxxxx	xxxxxx	none-A	none-A	h	h
	hepatic		xxxxxx	none-A	xxxxxx	h	h	xxxxxxxx	none
	renal		xxxxxx		xxxxxx		little-H	xxxxxxxx	none
	dermal/ocular	xxxxxxxxxxxxx	xxxxxx	h 3	xxxxxx	none-H (3)	h 3	h 7	
	other	9	xxxxxx	h 5	xxxxxx	none-A	9		h 9
	immunological	xxxxxxxxxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxxxx	h	h	h
	neurological		xxxxxx	h	xxxxxx			xxxxxxxx	
	developmental	xxxxxxxxxxxxx	xxxxxx	xxxxxx	xxxxxx			xxxxxxxx	
	reproductive	xxxxxxxxxxxxx	xxxxxx	xxxxxx	xxxxxx		11	xxxxxxxx	
	genotoxic	xxxxxxxxxxxxx	xxxxxx	xxxxxx	xxxxxx		h	xxxxxxxx	none
	carcinogenic	14	xxxxxx	none -H	xxxxxx	none- H	none-H	xxxxxxxx	24
		JP-4	***diesel 2***		***kerosene***		***toluene***	***CFS***	***PGVI***
	death		none in animals		none in animals		xxxxxxxx	none	none
systemic:	respiratory	xxxxxxxxxxxxx	h		none in animals			h	
	cardiovascular	xxxxxxxxxxxxx	none in animals		xxxxxxxxxxxxxxxx		12	xxxxxxxx	h
	gastrointestinal	xxxxxxxxxxxxx	little in humans		xxxxxxxxxxxxxxxx			xxxxxxxx	h
dermal	hematological	xxxxxxxxxxxxx	h				none-A	xxxxxxxx	none
exposure:	musculoskeletal	xxxxxxxxxxxxx	none in animals		xxxxxxxxxxxxxxxx		xxxxxxxx	h	h
	hepatic	none in animals (3)	xxxxxxxxxxxxx		none in animals (3)		none-A	xxxxxxxx	none
	renal	none in animals (3)			none in animals (3)		none-A	xxxxxxxx	none
	dermal/ocular		h 8		h 3		h 13	h 7	
	other	xxxxxxxxxxxxx	h 5		little in animals		xxxxxxxx		h 9
	immunological						xxxxxxxx	h	h
	neurological	xxxxxxxxxxxxx	h				xxxxxxxx	xxxxxxxx	
	developmental	xxxxxxxxxxxxx	xxxxxxxxxxxx		xxxxxxxxxxxxxxxx		xxxxxxxx	xxxxxxxx	
	reproductive	xxxxxxxxxxxxx	none in animals		xxxxxxxxxxxxxxxx		xxxxxxxx	xxxxxxxx	
	genotoxic	xxxxxxxxxxxxx	xxxxxxxxxxxxx		xxxxxxxxxxxxxxxx		none-A	xxxxxxxx	none
	carcinogenic		10		xxxxxxxxxxxxxxxx		xxxxxxxx	xxxxxxxx	24

Table 4-1: Matrix of Health Effects by Substance (continued)

substance, intermediate to chronic exposure to:

	symptoms	DEET (22)	pyridostigmine bromide	soman (GD)	sarin (GB)	tabun (GA)	CFS 21	PGVI 21
	death		none in humans				none	none
systemic	respiratory		**h**				**h**	
	cardiovascular		**h**				xxxxxxxx	**h**
	gastrointestinal		**h**				xxxxxxxx	**h**
	hematological	none-A	**h**		xxxxxxxx	xxxxxxxx	xxxxxxxx	none
oral	musculoskeletal		**h 17**				**h**	**h**
dosing:	hepatic		xxxxxxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx	none
	renal		**h**	xxxxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx	none
	dermal/ocular		**h**				**h 7**	
	other	**9**	**18**	na (15)	na (15)	na (15)		**h 9**
	immunological	xxxxxxxx	xxxxxxxxxxx	na	na	na	**h**	**h**
	neurological		**h 16**		na	na	xxxxxxxx	
	developmental		xxxxxxxxxxx	na	na	na	xxxxxxxx	
	reproductive		xxxxxxxxxxx	na	na	na	xxxxxxxx	
	genotoxic		xxxxxxxxxxx	na	na	na	xxxxxxxx	none
	carcinogenic	**25**	xxxxxxxxxxx	na	na	na	xxxxxxxx	**24**
	death	none-A	**23**				none	none
systemic	respiratory		I				**h**	
	cardiovascular		I				xxxxxxx	**h**
inhalation	gastrointestinal		I				xxxxxxx	**h**
dosing:	hematological		I		xxxxxxx	xxxxxxx	xxxxxxx	none
	musculoskeletal	xxxxxxx	I				**h**	**h**
	hepatic	xxxxxxx	I	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	none
	renal	xxxxxxx	I	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	none
	dermal/ocular		I				**h 7**	
	other	none-A	I	na (15)	na (15)	na (15)		**h 9**
	immunological	xxxxxxx	I	na	na	na	**h**	**h**
	neurological		I		na	na	xxxxxxx	
	developmental		I	na	na	na	xxxxxxx	
	reproductive	xxxxxxx	I	na	na	na	xxxxxxx	
	genotoxic		I	na	na	na	xxxxxxx	none
	carcinogenic	xxxxxxx	v	na	na	na	xxxxxxx	**24**
	death	20	**23**				none	none
systemic	respiratory	**h**	I				**h**	
	cardiovascular	none-H	I				xxxxxxx	**h**
	gastrointestinal	none-H	I				xxxxxxx	**h**
	hematological	**h**	I		xxxxxxx	xxxxxxx	xxxxxxx	none
dermal	musculoskeletal	none-H	I				**h**	**h**
exposure:	hepatic		I	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	none
	renal	little-H	I	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	none
	dermal/ocular	**h**	I				**h 7**	
	other	none-H	I	na (15)	na (15)	na (15)		**h 9**
	immunological	**h**	I	na	na	na	**h**	**h**
	neurological	20	I		na	na	xxxxxxx	
	developmental	none-A	I	na	na	na	xxxxxxx	
	reproductive		I	na	na	na	xxxxxxx	
	genotoxic	xxxxxxxx	I	na	na	na	xxxxxxx	none
	carcinogenic	none-A	v	na	na	na	xxxxxxx	**24**

Matrix key: intermediate to chronic effects

none-H	little or no effect in humans	little-A	little or no effect in animals
h	moderate effect in humans		moderate effect in animals
	severe effect in humans		severe effect in animals
		xxxxx	not studied, to date

notes:
- little/no effect is easily reversible in one day
- moderate effect is reversible
- severe effect is irreversible
- An effect studied in humans overrides that of animals
- Numbers inside boxes refer to notes found below

notes for Table 4-1:

