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# 9 Gulf War Syndrome: Questions, Some Answers, and the Future of Deployment Surveillance

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# I. INTRODUCTION

Ten years following the Persian Gulf conflict, uncertainty remains regarding potential exposures, health risks, and adverse outcomes in the 697,000 U.S. troops deployed to Operations Desert Shield/Desert Storm. While this was not the first wartime cohort to report medically unexplained symptoms, it is certainly the most studied. Somatic complaints such as fatigue, shortness of breath, headache, sleep disturbance, forgetfulness, and impaired concentration have been reported following armed conflicts since the Civil War (Table 9.1).<sup>1</sup> The authors described two general categories of war-related illness—a poorly understood group thought to be associated with physiological disease, and another group of psychological illnesses attributed to wartime stress. “War syndromes have not been consistently defined or identified by a pathognomonic physical sign or laboratory abnormality. As a result, the diagnosis of a physiological or psychological illness in individual patients has been imprecise and has depended on self-reported symptoms and the impression of the examining physician.”

Past wartime deployments have resulted in concerns over specific potential exposures as well. Following the Vietnam War, uncertainty relating to exposure to herbicides ultimately led to the Congressional passage of Public Law 102–4 (the “Agent Orange Act of 1991”). This legislation directed the National Academy of Sciences (NAS) to conduct a comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of these herbicides, including dioxin. The review was intended to determine, to the extent that available data permitted, whether there was: (1) a statistical association between herbicide exposure and disease outcomes, (2) an increased risk of the disease among those exposed to herbicides during Vietnam service, and (3) whether there was a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and disease.<sup>2</sup> The NAS committee faced considerable issues of cohort reconstruction and dose estimation in the absence of quantified exposure information, as well as difficulties in assessing causality. Ultimately, epidemiological studies were reviewed, and specific health outcomes were assigned to one of four categories of evidence based on “statistical associations,” not on causality.

Similarly, following the Persian Gulf War (PGW), the Department of Defense (DoD) and the Department of Veterans Administration (DVA) faced basic questions of exposure, outcome, and association. These questions address exposures that were known or possible for the deployed cohort, the potential outcomes of importance that might be associated with such exposures, and the studies and actions undertaken to evaluate these associations. Multiple expert boards and committees have studied PGW veterans and health consequences of service in the Gulf (Table 9.2).<sup>3–8</sup> The

**TABLE 9.1**  
**Somatic Symptoms Commonly Associated with War-Related Medical and Psychological Illnesses**

Symptom	War and Illness					
	U.S. Civil War DaCosta Syndrome	World War I	World War II Combat Stress Reaction	Vietnam Agent Orange Exposure	Vietnam Post-Traumatic Stress	Persian Gulf Unexplained Illness
Fatigue and exhaustion	+	+	+	+	+	+
Shortness of breath	+	+	+		+	+
Palpitations and tachycardia	+	+	+		+	
Precordial pain	+	+			+	+
Headache	+	+	+	+	+	+
Muscle or joint pain				+	+	+
Diarrhea	+		+	+	+	+
Excessive sweating	+	+	+			
Dizziness	+	+	+	+	+	
Fainting	+	+				
Disturbed sleep		+	+	+	+	+
Forgetfulness		+	+	+	+	+
Difficulty concentrating		+	+	+	+	+

*Note:* A plus sign indicates a commonly reported symptom.

*Source:* Hyams, K.C., Wignall, S.W., and Roswell, R., *Ann. Intern. Med.*, 125, 398, 1996. With permission.

Defense Science Board (DSB) panel was originally charged to evaluate the scientific and medical evidence relating to long-term health effects of low levels of neurotoxic agents, but expanded its scope to the full range of exposures to low levels of chemicals, as well as environmental pollutants, biological agents, and other health hazards.<sup>3</sup> The task force was unable to define the medical nature and cause or causes of a Gulf War Syndrome, and did not identify any cause-and-effect relationships between putative exposures and an undefined illness. The panel did not find evidence to suggest that illnesses suffered by PGW veterans were related to chemical or biological weapons.<sup>3</sup> In April 1994, the National Institutes of Health Technology Assessment Workshop was held to consider the evidence for increased incidence of unexpected illness attributable to service in the PGW and the components of a practical case definition. They further considered the plausible etiologies and biological explanations for any unexpected illness and future research deemed necessary.<sup>4</sup> The panel

**TABLE 9.2****Expert Panels Evaluating Health Effects of Gulf War Service**

<b>Panel</b>	<b>Funding</b>	<b>Report</b>
Task Force on PGW Health Effects, Defense Science Board	DoD	Report to the Under Secretary of Acquisition, DSB, 1994
National Institutes of Health Technology Assessment Workshop Panel	Interagency	NIH Technology Assessment Panel, 1994
Institute of Medicine Committee to Evaluate the Comprehensive Clinical Evaluation Program	DoD	IOM 1996, Evaluation of the U.S. Department of Defense Persian Gulf Comprehensive Clinical Evaluation Program
Presidential Advisory Committee on Gulf War Veteran's Illnesses	DoD	Presidential Advisory Committee on Gulf War Veteran's Illnesses Interim Report 1996, Final Report 1996
Institute of Medicine Committee to Review the Health Consequences of Service during the Persian Gulf War	DoD	Health Consequences of Service During the Persian Gulf War, IOM, 1996

was unable to formulate a case definition to determine whether plausible exposures were associated with outcomes (unexplained illnesses). The panel did note the lack of available data on exposures and made a series of recommendations regarding future research. Both the Institute of Medicine (IOM) and the Presidential Advisory Committee (PAC) noted that the formalized registries established by the DoD and the DVA, which provide free medical evaluation to concerned PGW veterans, served an important purpose but were not designed to answer epidemiological questions.<sup>5-8</sup> The PAC noted that the current scientific evidence did not support a causal link between the symptoms and illnesses reported by PGW veterans and exposures while in the Gulf to pesticides, chemical warfare agents, biological warfare agents, vaccines, pyridostigmine bromide, infectious diseases, depleted uranium, oil well fires and smoke, and petroleum products.<sup>8</sup> The PAC determined, however, that the investigation of possible exposures of troops to chemical and biological agents was "superficial and inadequate." They made a series of recommendations regarding improved communication, better data on baseline health conditions of troops, locations and exposures on deployments, and better services to veterans. The IOM reviewed the studies that were available to date and reported that the scope and focus was "of uneven depth and quality" and noted a series of potential biases.<sup>5,6</sup> They considered the initial research efforts "poorly organized both strategically and tactically." The committee identified a lack of reference population for many data collection and analysis activities, and noted that predeployment demographic information on health and medical interventions such as vaccinations was incomplete and possibly inaccurate. In the evaluation of health outcomes, there was little standardization and operationalization of data on disease symptoms and signs. Further, follow-up was difficult and incomplete, and

DoD and DVA databases did not communicate effectively. It was noted that very little personalized exposure information was available, and defining relevant control groups and obtaining data for them were very difficult. The committee also noted that the “full range of potential biases (selection bias, follow-up bias, dropout bias, observation bias, ascertainment bias, and recall bias) was operating. These problems further limit the ability of even the most expert and well-funded investigation to identify health outcomes linked to specific exposures or risk factors.”<sup>6</sup> The Government Accounting Office recommended a re-examination of research emphasis in 1997.<sup>9</sup> They noted that the majority of research focused on the prevalence and cause of Gulf War illnesses, rather than diagnosis, treatment, and prevention. “While this epidemiological research will provide descriptive data on veterans’ illnesses, methodological problems are likely to prevent researchers from providing precise, accurate, and conclusive answers regarding the causes of veterans’ illnesses. Without accurate exposure information, the investment of millions of dollars in further epidemiological research on the risk factors or potential causes for veterans’ illnesses may result in little return.”<sup>9</sup>

In summary, the panels and committees evaluating the available data noted a significant lack of exposure data on the population or populations at risk. Given these constraints, limited conclusions could be drawn concerning exposure and outcome relationships. The following sections discuss the population at risk and various subsets and provide an overview of outcomes reported in these populations.

