APPENDIX II

INDEPENDENT CONSULTANT REPORT

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Health effects of exposures to neurotoxic agents used in the Persian Gulf War

A report to the Committee on Veterans' Affairs of the United States Senate

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EXECUTIVE SUMMARY

The purpose of this report is to review in detail the known health effects of chemical agents potentially hazardous to the nervous system to which military personnel may have been exposed during the Persian Gulf War. This review is made with special attention to possible relationships between these agents and symptoms and health complaints that have been reported by a large number of Persian Gulf War veterans.

On August 2, 1990, Iraq invaded Kuwait and set in motion the events that would eventually lead to US military intervention in the Persian Gulf. On August 8, 1990, the first US Air Force planes arrived in Saudi Arabia and, on the following day, the first US ground forces arrived. The ground war began and ended in February, 1991. The last of the US service members who served in the ground war were returned to the United States in June, 1991.

In all, the United States had approximately 697,000 troops stationed in the Persian Gulf. Following their return, mounting concern has focused on symptoms and unexplained illness experienced by some. In response to concern about unexplained illness, the VA Persian Gulf Health Registry was created. As of June, 1994, over 17,000 veterans, either ill or concerned about illness, had enrolled. The ten most frequent complaints among those in the Registry were fatigue (17.4%), rash (16.8%), headache (14.1%), muscle and or joint pain (13.9%), neuropsychologic complaints (10.5%), shortness of breath (7.5%), sleep disturbances (4.9%), gastrointestinal disturbance (4.1%), cough (3.8%), and other respiratory complaints (3.3%). The registry has not shed light on any distinctive demographic, exposure, or geographic risk factor, with the possible exception that nearly half of the veterans with symptoms were reservists/National Guard personnel, a group that accounted for only 17% of all troops deployed in the Persian Gulf.

Numerous possible risks to health were present in the Persian Gulf at the time of the Gulf War. These included poor living conditions, characterized by heat and humidity, initially, and cold during the actual combat. Troops slept in temporary housing with little personal privacy. Food consisted mainly of prepackaged meals. Flies and other insects were prevalent. Chemical warfare alarms sounded frequently, although virtually all were false. Such alarms, nevertheless, resulted in donning of air purifying masks and chemical protective clothing. Attention has been paid to possible chemical warfare agent exposure in the Gulf occurring as a result of destruction of a chemical warfare agent facility at Kamisiyah. Iraq was reported to have stockpiled biological warfare agents as well. Concern about health effects from exposure to these weapons as well as to indigenous infectious diseases lead to an extensive vaccination program. In addition, an estimated quarter of a million troops took the chemical warfare agent protective drug

pyridostigmine bromide. Pesticides were used to control insect populations and insect repellents were provided to troops for personal use. Some troops were exposed to solvents from jet fuel, paint vapors, and other sources. Depleted uranium was used in special applications during the Gulf War and tetra-ethyl lead was formulated in gasoline used in motor vehicles. Finally, some troops were exposed to non-ionizing radiation from microwaves and radar installations.

In order to better characterize the health complaints of Gulf War veterans and to determine whether exposure to hazardous substances in the Gulf had caused them, health investigations of morbidity and mortality among Persian Gulf War veterans have been performed.

The largest and most methodologically sound study investigation included nearly five thousand subjects and involved inquiry about symptoms and exposure to known hazards in the Persian Gulf. Military personnel who served in the Persian Gulf War reported significantly more symptoms of depression, PTSD, chronic fatigue, cognitive dysfunction, bronchitis and asthma than non-Persian Gulf War personnel. Most of the self-reported exposures to hazards were statistically significantly related to virtually all of the health outcomes studied.

The results of the study indicate that subjective symptoms, including those consistent with nervous system impairment, occur more frequently among those who served in the Persian Gulf War than Persian Gulf War-era personnel who were not stationed in the Persian Gulf. The associations between multiple, unrelated exposures and multiple unrelated symptoms, however, is more consistent with differential recall of exposure as a function of symptoms experience than a toxic response to a single or even several agents.

Several other studies intended to characterize with more objective measures the neurological health of Gulf War Veterans have been published. Authors of some suggest that the results show neither increased nervous system impairment nor a consistent pattern of illness suggestive of a common etiology. Conversely, others conclude that their results show an increase in nervous system impairment and a pattern consistent with exposure to specific neurotoxicants. Unfortunately, nearly all of these studies were performed on "samples of convenience" and, as a result, cannot be used to draw conclusions about the larger but unstudied group of all Gulf War veterans. This body of literature has added little to the collective understanding of symptoms and health concerns among Persian Gulf War veterans.

Epidemiologic investigation of relationships between potentially toxic substances and ill

health require accurate and unbiased assessment, on an individual basis, of both health status *and* the intensity and type of exposures experienced among a sample of persons representative of the entire group at risk. Of these requirements, the task that appears nearly impossible at this time is a person by person estimation of the intensity and type of exposures experienced by military personnel who served during the Persian Gulf War. Characterization of exposure to hazards was, apparently, not performed during the actual deployment of troops. As a result, estimation of the magnitude of past hazardous exposure at this time requires either direct questioning of veterans with resulting reporting bias or historical exposure reconstruction of unknown validity. As indicated above, reporting bias likely accounts for the associations observed in one study between symptoms and a very wide range of potential hazards.

As an alternative to epidemiologic investigation, another approach to investigating associations between health and hazardous exposure is to focus separately on 1) health problems among veterans and 2) exposures which they might have experienced. If a characteristic illness is observed among Gulf War veterans, then known causes for it can be explored. If particular hazards were encountered by veterans in the Gulf, the known health effects of exposure to them can be reviewed and compared to reported health problems among veterans. As neither approach attempts to relate exposure to illness on an individual basis, considerable caution must be exercised in their execution and interpretation. This report employs the latter of these two approaches and provides a systematic review of health effects of substances potentially toxic to the nervous system to which military personnel may have been exposed during the Persian Gulf War. A summary of the review is provided below.

Pyridostigmine bromide is an anticholinesterase drug given to tens of thousands of military personnel in the Persian Gulf war as a protective pre-treatment for exposure to "nerve gas" type chemical warfare agents. It is a member of the carbamate class of chemical agents and has been used for decades in humans as a treatment for the neurological disorder *Myasthenia Gravis* as well as a short acting accelerator of recovery from certain anesthetic agents. Pyridostigmine bromide acts by binding reversibly to, and consequently inhibiting, the enzyme acetylcholinesterase, which is necessary for normal function of the nervous system. This action is the basis for its ability to protect against the lethal effects of nerve agents which bind irreversibly to this enzyme. Pyridostigmine bromide is known to cause short-term discomfort and its use in the Gulf War was associated with abdominal distress, nausea, and diarrhea. Little epidemiologic information is available about its long-term effects among healthy young human populations, however, several factors suggest few or no long term effects on the nervous system. First, it has been used for decades for treatment of neurological illness with no

systematic occurrence of symptoms resembling those experienced by Gulf War veterans. Second, the agent is not known to pass through the natural barrier that protect the brain from many drugs and chemicals (the "blood brain barrier"), thereby making effects on the brain unlikely. Third, the class of drugs and chemical agents to which Pyridostigmine belongs, carbamates, have been used extensively in agriculture for decades and are not known to cause persistent adverse effects on the nervous system in that setting.

Chemical warfare agents, known as "nerve gas", are members of the organophosphate class of chemical compounds. The organophosphate nerve agents act to irreversibly bind the enzyme acetylcholinesterase. Accumulation of the intended substrate of acetylcholinesterase, the neurotransmitter acetylcholine, results in a characteristic complex of symptoms. Unlike pyridostigmine, which also binds the enzyme acetylcholinesterase (reversibly, however), the organophosphate chemical warfare agents are capable of freely penetrating the brain and producing acute and chronic central nervous system toxicity.

Most of what is known about the effects of chemical warfare agents is a result of experimental studies of exposure to animals. However, several studies or case reports of acute human effects of exposure were identified in the literature. In addition, because of their chemical and toxicological similarity to organophosphate pesticides, some inferences about their toxicity can be made from the considerable literature about the organophosphate pesticides. Short term, acute exposure to chemical warfare agents produces a characteristic array of symptoms including sweating, diarrhea, urination, muscle twitching, pinpoint pupils, confusion, seizures, and, with sufficient exposure, death. Some credible medical evidence suggests that, upon recovery from toxic effects of acute exposure, chronic impairment of the central nervous system may occur. Little evidence is available to suggest that exposures insufficient to produce acute toxicity are associated with long term neurological effects. Reportedly, no military personnel were treated for acute effects of nerve agent exposure, making unlikely that chronic effects of such exposure are the cause of symptoms experienced by Persian Gulf War veterans.

Organophosphate pesticides were used in the Persian Gulf for control of insects. Because of widespread use of organophosphate pesticides worldwide, a larger body of literature about the acute and chronic health effects of organophosphate pesticides on human populations, including chronic effects on the CNS, is available than is available for organophosphate chemical warfare agent agents.

In addition to the organophosphate class of pesticides, carbamate, pyrethroid, and organochlorine pesticides were also used. Only the organophosphate pesticides are

known to cause, under certain exposure circumstances, long-term adverse effects on the nervous system. The carbamate pesticides, although similar in acute toxicity to organophosphates, are not known to result in long-term adverse neurological effects. Similarly, long-term adverse neurological effects of pyrethroid insecticides, and Lindane, the one organochlorine pesticide used in the Persian Gulf, have not been reported in the peer reviewed medical literature.

Exposure to organophosphate pesticides has been most convincingly associated with chronic adverse central nervous system health effects only when the exposure intensity is sufficient to produce acute toxicity consistent with acetylcholinesterase inhibition. Only one report in the literature related exposures to levels of organophosphate pesticides insufficient to produce acute effects to long-term adverse effects on the central nervous system. This finding has not been duplicated by other investigators. Given the apparent absence of documented signs and symptoms characteristic of acute organophosphate pesticide toxicity among soldiers deployed to the Persian Gulf, it unlikely that long-term health effects of pesticide toxicity is responsible for symptoms described by Persian Gulf veterans.

Lead, in the form of tetra-ethyl lead, was an octane boosting additive in gasoline used to fuel motor vehicles used by US forces in the Persian Gulf. Tetra-ethyl lead had been used in gasoline in the United States for decades and was widely discontinued from such use, for protection of the public health, beginning in the 1970's. Exposure to lead in the Persian Gulf War was limited to that emitted from vehicles in which leaded gasoline was used.

Both organic and inorganic lead are known to be toxic to the nervous system. Clinically, symptoms of lead intoxication include abdominal pain, fatigue, joint pain, headache, irritability and other mood disturbances, and muscle and joint pain. On clinical examination, physical signs of peripheral neuropathy, including paresthesias and motor weakness may be present. Clinical examination is insensitive to central nervous system impairment; however, when subjected to formal clinical neurobehavioral evaluation, patients with lead intoxication often show impairment of multiple central nervous system functions.

Although leaded fuels were used in the Persian Gulf, it is unlikely that exposures to tailpipe emissions were of sufficient duration or intensity to produce any kind of clinically apparent toxicity from lead exposure. While long-term exposure to lead does result in accumulation of lead in long-term storage pools in the human body, short-term exposures result in little long-term accumulation. Failure of symptoms to remit for years

following exposure is inconsistent with lead as an etiology of unexplained symptoms experienced by some Gulf War veterans. Furthermore, leaded fuels were used in the United States for decades and are still in use in many other countries worldwide. No reports of symptoms identical to those experienced by Persian Gulf veterans have emerged despite such widespread and long-term use.

Depleted uranium is a by-product of the extraction of uranium-235 (U235) from naturally occurring uranium. Military applications for this material include munitions production (armor piercing bullets and artillery shells) and armor for tanks and personnel carriers. The PGW was the first US use, in actual military conflict, of depleted uranium tipped shells and depleted uranium armored tanks and other vehicles.

At the current time, estimates of the total number of military personnel who had any exposure to depleted uranium are not available. Exposure may have occurred to personnel in vehicles penetrated by depleted uranium rounds as well as personnel involved in recovery and repair of vehicles damaged by depleted uranium containing rounds. The Army has identified 35 soldiers who were injured in combat vehicles damaged by depleted uranium munitions, 22 of whom likely were wounded by DU containing shrapnel. In addition, 27 soldiers involved in damage assessment and preparation for shipment of damaged combat vehicles have reported exposure to DU during those activities.

Exposure to uranium, depleted or non-depleted, is not known to produce adverse effects on the nervous system. Reports of exposure to depleted uranium to soldiers in the Persian Gulf, although uncertain, suggest limited numbers of involved personnel. These facts make extremely unlikely that exposure to depleted uranium during the Gulf War is responsible, wholly or in part, for the array of symptoms observed among Gulf War veterans.