1 C_t = 12,000 mg hour/m^3 intermediate dose [59]
2 data was for a variety of jet fuels [59]
3 acute, not chronic effects [59]
4 acute effects for JP-5 [59]
5 systemic edema [59:19]
6 intermediate JP-5 exposure [59]
7 fever, pulmonary complications [59]
8 ocular effects: subconjunctival hemorrhages [59]
9 decrease in body weight [59, 58, 56]
10 unspecified skin tumors; could be a trait of the particular species of mouse [59]
11 spontaneous abortions [61]
12 frequently fatal cardiac arrhythmia [61]
13 dry skin, eye irritation [61]
14 renal carcinoma in animals [60]
15 In cases of nerve agents, death from acute neurotoxicological and respiratory distress is the usual endpoint, so long term effects such as cancer and reproductive effects are not able to be studied [23]
16 used in the prescribed dosage of one 30 mg tablet every 8 hours [23, 34]
17 experienced primarily in women weighing 45 - 50 kg [34:694]
18 increased body core temperature and reduction in physical endurance [27, 42]
19 In case of oral DEET, overdose of >95% DEET solution [43, 19, 57, 58, 56]
20 especially in children [6:611]
21 symptoms of Chronic Fatigue Syndrome (CFS) and Gulf War Syndrome (GWS) are considered to be the same by all exposure routes (effect, not cause)
22 topically applied 75% solution [43, 19, 57, 58, 56]
23 not considered a route of exposure
24 carcinoma has been found in GWS veterans' children, but it is too soon to tell in GWS veterans themselves [19]
25 several studies done; results were inconclusive

a lesser degree, JP-4 and diesel 2. The primary route of exposure that I am concerned about with respect to these substances is the inhalation route (except for PB, which is orally administered). Although there are serious side effects associated with both the dermal and oral routes of exposure, the inhalation route is the primary route that most of these substances would have been introduced into the bodies of Gulf War personnel. Reasons for this are that most reported cases of oral ingestion are by children, and the military population are all adults. Dermal exposure is not my main concern either, due to the fact that protective clothing is generally worn by military personnel handling these substances or any substance that poses a health risk, even considering the hot climate of the AOR. If a military person did come into dermal contact with a hazardous substance, he would be trained sufficiently to know that he must thoroughly clean the exposure site. Once again, I must make the assumption that personnel handling hazardous substances are trained in hazardous material handling.

Therefore, for the contingency table analysis of these substances , I will concentrate on the inhalation route of exposure as my primary route of concern.

4.2 Comparison of CFS and PGVI Using Contingency Table Analysis

Chronic Fatigue Syndrome (CFS) and Persian Gulf Veterans' Illnesses (PGVI) have eight common symptoms, irrespective of exposure route. Table 4-2 shows the data used for the contingency table analysis. The CFS data comes from a medical report on symptoms and signs of CFS; the symptom prevalence of a sample of 30 people diagnosed

with CFS are the data I used to compare with the PGVI data **[11:2051]**. The PGVI data comes from the CCEP report on the initial examinations of 10,020 veterans and family members who have registered with the CCEP **[19:11]**. This data will form the basis for most of the following contingency table analyses also, as it is the most comprehensive and certainly the largest sample of people with PGVI available to date.

		frequency of symptoms							
disease	fatigue	headaches	arthralgias	myalgias	sleep disturbances	skin irritation	memory loss	depression	*N=*
CFS	30	25	21	23	16	8	19	15	**157**
PGVI	4709	3908	4709	4709	3206	2906	3307	2305	**29759**
ni	**4739**	**3933**	**4730**	**4732**	**3222**	**2914**	**3326**	**2320**	**29,916**

Table 4-2: Frequency of Symptoms for CFS vs. PGVI [11:2051; 19:11]

4.2.1 Analysis

There are **r = 2** populations (CFS, PGVI) and **c = 8** categories of symptoms. Therefore, there are (r-1)(c-1) = 7 degrees of freedom.

The rejection region of interest is $X^2_{1-\alpha} = 14.067$ at $\alpha = 0.05$ and df =7 **[21:676]**. If the test statistic T is larger than 14.067, we will reject the null hypothesis. Otherwise, the null hypothesis will be accepted.

H_o: the probabilities of symptoms in each of the two diseases are equal

H_a: at least two of the probabilities of symptoms are not equal to each other

4.2.2 Results and Discussion

The results of the chi-square analysis are shown below in Table 4-3. The original data analysis was run in the Statistix 4.1 program; the original printouts of that program can be found in Appendix C.

The T of 7.06 is less than the $X^2_{1-\alpha}$ of 14.067, so we accept H_o. This means that at our chosen significance level of 0.05, the probability of symptom occurrence in a particular health category for CFS is equal to the probability of that symptom occurring in PGVI. The expected values of cell observations are well above the required 5.0, so this is a good approximation of the chi-square distribution.

Inferences that can be drawn from these results are interesting. The symptom frequencies in all eight categories reported by PGVI patients are homogeneous with the symptom frequencies reported by patients diagnosed with Chronic Fatigue Syndrome. This can be interpreted to mean that a group of people manifesting these symptoms in the same frequencies could be diagnosed with either disease. Interestingly, the CCEP report shows that no PGVI veteran so far examined has been diagnosed with CFS. In fact, CFS is briefly discussed and then dismissed as a possible diagnosis **[19:19]**.

Case		PGVI	CFS	
1	observed	4709.00	30.00	4,739
fatigue	expected	4714.13	24.87	
	cell chi-sq	0.01	1.06	
2	observed	3908.00	25.00	3,933
headaches	expected	3912.36	20.64	
	cell chi-sq	0.00	0.92	
3	observed	4709.00	21.00	4,730
arthralgias	expected	4705.18	24.82	
	cell chi-sq	0.00	0.59	
4	observed	4709.00	23.00	4,732
myalgias	expected	4707.17	24.83	
	cell chi-sq	0.00	0.14	
5	observed	3206.00	16.00	3,222
sleep dist.	expected	3205.09	16.91	
	cell chi-sq	0.00	0.05	
6	observed	2906.00	8.00	2,914
skin irritation	expected	2898.71	15.29	
	cell chi-sq	0.02	3.48	
7	observed	3307.00	19.00	3,326
memory loss	expected	3308.55	17.45	
	cell chi-sq	0.00	0.14	
8	observed	2305.00	15.00	2,320
depression	expected	2307.82	12.18	
	cell chi-sq	0.00	0.66	
				N
		29,759	157	**29,916**
Overall chi-square:		**7.06** < 14.067		accept Ho
P-value:		**0.4228** > 0.05		
Degrees of freedom:		**7**		

Table 4-3: Results of Contingency Table Analysis of PGVI versus CFS

A graphic representation of the symptom frequencies of the two diseases are shown below in Figure 4-1. The percentage of the symptom frequencies are shown instead of the actual counts, due to the fact that the PGVI sampled population is so much larger than the CFS sample.