## II. THE POPULATION AT RISK

Although early epidemiological studies typically focused on infectious diseases and death, current epidemiology has a broader application as “the study of the distribution and determinants of health-related states and events in specified populations and the application of this study to the control of health problems.”<sup>10</sup> The population under study is logically dependent on the study question. Ideally, the two groups should differ only with respect to the exposure under study and have equal opportunity for the outcome under consideration. Differences between the two groups with respect to other relevant factors, for example, age, sex, general state of health, or smoking habits, known as confounding variables, should be addressed. Studies of a population exposed to a factor under study and the comparable unexposed control group must recognize known confounders for the outcome or outcomes of interest and measure the rate of exposure to confounders in both groups so that adjustment can be performed in the analysis. Apart from any relevant specific factors, consideration should be given to whether or not the exposed population has more frequent occupational or other relevant exposures, higher rates of disease or is otherwise more at risk for the outcome of interest due to reasons totally unrelated to the exposure under question. This information is typically not available when populations are studied at the community level—by county cancer rates, for example—and thus, differences in individual factors and their impact on the findings of the study cannot be known. Making inferences about individuals from studies of groups can be subject to error known as the “ecological fallacy.”<sup>11</sup>

The population at risk for adverse health outcomes associated with service during the war in the Persian Gulf is, in the broadest sense, the cohort of troops deployed to the Gulf. This population has been identified and considered the “exposed” population in a number of studies attempting to assess whether or not Gulf War veterans were at increased risk for adverse health outcomes, as compared with veterans from the same era who did not deploy to the Persian Gulf.<sup>12–17</sup>

Reconstructing this cohort required integration of a number of data sets. As one investigator reports, the data on service in the Gulf War and demographic variables were obtained from the Defense Manpower Data Center. Data on Gulf War Service were compiled from Army, Navy (including Marine Corps), and Air Force records of unit-deployment locations and pay for exposure to hostile fire.<sup>13</sup> Demographic data were obtained from routine data files on U.S. military personnel. Military personnel deployed to serve in the Gulf War for one or more days between August 8, 1990 and July 31, 1991 were considered Gulf War veterans. Approximately 83% of the approximate 697,000 U.S. Gulf War veterans served on regular active duty in the Army, Navy (including Marine Corps), or Air Force. The Defense Manpower Data Center also provided personal identifiers for the Gulf War veterans as well as data on their sex, age, race or ethnic group, marital status, branch of service, occupation, rank, pay grade, and total number of months of active duty service. The demographics of this population are provided in [Table 9.3](#).

Most of the studies of outcomes in this deployed or exposed cohort utilized the entire cohort of deployed troops for which data was complete.<sup>12–17</sup> The cohort thus identified as Persian Gulf veterans often excludes reservists and civilians. The completeness of the outcome data varied with the outcomes assessed (for example, reproductive outcomes vs. mortality outcomes). For most of the studies of outcomes in this cohort, rates were compared to a random sample of roughly an equal number of all personnel on active duty but not deployed to the Gulf, with the sampling percentage from each service proportional to the numbers from each service sent to the Gulf. The underlying assumption is that this non-deployed cohort represents a group with the same opportunity for outcomes of interest, apart from deployment, and as a group has no more or less of attributes that may be associated with these outcomes. Issues relating to whether or not this is a valid assumption are discussed specifically in the sections on health outcomes. A more basic question is whether or not the “population at risk” identified as the deployed cohort has any real meaning. In all reality, it is not a homogeneous group whose collective exposure was “the Gulf.” It is in actuality a composite of groups with differential experiences, exposures, and duties from locations throughout the Gulf theater. This is further discussed in the section addressing subsets of exposures.

### III. OUTCOMES IN THE POPULATION AT RISK

A variety of studies compared PGW veterans with non-deployed military personnel of the same era as a control group.<sup>12–17</sup> The selection of non-deployed military attempts to address the assumption that active duty military personnel are likely to be healthier than typical U.S. workers due to the physical demands of the military.<sup>8</sup> The

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**TABLE 9.3****Demographic Characteristics of the Persian Gulf War Population at Risk**

	PGW Participants
<b>Characteristic</b>	
<b>Gender (%)</b>	
Male	93
Female	7
<b>Race (%)</b>	
White	70
Black	23
Hispanic	5
Other/no data	2
<b>Age</b>	
Mean	26
Median	24
<b>Rank (%)</b>	
Enlisted	89
Officer	10
Other/no data	1
<b>Branch</b>	
Air Force	12
Army	50
Marines	15
Navy	23
<b>Status (%)</b>	
Active	83
Reserve component	17

*Note:* N = 697,000.

*Source:* Desert Shield/Storm Participation Reports Vol. 1 & 2, Defense Manpower Data Center, DoD, 1994

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ideal comparison population would be identical to the Gulf War veteran population in every aspect except deployment to the Gulf region. Therefore, concerns relate to whether some aspect of health resulted in non-deployed status and thus would be over-represented in the non-deployed group. Selected studies conducted to ascertain the frequency and scope of outcomes in troops and subpopulations of troops who served in the Gulf are summarized below.

### **A. MORTALITY**

Vital status was determined for all of the approximately 700,000 military personnel who served in the Gulf and compared with a roughly equal group of personnel on active duty who did not deploy to the Gulf for the period August–September 1990

to April 1991.<sup>12</sup> Potential confounders such as age, sex, race, and military variables were controlled. A 9% higher death rate in PGW veterans (exposed) was demonstrated as compared with other veterans of the same era, or “unexposed” (relative risk = 1.09, CI = 1.01–1.16) (Table 9.4). The excess mortality was entirely attributable to external causes with an excess of deaths from motor vehicle injuries (relative risk = 1.31, CI = 1.14–1.49) and unintentional injuries (RR = 1.25, CI =

**TABLE 9.4**  
**Deaths, Mortality Rates, and Mortality-Rate Ratios among the Study Subjects According to Cause of Death and Sex**