DEET, the common name for N,N-Diethyl-*m*-toluamide, is widely regarded as the most effective topical insect repellent available and is the major active ingredient in virtually all products marketed for this purpose. It was registered for use by the general public in 1957 and has been in civilian and military use since then. DEET has been a remarkably successful commercial product and is currently estimated to be used, in some form, by approximately 80 million persons in the United States, annually. Despite relatively long-term use by millions, only a few reports of toxicity were found in the medical literature. Most descriptions of human toxicity come from case reports of individual exposures or from small case series. Among the 20 individuals described in case reports, the group most frequently affected by DEET exposure were children and the most commonly

reported effects involved the nervous system.

Several factors suggest that DEET is not responsible for the symptoms reported by some veterans of the Persian Gulf War. First, the product appears to have adverse effects only on a very small proportion of those who use it. Second, the main adverse neurological effect appears to be seizures, a condition not reported commonly among Gulf War veterans, although one study of occupationally exposed workers has associated DEET with neurological symptoms with some similarity to those experienced by Gulf War veterans. The symptoms were experienced at the time of exposure to DEET, however; no long-term follow-up was reported. All clinical studies of adverse effects of DEET suggest full recovery occurs after withdrawal of exposure. No literature is available to suggest that topical use of DEET results in long-term health consequences.

Solvents are simple organic substances that are (1) liquid at room temperature, (2) relatively non-reactive, and (3) able to dissolve a wide range of organic compounds (i.e., lipophilic). Most solvents are quite volatile. The primary uses of solvents in the PGW were as motor vehicle and jet fuel, carriers for paint and coatings, and as an agent for control of airborne dusts blown from sand.

Solvents can affect the central nervous system (CNS), the peripheral nervous system (PNS), or both. Short term exposure to organic solvents can cause reversible anesthesia-like depression of the CNS. Long-term, heavy exposure to solvents may cause persistent, potentially irreversible impairment in cognitive function and affect, which may be associated with structural changes in neural tissue. Solvents can also cause impairment of peripheral nerve function.

Peripheral nervous system effects are well-established for a few specific solvents, none of which appear to have been used in the Persian Gulf. Acute, reversible CNS effects (i.e., acute intoxication) are common with all solvents. Chronic, apparently fixed, adverse effects of solvents on the CNS have been reported in the literature, with general agreement that long-term occupational exposure to solvents is associated with adverse effects on multiple CNS domains and that persons who suffer from such effects may report symptoms similar to those reported by some Persian Gulf War veterans, including depression, impaired concentration, and memory loss. The duration and intensity of exposure required to cause such effects and the potential severity of such effects is somewhat controversial, although most authorities agree that at least ten years of occupational (daily or near daily) exposure is required before effects are seen. Exposures to organic solvents in the Persian Gulf appear to be of insufficient duration, and may also have been of insufficient intensity, to produce chronic adverse effects on the CNS.

In summary, multiple agents with potential toxicity to the nervous system were used by military personnel in the Persian Gulf War. Such agents include pyridostigmine bromide, chemical warfare agents ("nerve gas"), pesticides, heavy metals, DEET, and organic solvents. Each of these agents or class of agents has been associated, in the biomedical literature, with acute or chronic toxicity to the central or peripheral nervous systems.

Soldiers returning from the Persian Gulf have reported numerous symptoms compatible with nervous system dysfunction including fatigue, headache, sleep disturbance, depression and memory impairment.

The concurrence of exposures with potential toxicity to the nervous system and the reporting of symptoms compatible with nervous system toxicity has lead to considerable scrutiny of a possible causal association between them. Review of the biomedical literature suggests, at this time, that neurotoxicity from exposure to pyridostigmine bromide, chemical warfare agents ("nerve gas"), pesticides, heavy metals, DEET, and organic solvents is not a likely explanation for symptoms experienced by Persian Gulf War veterans. Reasons for this conclusion vary for each individual agent or class of agents but include insufficient duration of exposure, evidence of insufficient intensity of exposure, incompatibility of effects of exposure with symptoms reported by military personnel, and the chronicity of illness following removal from exposure.

While currently available evidence does not support a neurotoxicological etiology for symptoms reported by many Persian Gulf War veterans, some key issues remain unclear. To close these gaps in knowledge, the following recommendations are made:

1. *To better characterize the neurological health status of Persian Gulf War veterans, a large study of a randomly selected sample of Persian Gulf War veterans and Persian Gulf War era veterans who did not serve in the Gulf in which objective measures of neurological and neurobehavioral function are used to assess neurological health should be performed.*

2. *Because clinical experience among healthy adults is limited, additional investigation of the long-term human health effects of pyridostigmine bromide in among healthy adults should be performed. Should pyridostigmine bromide be used by the US military in future conflicts, accurate records should be kept to permit fruitful long-term assessment of dose-effect relationships.*

3. *To determine whether exposure to pyridostigmine bromide altered military personnel responses to stress, investigation of the effect of pyridostigmine on physical and psychological responses to perceived threat of physical harm should be performed.*

4. *Because exposure to hazards rarely occurs in isolation, investigation of the effects of combined exposure to potentially toxic agents used in the Persian Gulf War should be performed. While such investigations may necessarily be performed on animals, the exposures used should be similar in route of administration, intensity, and duration to those experienced by humans under actual exposure conditions.*

5. *In the future, better efforts should be made to characterize objectively both health and hazardous exposures among US military personnel facing hazardous duty. Standardized, objective neurological and neurobehavioral testing of military personnel before deployment would provide useful baseline information about health status to which results of repeat testing, following deployment, could be compared. Quantitative assessment of exposure to potential hazards would provide information to compare to changes in health status that might be detected. The feasibility of such an effort should be explored.*

1. BACKGROUND: PERSIAN GULF WAR SYNDROME

On August 2, 1990, Iraq invaded Kuwait and set in motion the events that would eventually lead to US military intervention in the Persian Gulf. On August 8, 1990, the first US Air Force planes arrived in Saudi Arabia and, on the following day, the first US ground forces arrived. The ground war began and ended in February, 1991. The last of the US service members who served in the ground war were returned to the United States in June, 1991.

In all, the United States had approximately 697,000 troops stationed in the Persian Gulf. Following their return, mounting concern has focused on symptoms and unexplained illness experienced by some. In response to concern about unexplained illness, the VA Persian Gulf Health Registry was created. As of June, 1994, over 17,000 veterans, either ill or concerned about illness, had enrolled. The ten most frequent complaints among those in the Registry were fatigue (17.4%), rash (16.8%), headache (14.1%), muscle and or joint pain (13.9%), neuropsychologic complaints (10.5%), shortness of breath (7.5%), sleep disturbances (4.9%), gastrointestinal disturbance (4.1%), cough (3.8%), and other respiratory complaints (3.3%) (Persian Gulf Veterans Coordinating Board, 1995). The registry has not shed light on any distinctive demographic, exposure, or geographic risk factor, with the possible exception that nearly half of the veterans with symptoms were reservists/National Guard personnel, a group that accounted for only 17% of all troops deployed in the Persian Gulf (Persian Gulf Veterans Coordinating Board, 1995).

Numerous possible risks to health were present in the Persian Gulf at the time of the Gulf War. These included poor living conditions, characterized by heat and humidity, initially, and cold during the actual combat. Troops slept in temporary housing with little personal privacy. Food consisted mainly of prepackaged meals. Flies and other insects were prevalent. Chemical warfare alarms sounded frequently, virtually all were false alarms. Such alarms, nevertheless, resulted in donning of air purifying masks and chemical protective clothing. Attention has been paid to possible chemical warfare agent exposure in the Gulf occurring as a result of destruction of a chemical warfare agent facility at Kamisiyah. Iraq was reported to have stockpiled biological warfare agents as well. Concern about health effects from exposure to these weapons as well as to indigenous infectious diseases lead to an extensive vaccination program. In addition, an estimated quarter of a million troops took the chemical warfare agent protective agent pyridostigmine bromide. Pesticides were used to control insect populations and insect repellents were provided to troops for personal use. Some troops were exposed to solvents from jet fuel, paint vapors, and other sources. Depleted uranium was used in special applications in the Gulf War and tetra-ethyl lead was formulated on gasoline used

in motor vehicles. Finally, some troops were exposed to non-ionizing radiation from microwaves and radar installations.

In response to the reporting of illness and the possibility of exposure to hazardous conditions or agents, health investigations of morbidity and mortality among Persian Gulf War veterans have been performed.

A study of 4886 subjects randomly selected from among Persian Gulf War regular military, Persian Gulf War National Guard/Reserve, non-Persian Gulf War regular military, and non-Persian Gulf War National Guard/Reserve groups was conducted to assess the prevalence of self-reported symptoms and illness among military personnel deployed to the Persian Gulf and to compare the prevalence of these conditions to personnel on active duty during the Persian Gulf War but not stationed in the Gulf (Schwartz et al., 1997). In addition, associations between symptoms and self-reported exposures to a wide range of hazards were examined.

Persian Gulf War personnel (regular military and National Guard/Reserve personnel who served in the Persian Gulf War pooled into a single group for analysis) reported significantly more symptoms of depression, post traumatic stress disorder, chronic fatigue, cognitive dysfunction, bronchitis and asthma than non-Persian Gulf War personnel. The largest rate difference between Persian Gulf War and non-Persian Gulf War military personnel was for symptoms of cognitive dysfunction. Remarkably, most of the self-reported exposures to toxicants or hazards were significantly related to virtually all of the health outcomes studied. For example, among Persian Gulf War military personnel, symptoms of cognitive dysfunction were significantly associated with exposure to solvents, smoke and combustion products, sources of lead from fuels, pesticides, ionizing and non-ionizing radiation, chemical warfare agents, pyridostigmine use, sources of infectious agents, and physical trauma.

The results of the study indicate that subjective symptoms clearly occur more frequently among those who served in the Persian Gulf War than Persian Gulf War-era personnel who were not stationed in the Persian Gulf. However, the associations between multiple, unrelated exposures and multiple unrelated symptoms among Gulf War veterans is difficult to explain from a toxicologic perspective, but is consistent with differential recall as a function of place of service (recall bias). This methodological problem makes interpretation of associations between self-reported exposures and self-reported symptoms problematic.

Several other studies of neurological health among Persian Gulf War veterans have been conducted. To evaluate fatigue, weakness, and pain, twenty Persian Gulf War veterans with "severe" symptoms were evaluated with a variety of neurophysiological methods (Amato et al., 1997). The authors reported that 6 subjects had elevated levels of an enzyme (creatine kinase) released from damaged or inflamed muscles and that 5 subjects had "minor nonspecific abnormalities" on muscle biopsies. Despite these potential abnormalities, the authors concluded that "most of our patients had no objective evidence of neuromuscular disease" and remarked that the abnormalities found were "not believed to be clinically significant". They also concluded that "no evidence of specific neuromuscular disorder" was found among the twenty cases.

Interpretation of this study is made difficult by the absence of a comparison group. The reader is unable to determine whether the abnormalities observed would likely also be found in a group of 20 subjects who were not Persian Gulf War veterans, as is implied by the authors, or whether the abnormalities observed, in fact, suggest a problem among the Persian Gulf War subjects that would not be observed among non-Persian Gulf War veterans.

Another study intended to evaluate whether Persian Gulf War veterans were more likely to demonstrate peripheral neurological dysfunction was conducted in the United Kingdom among 14 Gulf War veterans selected from a pool of those with "unexplained illness" and a comparison group of "healthy" civilian subjects matched for age, sex, handedness, and physical activity (Jamal et al, 1996). The authors found significant group differences on three measures of peripheral nerve function, cold threshold, sural nerve latency, and median nerve sensory action potential. The authors were cautious in their conclusions and stated only that "The exact clinical relevance of these findings is unknown".

Although this study included a comparison group, the results are likely biased by differences in selection criteria used to create the two study groups. Specifically, *symptomatic* subjects were selected from among the Persian Gulf War veterans while *asymptomatic* subjects were selected from the non-Persian Gulf War population. That symptomatic subjects, from any group, have differences in health compared to asymptomatic subjects, is not surprising. Had symptomatic subjects been selected from among the civilian population and compared to asymptomatic subjects from the same civilian population, it would not be surprising if the symptomatic subjects were different from the asymptomatic subjects on tests of health, despite the fact that they came from the *same* population. To be unbiased, the same selection criteria need to be applied to

each group in order to assure that any differences observed are due to exposure or group status, and are not an artifact of the selection procedure.

A similar methodological error was made by Haley et al. (1997) when multiple neurological measures were performed on three groups of subjects: 23 Persian Gulf War veterans with a priori defined clinical "syndromes", 10 Persian Gulf War veterans without such syndromes, and 10 non-Persian Gulf War veterans without such syndromes. The authors observed that the 23 veterans with identified health complaints had more abnormalities on clinical evaluation than those without symptoms. Similar to the study of Jamal et al, (1996), the use by Haley et al. (1997) of different selection criteria for the Persian Gulf War veterans than was used for the other two groups of subjects produced a biased comparison in which the symptomatic Persian Gulf War veteran group selected was likely to have a greater prevalence of abnormalities than the other groups regardless of the actual prevalence of abnormalities in the populations from which they were selected.