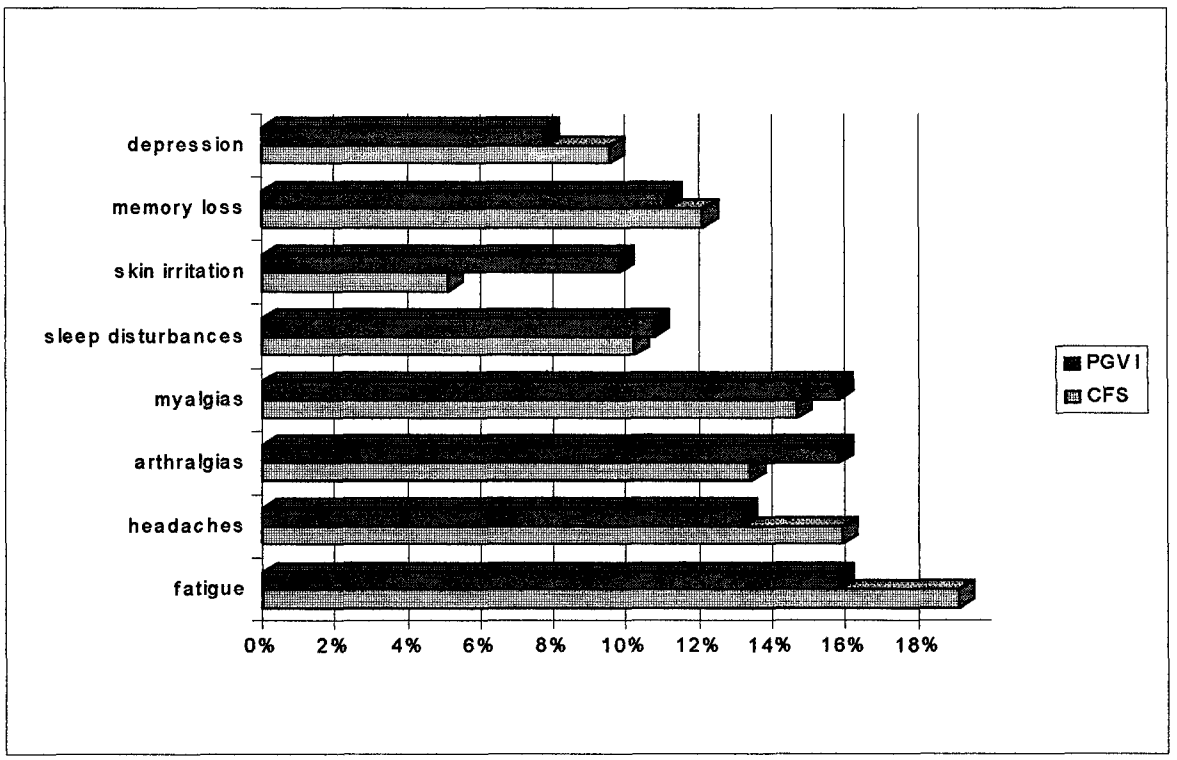

Figure 4-1: Frequency of Symptom Occurrence for CFS vs. PGVI [11:2051; 19:11]

As one can see when presented with the data in a visual format, each category of symptom frequency is similar for both diseases, although you must remember that you are looking at the frequency of symptoms reported *overall* versus symptoms reported *per individual*. But clearly, the frequency counts of symptoms are similar in both diseases.

One of the unusual aspects of CFS is that over 70% of the people diagnosed with CFS are white, middle-class women **[37:S9]**. In the CCEP database of 10,020 people (as of the date of the report), an estimated one-third of the reported symptoms are not associated with a definitive diagnosis after a medical evaluation **[19:19]**. Perhaps there is a reluctance on the part of military physicians to diagnose PGVI patients with a non-specific disorder such as Chronic Fatigue Syndrome or a similar disease such as fibromyalgia. Interestingly, some Gulf War veterans were diagnosed with Post-Traumatic Stress Disorder, so this may not be the case.

4.3 Comparison of PGVI and Solvents Using Contingency Table Analysis

The sample of solvent-exposed individuals is from a study of occupational workers exposed to a mixture of common solvents **[49:662]**. The study showed that the individuals reported several symptoms similar to symptoms reported by the PGVI participants **[19:11]**. Table 4-4 shows the frequency counts collected for the contingency table analysis:

	frequency of symptoms							
	fatigue	*depression*	*poor concentration*	*sleep disturbances*	*headaches*	*back pain*	*memory loss*	**N=**
solvents	21	5	3	40	2	17	11	99
PGVI	4709	2305	2705	3206	3908	200	3307	20340
	4730	**2310**	**2708**	**3246**	**3910**	**217**	**3318**	**20,439**

Table 4-4: Frequency of Symptoms of PGVI versus Solvents [19:11; 49:662]

4.3.1 Analysis

There are r = 2 populations (PGVI, solvent-exposed workers) and c = 7 categories of symptoms; therefore, there are (r-1)(c-1) = 6 degrees of freedom.

The rejection region of interest is $X^2_{1-\alpha} = 12.592$ at $\alpha = 0.05$ and df = 6 **[21:676]**. If the test statistic T is larger than 12.592, we will reject the null hypothesis. Otherwise, the null hypothesis will be accepted.

H_o: the probabilities of symptoms in PGVI and in solvent exposure are equal

H_a: at least two of the probabilities of symptoms are not equal to each other

4.3.2 Results and Discussion

The results of the chi-square analysis are shown below in Table 4-4. The original data analysis was run in the Statistix 4.1 program; the original printouts of that program can be found in Appendix C.

The original data run included eight categories of symptoms. One category was deleted from the data analysis because the expected value in that cell was less than one, and as discussed in Chapter III, a value of less than one indicates a poor approximation to the chi-square distribution. Therefore, I ran the data a second time after omitting the category that did not fit the distribution.

The second run resulted in better chi-square approximation, but the overall test statistic value of 309.13 is still much larger than X^2 of 12.592, so we reject the null

Case		PGVI	Solvents	
1	observed	4709.00	21.00	4,730
fatigue	expected	4707.09	22.91	
	cell chi-sq	0.00	0.16	
2	observed	2305.00	5.00	2,310
depression	expected	2298.81	11.19	
	cell chi-sq	0.02	3.42	
3	observed	2705.00	3.00	2,708
poor	expected	2694.88	13.12	
concentration	cell chi-sq	0.04	7.80	
4	observed	3206.00	40.00	3,246
sleep	expected	3230.28	15.72	
disturbances	cell chi-sq	0.18	37.49	
5	observed	3908.00	2.00	3,910
headaches	expected	3891.06	18.94	
	cell chi-sq	0.07	15.15	
6	observed	200.00	17.00	217
back	expected	215.95	1.05	
pain	cell chi-sq	1.18	242.01	
7	observed	3307.00	11.00	3,318
memory	expected	3301.93	16.07	
loss	cell chi-sq	0.01	1.60	
				N
		20,340	99	**20,439**
Overall chi-square:		**309.13** > 12.592, reject Ho		
P-value:		**0.0000** < 0.05		
Degrees of freedom:		**6**		

Table 4-5: Results of Contingency Table Analysis of PGVI vs. Solvents

hypothesis at significance level 0.05. When looking at the cells and examining the individual cell's chi-squares and comparing that value to the overall chi-square test statistic, we can see that "back pain", "headaches", and "sleep disturbances" are the symptoms in particular that do not appear to have an association to the symptom frequencies reported for PGVI, since those 3 categories' chi-squares all cause us to reject the null hypothesis.