Cause of Death	Gulf War Veterans		Other Veterans		Mortality-Rate Ratios	
	No. of Deaths	Mortality Rate <sup>a</sup>	No. of Deaths	Mortality Rate <sup>a</sup>	Crude	Adjusted (95% CI) <sup>b</sup>
<b>All Causes</b>						
Men	1437	10.7	1084	9.8	1.10	1.09 (1.01–1.18)
Women	70	5.8	84	4.1	1.41	1.32 (0.95–1.83)
<b>Disease-related causes</b>						
Men	238	1.8	286	2.6	0.69	0.87 (0.73–1.04)
Women	14	1.2	26	1.3	0.92	0.89 (0.45–1.78)
<b>All external causes</b>						
Men	1110	8.3	732	6.6	1.26	1.17 (1.07–1.29)
Women	47	3.9	41	2.0	1.95	1.78 (1.16–2.73)
<b>All accidents</b>						
Men	689	5.1	422	3.8	1.34	1.26 (1.11–1.42)
Women	25	2.1	22	1.1	1.91	1.83 (1.02–3.28)
<b>Motor Vehicle Accidents</b>						
Men	457	3.4	269	2.4	1.42	1.27 (1.09–1.48)
Women	21	1.7	19	0.9	1.89	1.81 (0.96–3.41)
<b>Suicide</b>						
Men	211	1.6	191	1.7	0.94	0.88 (0.72–1.08)
Women	11	0.9	12	0.6	1.50	1.47 (0.63–3.43)
<b>Homicide</b>						
Men	116	0.9	101	0.9	1.00	0.80 (0.61–1.05)
Women	11	0.9	6	0.3	3.00	2.66 (0.96–7.36)

*Note:* Data for men are based on 544,270 Gulf War veterans and 456,726 controls assigned to active units. Data for women are based on 49,919 Gulf War veterans and 84,517 controls assigned to active duty.

<sup>a</sup>Crude rates shown are per 10,000 person-years

<sup>b</sup>Adjusted rate ratios (and 95 percent confidence intervals [CI] were derived from the Cox proportional-hazards model after adjustment for age, race, branch of service, and type of unit.

*Source:* Kang, H.K. and Bullman, T.A., *N. Engl. J. Med.*, 335, 1498, 1996. With permission.



1.13–1.39). No excess of deaths from suicide, homicide, or specific disease was observed. Risk of death from infectious diseases was reduced in the deployed population ( $RR = 0.21$ ,  $CI = 0.11–0.43$ ). Mortality for both groups was less than half that of the U.S. general population. Precise reasons for the excess of deaths due to external causes among war veterans are not well understood. The findings of the extension of this study through 1997 indicated that, while the risk of disease-related deaths ( $RR = 0.65$ ,  $CI = 0.60–0.71$ ) in deployed veterans as compared to controls did not increase over time, the excess deaths from motor vehicle accidents persisted ( $RR = 1.32$ ,  $CI = 1.23–1.41$ ). Post-war mortality from external causes, including suicides and homicides, was greater among female veterans than males, and the risk of suicide and homicide was even greater among married female Gulf War veterans.<sup>18</sup>

This was a large study that compared broad outcomes in large populations without respect to specific risk factors. While it was critically important to describe mortality in the cohort deployed and have a comparison population, in the sense that “risk” was related to deployment, this makes the study ecological in nature. No attempt to differentiate exposure to any specific location or hazard was made due to lack of data. In this instance, risk was equated to deployment. Additionally, mortality represents an infrequent and rather serious outcome, and patterns of mortality might not reflect patterns of morbidity. Risks under consideration might not be substantial enough to lead to significant detectable changes in mortality. Nonetheless, all PGW veterans and almost half of all military personnel not deployed to the Gulf were included to minimize sampling biases. Interpretation of the study is somewhat limited by the possibility that the two populations are not comparable. Military personnel who were ill or recovering from surgery, and perhaps more at risk for morbidity outcomes, might be differentially represented in the non-deployed population, and this would confound the results. This further extension of the healthy worker effect, coined the “healthy warrior effect,” noted that lower mortality should be expected in those healthy enough to deploy; although the magnitude of the expected difference is not known, it is relevant to the interpretation of the results of morbidity and mortality studies.<sup>19,20</sup> This was a very complete study with several sources of mortality data. Death certificates were utilized that may vary in quality and completeness. In general, mortality data are suitable for some assessments of outcomes in broad categories, but less useful for diseases that are difficult to diagnose. Writer et al. reported similar findings for a comparison of deployed and non-deployed service members during the period of the Gulf War and shortly thereafter.<sup>17</sup>

## **B. MORBIDITY**

A study of hospitalization in military hospitals of 547,076 PGW veterans who had remained on active duty in the 2 years following the war compared 618,335 veterans who served elsewhere. All diagnostic categories were evaluated.<sup>13</sup> The study adjusted for the possibility that disease rates should be lower in the cohort that was deployed. This considers that individuals with pre-existing illness might differentially not deploy, and thus the rate of hospitalization in this cohort might be expected to differ. The study noted that PGW veterans were at a slightly lower risk for hospitalization for any cause than the non-deployed cohort before the war, but not after the war.

Higher rates of hospitalization for alcohol and drug use and adjustment disorders were noted in PGW veterans in 1992 and 1993. Gulf War veterans were at increased risk of hospitalization for benign neoplasms in 1991, diseases of the genitourinary system in 1991, and diseases of the blood and blood-forming organs in 1992. Further analysis indicated that most of these were anemias associated with pregnancy. This study did not demonstrate an emerging illness requiring increased hospitalization in troops deployed to the Gulf. However, this study also equated deployment to the Gulf to exposure and did not attempt to differentiate hospitalization rates among various subpopulations of deployed troops with different exposures or experiences. Outcomes were obtained from computerized military hospital discharge data. While hospitalization of virtually all active-duty troops takes place in military hospitals, hospitalizations after discharge may occur in private, public, or DVA facilities.<sup>6</sup> For certain outcomes of interest such as obstetrical outcomes, civilian sector care may be frequently utilized. Also to be considered is that hospitalization outcomes on those who remain on active duty may be biased if health-status-specific discharges differ for the two cohorts.<sup>19,21</sup>

### C. SYMPTOM PREVALENCE

The Iowa Persian Gulf Study Group evaluated symptom prevalence in a cross-sectional telephone interview survey of 3,695 PGW and non-PGW military personnel from the state of Iowa.<sup>22</sup> The study tool was a validated questionnaire which attempted to gather information on the prevalence of self-reported medical and psychiatric conditions in PGW veterans compared to military personnel on active duty at the same time but non-deployed. The PGW veterans reported a significantly higher prevalence of depression, post-traumatic stress disorder, fatigue, cognitive dysfunction, bronchitis, asthma, alcohol abuse, anxiety, and sexual discomfort. The relationship between self-reported exposures and conditions suggested that no single exposure was related to the medical and psychiatric conditions among PGW personnel (Table 9.5). The most commonly reported exposures in symptomatic PGW personnel were solvents, smoke, pesticides, pyridostigmine bromide, and chemical warfare agents. However, this study suffered from recall bias related to self-reporting, and the number and variety of units involved precluded the focus on any subpopulations with specific exposures. Telephone interviewing may result in a select group who is willing to participate, and generalizability is also somewhat limited by restricting eligibility to those from Iowa.