At this time, little objective information is available about the actual neurological health status of Persian Gulf War veterans. One large study of a representative sample of Persian Gulf War veterans showed increased reporting of symptoms among this group but did not include objective measures of health. Smaller studies in which objective measures were used were not performed on representative samples and therefore contribute little to knowledge of health problems among Persian Gulf War veterans, as a group.

2. OVERVIEW OF EXPOSURES TO NEUROTOXICANTS DURING THE PERSIAN GULF WAR

Multiple agents with known acute or chronic effects on the central and peripheral nervous systems were used in the Persian Gulf War with resultant exposure to US service members. Such exposures include pesticides, chemical warfare agents, pyridostigmine bromide, heavy metals and organic solvents (PAC, 1996). Agents with neurotoxic potential used, or suspected of use, in the Persian Gulf are provided in Table 1 and reviewed briefly, below.

Pesticides and insect repellents. Pesticides and insect repellents provided to US service personnel in the Persian Gulf include agents in the carbamate (carbaryl, methomyl, propoxur), organophosphorus (chlorpyrifos, diazinon, dichlorvos, malathion) , chlorinated hydrocarbon (lindane), pyrethroid (permethrin and others), and other classes (e.g., DEET, rodenticdes) (PAC, 1996). In sufficient dose, a number of these agents are known to have acute and chronic effects on the human nervous system. Actual amounts of exposure of individual US service members to individual agents is reported to be

unknown or uncertain. At this time, only self report of use of specific agents is available for use in studies of Persian Gulf War veterans.

Chemical warfare agents. Information about US military personnel exposure to chemical warfare agents is limited and of unknown accuracy (PAC, 1996; CIA, 1997). Recent revelations about possible releases of chemical warfare agents following destruction of chemical warfare facilities at Muhammadiyat and Al Muthanna (reported to have resulted in no exposure to US troops), as well as following demolition of an ammunition depot at Kamisiyah, has increased concern that these agents may have a role in illness reported by many Gulf War veterans.

Pyridostigmine bromide. This is a carbamate class agent which has a *cholinergic agonist* effect on the nervous system. This occurs as a result of blockade of the enzyme *acetylcholinesterase*, necessary for regulation of the levels of the neurotransmitter acetylcholine in the nervous system. Pyridostigmine bromide, in the form of 30 mg tablets, was issued to all US service members in the Persian Gulf. DOD has estimated that 250,000 troops took this drug during the Persian Gulf War. As is the case with pesticide exposure, only self-report of pyridostigmine use is available as an estimate of the actual amount of pyridostigmine taken by any individual; no records of its use were kept during the conflict.

Heavy Metals.

Depleted uranium. The PGW was the first US use, in actual military conflict, of depleted uranium tipped shells and depleted uranium armored tanks and other vehicles. Estimates of unknown reliability from the lay press and from grass-roots advocacy groups are that at least 5000 rounds of 120mm DU-containing artillery were fired from US tanks and that tens of thousands of rounds of DU-containing armor piercing bullets were fired from US aircraft (Bukowski et al., Uranium Battlefields Home and Abroad: Depleted Uranium Use by the US Department of Defense, 1993).

Lead. Lead, in the form of tetra-ethyl lead, was an octane boosting additive in gasoline used to fuel motor vehicles used by US forces in the Persian Gulf. Tetra-ethyl lead is one of several "organo-lead" compounds. It had been used in gasoline in the United States for decades, beginning in the 1920's, and was widely discontinued from such use, for protection of the public health, beginning in the 1970's. Exposure to lead from motor vehicle emissions experienced by Persian Gulf veterans is difficult or impossible to estimate at this time. Lead is a cumulative toxicant, however, and can be measured in bone or blood years after exposure. Should it be necessary, efforts could be made to measure accumulated lead burdens in Persian Gulf veterans in an attempt to evaluate past

lead exposures. Given the short duration of exposure and the likely low intensity of exposure, such efforts would likely show no lead accumulation.

Organic Solvents. Solvents are simple organic substances that are (1) liquid at room temperature and under standard atmospheric conditions, (2) relatively non-reactive, and (3) able to dissolve a wide range of organic compounds (i.e., lipophilic). Most solvents are quite volatile. Solvents may be used for the selective dissolution of one substance from a mixture (i.e., chemical extraction), for reduction of the viscosity of another substance, or as feedstock for the production of synthetics. Some solvents, such as gasoline and other aliphatic compounds, are used as fuels. The primary uses of solvents in the PGW were as motor vehicle and jet fuel, carriers for paint and coatings, and as an agent for control of airborne dusts blown from sand.

3. OVERVIEW OF NEUROTOXICITY

3.1. Description of nervous system structure and function

The fundamental purpose of the nervous system are 1) reception (transduction) of stimulation from the environment; 2) rapid communication within the organism, including regulation of body function; 3) initiation and coordination of motor responses; and 4) "higher functioning" such as cognition, thought, emotion, and learning.

The main cellular "building-block" of the nervous system is the nerve cell or neuron (Figure 1). The neuron is capable of receiving chemical information, transducing it into bio-electrical impulses (action potentials or nerve signals), propagating those impulses over long distances along its cellular projections (axons), and converting them into chemical information for communication (neurotransmission) with other cells. Proper function of the nervous system requires maintenance of the functional integrity of neurons.

Some knowledge of neuron structure and function is useful for understanding certain kinds of neurotoxicity. The neuron is composed of 1) the cell body, the center of its metabolic activity, 2) the axon, the long cellular projection responsible for transmission of nerve impulses over long distances, and 3) the cell membrane, the barrier between the cell and its environment which is responsible for converting nerve signals into chemical signals and vice-versa. Finally, many nerve cells are surrounded by so-called "ensheathing cells" which protect the neuron and provide, in some parts of the nervous system, a form of insulation, known as myelin (a lipid rich substance) that assists in nerve transmission.

Because the nervous system contains many billions of nerve cells, they must have an efficient means of communicating with each other as well as with target tissues such as the muscles of voluntary movement. Nerve cells that communicate with one another do not actually make physical contact. Rather, they have cellular projections, called dendrites, that extend from the axon and cell body and come very near to one another, but do not touch. The dendrites contain chemicals, known as neurotransmitters (e.g., acetylcholine), that are released into the small gap (the synaptic cleft) between the cells (Figure 2). The chemicals diffuse across the synaptic cleft and stimulate receptors on the other cell. Once stimulated, the receptors cause the other cell to "fire" a nerve impulse (action potential). The neurotransmitter is removed from the cleft by enzymes responsible for destroying it (e.g., acetylcholinesterase), so that the signal can be "turned off". This form of transmission of nerve signals occurs between nerve cells as well as between nerve cells and other tissues such as muscles of voluntary movement.

The nervous system is uniquely vulnerability to toxic insult. Specific factors that may contribute to this vulnerability include 1) inability to replace lost cells, 2) long distances over which neurons must transport cellular products, 3) great surface area of the nervous system, 4) high sensitivity of neurons to energy and oxygen deficits, 5) tendency for certain nervous system components to accumulate lipophilic ("fat-seeking") substances.

The nervous system is divided structurally and functionally into the peripheral and central nervous systems. They will be discussed separately.

3.2. Peripheral nervous system

The peripheral nervous system includes the dorsal and ventral spinal roots, spinal and cranial nerves, dorsal root and other sensory ganglia, sensory and motor terminals, and the bulk of the autonomic nervous system. The peripheral nervous system has the physiologic task of 1) transmitting sensory information from receptors in the skin, soft tissues, bone and specialized sensory organs to the central nervous system for regulatory purposes or consciousness awareness, and 2) transmitting information from the central nervous system to effector organs for regulatory purposes or voluntary movement.

Exposure to toxic substances can cause both acute and chronic adverse effects on the peripheral nervous system.

3.2.1. Acute effects

Several types of chemical have immediate effects on the peripheral (and central) nervous system because of their ability to disrupt orderly transmission of nerve signals from one cell to another. Specifically, these agents act to inhibit the enzyme acetylcholinesterase,

responsible for termination of chemical transmission from one cell to another by the action of the neurotransmitter, acetylcholine. By inhibiting the acetylcholinesterase enzyme, the neurotransmitter acetylcholine remains in the synaptic cleft for a prolonged period of time, and the nerve signal it triggers is never terminated. The result is an excess of activity of the nervous system, resulting, in severe cases, in a characteristic pattern of symptoms and signs, provided in Table 2. Agents capable of producing some or all of these effects include pyridostigmine bromide, organophosphate pesticides, and chemical warfare agents of the "nerve-gas" type (which are themselves organophosphate compounds). These acute effects may be manifested within minutes of exposure to the offending agent and their severity is proportional to the amount of acetylcholinesterase inhibition induced.

3.2.2. Chronic effects

Chronic disorders of the of the peripheral nerves are known as peripheral neuropathies. Several types of peripheral neuropathy are recognized. Only one form of peripheral neuropathy, however, *distal axonopathy* or *distal axonal neuropathy*, is commonly observed following exposure to certain neurotoxicants. Distal axonopathy is characterized by disintegration of the distal portion of the largest, longest axons, with concomitant dissolution of the myelin (insulation) sheath that surrounds it. Persons with distal axonal neuropathy experience tingling, "pins and needle" sensations (i.e., paresthesias), numbness (loss of sensory acuity), muscular weakness or clumsiness, and loss of balance, especially with eyes closed or in dim light. On physical examination they may have diminished or absent deep tendon reflexes (especially in the lower extremities), loss of vibration perception and proprioception (perception of position of limbs and joints) occurring in a "stocking-glove" distribution, and, in advanced disease, diminished motor strength, especially in the lower extremities. Confirmation of the diagnosis is provided by nerve conduction study and electromyography. Substances known to produce distal axonal neuropathy are provided in Table 3.

3.3. Central nervous system

The central nervous system is composed of the brain and spinal cord. Brain neuroanatomy is complex. The brain contains between 10^{10} and 10^{11} cells which form a network consisting of 10^{15} inter-neuronal connections. Brain functions include 1) cognition, e.g., intelligence, concept formation, attention, memory, and language skills, 2) affect, e.g., mood and emotions, 3) level of consciousness, e.g., alertness and concentration, 4) coordination of motor activity, e.g., complex motor behavior such as standing erect, walking, and fine motor control of the hands, 5) conscious perception of sensory information, e.g., taste, smell, sight, and touch.

The best available system for classifying responses of the CNS to toxic insult is provided by the WHO. The system separates acute from chronic effects and provides some classification of severity for each.

3.3.1 Acute effects

Acute effects on the central nervous system are characterized by confusion, headache, dizziness, poor concentration, errors in judgment, and motor incoordination. These effects are pharmacologic in nature, and can occur after minutes to hours of exposure. The intensity of the disorder is a function of the actual amount of the toxicant present in the nervous system. This category includes the most common form of acute CNS intoxication, that which occurs following consumption of alcohol containing beverages. Like the effects of alcohol, acute intoxication by solvents is relatively rapidly reversible upon cessation of exposure (i.e., several hours). This condition follows exposure to organic solvents which are sometimes abused in order to experience the intoxicating effects. It may also follow exposure to carbon monoxide as well as other causes of oxygen depravation.

Acute exposure to high doses of neurotoxicants can produce an immediate severe impairment of brain function (acute toxic encephalopathy) which may be associated with only partially reversible structural changes such as brain edema (swelling) or profound brain disorder such as seizures or death. Depending upon the intensity of the exposure, the disorder can occur over hours to days. After removal from exposure persistent dysfunction may remain. This condition occurs following exposures of substantial magnitude to solvents, lead, and certain pesticides.

3.3.2 Chronic effects

The WHO has established three categories of increasing severity of chronic effects of exposure to neurotoxicants: organic affective syndrome, mild chronic toxic encephalopathy, and severe chronic toxic encephalopathy.

Organic affective syndrome is characterized by subjective reports of easy fatiguability, irritability, memory complaints, and difficulty concentrating. Objective neurobehavioral tests often fail to reveal measurable cognitive impairment. The onset latency varies from weeks to months. It is considered reversible following cessation of exposure. Neurotoxic substances implicated in the development of this disorder include organic solvents, lead, and organophosphate pesticides.

Mild chronic toxic encephalopathy includes many of the features of organic affective syndrome described above but also requires objective evidence of impaired cognitive

function on formal neuropsychological testing. Short-term memory is often impaired and psychomotor function may be slowed. Deterioration of personal and social functioning is also found. It occurs over months to years, depending upon the intensity of exposure, and is variably reversible. Substances implicated in the development of this disorder include organic solvents, lead, organophosphate pesticides, and possibly carbon monoxide.