The results are interpreted to mean that the symptom frequencies seen by occupational exposure to solvents have no proportional relationship with the symptom frequencies shown by PGVI patients, particularly with respect to back pain, headaches, and sleep disturbances. Solvents do not appear to be a major concern of researchers looking for causes of PGVI. As I had discussed earlier in this chapter, I do not believe that toluene inhalation associates with PGVI symptoms and severity; this result backs up my original assertion. As one can see in Figure 4-2 below, the symptom frequencies of the two samples have no association.

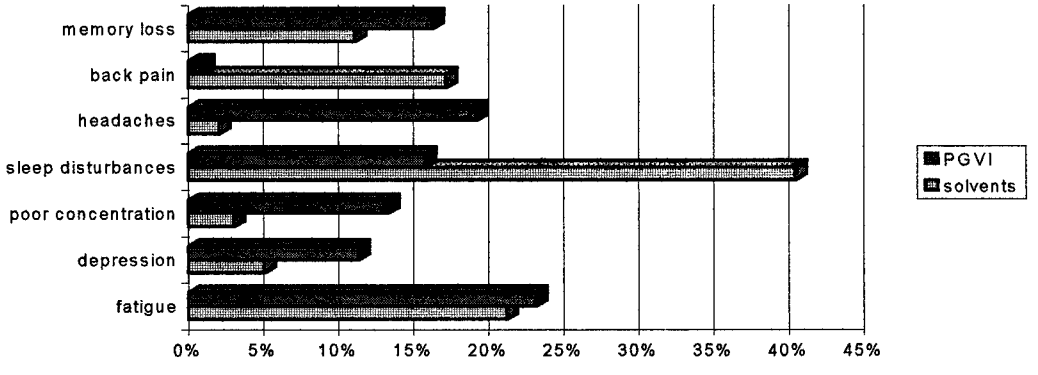

Figure 4-2: Frequency of Symptom Occurrence for PGVI vs. Solvents [19:11; 49:662]

4.4 Comparison of PGVI and Pyridostigmine Bromide Using Contingency Table Analysis

Pyridostigmine bromide (PB) was only distributed to Persian Gulf personnel in the form of 30 mg tablets **[46:9]**. Therefore, this analysis will be of oral side effects from PB, as opposed to inhalation. The PB data used in this analysis is from a survey given to a sample of Army personnel shortly after Operation Desert Storm, conducted by the U.S. Army Aeromedical Research Laboratory. The 148 participants were mostly aviators, and over two-thirds were officers. One part of the survey consisted of questions regarding side effects of PB administration. 90% of the officers and 87% of the enlisted had taken PB tablets, and none had taken atropine, so all the reported side effects would be from PB only, discounting any other health problems the personnel may have had **[12:277]**. This contrasts with 70% of the CCEP participants who have reported taking PB **[19:10]**. Table 4-6 below shows the common symptoms and their respective frequency counts for PB and PGVI.

frequency of symptoms

	gastro-intestinal	*headache*	*diarrhea*	*muscle cramps*	*stiff joints*	***N=***
PB	22	9	7	2	2	42
PGVI	1603	3908	1804	2204	4709	14228
	1625	**3917**	**1811**	**2206**	**4711**	**14,270**

Table 4-6: Frequency of Symptoms for PGVI vs. PB [19:11; 12:277]

4.4.1 Analysis

There are **r = 2** populations (CFS, PGVI) and **c = 5** categories of symptoms; therefore, there are (r-1)(c-1) = 4 degrees of freedom.

The rejection region of interest is $X^2_{1-\alpha} = 9.488$ at $\alpha = 0.05$ and df =4 **[21:676]**. If the test statistic T is larger than 9.488, we will reject the null hypothesis. Otherwise, the null hypothesis will be accepted.

H_o: the probabilities of symptoms for PGVI is equal to the probabilities of symptoms from oral exposure to pyridostigmine bromide

H_a: at least two of the probabilities of symptoms are not equal to each other

4.4.2 Results and Discussion

The results of the contingency table analysis for PGVI versus PB are shown below in Table 4-7. The original data analysis was run in Statistix 4.1; the results can be found in Appendix C.

The overall T of 76.55 is larger than the chi-square value of 9.488; therefore, we reject H_o at significance level of 0.05. If you look closely at the cells of the analysis, we can see that most of the test statistic T is located in one category: "gastrointestinal effects". However, even if we did remove that category from this analysis, there are other sufficiently large values of T that would still cause us to reject H_o.

We can conclude from this analysis that PB, when used in its prescribed oral dose of 30 mg three times a day, does not seem to have the same frequencies of symptoms that

Case		PGVI	PB	
1	observed	1603.00	22.00	1,625
gastro-	expected	1620.22	4.78	
intestinal	cell chi-sq	0.18	61.98	
2	observed	3908.00	9.00	3,917
headache	expected	3905.47	11.53	
	cell chi-sq	0.00	0.55	
3	observed	1804.00	7.00	1,811
diarrhea	expected	1805.67	5.33	
	cell chi-sq	0.00	0.52	
4	observed	2204.00	2.00	2,206
muscle	expected	2199.51	6.49	
cramps	cell chi-sq	0.01	3.11	
5	observed	4709.00	2.00	4,711
stiff	expected	4697.13	13.87	
joints	cell chi-sq	0.03	10.15	
				N
		14,228	42	**14,270**
Overall chi-square:		**76.55** > 9.488, reject Ho		
P-value:		**0.0000** < 0.05		
Degrees of freedom:		**4**		

Table 4-7: Results of Contingency Table Analysis for PGVI vs. PB

are associated with the PGVI patients, particularly with respect to gastrointestinal complaints.

Of course, it would be prudent to conduct further study in this area, particularly scientific human studies on oral side effects of PB, concentrating on the types of symptoms manifested particularly in PGVI patients, to see if there is any association. One survey does not provide conclusive proof of a disassociation.

Figure 4-3 below shows a visual representation of the percentage of symptom frequencies shown by the two samples.