The Veterans Administration's "National Health Survey of Gulf War Era Veterans and Their Families" is a three-phased project currently underway.<sup>23</sup> Phases I and II collected self-reported health data using mail and telephone interviews with about 21,000 veterans. Phase III involves a comprehensive, in-person examination on a stratified random sample of Phase I and II participants and their families. Participants are currently being recruited. The study's aim is to test the hypothesis that the prevalence of chronic fatigue syndrome, fibromyalgia, post-traumatic stress disorder, selected neurological abnormalities, and general health status of deployed and non-deployed veterans and their families are not significantly different.

**TABLE 9.5****Reported Exposures among Persian Gulf Military Personnel**

	<b>Regular Military (N = 985)</b>	<b>National Guard/Reserve (N = 911)</b>
Estimated days in theater Mean (SE)	167.8 (2.5)	138.1 (1.2)
Number of assigned units	820	137
Number of vaccinations (injections and oral)		
% of subjects		
0	1.5	1.1
1–5	28.3	26.8
6–10	31.1	35.8
>10	33.6	27.1
missing data	5.5	9.2
Number of pyridostigmine tablets used % of subjects		
0	45.7	40.8
1–10	17.7	27.0
11–30	14.6	15.0
>30	33.6	27.1
missing data	2.3	4.3
Smoking history		
% of subjects		
Never	44.9	45.1
Former	21.0	22.4
Current	34.1	32.5
Agent, % of subjects		
Solvents/petrochemicals	88.7	91.2
Smoke/combustion products	85.2	96.0
Sources of infectious agents	84.0	92.6
Psychological stressors	82.6	96.3
Sources of lead from fuels	78.2	88.5
Pesticides	43.8	63.4
Ionizing/nonionizing radiation	27.2	16.0
Chemical warfare agents	4.6	6.4
Physical trauma	3.7	5.6

Source: JAMA, 277, 238, 1997. With permission.

**D. REPRODUCTIVE OUTCOMES**

Birth outcomes for 579,931 active duty military personnel deployed for at least one day to Operations Desert Shield/Desert Storm from August 8, 1990, to July 31, 1991, were compared to that for 700,000 service members occurring in a similar time frame.<sup>15</sup> Information was obtained from hospital-recorded, International

Classification of Disease codes coded to five digits and included up to eight diagnoses. The primary outcome assessed in the study was the occurrence of birth defects with the number of live births per 1,000 population and the ratio of male to female babies as secondary outcome. Birth defects were defined in two ways—a sensitive definition of “any birth defect” and a second “severe birth defect” as defined by the Centers for Disease Control (CDC). Birth rates were comparable in the two populations. The hypothesis that children born to PGW veterans were at increased risk of overall birth defects was not supported. For male service members, no positive association was noted between PGW service and any birth defects. For female PGW veterans, the risk of any birth defect was slightly higher, but appeared to be the result of confounding by race, ethnicity, marital status, or length of service, and did not persist after adjustment. The risk of birth defects in both the deployed and the non-deployed military populations approximated the risk in a civilian population. No linear trend of increasing risk with increasing length of time spent in the Gulf was demonstrated. The study was limited by gross classification of exposure simply as service in the Gulf. Further, only 68% of all births to military personnel occurred in military hospitals and were studied. Births to reserve component members or individuals who left active duty after the study period were excluded. Also, only defects evident at birth and coded before discharge were included. Nonetheless, this study provides substantial evidence that PGW veterans do not have decreased fertility or increased risk of birth defects. Another study identified 17,182 live births to military personnel in the state of Hawaii between 1989 and 1993. The Hawaii Birth Defects Program records were utilized to identify birth defects. A total of 3,717 infants were born to PGW veterans and 13,465 to non-deployed veterans. Of these, 367 infants (2.14%) were identified with one or more of 47 major birth defects diagnoses. The prevalence of birth defects was similar between both groups and was similar among infants conceived prior to and after the Gulf War. Although the number of infants in the birth defects categories was small, this study eliminates some of the limitations of previous studies that utilized information only from military hospitals and included diagnoses made during the first year of life.

#### **IV. SUBSETS OF THE POPULATION AT RISK: SYMPTOM-BASED CLUSTERS**

Another subset of the deployed population at risk was identified on the basis of symptoms. Within a few months of the return of troops in 1991, complaints of fatigue, headaches, joint pains, rashes, sleep disturbances, and other cognitive difficulties began to arise.<sup>25</sup> A concern was raised that perhaps there was something unique to the Gulf or the war fought there that was linked to a specific illness. These concerns were raised initially by individuals and then by other outbreak or cluster investigations that reported a high prevalence of a cluster of symptoms later proposed to be a characteristic of a “Gulf War Syndrome.”<sup>26–29</sup>

Cluster investigations are typically initiated to evaluate reported rates of symptoms in a group of individuals. The “cluster” is first identified on the basis of

symptoms or conditions. Typically, the individuals are linked by a common workplace, community, or experience and have some concern about an “excess” of symptoms or findings that they believe are linked to a poorly defined exposure. A key difficulty with a systematic approach to cluster evaluations is identifying the correct denominator, that is, the population at risk. “Clusters sometimes arise, are publicized, generate interest, and often lead to the collection of cases (numerator data) that are poorly defined with little knowledge of the population at risk (denominator data).”<sup>6</sup> Selection of the participants for study may be problematic, as is the selection of a control group for comparison, if one is used, because it depends on correct classification of exposure, although the exact exposure of concern might not be identified. “Even if the disease is well defined and its diagnosis properly operationalized, clusters cannot be used to evaluate causation because it is virtually impossible to identify a reference population. Clusters will arise in the absence of causation; indeed, they are inevitable in any large and complex collection of study participants and data. It is the task of the investigating analyst to sort out clusters that occur by chance from those that occur as a result of some exposure of interest.” These studies are also limited by sample size and have a significant potential for bias resulting from respondent awareness of the underlying concern.

The initial reports of symptom clusters (fatigue, headache, muscle aches) helped to formulate hypotheses for subsequent studies and served as a starting point for survey questions. Clusters of disease have been reported among various units deployed to the Gulf.