Severe chronic toxic encephalopathy is a dementing condition with profound adverse effects on all activities of life. It is characterized by severe loss of intellectual ability including marked impairments of abstract thinking and judgment. Personality changes are common. It is known to occur following long-term solvent abuse; its prevalence following exposure to neurotoxicants at doses encountered in other settings (i.e., the workplace) is controversial. It is likely that risk of this condition is limited only to those with massive moderate-term or substantial long-term exposures. The condition is considered irreversible. The literature suggests that it may follow long term exposure to lead and organic solvents.

4. HEALTH EFFECTS OF NEUROTOXIC AGENTS USED IN THE PERSIAN GULF WAR

4.1. Pyridostigmine bromide

Pyridostigmine bromide is an anticholinsterase drug used in the Persian Gulf war as a protective pre-treatment for personnel at risk of exposure to "nerve gas" type chemical warfare agents. Its protective action from lethal effects of nerve agents has been demonstrated in non-human primates (Dirnhuber et al, 1979). It is a member of the carbamate class of chemical agents and has been used for decades in humans as a treatment for the neurological disorder *Myasthenia Gravis,* as well as a short acting accelerator of recovery from certain anesthetic agents. It is currently under investigation for use as treatment of the long term effects of poliomyelitis on muscle strength and fatigue (Trojan and Cashman, 1995). Related carbamate compounds are being evaluated for use in treatment of Alzheimer's disease (Winker, 1991).

Pyridostigmine bromide acts by binding to, and consequently inhibiting, acetylcholinesterase, an enzyme necessary for normal function of the nervous system. Inhibition of this enzyme permits the accumulation of the neurotransmitter acetylcholine at the cellular site of transmission of signals from one nerve cell to another or from a nerve cell to a muscle cell. Inhibition of acetylcholinesterase leads to predictable and well-established acute effects, the occurrence and severity of which are depend on the dose of pyridostigmine administered. The binding of pyridostigmine to the enzyme is reversible and of relatively short duration. This reversibility of its binding is essential to its use as a protective pretreatment for chemical warfare "nerve gas" exposure. Specifically, pyridostigmine occupies, temporarily, the location on the enzyme that nerve agents occupy permanently when they have access to it. Thus, pyridostigmine acts to block the nerve agent from binding to the enzyme, which would destroy it.

4.1.1. Acute effects

At high doses of pyridostigmine bromide, acetylcholinesterase activity levels can be inhibited to values as low as 10% or less of non-exposed levels (i.e., 90% or greater inhibition). Such individuals experience symptoms of severe poisoning, consisting of the classic syndrome of acetylcholinesterase inhibition: salivation, lacrimation (tearing of the eyes), rhinorrhea (excessive secretions from the nose), diarrhea, urination, sweating, pinpoint pupils, instability of blood pressure and heart rate, and muscle twitching (Table 2). Unlike the organophosphorus class of pesticides which also inhibit the enzyme acetylcholinesterase, pyridostigmine does not enter the brain and is not reported to cause acute effects on central nervous system function.

Pyridostigmine bromide was used at much lower doses in the Persian Gulf war than those that cause the acute toxic effects described above. Specifically, at the recommended dose

of 30 mg taken orally three times each day, acetylcholinesterase activity levels were reduced to levels 60-80% of normal (20-40% inhibition). Symptoms associated with this level of exposure are mild and variable across individuals. Several investigations of symptoms associated with use of pyridostigmine bromide among those who served in the Persian Gulf as well as among others are available in the literature and are reviewed below.

Reports of Symptoms from the Persian Gulf War: Investigations of symptoms experienced among soldiers taking pyridostigmine during the Persian Gulf War were performed by United States Army (Keeler et al., 1991) and the Israel Defense Forces (Sharabi et al., 1991).

The US Army investigation (Keeler et al., 1991) was "based on reports from medical personnel providing care to 41,650 soldiers (6.5% women) who took pyridostigmine bromide orally at 30 mg every 8 hours for periods of 1 to 7 days." Elsewhere in the article, the authors indicate that they "queried approximately 30 medical officers" to obtain the results presented. The authors reported that approximately half of all US troops who took pyridostigmine were reported by the medical officers to have experienced gastrointestinal symptoms, including gas, loose stools, abdominal cramps, and nausea. According to the medical officers, symptoms of urinary urgency and frequency were reported by 5-30% of troops, and headaches, rhinorrhea ("runny nose"), sweating, and tingling of the extremities were reported by 1% of troops. Symptoms were of sufficient severity to result in 483 clinical contacts related to pyridostigmine administration. A total of 453 of these visits were for either gastrointestinal complaints or urinary urgency. The remaining 30 visits included complaints of bad dreams, worsening of bronchitis, headache, slurred speech, rash, and vertigo. Symptoms or other problems resulted in discontinuation of pyridostigmine treatment for 28 soldiers. In their conclusion, the authors stated that "The pyridostigmine regimen followed by soldiers under wartime conditions caused a higher incidence of adverse physiologic events than had been reported in earlier peacetime evaluations." They speculated that stress, sleep deprivation, and living under field conditions may have affected responses to pyridostigmine use.

The Israel Defense Forces study (Sharabi et al., 1991) was performed on 250 soldiers of one unit who were examined 24 hours after starting to take 30 mg of pyridostigmine three times daily. The reporting of the results obtained during this study is confusing. Specifically, the authors present the frequency of selected symptoms (i.e., present or absent) and then categorize the severity of each symptom among subjects reporting the symptom as present. The first symptom severity category is called "no effect", however,

causing difficulty in interpretation of frequencies of symptoms reported. For purposes of this review, only the frequencies of those experiencing "mild/moderate" or "severe" symptoms will be presented. Among the participants, 61% reported at lest one symptom of any kind of "mild/moderate" severity. The single most common symptom was dry mouth, reported by 50% of the participants. General malaise was reported by 44.7% of the participants, weakness by 42%, and fatigue and numbness (as a single category) by 39.1%. Nausea was reported by 24% of the participants, abdominal pain by 22.1% and diarrhea by 7.7%. Symptoms were reported to occur an average of 1.6 hours after taking the medication. The authors concluded that "the frequency and severity of subjective symptoms following administration of pyridostigmine during wartime were increased", presumably in comparison to the frequency and severity of symptoms among those taking similar doses in peacetime. The authors speculated that that the "state of anxiety often accompanying war situations" might have contributed to the symptoms experienced by the soldiers.

Reports of symptoms from other sources:
Several studies have investigated symptoms, in addition to other health outcomes, in relatively short-term experimental studies of effects of pyridostigmine use. Virtually all were conducted by military organizations on healthy enlisted personnel.

In a study of the effect of pyridostigmine on acceleration tolerance, five subjects were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled, crossover experimental study (Forster et al., 1994). No significant differences were observed in reporting of fatigue or other symptoms. The authors did not specify what symptoms, in particular, were evaluated, however.

In a study of the effects of pyridostigmine on exercise tolerance in hot environments, seven subjects were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled, crossover experimental study (Cook and Kolka, 1992). Headaches were reported less frequently during treatment with pyridostigmine than with placebo. No other significant differences in symptoms were observed although the authors did not specify what other symptoms were investigated. When questioned, subjects were not able to indicate correctly whether they were treated with pyridostigmine or placebo, further suggesting that subjective symptoms were absent or insignificant in severity.

In a study of pyridostigmine use on in-aircraft performance of flight crews, 21 subjects were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled study (Gawron et al., 1990). Subjective symptoms were not reported.

However, when subjects were asked to guess whether they had taken placebo or pyridostigmine, 52% of their responses were correct, suggesting that few or no symptoms were present.

Studies of objective outcomes: Several short-term experimental studies have investigated the effects of pyridostigmine on performance of selected tasks as well as on changes in physiology in humans and non-human primates. In one observational study, effects of pyridostigmine on blood pressure were found and discussed.

In a study of the effects of pyridostigmine on pilot performance in an aircraft flight simulator, ten experienced pilots between ages 21 and 33 years were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled, crossover experimental study (Izraeli et al., 1990). Average whole blood cholinesterase inhibition was 29% (SD=6.5%). The outcomes examined were the percent of time outside of prescribed acceptable performance limits of simulated flight and the magnitude of such deviations. No significant differences in performance were observed for any of the outcomes examined. The average number of symptoms reported by subjects was nearly significantly greater while taking pyridostigmine (mean symptoms=1.08) than while taking placebo (mean symptoms=0.7; $p<0.10$). The authors reported that symptoms were categorized as "minor" by all subjects.

In a study of the effects of pyridostigmine on neuromuscular function, 34 subjects between the ages of 18 and 20 years were administered 30 mg of pyridostigmine daily in a double blind, placebo controlled experimental study (Glikson et al., 1991). Average whole blood cholinesterase inhibition was 23%. Strength tests were performed of handgrip, knee flexor and extensor muscles, and elbow flexor and extensor muscles. In addition, muscle endurance tests were administered. Finally, motor nerve conduction measures, repetitive stimulation, and electromyography tests were administered to a subgroup of participants. After eight days of treatment, a slight improvement in test results in the placebo group, but not the treatment group, resulted in a subtle trend towards a difference in performance between the groups. Repeat testing five days after the termination of treatment showed no difference in performance between the two groups.

In a study of the effects of pyridostigmine on exercise tolerance in hot environments, seven subjects (mean age 21.4 years) were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled, crossover experimental study (Cook and Kolka, 1992). Average red blood cell acetylcholinesterase inhibition was 32.3%. Diastolic blood pressure, pupil size, core body temperature, and grip strength were

statistically significantly affected by pyridostigmine treatment. Specifically, mean blood pressure was slightly lower, pupil size was smaller, temperature was slightly higher, and grip strength was slightly lower during pyridostigmine administration than during placebo administration. The authors concluded that use of pyridostigmine as pretreatment for protection against nerve agent poisoning "was shown to induce few side effects of clinical significance among young, healthy, soldiers performing moderate intensity exercise in the heat."

In a study of pyridostigmine use on in-aircraft performance of flight crews, 21 subjects age 25 to 44 years (mean 32.9 years) were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled study (Gawron et al., 1990). Of the 12 aircraft control and mission completion tasks evaluated, differences between pyridostigmine and placebo were observed for two, and a drug by task interaction was observed for a third. The pattern of effects was heterogeneous with respect to adverse or beneficial effects of pyridostigmine administration. The authors concluded that "Overall, pilot flight performance and crew coordination were not degraded by pyridostigmine."

In a study of the effects of pyridostigmine on acceleration tolerance, five subjects (mean age 26 years) were administered 30 mg pyridostigmine three times daily in a double blind, placebo controlled, crossover experimental study (Forster et al., 1994). Performance tasks evaluated under both conditions (drug and placebo) following exposure to whole body acceleration were selected to permit evaluation of sensory, cognitive, and motor function. No significant differences were observed between pyridostigmine and placebo on the performance tasks. The authors concluded that no "significant degradation in optimum tolerance and performance of normal aircrew taking prophylactic doses of pyridostigmine" were expected.

The US Army investigation (Keeler et al., 1991) reported only one physiologic consequence of pyridostigmine bromide use. Specifically, clinically important blood pressure elevations were observed in two soldiers. Because these cases of elevated blood pressure came to medical attention as a result of symptoms associated with the disorder, and because no screening program was in place for identification of asymptomatic cases of elevated blood pressure, the authors included that the two cases "may have represented a more prevalent phenomenon."

4.1.2. Chronic effects

No studies of the long-term effects of pyridostigmine bromide on healthy human populations were found.

4.1.3. Relationship to Gulf War Veterans' health conditions

Pyridostigmine bromide is a carbamate compound used in the Persian Gulf War as a prophylactic pre-treatment for protection against attack with chemical warfare agents. Pyridostigmine is known to cause acute symptoms including abdominal discomfort, diarrhea, and urinary urgency consistent with its pharmacologic action; such symptoms were documented among troops in the Persian Gulf. No evidence was found in the literature that pyridostigmine bromide causes long term adverse effects on the central nervous system; however, no clinical or epidemiological studies were found to demonstrate this conclusively among healthy young adults. In support of the absence of long-term effects of pyridostigmine on the brain is that fact that it is not able to penetrate the blood brain barrier and therefore does not have access to the brain. Additional anecdotal evidence for the safety of pyridostigmine comes from its use, at doses considerably higher than those used by troops in the Persian Gulf, by persons with the neurological disorder Myasthenia Gravis. Among those with this disease, symptoms similar to those reported by Gulf War veterans have not been reported. Finally, the class of chemical agent to which pyridostigmine belongs, carbamates, widely used in agriculture, are not known to have long-term effects on the nervous system.