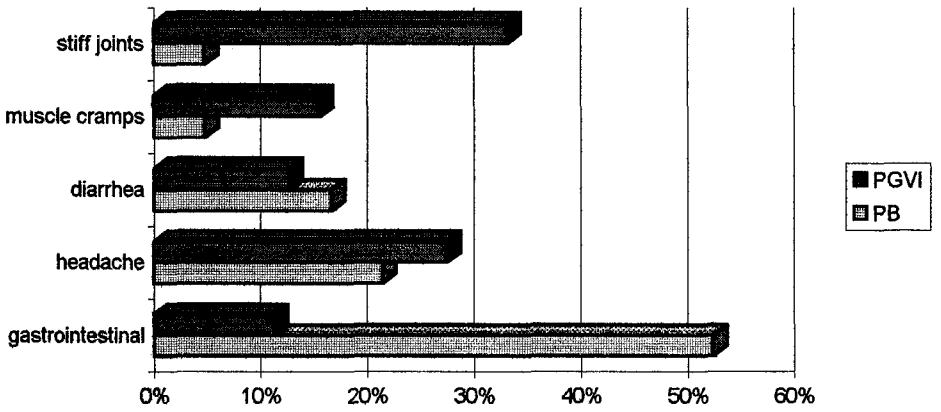

Figure 4-3: Frequency of Symptom Occurrence for PGVI vs. PB [19:11; 12:277]

From the figure we can see that the "gastrointestinal effects" and "stiff joints" categories of symptoms do not associate to each other. I would conclude that PB side effects are not similar in frequency to the symptom frequency of PGVI personnel. Considering that over 70% of Gulf War veterans examined to date say they took PB, and only 17% of those veterans still remain undiagnosed, it is unlikely that PB is the underlying common cause of PGVI.

4.5 Summary

Contingency table analysis is a useful tool to make inferences regarding two or more samples from different populations. I have shown this by comparing Persian Gulf

Veterans' Illnesses to Chronic Fatigue Syndrome, solvents, and pyridostigmine bromide. Unfortunately, I am unable to analyze several of the areas of study that I desired to, due to the fact that at this point in time, no sufficient human data exists. Diesel and JP-4 data found in the matrix are almost entirely from animal studies. Kerosene data is sporadic, consisting of single-case studies, not samples. Data from DEET consists mainly of single-case studies of children who have swallowed DEET, which is not the type of information I need to be useful to PGVI veterans. Soman, sarin, and tabun similarly have no human studies available; obviously, that is not possible. In almost all cases of nerve agent exposure, the people exposed die, so symptoms are not known, just pathological findings are known. Therefore, I could only conduct contingency table analysis using the data I do have available; that for PB, solvents, and Chronic Fatigue Syndrome.

V. Conclusions and Recommendations

5.1 Conclusions

Conclusions for each research activity conducted are presented in the following sections, followed by overall conclusions.

5.1.1 Literature Search

The extensive literature search revealed many areas where there are data gaps in the study of health effects, both in human studies and in animal studies. Although I did find many adverse health effects caused by the substances studied, many of the literature sources are considered to be inadequate; for example, the health effects studies for DEET contained in the EPA Pesticide Registration Standard **[63]** are included in the standard, with the caveat that the studies, as they now exist, are inadequate to draw conclusions. I included this type of information when there were no other studies to contradict the results, although I attempted to also caveat the results with that disclaimer.

The substances that were identified by the Institute of Medicine as being possible causes of PGVI (but were not included in my thesis due to the need to limit the scope of study and unavailability of data) should be investigated also. These substances include anthrax vaccine, botulinum toxoid, depleted uranium from munitions, and the oily residue from the Kuwait oil fires. Some of this information is classified, and some of the

information has not been published yet. However, these areas of study that I was unable to research should be looked into.

Additionally, health effects associated with reproduction and long-term health effects such as cancer were not studied in depth in this report due to limiting of the scope and also because PGVI is only 5 years old; it is not possible to study long-term effects yet. From my preliminary research in these areas, it appears that these types of health effects could potentially be even more devastating than the chronic illnesses being experienced now.

There needs to be further research in the area of inhalation studies on humans, for all types of fuel oils. There also needs to be more study done in the area of pyridostigmine bromide by oral dose, since the only scientific studies done to date involve myasthenia gravis patients, and the adverse side effects of the drug mirror the symptoms of the disease, so there is no definitive way to draw conclusions regarding its safety. The nerve agents soman, sarin, and tabun should also be further investigated in chronic animal studies, to determine long-term types of health effects associated with exposure to them.

5.1.2 Health Effects Matrix

The health effects matrix (Table 4-1) shows visually the extensive health information collected by the literature search. The matrix not only clearly shows the data gaps of the current literature for all the substances examined, it shows which substances

have the most potential for human health risks. The matrix also shows in what areas no human studies have been done.

The health effects matrix allowed me to narrow down the scope of further study to primarily the inhalation route of exposure, and to look at the health effects from PB (oral exposure), solvents, the nerve agents soman, sarin, and tabun, and also, Chronic Fatigue Syndrome as a possible diagnosis.

5.1.3 Contingency Table Analyses

The contingency table analyses of the substances of concern indicated by the health effects matrix had some interesting results. First, I compared the frequency of symptoms of CFS versus those of PGVI. The null hypothesis was not rejected, indicating that the symptom frequencies of the two diseases are homogeneous. In other words, the symptoms could be caused by either disease; all the symptoms could be said to come from one population, not two. This is significant in that to date, no Gulf War veteran registered with the CCEP has been diagnosed with CFS. I would recommend that these veterans be examined more thoroughly, especially those that have not been diagnosed with any type of ailment. The current population of veterans should be broken down into subcategories, such as men vs. women, smokers vs. nonsmokers, etc. to compare their symptoms to those of other diseases such as CFS.

The contingency table analysis of inhalation of solvents did result in rejection of the null hypothesis. This means that there appears to be no association between the

symptom frequencies of the two samples. The two samples could easily be distinguished from one another. However, this is a finding; it suggests that solvent exposure is not an area for concern when looking for causes of PGVI. It also suggests that "paint sniffing" may not have been a widespread pastime among soldiers deprived of alcohol for a long period of time.

The analysis of symptom frequencies of PGVI versus those of pyridostigmine bromide also resulted in rejection of the null hypothesis of independence. This finding is significant because a vast majority of soldiers stationed in the Persian Gulf did take the prescribed PB tablets, and apparently, this common link does not appear to be a cause of PGVI. The small sample size of the PB survey, plus the fact that no scientific experiments have been conducted on humans to date, does not rule out the possibility that PB is not a contributing factor. It does appear that PB, when used properly, does not result in symptom frequencies similar to that reported by Gulf War veterans.

5.2 Recommendations for Further Research

There are numerous avenues of further research pertaining to this area of study. First and foremost, the results of this study could be used to narrow the scope of a toxicology study being proposed by the U.S. Army Medical Research and Materiel Command to look at effects of inhalation exposure of rats to various fuels and solvents, combined with exposure to PB and DEET.