## **A. 123RD ARCOM**

Early in 1992, the staff of the 123rd ARCOM Surgeon’s Office became aware of symptomatic complaints among reservists belonging to the 123rd ARCOM, Lafayette, Indiana. Similar complaints were later reported from the members of the 417th Quartermaster Company in Scottsburg, Indiana. A team from the Walter Reed Army Institute of Research evaluated 79 reservists with medical questionnaires; 78 completed a brief symptom inventory and a detailed interview. Other components of the evaluation included a brief psychiatric intake interview, a dental exam, vital signs, a laboratory evaluation that included a complete blood count with differential, an erythrocyte sedimentation rate, and liver function studies. All sera were tested for antibodies to *Leishmania tropica*, and sera from selected individuals were tested for antibodies to brucellosis. The most common complaint was fatigue (70%); other less-common symptoms included fever, abdominal pain, and diarrhea. The onset of fatigue and other associated symptoms were related to redeployment from the Gulf, although diarrhea was more frequent during the deployment. Blood testing revealed no cases of leishmaniasis, brucellosis, Lyme disease, nor any characteristic pattern of other laboratory measures. There was no documented exposure to microwaves, chemicals, radiation, or other suspected environmental hazards. High levels of stress were reported, although Post-Traumatic Stress Disorder (PTSD) was present in few, if any, of the reservists. No common pattern of illness was noted among study group members. This study provided no basis for identifying a “case” of disease, and no evidence of a common exposure was found.<sup>25</sup>

**B. AIR NATIONAL GUARD**

In 1994, an evaluation of unexplained illness among PGW veterans of the Pennsylvania Air National Guard unit was conducted.<sup>26</sup> The initial cluster investigation expanded into a three-stage study. To identify and characterize the signs and symptoms of disease in these veterans, 59 identified symptomatic PGW veterans received standardized interviews and physical examinations. Gulf War veterans reported a higher prevalence of symptoms identified as “moderate” or “severe” (Table 9.6). Overall, the patients reported that symptoms began in the Gulf or 2 to 3 months following return and persisted for greater than 6 months. No consistent abnormalities were noted on physical examination or medical records’ review. To establish the frequency of reported symptoms in PGW veterans as compared to guardsmen who had not deployed to the Gulf, a second stage surveyed 3,927 members of the index unit and three comparison units. In all units, the prevalence of 13 symptoms lasting greater than 6 months was higher among deployed personnel. The index unit had a higher prevalence of chronic diarrhea, other gastrointestinal complaints, difficulty remembering, “trouble finding words,” and fatigue, but also had twice the deployment rate of comparison units. Deployment rate appeared to account for the higher rates of symptoms. All outcomes or symptoms were self-reported in this stage of the evaluation. Similar increases in symptom prevalence were noted in a study of Navy Seabees.<sup>27</sup>

**C. SEABEES**

Haley et al. studied 249 (61%) of the members of a Reserve Naval Mobile Construction Battalion that served in the Gulf. Illness had been common in this group, and some members had previously undergone evaluation of cognitive function.<sup>28–30</sup> The 249 veterans were evaluated through the administration of a detailed

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**TABLE 9.6**  
**Ten Most Frequently Reported Symptoms**  
**in 59 PGW Veterans, Air National Guard**

Symptom	% Reported
Fatigue	61%
Joint Pain	51%
Nasal/Sinus Congestions	51%
Diarrhea	44%
Joint Stiffness	44%
Unrefreshing Sleep	42%
Excessive Gas	41%
Difficulty Remembering	41%
Muscle Pains	41%
Headaches	39%

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questionnaire that included anatomic distribution of symptoms, wartime exposures, and a standard personality assessment inventory. Seventy percent of the veterans reported "serious health problems" that most attributed to the war; 30% reported no such problems. The results were subjected to factor analysis, and the authors identified six clusters of self-reported symptoms that were grouped into syndromes. Sixty-three of the 249 veterans were classified as having one of the six syndromes. The three syndromes with most strongly clustered syndromes were characterized as impaired cognition, confusion ataxia, and arthromyoneuropathy.<sup>28</sup> Twenty-three veterans with clinical symptoms were further evaluated with detailed neuropsychological studies, as were 10 PGW veterans without symptoms, and 10 non-deployed controls. Thirteen veterans identified as having the "confusion ataxia syndrome" had significantly higher mean brain dysfunction scores than the 20 controls. These scores were based on the Halstead impairment index, General Neuropsychological Deficit Scale, and Trail Making Test Part B. Individuals classified as having the other two syndromes demonstrated impairment more frequently on other scales. The author concluded that individuals found by factor analysis to have one of these three syndromes "consistently scored in the abnormal direction on objective tests of neurological function than control veterans of the same battalion who were matched for age, sex, and education and were either deployed to the war zone and remained well, or who were not deployed." The study was not population-based, but limited to a single battalion that was the focus of a cluster evaluation and whose experiences and exposures may not be widely generalizable. The rate of participation (41%) may indicate some selection bias, and exposure and outcome information was self-reported. Finally, the study involved very few participants for the detailed neuropsychological evaluations.<sup>28</sup>

#### **D. REPRODUCTIVE EFFECTS**

A cluster investigation evaluated a perceived excess of birth defects and health problems in children born to two National Guard units from Southwest Mississippi. The two units, both deployed to the Gulf, consisted of 282 veterans. Initial contact was by telephone, and it was learned that 67 pregnancies had occurred since return from the Gulf. Medical records on 54 of the children were available and reviewed. The children ranged in age from 3–26 months at the time of the review. Records were reviewed for evidence of serious birth defect, minor birth defects, low birth weight, or premature birth. Baseline rates for comparison were obtained from three major U.S. birth defect surveillance systems. The rate of birth defects of all types in children born to this group of veterans was similar to that expected in the general population. The small size of the study population and the occurrence of only one case of each of five different types of birth defects (three major and two minor) made calculation of individual rates for the purpose of comparison difficult. Clustering of any one type or affected system was not noted. The amount of morbidity observed during the first year of life was not excessive.<sup>16</sup>

Taken as a whole, these studies support claims that deployed troops reported high rates of a variety of non-specific symptoms. However, they were initiated in

essentially “self-selected” groups who had reported concerns and, as such, provide little information about the larger cohort of troops who deployed to the Gulf. Self-reported symptoms may in some part result from recall bias. This bias has been commonly reported in epidemiological investigations of health effects associated with exposure to hazardous waste sites. In the context of an ill-defined exposure possibly linked to health effects, concerned individuals tend to report more symptoms, or differentially recall exposures.<sup>31,32</sup> Troops may have been aware of the general public debate regarding Gulf War Syndrome and medical concerns of others in their units. Additionally, concerns about service-connected disorders may have sensitized troops to report conditions for fear that the symptoms might progress in severity.<sup>6</sup> Thus, defining a general population to compare the prevalence of symptoms may be inappropriate if the general population does not share the same general concerns.

## **V. SUBSETS OF POPULATION AT RISK: COMMON EXPOSURES**

As previously discussed, the identification of an exposed population to compare with an unexposed population is fundamental to cohort studies attempting to evaluate differential rates of outcomes. While there have been many assessments of potential and known exposures that are related to PGW service, quantitative data with which to distinguish the exposed from the unexposed is lacking.<sup>3-8</sup> The environment of the Gulf was described as hostile, with uncomfortable temperatures and extreme rainfalls, and desert conditions with blowing sand, insects, animals, fumes, and smoke.<sup>6</sup> Troops were exposed to vaccines to protect against biological warfare and other infectious diseases, pyridostigmine bromide to protect against chemical warfare, and pesticides to protect against insects carrying diseases such as sandfly fever and leishmaniasis. Depleted uranium was used in munitions and tank armor, and subsets of troops faced occupational exposures to fuel, solvents, chemical-agent-resistant coating (CARC) paint, and vehicle exhaust fumes. Additionally, oil wells set on fire south of Kuwait City created a superplume of smoke. Hazardous exposures have been considered by many of the expert panels evaluating consequences of PGW service<sup>6</sup> (Table 9.7).