4.2. Nerve agents

Chemical warfare agents known as "nerve gas" are members of the organophosphate class of chemical compounds and act on the human body in the same way as do organophosphate pesticides. Specifically, the organophosphate nerve agents act to bind irreversibly the enzyme acetylcholinesterase. Accumulation of the intended substrate of acetylcholinesterase, the neurotransmitter acetylcholine, results in the characteristic complex of symptoms described for this class of compounds (Table 1). Unlike pyridostigmine, the organophosphate chemical warfare agents are capable of freely penetrating the brain and can cause acute and chronic central nervous system toxicity.

Most of what is known about the effects of chemical warfare agents is a result of experimental studies of exposure to animals. However, several studies or case reports of acute human effects of exposure were identified in the literature and are reviewed. Studies of non-human primates exposed to nerve agents are of some relevance to questions of human health effects of exposure to organophosphates, and are also reviewed.

4.2.1. Acute effects

The acute effects of the nerve agent sarin (GB, isopropyl methyl phosphonofluoridate) were studied during an experiment in which ten subjects were repeatedly administered the agent (Grob and Harvey, 1957). The inhibitory activity of sarin for cholinesterase

enzymes was observed to be greater that that the organophosphate compounds tabun, TEPP, DFP, and parathion by factors of 5 (tabun) to 4000 (parathion). In addition, the binding of sarin to acetylcholinesterase was almost completely irreversible after the first hour of mixing.

Sarin was administered to the ten subjects over a three day period. When administered in a single dose, mild symptoms were produced with 0.022 mg/kg of sarin and moderate symptoms were produced with 0.028 mg/kg. These correspond to total doses of 1.54 mg and 1.96 mg to produce mild and moderate symptoms in a 70 kg (154 lb.) human. Symptoms began 20-60 minutes after oral administration of sarin. Mild symptoms lasted up to 6 hours and moderate symptoms up to 24 hours. During the 24 hour period following the disappearance of symptoms, subjects were more susceptible to the effects of an additional does of sarin than subjects who had not been recently dosed. At the time that mild symptoms were observed, a diminution in the voltage of the electroencephalogram was also observed. Following cessation of sarin administration, the electroencephalographic changes decreased gradually, but could still be detected for 4 to 18 days after the disappearance of symptoms. No long-term health effects were reported.

Behavioral toxicity of soman in non-human primates was demonstrated in a study of rhesus monkeys (Blick et al, 1994). Soman was given over a five day period. With chronic exposure, serum cholinesterase levels were inhibited to at least 85% from baseline activity level before performance decrements on an equilibrium platform (a neurobehavioral task) were observed. In other investigations, performance decrements associated with acute exposure occurred at doses that produced 65-70% inhibition of cholinesterase activity.

In order to investigate whether pretreatment with pyridostigmine prevented behavioral toxicity associated with soman exposure, rhesus monkeys were first treated with pyridostigmine in doses sufficient to inhibit 30% and 60% of serum cholinesterase activity (Blick et al., 1991). They were subsequently dosed with low levels of soman over a five day period. The pretreatment appeared to provide small and variable protection from the effects of low dose soman on an equilibrium platform task.

Acute changes in performance on an equilibrium platform task of the two cholinesterase inhibitors, pyridostigmine and soman, were compared among 16 adult rhesus monkeys (Blick et al, 1994). Soman was observed to disrupt performance at levels of acetylcholinesterase inhibition that were not associated with impaired performance when induced by pyridostigmine. This result is consistent with the known differences in brain

penetration of soman and pyridostigmine, with soman freely entering the brain and pyridostigmine blocked from the brain by the blood brain barrier.

4.2.2. Chronic effects

Five cases of accidental human poisoning with the organophosphate nerve agents soman and saran were reported by Sidell (1974). Two of the cases involved severe effects requiring hospitalization and intensive treatment, including large doses of atropine. One required endotrachial intubation and mechanical ventilation. Three cases were less severe and were observed but given no pharmacologic treatment after removal from exposure. The author was impressed by persistent psychiatric sequella following recovery from the acute effects of exposure. In both cases, marked depression requiring psychiatric intervention was observed. The three cases for whom poisoning was less severe did not experience any psychiatric sequella. The author stated that "the prolonged period of mental depression...may have been a direct effect of [sarin]". The three workers with milder symptoms of intoxication were not reported to have experienced psychiatric effects following recovery. Because of the small size of the series and the absence of information about the effects of acute life threatening illness (other than ones associated with organophosphate exposure) on mood, in general, it is not possible to distinguish between depression as a specific toxic effect of the nerve agents, *per se*, or whether it was a generalized reaction to sudden near fatal illness.

An epidemiologic study of 77 industrial workers with a history of at least one exposure to sarin and 38 unexposed industrial workers was performed to allow comparison of electroencephalogram (EEG) results at least one year after cessation of exposure (Burchfiel and Duffy, 1982). A subgroup of exposed workers called the "maximum exposure group" were required to have 1) a documented history of exposure (required for inclusion in the exposed group), 2) resultant clinical signs and symptoms consistent with exposure, and 3) inhibition of erythrocyte cholinesterase activity to a level 25% or more below the individual's pre-exposure baseline. For purposes of analysis, the mean energy within each frequency band of the EEG was compared across groups. Statistically significant differences in EEG outcomes were observed between the two exposure groups and the unexposed group. The authors concluded that the effects observed may be the "unexpected persistence of the well-known effects of acute organophosphate exposure." The study was flawed by failure to provide participation rates from among any of the exposure groups, absence of information about the demographics of any of the participants, and no apparent to efforts to control for potential confounding. Despite the fact that no firm conclusions can be made as a result of these major shortcomings, the finding of persistent effects on an objective measure of CNS activity (the EEG) in

formerly exposed workers when compared to unexposed workers is consistent with long-term effects of exposure at levels that did not cause acute toxicity.

4.2.3. Relationship to Gulf War Veterans' health conditions

Reports of exposure to nerve agents have evolved over the years following the Persian Gulf War. Most recently, it appears that some release with possible exposure to chemical warfare agents occurred following destruction of an Iraqi munitions depot at Khamisiyah. Examination of the likely magnitude of exposure and the likely direction taken by the airborne plume smoke created by the destruction of the munitions depot at Khamisiyah may shed some light on which troops were at possible risk of exposure. However, it appears that no reports of unexplained or sudden acute illness consistent with the acute effects of exposure to nerve gas were made by medical personnel in the Gulf. In the absence of exposure sufficient to produce observable acute health effects, there is no medical basis to infer that exposures to nerve agents were of sufficient magnitude to result in long-term health effects. Like the organophosphate pesticides, discussed below, the majority of medical evidence suggests that long-term health effects of exposure to chemical warfare agents occurs only when exposure intensity is sufficient to cause acute effects.

4.3. Pesticides

Organophosphate class pesticides were used in the Persian Gulf for control of insects. These substances are of the same chemical class as chemical warfare nerve agents and, in sufficient dose, have similar biological effects. Because of widespread use of organophosphate pesticides worldwide, a larger body of literature about their acute and chronic health effects on humans is available than is available for organophosphate chemical warfare agent agents.

In addition to the organophosphate class of pesticides, carbamate, pyrethroid, and organochlorine type pesticides were also used. Only the organophosphate pesticides are known to produce, under certain exposure circumstances, long-term adverse effects on the nervous system. The carbamate pesticides, although similar in acute toxicity to organophosphates, are not known to result in long-term adverse effects. Similarly, long-term adverse neurological effects of pyrethroid insecticides, and Lindane, the one organochlorine pesticide used in the Persian Gulf, have not been reported in the peer reviewed medical literature.

4.3.1. Acute effects

The acute effects of exposure to organophosphate pesticides are similar to the acute effects of pyridostigmine and nearly identical to those of chemical warfare agents (which

are also members of the organophosphate class of compounds). The reason for the similarity of effect is that all three classes of compound (carbamates, organophosphate pesticides, and organophosphate chemical warfare agents) have the same biochemical target in the nervous system, i.e., the enzyme acetylcholinesterase. Like the carbamates and organophosphate nerve agents, organophosphate pesticides are capable of binding to the acetylcholinesterase molecule and antagonizing its normal function. Unlike the carbamate class of acetylcholinesterase inhibiting agents, the binding between the organophosphate pesticide and the enzyme will become permanent and the enzyme molecule lost permanently (a process known as "aging") unless medical intervention separates the two.

Another difference between the organophosphorus class of acetylcholinesterase inhibitors and the carbamate class of acetylcholinesterase inhibitors is that the organophosphate agents are capable of entering the brain by crossing the "blood-brain barrier", a property of the brain that results in the exclusion from it of many drugs and toxic agents, including pyridostigmine (a carbamate). The result of this access to the brain is that, acutely, organophosphate agents can produce severe CNS effects, including confusion, delirium, seizures, coma, and death. In addition to these acute effects of organophosphate pesticides on the CNS, investigators have begun to examine the long-term consequences of exposure to these agents.

The acute picture of organophosphate pesticide poisoning is that of excessive cholinergic activity in the peripheral and central nervous systems. It is nearly identical to that of the organophosphate nerve agents, although the time course for onset and the severity of symptoms is different. Following exposure to sufficient doses to produce acute effects, the full clinical picture of organophosphate toxicity (Table 2) includes anxiety, restlessness, tremor, confusion, seizures, rhinorrhea (excess nasal secretions), wheezing, sweating, salivation, lacrimation (tearing of the eyes), abdominal cramps, diarrhea, vomiting, involuntary urination, heart rate instability, weakness and muscle twitching (Abou-Donia, 1992; Bardin et al., 1994; Goldfrank et al, 1981; Marrs, 1993; Namba et al., 1971). Treatment of acute organophosphate pesticide poisoning requires decontamination, support of vital functions (respiration, circulation), control of seizures, and pharmacologic reversal of the effect of organophosphate pesticides with the anticholinergic agent atropine. In addition, the binding of the organophosphate to the acetylcholinesterase molecule can be reversed prior to "aging" by administration of drugs known as oximes, the most commonly used of which is pralidoxime (2-PAM).

Exposure at doses lower than those required to produce the full clinical picture of organophosphate poisoning still result in some inhibition of the activity of the

acetylcholinesterase enzyme. This decrement in enzyme activity may be asymptomatic and can be detected by testing of blood. Such asymptomatic decrements in acetylcholinesterase levels are the basis for monitoring of agricultural workers for evidence of excessive exposure to these agents.

4.3.2. Chronic effects

Because of the extremely common use of these agents, considerable attention has been paid to the possibility of long term effects of exposure. Two types of long-term effects have been described; those involving the peripheral nervous system and those involving the central nervous system.

Peripheral nervous system effects. Exposure to some, but not all, organophosphate agents results in the disorder of the peripheral nerves known as distal axonopathy. When distal axonopathy occurs as a result of exposure to organophosphate compounds, it is called *organophosphate-induced delayed neuropathy* (OPIDN). This disorder is characterized clinically by numbness, tingling, and loss of sensation in the feet and hands, weakness of the muscles in the limbs, and, when severe, impaired balance and gait. It is the result of selective impairment of the large, heavily myelinated nerve fibers that carry sensory information associated with perception of light touch, vibration, and position of the joints and limbs in space (proprioception) as well as motor signals to the voluntary skeletal muscles. The nerve injury is characterized by degradation of the axon, the long projection of the nerve cell that functions as the "wire" along which nerve impulses travel. The axon undergoes this degradation at its most distal locations, which then progresses back towards the spinal cord (hence the name "distal axonopathy").

The ability of specific organophosphate agents to produce OPIDN is variable and does not appear to be related to the potency of their anticholinesterase activity. The induction of OPIDN appears to be a result of binding of the organophosphate with another enzyme called *neuropathy target esterase* (NTE). The affinity of various organophosphate compounds for this enzyme is independent of their affinity for acetylcholinesterase. To allow quantitative comparison of the relative capacity of organophosphates to produce OPIDN, one investigator has measured the concentration of selected organophosphates required, *in vitro*, to produce 50% inhibition (I50) of the activity of acetylcholinesterase as well as of NTE (Gordon et al,, 1983). The number produced by division of I50 for acetylcholinesterase by the I50 for NTE can be used as an index of potency to produce OPIDN standardized for potency to produce acute toxic cholinergic effects. The larger the number, the more potent the agent for production of OPIDN. The ratio was greater than one for two agricultural organophosphates (mipafox and DFP) but was 0.0056 for sarin, 0.0012 for soman, 0.0005 for tabun and 0.000001 for VX.

The results of these investigations and others showing similar low potency of nerve agents to produce OPIDN has lead the author of one major review to state: "Thus, overwhelmingly, the expectation is that nerve agents would not produce OPIDN" (Marrs, 1993). Given the relatively poor potency of nerve agents for production of OPIDN in humans, it is clear that development of OPIDN would be virtually impossible in the absence of severe overexposure to nerve agents requiring aggressive medial efforts to support life through the period of acute poisoning.