Secondly, the area of reproductive effects of PGVI is a "hot" topic in current literature. There appears to be some clustering of rare congenital birth defects, and many instances of sudden death among children born to Persian Gulf veterans upon their return. This is an area of deep concern for military members, their families, and for the taxpayers who must now support these children with severe physical and often psychological problems. It is imperative that something be done about this problem.

The health effects matrix contains a visual record of a number of areas of research that so far has been virtually ignored up to now. For example, the human health effects of jet fuel JP-4 has been virtually not researched at all. Inhalation of the insecticide DEET has also been only sparsely studied, despite a number of commercial products that are on the market consisting of aerosol sprays.

A larger emphasis must be placed on determining health effects to humans, either by drawing conclusions and interpolating from animal data, or by conducting human exposure studies under reasonable exposure scenarios.

It is obvious that there are numerous "what ifs" concerning what is causing Persian Gulf Veterans' Illnesses. The immediate task is to narrow down the field of study through planned experimentation, to rule out those factors that do not appear to be of concern.

Appendix A: Terminology Used In This Report

absolute (vs. relative) organ weights -- a relative organ weight is in comparison with total body weight; the absolute organ weight is not compared to total body weight

acidosis -- a state of increased acidity of body tissues and fluids **[22]**

adenoma -- an epithelial tumor composed of glandular tissue **[22]**

albumin -- one of a class of simple proteins, which are soluble in water, that occur in blood plasma, serum, and muscle **[22]**

albuminuria -- presence in the urine of serum albumin or serum globulin **[22]**

alopacia -- hair loss from normally hairy parts of the body **[22]**

alveolae -- thin walled chamber of the lung, surrounded by capillaries, where carbon dioxide and oxygen are exchanged **[22]**

anaphylaxis -- exaggerated skin reaction to a foreign substance to which one has previously been sensitized **[22]**

angioedema -- abnormal accumulation of fluid in the blood vessels **[22]**

anomalies -- deviations from normal conditions **[22]**

anorexia -- loss of appetite for food **[22]**

anticholinesterase -- a class of drugs, including pyridostigmine bromide, that

> "...bind reversibly with acetylcholinesterase. This allows the temporary and partial buildup of acetylcholine, which may allow continuous stimulation of cholinergic receptors throughout the central and peripheral nervous system. This pharmacological action has been taken advantage of in the protection of military personnel from the effects of organophosphate toxic gases..." **[806:56]**.

aortic plaque -- small, disk-like raised patches consisting of the innermost lining of the aorta (great artery rising from the left ventricle) **[50, 22]**

Area of Responsibility (AOR) -- term used to refer to the entire Persian Gulf War area of operations, including Saudi Arabia, Oman, United Arab Emirates, Kuwait, and Iraq.

arthralgia -- joint pain **[22]**

asphyxia -- cessation of life due to interruption of gaseous exchange in the lungs; suffocation **[22]**

ataxia -- spastic or involuntary movements and rigidity **[22]**

atherosclerosis -- a condition characterized by degeneration and hardening of the walls of arteries and sometimes valves of the heart **[22]**

audiological -- relating to hearing **[22]**

blood lactate -- a salt of lactic acid present in the blood **[22]**

bradycardia -- abnormal slowness of heart rate and pulse **[22]**

bronchitis -- inflammation of the larger passages conveying air to and within the lungs (bronchi). **[22]**

bronchoconstriction -- narrowing or contraction of the bronchi **[22]**

bronchopneumonia -- inflammation of the bronchi and lungs **[22]**

bullous -- fluid-containing elevated skin lesions **[22]**

cardiomegaly -- enlargement of the heart **[22]**

chromodacryorrhea -- shedding of colored tears **[22]**

conjunctival epithelium -- cellular substance of the eyelids' inner membrane **[22]**

conjunctivitis -- inflammation of the conjunctiva **[22]**

craniofacial -- pertaining to the skull and face structure **[22]**

creatinine -- a waste product formed from creatine (a crystallized nitrogenous compound synthesized in the body) and phosphocreatine (a creatine-phosphoric acid compound occurring in muscle) **[22]**

cyanosis -- bluish discoloration of the skin and mucous membranes due to excessive concentration of reduced hemoglobin in the blood **[22]**

cytolysis -- dissolution of cells **[22]**

cytopenia -- a deficiency in the cells of the blood **[22]**

dermatitis -- inflammation of the skin **[22]**

dermatosis -- any disorder of the skin **[22]**

dynamic lung compliance -- the measure of the lungs' ability to distend without disruption, expressed in terms of unit of volume per unit of pressure **[22]**

dysmorphism -- deformity **[22]**

dyspnea -- difficulty breathing **[22]**

edema -- an abnormal accumulation of fluid in intercellular spaces of the body **[22]**

electrophysiology -- observation of the effects of electricity upon the body in health **[22]**

emphysema -- abnormal presence of air or gas in body tissue **[22]**

encephalitis -- inflammation of the brain **[22]**

encephalopathy -- any disorder of the brain **[22]**

epigastric -- upper abdominal region **[22]**

epithelial -- membranous cellular tissue that lines a tube or cavity inside the body

erythema -- redness of the skin due to congestion of the capillaries **[22]**

erythrocyte -- one of the formed elements in peripheral blood, containing hemoglobin and transporting oxygen **[22]**

etiology -- the study of the causes and origins of diseases **[22]**

exudate -- material which has escaped from blood vessels and been deposited on tissue surfaces, usually as a result of inflammation **[22]**

fibrosarcoma -- a tumor composed of both fully developed connective tissue (fibroma) and of the meshwork of embryonic connective tissue in the mesoderm (sarcoma) **[22]**

focal tubular necrosis -- pathologic cell death in renal tubes **[22]**

folliculitis -- inflammatory cells within hair follicles **[32:251]**

foot splay -- absence of arch in the foot

gastroenteritis -- inflammation of stomach and intestines **[22]**

gonadotropic -- pertaining to dominance of the gonads in the endocrine make-up **[22]**

hematology -- study of the blood **[22]**

hematuria -- excretion of urine containing blood **[22]**

hemoglobin -- the oxygen-carrying pigment of the blood **[22]**

hepatic -- pertaining to the liver **[22]**

histological -- microscopic study of the form and structure of the various tissues that make up the body **[22]**

histopathological -- microscopic study of the form and structure of the various body tissues, in order to assess the effects of a disease on the body **[22]**

hyaline droplets -- translucent nitrogenous substance found around cells that is readily stained by eosin dye **[22]**

hyperemia -- excess of blood in a part **[22]**

hyperemic conjunctiva -- excess of blood in the eyelid's thin inner membrane **[22]**

hyperglycemia -- excess of glucose in the blood **[22]**

hyperplasia -- increase in volume of a tissue or organ caused by the formation and growth of new cells **[22]**

hypertension -- abnormally increased blood pressure **[22]**

hypertrophy -- increase in volume of a tissue or organ produced entirely by enlargement of existing cells **[22]**