As noted by the IOM, “Although a wide range of possible exposures might be associated with adverse health outcomes in PGW veterans, data on these exposures are often not available; when they are available, they are poorly documented. This lack of exposure information is at the core of the frustration in obtaining answers from epidemiological studies. Self-reports of exposure and estimates of individual exposure from unit level measurements will be subject to so much error that they are likely to yield inconclusive results and additional questions.”<sup>6</sup>

### **A. INFECTIOUS DISEASES**

With respect to individual exposures of interest, infectious diseases such as shigellosis, malaria, sandfly fever, and cutaneous leishmaniasis were a known threat in the region.<sup>33-35</sup> However, infectious disease did not exert a major toll on deployed troops. This success has been attributed to preventive medicine efforts and the timing of



**TABLE 9.7****Exposures of Interest in the Gulf War and Availability of Exposure Information**

<b>Exposure</b>	<b>Available Data</b>
Infectious Diseases	Case reports and summaries
Pyridostigmine Bromide	No centralized record of recipients Toxicological studies of effects Toxicological studies of interactions
Immunizations	No centralized database of recipients
Pesticides	Amount shipped to theater
Chemical Agent Resistant Coating Paint	No industrial hygiene monitoring data
Depleted Uranium	Clinical follow-up of soldiers with imbedded shrapnel Health risk assessment in progress based on modeled exposures
Petroleum Products	No industrial hygiene monitoring data
Oil-Well Fires	Human Health Risk Assessment based on monitoring data
Biological Warfare Agents	No data
Chemical Warfare Agents	Modeled data based on Khamisayah

major troop strengths in the region when insect populations were decreased due to cooler weather. Short-term diarrhea was common initially, but gastroenteritis rates decreased from 4% per week early in the deployment to less than 0.5% per week once controls over food sources, particularly locally grown produce, were instituted.<sup>7</sup> Seven cases of malaria and one case of West Nile fever were diagnosed, but there were no cases of sandfly fever, rickettsial illnesses, or arthropod-borne viral illness diagnosed. Visceral leishmaniasis and cutaneous leishmaniasis appeared to be the only endemic infectious disease associated with chronic morbidity in deployed troops.<sup>35</sup> Twelve cases of visceral leishmaniasis and 20 cases of cutaneous leishmaniasis were reported.<sup>36</sup>

## **B. IMMUNIZATIONS, PESTICIDES, AND OCCUPATIONAL EXPOSURES**

Distinguishing the exposed from the unexposed with respect to immunizations is not possible due to incomplete documentation and the lack of a centralized database. Although it is estimated that at least 250,000 troops took at least some pyridostigmine bromide, no records of self-administered medications were kept.<sup>8</sup> Pesticide volumes shipped to theater are known, but estimating an individual's exposure is not possible, nor is it possible to identify those who used topical repellents (DEET) and impregnated their uniforms with permethrin or to what degree. Certain subsets of soldiers performed occupational duties that exposed them to unique hazards such as fuels, solvents, metals, and chemical-agent-resistant coatings applied to vehicles. Industrial operations performed in field settings are not subjected to strict industrial hygiene oversight. Modifications to procedure, lack of fixed ventilation, and the lack of recommended protective equipment may lead to exposures of individuals in excess of

permissible workplace standards. One episode of overexposure to CARC paint was reported, but reliable monitoring information is not available to define a subset of exposed individuals.<sup>37</sup>

### C. DEPLETED URANIUM

Depleted uranium (DU) is a heavy metal that contains decreased amounts of the most radioactive isotopes of uranium. It is 40% less radioactive than naturally occurring uranium, but chemically and toxicologically similar to natural uranium. The health effects are considered to be generally comparable to other heavy metals such as lead and tungsten.<sup>38–41</sup> Depleted uranium is created as a by-product of the nuclear energy industry. The U.S. employed steel-encased DU for increased armor protection, and the M2/3 Bradley Fighting Vehicle, M1 Abrams Tank and the M60 series tank can fire penetrating munitions containing DU.<sup>38</sup> There are no additional safety procedures required for intact DU and armor beyond those required for all munitions. When a DU munition pierces a target, it pyrolyzes, resulting in high concentrations of airborne oxides of uranium and metallic shards. Concerns arose over exposure to DU in the Gulf relating to proximity to a vehicle at the time of impact by DU munitions or a DU-armored vehicle at the time of impact by munitions. Other scenarios of concern involved proximity to actively burning fires involving DU, or routinely entering vehicles with penetrated DU armor or vehicles that had been struck by DU munitions. Exposure may occur through retained fragments, inhalation, or wound contamination. A health risk assessment addressing human health risk to modeled exposures is currently near completion. Toxicity related to DU exposures is expected to be related to heavy-metal-like effects on the kidneys. Renal toxicity occurs only at very substantial doses but was at least a theoretical concern relating to soldiers exposed in the Gulf. Surveillance was conducted on several small populations of troops considered at risk for exposure.<sup>39–41</sup> Twelve military personnel who helped salvage disabled tanks were studied by whole body counts and eight received urine analysis for uranium approximately 1 year after exposure. None were found to have increased body burdens of uranium.<sup>39</sup> A surveillance program was initiated in 1993 for referral of soldiers identified at increased risk from DU exposure. Thirty-three personnel were evaluated in 1993–1994. Testing included complete history to include medical, reproductive, occupational components, laboratory examinations to include complete blood count (CBC), chemistries, renal function tests, urinary uranium levels, and neuroendocrine measures. These individuals also received detailed physical examinations, neuropsychological tests, and radiologic tests. These initial evaluations demonstrated some persistent health problems related to wounds. Those with evidence of retained fragments (shrapnel) had increased urinary uranium, but no association between uranium excretion and clinically detectable adverse health effects was documented. Twenty-nine of this original cohort were re-evaluated in 1997. Controls without DU exposure were included at this time to provide a point of comparison for some of the clinical parameters and to assess the range of urinary and other uranium from natural sources. The evaluation was expanded to include genotoxicity assessments, neurocognitive evaluations, psychiatric and psychosocial

evaluations, and risk communication. An additional focus at this point was to identify the most sensitive and relevant biologic measures of uranium such as spot and 24-h urines, seminal fluid, and whole-body radiation. It has been determined that 24-h urine collection and analysis is the most sensitive biologic exposure indice for uranium.<sup>40</sup> Thus far, the highest urinary uranium values were found in those with retained fragments; individuals who had fragments removed still had uranium levels somewhat above controls. On clinical examination, the exposed and unexposed groups were similar, although the unexposed had more genitourinary (GU) and nervous system complaints. Psychiatric complaints were similar. Exposed individuals were more likely than controls to have normal laboratory parameters such as CBC, urinalysis (UA), semen parameters, and blood chemistries. No renal abnormalities were noted. The most common abnormality in both groups was triglyceride levels. Only prolactin levels were found to be more elevated in exposed individuals as a group. This surveillance will continue, and the statistically significant differences between the two groups with respect to reproductive hormone and neurocognitive function will be further investigated.