Central nervous system effects. While effects of organophosphate pesticides on the peripheral nervous system are well-described and universally accepted, effects of organophosphate pesticides on the central nervous system, especially at moderate doses, are not as well described nor universally accepted. Several investigations have been performed to evaluate the chronic CNS effects of organophosphate pesticide exposure.

In a cross sectional study of neurological and neurobehavioral function, 128 subjects identified by a state surveillance system to have been poisoned by organophosphate pesticides between 1982 and 1990 were compared to 90 referents without such history (Steenland et al, 1994). The poisoned group was divided into two subgroups; 83 "definite" cases (required to have symptoms compatible with organophosphate toxicity and documentation of inhibition of acetylcholinesterase enzyme activity) and 45 "probable" cases. Additional analyses were performed on 36 "hospitalized" cases (one or more night). Outcomes included peripheral neurological measures (nerve conductivity and vibrotactile threshold measures), neurobehavioral tests, and a test of postural stability. When analyses were performed on all poisoned subjects, performance on a test of sustained visual attention was significantly poorer among the cases than the referents. In addition, the cases reported significantly more tension and confusion than the referent subjects. When analyses were restricted to the 83 "definite" cases, significantly poorer vibrotactile threshold performance was observed in addition to the decrements observed for all poisoned subjects. Finally, when analyses were restricted to the 36 hospitalized subjects, significantly poorer performance was observed for vibrotactile thresholds, a test of sustained visual attention, and a coding speed test (symbol digit substitution). The results of the study suggest that chronic impairment of the central nervous system is detectable years following a clinically apparent episode of organophosphate pesticide poisoning.

To test the hypothesis that organophosphate pesticide exposure sufficient to cause cholinesterase inhibition, but not overt poisoning, was associated with chronic adverse neurological effects, a cross-sectional study of 45 subjects with a history of organophosphate-related inhibition of acetylcholinesterase activity and 90 unexposed

referents was performed (Ames et al., 1995). Exposed subjects were eligible for inclusion in the study if they had a history of red blood cell cholinesterase of 70% or less of baseline or plasma cholinesterase of 60% or less of baseline. In addition to meeting the criteria for cholinesterase inhibition, the subjects were required to have not had prior episodes of overt pesticide poisoning. Outcomes included peripheral neurological measures (nerve conductivity and vibrotactile threshold measures), neurobehavioral tests, and a test of postural stability. Only one measure, serial digit learning, was significantly associated with exposure group status. Paradoxically, performance on the test was better among those with a history of cholinesterase inhibition than among the unexposed. The authors concluded that the results "provide some assurance that preventing acute organophosphate poisoning may also prevent chronic neurologic sequelae."

A cross sectional study of the effect of a past episode of acute organophosphate poisoning on central neurological function was performed on 100 subjects with such a past episode and 100 referents matched for age, education, occupation, and "social position" (Savage et al., 1988). Outcomes investigated included electroencephalogram examination of brain wave patterns, tests of neurobehavioral and neuropsychological functioning, and a personality inventory. Summary measures were constructed to streamline data reporting and analyses of effect. A nonsignificant differences in EEG parameters was observed between former poisoned subjects and referents. Significant differences were observed between former exposed subjects and referents for 18 of 34 individual neurobehavioral test scores and for 4 of 5 summary measures. In addition, significant differences on several scales of the personality inventory were also observed. The results of the study are consistent with the hypothesis that prior episodes of clinically overt organophosphate poisoning are associated with persistent subtle impairment of neurobehavioral function.

In a cross-sectional study the neuropsychological performance of 146 sheep farmers exposed to organophosphate pesticides in the course of "sheep dipping" was compared to that of 143 non-exposed quarry workers (Stephens et al., 1995). Farmers were selected from a registry maintained by a trade organization; they were not selected on the basis of past health effects. A lifetime dose estimate was constructed that included the number of sheep in the farmer's flock, the number of "dips" per year performed, and the number of years using organophosphates. After controlling for effects of covariates, the farmers were observed to have significantly poorer performance on tests of sustained attention and speed of information processing. The authors stated that "It seems reasonable to conclude that chronic effects on the nervous system have occurred in this group of farmers and that these effects are likely to be associated with long-term exposure to organophosphates." No information was provided about past episodes of acute toxicity among the farmers.

A nested case-control study to evaluate neurological function was performed among the subjects of the previously described study (Beach et al., 1996). The ten most symptomatic and the ten least symptomatic farmers were selected as were ten unexposed quarry workers. Few differences in neurological examination abnormalities were observed. Only two point discrimination and calf circumference were significantly different between the two groups. Inferences made from the study are limited by its small sample size.

Fifty nine subjects with "varying degrees" of occupational exposure to organophosphate pesticides were examined with neurobehavioral tests and electroencephalogram recordings (Korsak and Sato, 1977). The specific tasks, occupations, and duration of exposures were not provided. Exposure to organophosphate pesticides was graded by one investigator blinded to health outcomes. Following grading, a median split on the distribution of exposure grades was performed to create "high" and "low" categories of exposure. After controlling for selected confounders, chronic organophosphate exposure was significantly related to performance on the Bender Visual Motor Gestalt test and the Trails B test. In addition to differences in neurobehavioral test performance, significant differences in quantitative EEG outcomes was also observed. The authors concluded that "chronic and clinically nontoxic exposure to organophosphate pesticides have definite and quantifiable effects upon apparently asymptomatic human beings."

In a study of 36 agricultural workers with a past history of hospitalization for organophosphate toxicity, results of neurobehavioral tests and symptoms survey instruments were compared to those of a non-poisoned comparison group (Rosenstock et al., 1991). Significant differences were observed for six of the neurobehavioral outcomes. In addition, the poisoned subjects reported significantly more symptoms than the referents. When the results were controlled for potential confounding by pre-morbid intellectual function by adjusting for vocabulary score, the contribution of poisoning status was reduced, but was still statistically significant. The authors concluded that "even single episodes of clinically significant organophosphate intoxication are associated with a persistent decline in neuropsychological function."

4.3.3. Relationship to Gulf War Veterans' health conditions

Exposure to organophosphate pesticides has been most convincingly associated with chronic adverse central nervous system health effects only when the exposure intensity is sufficient to produce acute toxicity consistent with acetylcholinesterase inhibition. Only one report in the literature related exposure to levels of organophosphate pesticides insufficient to produce acute effects to long-term adverse effects on the central nervous

system (Korsak and Sato, 1977). This finding has not been duplicated by other investigators.

Given the apparent absence of documented signs and symptoms characteristic of episodic acute organophosphate pesticide toxicity among soldiers deployed to the Persian Gulf, it unlikely that long-term health effects of organophosphate pesticide toxicity is responsible for the experience of symptoms described by Persian Gulf veterans.

4.4. Lead

Lead, in the form of tetra-ethyl lead, was an octane boosting additive in gasoline used to fuel motor vehicles used by US forces in the Persian Gulf. Tetra-ethyl lead is one of several "organo-lead" compounds. It was used in gasoline in the United States for decades, beginning in the 1920's, and was widely discontinued from such use, for protection of the public health, beginning in the 1970's.

Exposure to lead in gasoline occurs either during production of leaded gasoline or from exposure to tailpipe emissions from vehicles in which leaded gasoline is used. Tailpipe emissions are known to contain both organic lead and inorganic lead. Exposure to lead in the Persian Gulf War was limited to that emitted from vehicles in which leaded gasoline was used.

Both organic and inorganic lead are known to be toxic to the nervous system. Clinically, symptoms of lead intoxication include abdominal pain, fatigue, joint pain, decreased libido, headache, irritability, impotence, depression, anorexia, muscle pain, and weight loss (Culen et al., 1983). On clinical examination, physical signs of peripheral neuropathy, including paresthesias and motor weakness have been observed. Clinical examination is insensitive to central nervous system impairment; however, when subjected to formal clinical neurobehavioral evaluation, patients with lead intoxication often show impairment of multiple central nervous system functions, including visual-motor coordination, rapid motor control, memory, and nonverbal intelligence. Removal from exposure generally results in symptomatic and measurable functional improvement (Cullen et al., 1983).

Numerous epidemiologic studies have been performed to assess the effects of lead exposure on peripheral and central nervous system function. In a recent study of 60 workers from a lead-acid storage battery manufacturing facility with an average of 17 years of occupational lead exposure, sural sensory nerve evoked response amplitude and median motor nerve evoked response amplitude were significantly negatively related to time integrated blood lead concentration after adjusting for age (Kovala et al., 1997).

Sural sensory nerve evoked response amplitude was also significantly negatively related to tibial bone lead concentration. Conduction velocities were weakly, and not statistically significantly, negatively related to indices of lead exposure. Vibrotactile thresholds were also significantly related to indices of lead exposure. In addition to physiological measures of peripheral nervous system function, quantitative electroencephalograms (EEGs) were performed to investigate physiological changes in brain function. Several parameters derived from the EEG were significantly related to indices of lead exposure.

Tests of peripheral and central nervous system function were administered to 99 lead exposed foundry workers and 61 unexposed comparison workers (Baker et al., 1984). After controlling for potential confounders, ulnar motor nerve evoked response amplitude, and sural sensory nerve conduction velocity and evoked response amplitude were significantly associated with current blood lead level. Among tests of central nervous system function, exposure level was significantly correlated with performance on tests of visual intelligence, memory, and several items on a test of mood.

A prospective follow-up study of newly hired workers at a lead-acid battery manufacturing facility was performed to determine whether nerve conduction velocity changed with changes in blood lead level (Seppalainen et al., 1983). Of 89 workers initially examined with electrophysiological tests of peripheral nerve function, 23 were available for follow-up examination after one year of exposure. Workers whose blood lead levels increased over one year to greater than 30 ug/dL had significantly poorer median motor nerve conduction velocity, median sensory nerve conduction velocity, ulnar motor nerve conduction velocity, and ulnar sensory nerve conduction velocity.

Numerous additional investigations over the past thirty years have often found decrements in central and peripheral neurological function among adults with occupational exposure to lead (Bordo et al., 1982; Baloh et al., 1980; Valciukas et al., 1978a. Valciukas et al., 1978b. Stollery et al., 1989;. Hanninen et al., 1979; Mantere et al., 1984; Baker et al., 1985. Ashby, 1980) although occasional inconsistency has been observed (Spivey et al., 1980.)

4.4.1. Relationship to Gulf War Veterans' health conditions

Although leaded fuels were used in the Persian Gulf, it is unlikely that exposures to tailpipe emissions were of sufficient duration or intensity to produce any kind of clinically apparent toxicity from lead exposure. While long-term exposure to lead does result in accumulation of lead in long-term storage pools in the human body, short-term exposures result in little long-term accumulation. Neurological effects of lead exposure among adults have generally been observed only among those with daily occupational

exposure likely to be much greater than military personnel experienced as a result of tailpipe emissions. In addition, failure of symptoms to remit for years following exposure is inconsistent with lead as an etiology of unexplained symptoms experienced by some Gulf War veterans. Finally, leaded fuels were used in the United States for decades, and are still in use in many other countries worldwide. No reports of symptoms identical to those experienced by Persian Gulf veterans have emerged despite such widespread and long-term use.

4.5. Depleted uranium

Depleted uranium is a by-product of the extraction of uranium-235 (U235) from naturally occurring uranium. The U235 extracted from naturally occurring uranium is "fissionable" and is therefore used in nuclear power and nuclear arms industries. The remaining uranium, depleted of the more radioactive U235, is known as depleted uranium and is sometimes referred to as the "uranium tailing". Depleted uranium is radioactive, although less so than natural uranium, and it is chemically toxic as well, with effects primarily limited to the kidneys. Depleted uranium has, previously, had little military or industrial application.

All uranium isotopes are very dense, having nearly twice the density of lead. As a result, uranium can be used in applications where a metal of very high density is required. Military applications suitable for such this material include munitions production (armor piercing bullets and artillery shells) and armor for tanks and personnel carriers (United States General Accounting Office, 1993.). The PGW was the first US use, in actual military conflict, of depleted uranium tipped shells and depleted uranium armored tanks and other vehicles. Estimates of unknown reliability from the lay press and from grass-roots advocacy groups are that at least 5000 rounds of 120mm DU-containing artillery were fired from US tanks and that tens of thousands of rounds of DU-containing armor piercing bullets were fired from US aircraft (Bukowski et al., 1993).

At the current time, estimates of the total number of military personnel who had any exposure to depleted uranium are not available. Exposure may have occurred to personnel in vehicles penetrated by depleted uranium rounds as well as personnel involved in recovery and repair of vehicles damaged by depleted uranium containing rounds. The Army has reportedly identified 35 soldiers who were injured in combat vehicles damaged by depleted uranium munitions, 22 of whom likely were wounded by DU containing shrapnel. In addition, 27 soldiers involved in damage assessment and preparation for shipment of damaged combat vehicles have reported exposure to DU during those activities. Other with potential exposure to DU include maintenance

personnel who worked on damaged vehicles (United States General Accounting Office, 1993).