hypoactivity -- diminished activity **[22]**

hypotension -- low blood pressure **[22]**

immunology -- study of the body's resistance to diseases **[22]**

in vitro -- occurring outside the body, in an artificial environment (such as a test tube) **[22]**

in vivo -- occurring in a living body of a plant or animal **[22]**

karyolysis -- the dissolution of a nucleus of a cell **[22]**

karyopyknosis -- shrinkage of a cell nucleus, with condensation of the chromatin **[22]**

lacrimation -- secretion of tears **[22]**

LD_{50} -- the chemical dosage needed to produce death in 50% of the treated animals **[35:12]**

leishmania tropica -- the predominate Leishmaniasis species in the Persian Gulf region, responsible for thirty-one reported cases among military members. **[20:47]**

leishmaniasis (cutaneous) -- chronic ulcerative granuloma (a mass of histiocytes) caused by *l. tropica* **[22]**

leishmaniasis (visceral) -- also known as kala-azar, a fatal epidemic fever of tropical Asia, resembling malaria, caused by *l. donovani*. **[22]**

leukocyte -- a colorless blood corpuscle capable of ameboid movement, whose chief function is to protect the body against microorganisms causing disease **[22]**

lipoidal pneumonia -- patchy or diffuse consolidation of lung tissue caused by the aspiration of oil **[22]**

LOAEL -- lowest observed adverse effect level; refers to the lowest dosage of a substance at which an adverse effect is seen, usually pertaining to animal experiments **[47:61]**

lymphocytes -- a variety of leukocyte that arises in the reticular tissue of the lymph nodes **[22]**

microcephaly -- small size of head in relation to the rest of the body **[22]**

miosis -- excessive contraction of the pupil **[22]**

mitogen -- an agent that stimulates indirect cell division **[22]**

myalgia -- muscular pain **[22]**

myalgic encephalomyelitis -- inflammation of the brain and spinal cord, accompanied by muscular pain **[22]**

myocardial fibers -- fibers of the muscular substance of the heart **[22]**

narcosis -- a sleeplike, stuporous state induced by a sedative drug **[22]**

necrosis -- death of a cell as a result of disease or injury **[22]**

neurasthenia -- excessive fatigue of neurotic origin **[22]**

neutrophils -- a medium-sized leukocyte, composing about 60-70% of all the leukocytes in the blood **[22]**

NOAEL -- no observed adverse effect level; refers to the highest dosage at which no toxic effect is observed, usually pertaining to animal experiments **[47:61]**

nocturia -- excessive night time urination; bedwetting

olfactory -- pertaining to the sense of smell **[22]**

oliguria -- diminished urine secretion, to 100 - 400 milliliters in 24 hours **[22]**

opto-vestibular -- relating to the eye socket **[22]**

osmolality -- concentration of the solute in a solution per unit of solvent

ototoxicity -- having a detrimental effect upon hearing and balance **[22]**

paresthesia -- an abnormal or perverted sensation due to disorder of the sensory nervous system **[22]**

perivascular cuffing -- formation of a cufflike border around a blood vessel **[22]**

pharyngitis -- inflammation of the pharynx (the musculomembranous cavity behind the nose, mouth, and larynx) **[22]**

pneumonia -- an acute inflammatory condition of the lung marked by material from the blood vessels being deposited in the interstitial and cellular portions of the lung **[22]**

pneumonitis -- inflammation of lung tissue **[22]**

pneumothorax -- the presence of air or gas in the pleural cavity, or between the pleura (membrane enveloping the lungs and lining the walls of the thoracic cavity) and the chest wall **[22]**

polyneuropathy -- disease involving several nerves **[22]**

promoters -- agents that facilitate the growth of dormant neoplastic cells into tumors. Promoters can be noncarcinogenic, but most are generally considered weak carcinogens that cause a synergistic effect when combined with another carcinogen. **[35:131]**

proteinuria -- protein in the urine **[22]**

pyruvate -- a salt or ester of pyruvic acid **[22]**

pyruvic acid -- a 3-carbon keto acid $C_3H_4O_3$ that is an intermediate in carbohydrate metabolism

retinal arteriole constriction -- narrowing of the arteries in the retina (innermost part of the eye) **[22]**

rhinorrhea -- discharge from the nasal mucous membranes

septal muscle (heart) -- the muscle in the heart that serves to divide the chambers **[22]**

squamous cell carcinoma -- a rapidly growing and readily metastasizing (spreading throughout the body) carcinoma originating in the epidermis **[22]**

subconjunctival -- beneath the conjunctiva (eyelid's thin inner membrane) **[22]**

subcutaneous hemorrhage -- blood escaping from a ruptured blood vessel under the surface of the skin **[22]**

tachycardia -- abnormally rapid heart rate **[22]**

tachypnea -- very rapid respiration **[22]**

tenesmus -- straining at stool or in urinating **[22]**

teratogenicity -- refers to the subcategory of pathological effects during the sensitive development phase after implantation of the embryo up to the first three months of pregnancy in humans when major tissues and organs differentiate and develop. **[38:245]**.

tetanic contracture -- sustained convulsive contractions of a voluntary muscle **[22]**

thymus -- a two-lobed ductless gland in the cavity of the chest, just above the heart **[22]**

tracheitis -- inflammation of the trachea **[22]**

triglicerides -- compound consisting of 3 molecules of fatty acid esterified to glycerol; a neutral fat that is the usual storage form of lipids in animals **[22]**

tubular interstitial nephritis -- inflammation of the tubules, with increase of interstitial tissue and thickening of vessel walls **[22]**

urinary calculi -- small hard masses formed in the urinary tract **[22]**

urticaria -- a vascular reaction of the skin marked by transient appearance of slightly elevated patches which are redder or paler than surrounding skin and often accompanied by severe itching **[22]**

vacuolization -- the formation of vacuoles, which are a space or cavity in the protoplasm of a cell **[22]**

vasculitis -- inflammation of a vessel **[22]**

vasodilation -- increase in the diameter of a blood vessel's opening **[22]**

ventricular heart muscle -- muscles of the ventricles of the heart **[22]**

Appendix B: Informal Survey Results

An informal survey was sent out to a list of Air Force site engineers who were stationed in the Area of Operations during Operations Desert Shield/Storm. The primary purpose of this survey was to get an indication of what type of occupational chemicals and substances were in use during these operations, not to make inferences from the results. The original survey is presented at the conclusion of this Appendix.

The replies are presented anonymously, so that survey respondents would not temper their answers. The results of each question are presented below. Eight people replied to this survey out of 14 solicitations. Some respondents listed multiple answers, which accounts for more than 8 responses to a question. Also, one respondent filled out 2 surveys for two different deployments to the Gulf.

Question 1: Did your squadron ever conduct any type of area-wide spraying of insecticide by either truck-mounted foggers or hand-held units?

Truck-mounted	2
Hand-held	1
No	6
Locals did spray, not US	1

Question 2: If yes, do you know what type of insecticide was used (brand name or chemical name)? Ex: malathion.