#### **D. OIL WELL FIRES**

Of all of the exposures in the Gulf, the oil well fires are the most studied. A U.S. Interagency Air Assessment team of scientists studied the potential health effects of the oil well fires.<sup>42,43</sup> The U.S. Army Environmental Hygiene Agency collected nearly 4,000 ambient air and soil samples from May to December 1991.<sup>44</sup> These data were collected after a number of the fires had been extinguished, but were utilized in a health-risk assessment performed to assess the potential for health effects from exposure. Analyses were performed for criteria pollutants such as particulates, nitrogen oxides, sulfur dioxide, carbon monoxide, and lead. Other pollutants measured included volatile organic compounds and semi-volatile organic compounds, such as polycyclic aromatic compounds and metals. Results indicated that most contaminants did not exceed findings in a typical U.S. industrialized city, and the risk of long-term adverse health effects was minimal. The total predicted excess carcinogenic risks did not exceed 3 excess cancers per 1,000,000 attributable to this exposure.<sup>44</sup> The Environmental Protection Agency considers this level of risk to be *de minimus*, or indistinguishable from background. Non-carcinogenic risks were also predicted to be minimal following health risk assessment methodology. While particulate levels were high, analysis indicated that they resulted from sand-based material typical for the Gulf, and levels of associated metals and organic compounds were low.

#### **E. CHEMICAL AND BIOLOGICAL WARFARE AGENTS**

While there was no available evidence from the Gulf to indicate a subpopulation of troops exposed to biological warfare agents, data reconstruction was performed to identify troops potentially exposed to chemical weapons.<sup>6-8</sup> This effort and the associated study are discussed in some detail here.

## F. KHAMISIYAH, IRAQ

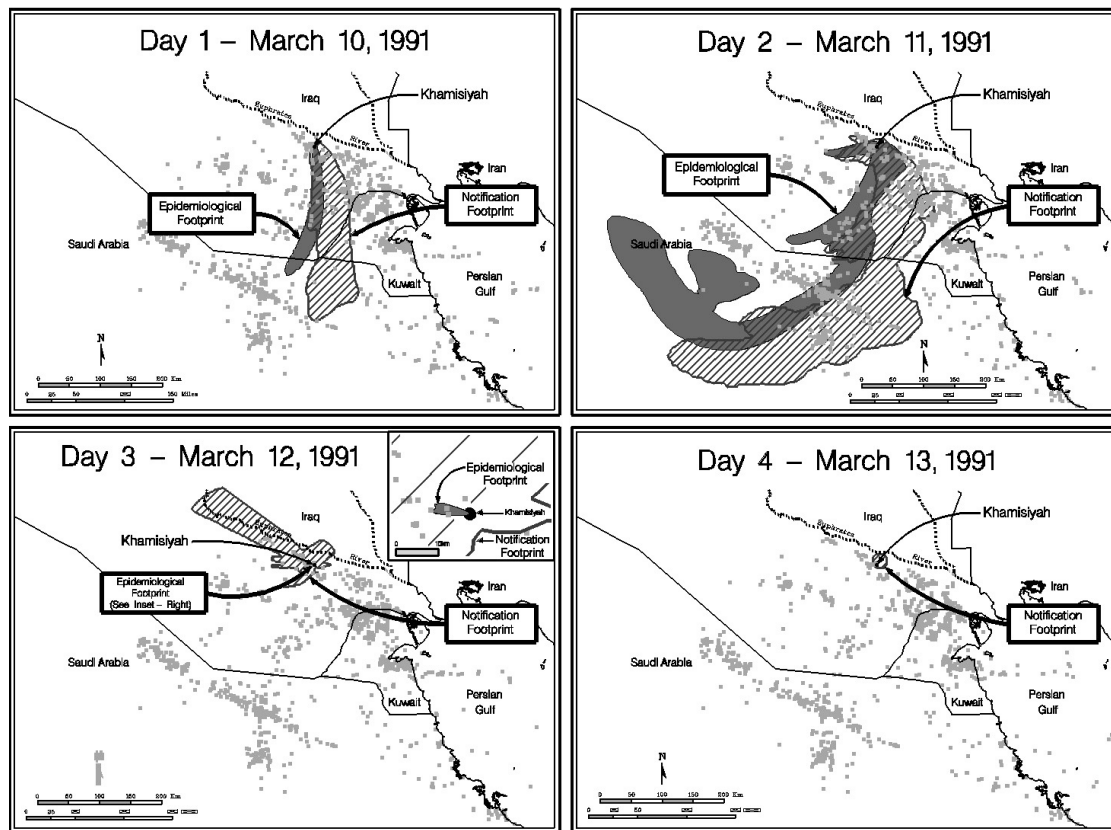
While Iraq was known to possess chemical weapons, review of the available exposure and medical data from the Gulf concluded that there was no evidence that these weapons were used during the conflict.<sup>3</sup> However, in June 1996, the U.S. Department of Defense announced the United Nations' findings that U.S. forces near Khamisiyah, Iraq, had destroyed chemical agents in March 1991. Attempts were made to identify a possibly exposed population and compare their hospitalization experience with that of PGW veterans who were not likely exposed.<sup>45</sup>

Khamisiyah was a large ammunition storage facility located in southern Iraq and contained numerous ammunition bunkers, storage buildings, and pits and sand mounds to protect stored weapons. During March 1991, engineers operating from remote sites destroyed much of this. On March 10, 1991, a cache of 1,250 rockets stored in an open pit was destroyed. At the time, it was not known that any of the munitions at Khamisiyah contained chemical agents. In May 1996, the United Nations Special Commission inspectors determined from debris that some of the destroyed rockets contained the nerve agents sarin and cyclosarin. Although quantitative exposure data was not available, concerns about the possible health implications to troops were raised. Utilizing available data regarding numbers of rockets and nerve agent concentrations, the DoD and Central Intelligence Agency jointly conducted destruction testing of simulated rockets containing simulated nerve agent. The simulations and intelligence data led to an estimate that 342 gallons (1,294.57 liters) of nerve agent were released on March 10, 1991. Further analysis estimated the percentages released instantaneously and over time by evaporation. Meteorological, transport, and diffusion modeling were performed by an expert panel of federal and nonfederal experts using meteorological data from a number of sources and three transport and diffusion models. These were combined to generate five estimates of simulations of daily plume coverage.<sup>46</sup>

Although no U.S. personnel casualties were associated with the event of March 10, the DoD defined two nerve agent concentrations to be used in modeling to estimate the population potentially at risk. "The first noticeable effects concentration, 1 mg-minute/m<sup>3</sup>, was defined as the dosage expected to cause mild symptoms such as rhinorrhea, muscle twitching, chest tightness, and headache."<sup>45</sup> The general population limit concentration is defined as "The dosage below which the general population, including children and the elderly, could endure for at least 72 hours without symptoms."<sup>45</sup> Following an independent review panel, a notification plume was determined combining the five meteorological/dispersion model simulations. These model simulation contours "represent a 99% probability that persons exposed to the general population limit dosage would fall within that perimeter."<sup>45</sup> Another independent panel recommended the construction of an epidemiological plume from the "best" meteorological and dispersion models for unit-specific dose estimates. This plume "enabled epidemiologists to estimate nerve agent concentration at specific troop locations over time." The troop location data was obtained from a geographical information system that contained all available daily unit locations in latitude and

longitude. This data was not available for all units and was reconstructed after the war, and therefore subject to some limitations. Plumes were estimated for each day from March 10 to 13, 1991 and overlaid on the geographic information system troop unit location map (Figure 9.1).