Health risks associated with exposure to depleted uranium include chemotoxicity as well as those associated with radiation exposure. The main long-term health effect of exposure to radiation is cancer. The actual risk is proportional to the delivered dose of radioactivity. Long-term, low dose radiation is not known as a neurotoxicant and is not likely related to neurological complaints observed among PGW veterans.

The primary non-radiation health effect of exposure to uranium (depleted or non-depleted) is toxicity to the kidneys (Thun et al., 1985; Leggett, 1989; Morris and Meinhold, 1995). Renal toxicity of DU is the basis for limits on occupational exposure to un-enriched uranium (Voelz, 1992). One recent report of kidney histopathology obtained at autopsy from workers with low level occupational exposure to uranium, however, failed to identify tissue effects (Russell et al., 1996). Exposures in that study were an order of magnitude lower than the current accepted permissible exposure level for occupational exposure to uranium.

4.5.1. Relationship to Gulf War Veterans' health conditions

Exposure to uranium, depleted or non-depleted, is not known to produce adverse effects on the nervous system. Reports of exposure to depleted uranium among soldiers in the Persian Gulf, although uncertain, suggest limited numbers of involved personnel. These facts make extremely unlikely that exposure to depleted uranium as appears to have occurred in the Gulf War is responsible, wholly or in part, for the array of symptoms observed among Gulf War veterans.

4.6. DEET personal insect repellent

The insect repellent N,N-Diethyl-*m*-toluamide, commonly known in the United States as DEET, is widely regarded as the most effective topical insect repellent and is the major active ingredient in virtually all products marketed for this purpose (Robbins and Cherniack, 1986; Osimitz and Murphy, 1997). The literature is inconsistent regarding when DEET was developed and by whom. Authors of one report state that it was developed by the US Department of Agriculture for use by the military in 1946 (Osimitz and Murphy, 1997) whereas those of another report state that it was "introduced" by the Hercules Chemical Corporation in 1955. It was registered for use by the general public in 1957 and has been in civilian and military use since then.

DEET is one of only two insecticides approved by the US Environmental Protection Agency for topical application to humans. The other, citronella, is considered less

effective (Osimitz and Murphy, 1997). DEET has been a remarkably successful commercial product and is currently estimated to be used, in some form, by some 80 million persons in the United States, annually (Stinecipher and Shah, 1997). Although intended for topical use, DEET is known to be partially absorbed through the skin, resulting in systemic distribution. It is metabolized and excreted relatively rapidly, although some of the absorbed dose may be retained in the skin for longer periods.

Despite relatively long-term use by millions of people, only a few reports of toxicity were found in the medical literature. Most descriptions of human toxicity come from case reports of individual exposures or from small case series. One article reports the experience of regional poison control centers regarding this agent. A Health Hazard Evaluation performed by NIOSH is reviewed by authors of two papers but is not available in the peer-reviewed medical literature.

Among the 20 individuals described in case reports, children were the most frequently affected age group and neurological effects were the most commonly reported adverse consequence of exposure, with the majority experiencing seizures. Of the fourteen case reports of major neurological consequences of DEET exposure, three are known to have died, nine recovered, and one was unknown (Osimitz and Murphy, 1997).

A review of 9,086 reports to regional poison control centers of human DEET exposure between 1985 and 1989 found that 98.9% experienced either no effect or had short lived "minor" effects (Veltri et al., 1994). The majority of effects in this group were irritation of the skin or mucous membranes. Sixty-six reports to poison control centers involved persons with "moderate" effects, i.e., more severe or more prolonged than minor effects, but still resolving fully without sequelae. Five reports involved persons with "major" effects, including seizures and death.

The only report of occupationally related DEET toxicity comes from a non-peer-reviewed Health Hazard Evaluation performed by NIOSH and described by Osimitz and Murphy (1997) and Robbins and Cherniack (1986). According to these authors, National Park Service workers in the Florida Everglades reported episodes of confusion and a sensation of decreased sweating while using DEET. A questionnaire provided to 143 workers showed a significant increase in the prevalence of muscle cramping, insomnia, irritability and depression among those who had an estimated dermal exposure to 4.25 grams or more of DEET in comparison to those with lower exposures. The more highly exposed group also reported more skin rashes and difficulty starting and stopping the urinary stream. Inadequate control of confounding and failure of the investigators to replicate the

results in a follow-up survey were criticisms of the initial results cited by Osimitz and Murphy (1997).

4.6.1. Relationship to Gulf War Veterans' health conditions

The insect repellent DEET has been used by tens of millions of Americans for several decades. It is intended for topical use but is absorbed through the skin and distributed throughout the body. Given the widespread use of this substance, however, the literature describing adverse effects associated with its use is remarkably small. The primary severe adverse effect appears to be neurological, however, with seizures as the most commonly reported event. Only one study of adult occupational exposure is described, with neurological symptoms occurring among the most heavily exposed group of workers. No attempts to reproduce the results obtained from the NIOSH study of workers exposed to DEET have been reported in the peer-reviewed literature.

Several factors suggest that DEET is not responsible for the symptoms reported by some veterans of the Persian Gulf War. First, the product appears to have adverse effects only on a very small proportion of those who use it. Second, the main adverse neurological effect appears to be seizures, a condition not reported commonly Gulf War veterans, although one study of occupationally exposed workers has associated DEET with neurological symptoms with some similarity to those experienced by Gulf War veterans. The symptoms were experienced at the time of exposure to DEET, however; no long-term follow-up of the workers was reported. All clinical studies of adverse effects of DEET suggest full recovery occurs after withdrawal of exposure. No literature is was found that suggests that topical use of DEET results in long-term health consequences.

4.7. Solvents

Solvents are simple organic substances that are (1) liquid at room temperature, (2) relatively non-reactive, and (3) able to dissolve a wide range of organic compounds (i.e., lipophilic). Most solvents are quite volatile. Solvents may be used for the selective dissolution of one substance from a mixture (i.e., chemical extraction), for reduction of the viscosity of another substance (i.e., solvents used as "thinners"), or as feedstock for the production of synthetics. Some solvents, such as gasoline and other aliphatic compounds, are used as fuels. The primary uses of solvents in the PGW were as motor vehicle and jet fuel, carriers for paint and coatings, and as an agent for control of airborne dusts blown from sand.

Solvents can affect the central nervous system (CNS), the peripheral nervous system (PNS), or both. Short term exposure to organic solvents can cause reversible anesthesia-like depression of the CNS. Long-term, heavy exposure to solvents may cause persistent,

potentially irreversible impairment in cognitive function and affect, which may be associated with structural changes in neural tissue (NIOSH, 1987). Solvents can also cause impairment of peripheral nerve function. The effects of organic solvent exposure on the PNS and CNS are reviewed below.

4.7.1. Peripheral Nervous System

4.7.1.1. Acute effects. Organic solvents are not known to have clinically apparent acute toxicity to the peripheral nervous system.

4.7.1.2. Chronic Effects. Widespread agreement exists that the solvents *n*-hexane, methyl-n-butyl ketone, and carbon disulfide can cause peripheral neuropathy of the distal axonal type. Other solvents suspected of having peripheral nerve effects include styrene and tetrachloroethylene (Spencer and Schaumburg, 1985). Little evidence exits that other solvents cause peripheral neuropathy.

Clinically, the initial complaint associated with solvent-related peripheral neuropathy is usually symmetric numbness of the fingers and toes. Loss of cutaneous sensibility to light touch, vibration, pin prick, and temperature are present on physical examination, as are proprioceptive abnormalities and loss of the Achilles tendon reflex. Severe disease can include motor weakness and atrophy (Schaumburg et al, 1983, Buiatti et al., 1978). Electrophysiologic evaluation discovers symmetric distal electromyographic abnormalities consistent with denervation as well as mild to moderate slowing of both motor and sensory nerve conduction velocity (Mutti et al, 1982).

A characteristic feature of hexacarbon-induced peripheral neuropathy is the tendency for the disease to progress for up to 4 months following cessation of exposure (Schaumburg et al, 1983). There is no specific treatment for solvent induced peripheral neuropathy, and the degree of recovery that follows removal from exposure is proportional to the severity of disease.

4.7.2. Central Nervous System

4.7.2.1. Acute Effects. The depressant effects of solvents are well-recognized; historically, some have been used as general anesthetics. The ability of solvents to rapidly produce narcotic effects constitutes their main acute health hazard (Laine and Riihimäki, 1986). Acute effects of exposure to solvents are pharmacologic and their intensity is generally proportional to their concentration in the brain. There may be initial euphoria and disinhibition. Higher intensity exposure may result in prenarcosis symptoms such as dizziness, nausea and vomiting, incoordination, paresthesias, and slurred speech. The symptoms are generally transient, disappearing quickly after exposure is terminated.

Overexposure can lead to seizures, coma, and death in severe cases. The likely mechanism is anoxia following depression of central control of respiration.

Subclinical effects of acute exposure to solvents in humans have been studied in the laboratory under experimental control. Typically, healthy volunteers are exposed for a few hours in chambers to well-controlled concentrations of solvent at or below the occupational permissible exposure limit. At least 50 experimental studies of effects in humans of acute exposure to solvents have been published. The most-studied solvents have been toluene, xylene, styrene, trichloroethylene, perchloroethylene, and methylene chloride. These studies have typically shown, at most, subtle effects of short-term exposure at the current exposure limit values (Gamberale, 1986, Iregren, 1988, Dick, 1988). The reader should be aware of some limitations in interpreting the results of short-term experimental studies of solvent exposure, however. Specifically, information on extrapolation from effects of short-term exposure to those from chronic exposure or from subtle effects to more severe effects is lacking.

4.7.2.2. Chronic Effects. The nonspecific effects of long-term exposure to solvents range from a general negative affective state to a subtle reduction in functional reserve capacity to perform well when fatigued or in a distracting environment, to mild slowing of psychomotor performance, to memory disturbance, and finally to severe intellectual deficits (Hanninen, 1986). The most severe condition, which has been called psychoorganic syndrome, presenile dementia, and severe chronic toxic encephalopathy, is also the most controversial. Although the existence of chronic solvent encephalopathy has been questioned (Grasso et al, 1984), experts now generally agree that it occurs but not on its prevalence (Danish Ministry of the Environment, 1991, Hogstedt, 1994). Epidemiologic studies of the effects of solvents on the central nervous system have been either registry-based studies of neuropsychiatric disability or cross-sectional studies comparing exposed and unexposed groups for differences in prevalence of symptoms, neurobehavioral performance level, or other measures of CNS function.

Neuropsychiatric Disability. A number of studies based on pension or disability registries in relation to solvent exposure have been published (Axelson et al, 1976, Millelsen, 1980, Lindstrom et al, 1984; van Vliet et al., 1989; Brackbill et al., 1990; Riise et al., 1995). In general, risk of disability award on the basis of neuropsychiatric illness was found to be elevated about twofold among solvent-exposed groups such as painters and floorlayers in comparison to non-solvent exposed groups such as carpenters and electricians, although there have been some exceptions to this trend (Cherry and Waldron, 1984). In addition to registry based studies, case-control studies of the association between occupational solvent exposure and 1) psychiatric disorders requiring hospitalization (Labreche et al.,

impairment at the initial examination

1992), 2) medical disability retirement resulting from chronic neurological and psychiatric disease (Nelson et al., 1994), and 3) organic brain damage (Cherry et al., 1992) have been published. Only in the study of organic brain damage was a significant association with solvent exposure observed.

Symptoms: The rates of reporting of some symptoms were elevated above the rate reported by comparison groups in the vast majority of published epidemiologic studies of solvent-exposed workers. Those symptoms most often elevated were fatigue, irritability, depression, headaches, poor concentration, and forgetfulness.

Neurobehavioral tests: Tests of neurobehavioral function permit noninvasive assessment the functional integrity of the CNS. It is generally accepted that the tests administered should sample from the perceptual, motor, psychomotor, learning-memory, attentional, and affective functional domains.

In the last 15 years at least 16 epidemiologic studies of solvent-exposed painters (car, industrial, construction, and combinations of the three) and four studies of solvent-exposed paint-manufacturing workers exposed to mixed solvents have been published. At least 11 studies of fiberglass fabrication workers exposed almost exclusively to styrene and at least four studies of printers exposed primarily to toluene have been published. Many other epidemiologic studies of heterogeneous groups of solvent-exposed workers have also been reported. Although some inconsistencies exist, neurobehavioral performance was reported to be poorer in the solvent-exposed groups than in the referent groups in most of these studies (e.g., Spurgeon et al., 1992; Rasmussen et al., 1993; White et al., 1995; Daniell et al., 1993; Hänninen et al., 1991).