Resmethrin	1
Malathion	1
Cypermethrin	1
Don't know	1
Not applicable	6

Question 3: Was the chemical(s) provided by the U.S. or by the Saudis?

U.S.	2
Saudis	2
UAE locals	1
Not applicable	5

Question 4: Did you observe any use of diesel fuel, JP-4, or JP-8 being sprayed on the ground as a dust suppressor? If so, what type of fuel.

No	6
Diesel	2
Waste motor oil	1
Diesel used as dispersion agent for cypermethrin	1

Question 5: Do you know whether JP-4 or JP-8 was used as a primary aircraft fuel in your area?

JP-4	5
JP-8	0
Don't know	3

Question 6: Was your group given pyridostigmine kits as a measure against chemical attacks? Did anyone in your group ever use them?

No	5
Yes/No one used them	4
Yes/We used them	1

Question 7: Are there any other chemicals or fuels that you know of or that you and your group were exposed to that you would like us to include in our study?

No	7
Anthrax vaccine	2
Kuwait oil smoke/residue	1

Original survey:

Dear sir, my name is Captain Rebecca Nelson and I am a student at the Air Force Institute of Technology in the engineering and environmental management program. I am writing to you regarding your experience in the Gulf War, for my thesis work. I received your name from Maj Wayland Patterson, who was on CENTAF staff during the war.

Basically what my thesis involves is a toxicological study, sponsored by the US Army, to either find or disprove associations between certain airborne exposure scenarios and any incidences of Gulf War Syndrome. This project is in a very preliminary stage and I would greatly appreciate your help in answering several questions, so that we can be more accurate in our selection of chemicals to use for the exposure scenarios.

No names will be used in my thesis; however, if you would like a copy of my thesis please provide me your mailing address. I need specific answers to the following questions:

1) Did your squadron ever conduct any type of area-wide spraying of insecticide by either truck-mounted foggers or hand-held units?

2) If yes, do you know what type of insecticide was used (brand name or chemical name)? Ex: malathion.

3) Was the chemical(s) provided by the U.S. or by the Saudis?

4) Did you observe any use of diesel fuel, JP-4, or JP-8 being sprayed on the ground as a dust suppressor? If so, what type of fuel.

5) Do you know whether JP-4 or JP-8 was used as a primary aircraft fuel in your area?

6) Was your group given pyridostigmine kits as a measure against chemical attacks? Did anyone in your group ever use them?

7) Are there any other chemicals or fuels that you know of or that you and your group were exposed to that you would like us to include in our study?

8) If you were not able to answer any of these questions, do you know of someone else who was in your group that I could contact?

I thank you very much for your help, it will make our study more accurate. If this survey was sent to you by mistake, because of similar names, please let me know so I can send it to the correct individual.

Appendix C:

Statistix 4.1 output for Contingency Table Analysis

STATISTIX 4.1 CONT1DATA, 11/05/95, 20:32

CHI-SQUARE TEST FOR HETEROGENEITY OR INDEPENDENCE

CASE		VARIABLE PGVI	CFS	
1	OBSERVED	4709	30	4739
	EXPECTED	4714.13	24.87	
	CELL CHI-SQ	0.01	1.06	
2	OBSERVED	3908	25	3933
	EXPECTED	3912.36	20.64	
	CELL CHI-SQ	0.00	0.92	
3	OBSERVED	4709	21	4730
	EXPECTED	4705.18	24.82	
	CELL CHI-SQ	0.00	0.59	
4	OBSERVED	4709	23	4732
	EXPECTED	4707.17	24.83	
	CELL CHI-SQ	0.00	0.14	
5	OBSERVED	3206	16	3222
	EXPECTED	3205.09	16.91	
	CELL CHI-SQ	0.00	0.05	
6	OBSERVED	2906	8	2914
	EXPECTED	2898.71	15.29	
	CELL CHI-SQ	0.02	3.48	
7	OBSERVED	3307	19	3326
	EXPECTED	3308.55	17.45	
	CELL CHI-SQ	0.00	0.14	
8	OBSERVED	2305	15	2320
	EXPECTED	2307.82	12.18	
	CELL CHI-SQ	0.00	0.66	
		29759	157	**29916**

OVERALL CHI-SQUARE 7.06
P-VALUE 0.4228
DEGREES OF FREEDOM 7

STATISTIX 4.1 SOLVDTA, 11/08/95, 15:08

CHI-SQUARE TEST FOR HETEROGENEITY OR INDEPENDENCE

CASE		VARIABLE **PGVI**	**SOLVENTS**	
1	OBSERVED	4709	21	4730
	EXPECTED	4707.09	22.91	
	CELL CHI-SQ	0.00	0.16	
2	OBSERVED	2305	5	2310
	EXPECTED	2298.81	11.19	
	CELL CHI-SQ	0.02	3.42	
3	OBSERVED	2705	3	2708
	EXPECTED	2694.88	13.12	
	CELL CHI-SQ	0.04	7.80	
4	OBSERVED	3206	40	3246
	EXPECTED	3230.28	15.72	
	CELL CHI-SQ	0.18	37.49	
5	OBSERVED	3908	2	3910
	EXPECTED	3891.06	18.94	
	CELL CHI-SQ	0.07	15.15	
6	OBSERVED	200	17	217
	EXPECTED	215.95	1.05	
	CELL CHI-SQ	1.18	242.01	
7	OBSERVED	3307	11	3318
	EXPECTED	3301.93	16.07	
	CELL CHI-SQ	0.01	1.60	
		20340	99	**20439**

OVERALL CHI-SQUARE **309.13**
P-VALUE 0.0000
DEGREES OF FREEDOM **6**
CASES INCLUDED 14 MISSING CASES 0

STATISTIX 4.1 PBDATA, 11/08/95, 16:15

CHI-SQUARE TEST FOR HETEROGENEITY OR INDEPENDENCE

CASE		VARIABLE PGVI	PB	
1	OBSERVED	1603	22	1625
	EXPECTED	1620.22	4.78	
	CELL CHI-SQ	0.18	61.98	
2	OBSERVED	3908	9	3917
	EXPECTED	3905.47	11.53	
	CELL CHI-SQ	0.00	0.55	
3	OBSERVED	1804	7	1811
	EXPECTED	1805.67	5.33	
	CELL CHI-SQ	0.00	0.52	
4	OBSERVED	2204	2	2206
	EXPECTED	2199.51	6.49	
	CELL CHI-SQ	0.01	3.11	
5	OBSERVED	4709	2	4711
	EXPECTED	4697.13	13.87	
	CELL CHI-SQ	0.03	10.15	
		14228	42	**14270**

OVERALL CHI-SQUARE **76.55**
P-VALUE 0.0000
DEGREES OF FREEDOM **4**
CASES INCLUDED 10 MISSING CASES 0

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Vita

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