Other tests: Testing of three sensory systems, olfactory, auditory, and visual, that may be early targets for solvent toxicity have been reported in the literature. Decrements in "smell identification" among nonsmoker paint-manufacturing workers were observed in one study in the US (Schwartz et al., 1990) but the findings were not observed in a Swedish study of similarly exposed workers (Sandmark et al., 1989). Loss of hearing has been associated with occupational exposure to solvents. In one study of self-reported hearing difficulty, a significant association was observed with self-reported occupational solvent exposure (Jacobsen et al., 1993). Authors of another study, in which audiometry was performed to characterize auditory function, observed a strong effect of solvent exposure on hearing (Morata et al., 1994; Morata et al., 1995; Johnson et al., 1995). In addition, a statistically significant interaction between solvent exposure and noise exposure was observed. Deficits in performance of a simple color vision test have been reported among several solvent-exposed groups (Riatta et al., 1981; Mergler and Blain,

1987; Mergler et al., 1988; Mergler et al., 1990), however, these results have not been replicated in other investigations (Ruijten et al., 1990; Baird et al., 1994; Nakatsuka et al., 1992). Changes in visual contrast sensitivity have also been reported for solvent-exposed microelectronics workers (Frenette et al., 1991) and a series of solvent-exposed patients (Donoghue et al., 1995).

Many of the studies of chronic effects of solvent exposure, particularly those not reporting effects, may not have included in the exposed group enough subjects with sufficiently intense exposure to produce impairment of the nervous system. This explanation requires the assumption of an effective threshold of cumulative exposure, which many experts have estimated informally to be about 10 years of relatively "heavy" exposure. Authors of one study (Mikkelsen et al., 1988) have estimated that there may be little risk of organic brain damage with less than 13 years' exposure to the equivalent of a time-weighted average of 40 PPM of white spirit.

Follow-up observation of patients diagnosed as having chronic toxic encephalopathy have indicated that this condition is persistent in most cases even after exposure has stopped, but it does not appear to be rapidly progressive. Among 32 such patients in Sweden followed an average 4 years after diagnosis, findings at follow-up were very similar to those at their initial evaluations for physical examination and neurobehavioral performance (Ørbaek and Lindgren, 1988), CT (Ørbaek et al., 1987), peripheral nerve conduction measures (Ørbaek et al., 1988), and regional blood flow (Hagstadius et al., 1989). In a recent multicenter long-term follow-up study of another 111 solvent-exposed workers in Sweden (Edling et al., 1990), the workers who showed neurobehavioral impairment at the initial examination showed persistence of effects after removal from exposure for at least 5 years, but rapid progression of impairment was not evident. There was evidence that removal from exposure led to symptomatic improvement in workers who had symptoms but no signs of impaired intellectual function. Finally, a Danish study has observed continued elevated reporting of symptoms of impaired memory and concentration in a group of more than 50 solvent-exposed workers at 5- and 10-year follow-up (Gregersen, 1988).

4.7.3. Relationship to Gulf War Veterans' health conditions

Chronic peripheral nervous system effects are well-established for a few selected solvents. Acute, reversible central nervous system effects are common with all solvents. Chronic, apparently fixed, adverse effects of solvents on the central nervous system have been reported in the literature, with general agreement that long-term occupational exposure to solvents is associated with adverse effects on multiple central nervous system domains and that persons who suffer from such effects report symptoms of the type

reported by some Persian Gulf War veterans, including depression, impaired concentration, and memory loss. The duration and intensity of exposure required to cause such effects and the potential severity of such effects is somewhat controversial, however, although most authorities agree that at least ten years of occupational (daily or near daily) exposure is required before chronic central nervous system effects are seen.

Except for cases of massive solvent overexposure resulting in severe acute effects (loss of consciousness, seizures, respiratory arrest) or deliberate inhalational abuse of organic solvents, exposures of less than ten years duration are generally considered inadequate to produce long-term or permanent impairment of the central nervous system. Exposures to organic solvents in the Persian Gulf appear to be of insufficient duration, and may have been of insufficient intensity, to produce chronic adverse effects on the CNS. Furthermore, following abatement of exposure, symptoms from these exposures are expected to stabilize or show some improvement.

4.8. Combined effects of agents used in the Persian Gulf War

No studies of the combined effects on humans of neurotoxic agents used in the Persian Gulf War were found. Two studies performed on non-primate animals examined the effects of concurrent exposure to several agents used in the Persian Gulf War.

In one study, groups of five adult leghorn laying hens (*Gallus gallus* domesticus) were dosed with DEET, pyridostigmine bromide, and permethrin, as single agents and in several combinations (Abou-Donia et al., 1996a). The dose and route of administration for each of the agents were: pyridostigmine bromide - 5 mg/kg/d given by mouth; DEET 500mg/kg/d administered by subcutaneous injection; and permethrin 500 mg/kg/d administered by subcutaneous injection. Health outcomes included survival time, tremor, locomotor dysfunction, and histopathological alterations of nervous system tissue after death or sacrifice. In general, greater abnormality was observed following administration of multiple agents as opposed to single agents. The greatest frequency of abnormality was observed following administration of all three agents simultaneously. The authors concluded that co-exposure to relatively high doses of pyridostigmine bromide, DEET, and permethrin results in neurotoxicity not observed when each substance was administered individually.

In another study of essentially identical experimental design, pyridostigmine bromide, DEET, and chlorpyrifos were administered to groups of five hens (Abou-Donia et al., 1996b). Results were similar to those obtained in the original study. They concluded that the study "confirmed our previous finding that co-exposure to sub-neurotoxic doses of PB and pesticide chemicals resulted in increased neurotoxicity". They also concluded

that "Further studies are needed to investigate the potential neurologic deficits resulting from co-exposure to these chemicals at dosages to which the Gulf War veterans may have been exposed."

The relevance of these two studies to health complaints of Gulf War veterans is substantially limited. First, although the hen is considered a useful model for human peripheral neuropathy induced by organophosphate compounds, the relevance of this specie to humans regarding multiple symptoms experienced by Persian Gulf War veterans is unknown. Second, illnesses experienced by Persian Gulf War veterans appear to be mainly characterized by chronic symptoms rather than overt acute signs of disease or short-term mortality, the main outcomes employed in these studies. Third, doses of potentially toxic agents administered in these two studies were of sufficient magnitude to result acutely in observable behavioral pathology and, in when administered in combination, substantial short-term mortality. On a per-kilogram basis, personnel in the Persian Gulf were exposed to much lower doses than were used in these studies. These factors suggest limited relevance of these studies to health concerns of Persian Gulf War veterans.

5. Conclusions and Recommendations

Multiple agents with potential toxicity to the nervous system were used by military personnel in the Persian Gulf War. Such agents include pyridostigmine bromide, chemical warfare agents ("nerve gas"), pesticides, heavy metals, DEET, and organic solvents. Each of these agents or class of agents has been previously associated with toxicity to the central or peripheral nervous systems.

Soldiers returning from the Persian Gulf have reported numerous symptoms compatible with nervous system dysfunction including fatigue, headache, sleep disturbance and "neuropsychologic complaints" including depression and memory impairment.

The concurrence among Persian Gulf War veterans of 1) exposures to a variety of agents with potential toxicity to the nervous system while serving in the Gulf and 2) the reporting of symptoms compatible with nervous system toxicity after returning from the Gulf has lead to considerable scrutiny of a possible causal association between them. In this report, detailed review is provided of the known human health effects of neurotoxicants to which personnel who served in the Persian Gulf may have been exposed. Such review has shown that neurotoxicity from exposure to pyridostigmine bromide, chemical warfare agents ("nerve gas"), pesticides, heavy metals, DEET, and organic solvents is not a likely explanation for symptoms experienced by Persian Gulf War veterans. Reasons for this conclusion vary for each individual agent or class of

agents but include insufficient duration of exposure, evidence of insufficient intensity of exposure, incompatibility of effects of exposure with symptoms reported by military personnel, and the chronicity of effects given removal from exposure.

Some concern has been focused on possible interactions of neurotoxic agents resulting in effects not observed in studies of individual agents. Scientific investigation of such interactions is extremely limited at this time. However, the factors described above, duration of exposure, intensity of exposure, compatibility of effects with exposure and chronicity of effects after removal from exposure suggest a non-neurotoxicologic mechanism for symptoms experienced by veterans from the Persian Gulf War.

Despite the current lack of evidence that exposure to neurotoxic agents in the Persian Gulf is responsible for the experience of symptoms reported by many Gulf War Veterans, many questions remain unanswered. The following recommendations are made for additional investigations to better clarify the relationship between service in the Persian Gulf and health of the nervous system.

1. Because no large formal characterization of neurological status among a representative sample of Persian Gulf War veterans is available, the actual prevalence of neurological impairment among Persian Gulf War veterans is not known. To fill this gap in knowledge, *a large study of a randomly selected sample of Persian Gulf War veterans and Persian Gulf War era veterans who did not serve in the Gulf in which objective measures of neurological and neurobehavioral function are performed should be performed.*

1. The drug pyridostigmine bromide has an impressive history of safety and efficacy among patients with the neurological disease Myasthenia Gravis. Large scale experience with the drug among healthy adults is not available, however. For this reason, *additional investigation of the long-term human health effects of pyridostigmine bromide among healthy adults should be performed. The logistics and ethical considerations of such a study may be considerable. However, should pyridostigmine bromide be used by the US military in future conflicts, accurate records should be kept to permit fruitful long-term follow-up of dose-effect relationships.*

1. The suggestion has been made elsewhere that the psychological stress of service in the Gulf may be, at least in part, responsible for chronic symptoms among Persian Gulf war veterans. While stress has been associated with adverse physical and psychological health effects, nothing is known about the effect of pyridostigmine

bromide on physical and psychological responses to perceived threat of physical harm. Because this potential interaction is virtually completely unexplored, *investigation of the effect of pyridostigmine on physical and psychological responses to perceived threat of physical harm should be performed.*

1. Little evidence suggests that symptoms experienced by Persian Gulf War veterans are due to unforeseen consequences of multiple exposures. However, this area of toxicology is not well understood and the possibility remains open. For this reason, *investigation of the effects of combined exposure to agents used in the Persian Gulf War should be performed. Whole such investigations may necessarily be performed in animals, the exposures used in such should be similar in intensity and duration to those experienced by humans under actual exposure conditions.*

1. *In the future, better efforts should be made to characterize objectively both health and hazardous exposures among US military personnel deployed to potentially hazardous duty.* Standardized, objective neurological and neurobehavioral testing of military personnel before deployment would provide useful baseline information about health status to which results of repeat testing, following deployment, could be compared. Quantitative assessment of exposure to potential hazards would provide information to compare to changes in health status that might be detected. Automated methods of neurological and neurobehavioral testing now available would allow efficient collection and storage of health information. Better record-keeping of medication administration and toxic substance allocations, and use of passive exposure dosimetry would provide quantitative information about exposure potentially toxic substances. While such efforts would require some expenditure of resources, their utility in the understanding and resolution of concerns about health following future deployments would likely show them to be wise investments.

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Table 1. Agents with neurotoxic potential to which US military personnel may have been exposed during the Persian Gulf War

1. Pyridostigmine Bromide

2. Chemical Warfare Agents
   - Sarin

3. Pesticides
   - Carbamates
   - Chlorinated hydrocarbons
   - Organophosphates

4. Depleted uranium

5. Lead

6. Insect repellents (DEET)

7. Organic solvents

8. Chemical mixtures

Table 2. Clinical effects of inhibition of the enzyme acetylcholinesterase

Effect	Carbamate*	Organophosphate	CW Nerve agents
Nicotinic (sympathetic and somatic motor activity)			
fasiculations	x	x	x
cramps	x	x	x
weakness	x	x	x
hypertension	x	x	x
rapid heart beat	x	x	x
Muscarinic (parasympathetic activity)			
salivation	x	x	x
vomiting	x	x	x
diarrhea	x	x	x
urinary incontinence	x	x	x
pupillary constriction	x	x	x
CNS			
restlessness		x	x
emotional lability		x	x
headache		x	x
confusion		x	x
slurred speech		x	x
impaired coordination		x	x
coma		x	x
seizures		x	x

* Including pyridostigmine bromide

Table 3. Substances known to produce distal axonal neuropathy

Metals
- lead
- arsenic
- mercury
- thallium

Solvents
- hexacarbons (2,5-hexanedione)
  - n-hexane
  - methyl-n-butyl ketone
- carbon disulfide

Organophosphorous esters (OPs)
- selected organophosphate pesticides
- triorthocresyl phosphate (TOCP)

Plastic monomers
- acrylamide
- styrene
- dimethylaminopropionitrile (DMAPN)

Figure Legend

Figure 1. Cellular components of the neuron.

Figure 2. Components of synaptic transmission.

Figure 1

Figure 2