Although no units were identified as having been exposed to the first noticeable effects of vapor concentration or higher in vapor plume modeling, 124,487 Army PGW veterans were identified as having the possibility of at least low-level exposure under either the notification or epidemiological plumes. This group was stratified into four dose groups: uncertain low dose ( $n = 75,717$ ); exposure 1 defined as  $0.0\text{--}0.01256$  mg-minute/ $m^3$  ( $n = 18,952$ ); exposure 2 defined as  $0.01257\text{--}0.09656$  mg-minute/ $m^3$  ( $n = 23,0610$ ); and exposure 3 defined as  $0.09657\text{--}0.51436$  mg-minute/ $m^3$  ( $n = 6,757$ ). These U.S. Army personnel were compared with 224,804 other Army PGW veterans who were deployed to the Gulf at the same time but were not under the vapor plumes. Hospitalization data was obtained from all DoD hospitals for the period of March 10, 1991 to September 30, 1995 for all study participants. Data included date of admission, up to eight individual International Classification of Diseases, Ninth Revision discharge codes, and disposition. Diagnoses with the same major diagnostic category codes were considered the same. Further, specific diagnoses determined by an expert panel to be possible manifestations of subtle, nerve-agent-induced neurophysiologic effects were examined. These included mononeuritis, peripheral neuropathy, toxic neuropathy, and myoneural disorders and myopathies. Cox proportional hazard modeling was performed for each of the 15 diagnostic categories over 54 months. Possible nerve-agent exposure was not associated with post-war hospitalizations. Analysis of the specific diagnoses between dose groups did not reveal increased risk for personnel possibly exposed to vapor plume. Further analysis of a dichotomous yes/no exposure and yes/no hospitalizations for any cause and for the 15 major codes found only a slight risk for adjustment reaction and nondependent drug abuse. The authors concluded that "These data do not support the hypothesis that PGW veterans who were possibly exposed to nerve agent plumes . . . experienced unusual post-war morbidity." This study was a unique effort to combine operational data (temporal and geographic) with dispersion and meteorological data to estimate an exposure. The accuracy of these models and estimates cannot be known, but represent considerable effort to determine the magnitude and scope of possible nerve agent exposure to deployed troops. The study also compared PGW veterans possibly exposed to all other PGW veterans, eliminating some of the concerns raised regarding the inappropriateness of comparing PGW veterans with non-deployed cohorts of the same era. Finally, dose gradients were estimated to enable dose-response trends to be evaluated. Limited only to hospitalization data, the study could not address symptoms or complaints not resulting in hospitalizations, and available information was limited to personnel remaining on U.S. Army active duty. Nonetheless, this innovative use of available information serves to rule out significant morbidity in a subset of the population at risk when quantitative exposure information was not available.



**FIGURE 9.1** Modeled chemical agent plumes and troop locations, March 10–13, 1991, Khamisiyah, Iraq. (Source: Gray, G., Knoke, J., Berg, S.W., Wignall, S., and Barrett-Conner, E., Counterpoint: responding to suppositions and misunderstandings, *Am. J. Epidemiol.*, 148, 328, 1998.)

## **G. MIXED EXPOSURES AND SYNERGISTIC, ADDITIVE, OR OTHER COMBINED EFFECTS**

It has been noted by many of the review panels that a further issue of consideration is the potential for additive or synergistic or other complex effects from exposures. This has been a particular focus of study with respect to the combination of neurotoxic compounds such as pyridostigmine bromide, DEET, and permethrin, as well as possible nerve-agent exposure.<sup>47–48</sup> While these interactions are complex and not discussed here, the issue of additive effects has importance for a number of reasons. Most of the evaluations of individual exposures and their likelihood of producing health effects of significance addressed individual exposures. Therefore, the conclusions of such evaluations are often questioned because they do not address additive or other combined effects. As noted by the IOM, “Service personnel stationed in the Gulf were exposed to an extraordinary array of environmental conditions. Their complex experiences combined to yield what is truly a varied and sometimes confusing picture of exposure that has proven difficult to understand, much less reconstruct.”<sup>46</sup> It was noted that the exposures combined to produce an environment are not easily described or evaluated. Environmental exposure reports for a variety of hazards encountered during the Persian Gulf conflict can be obtained from [http://www.gulflink.osd.mil/cia\\_092297](http://www.gulflink.osd.mil/cia_092297). The Office of the Secretary of Defense, Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses, also commissioned eight literature reviews on potential health hazards in the Gulf. The series addresses infectious diseases, pyridostigmine bromide, immunizations, stress, chemical and biological warfare agents, oil well fires, depleted uranium, and pesticides. These reviews describe available data on exposure to these hazards in the context of the Gulf War and published literature on possible health effects.<sup>38,49–55</sup>

## **VI. SUBSETS ENROLLED IN REGISTRIES**

Other populations of Gulf War veterans have been described and have provided data with respect to health outcomes in Gulf War veterans. However, they are not random samples of deployed veterans; rather, they are subsets of the population at risk. Two such subsets are the DoD Comprehensive Clinical Evaluation Program (CCEP) registrants and the Department of Veterans Affairs Persian Gulf Health Registry (PGHR) participants.<sup>56,57</sup> To address the health concerns of PGW veterans, to enable them to receive a clinical evaluation, and to assemble information regarding patterns of illness on a large scale, health registries and referral services were developed. The Department of Veterans Affairs established the National Referral Center and PGHR. Similarly, the Department of Defense created the CCEP. Participation in CCEP is open to Gulf War veterans who are active duty, military retirees, full-time National Guard personnel, members of the reserve units who are placed on orders, family members of above categories who are eligible beneficiaries for military health care, and DoD civilians (current and former) who were in the Persian Gulf between August 1990 and July 1991. Gulf War veterans who have separated or are in a Reserve Component are not eligible but may request a medical evaluation through the

DVA PGHR. The PGHR offers a free complete physical examination with basic laboratory studies to every PGW veteran. In 1996, Public Law 103–446 established a special program to fund health examinations for some spouses and children of PGW Veterans Registry participants. The results of these examinations are included in the PGHR. The demographics of these registry participants are noted in Table 9.8.

The most obvious indication that the registries do not represent a random sample of those veterans who deployed to the Gulf is that the inclusion of family members does not restrict participation to those who actually deployed to the Gulf. Further, the group is self-selected, in that participation is not mandatory. Reasons for requesting a medical evaluation might include diagnosis and treatment of a symptom or illness or perhaps a desire for a complete medical evaluation. Others might wish to obtain information about the health of other Gulf War veterans or to register in case of future health problems that might be compensated. Other individuals might not

**TABLE 9.8**  
**Demographic Characteristics of Gulf War Participants Enrolled in the DoD CCEP and DVA Registry**

	Total Gulf War Participants (N = 697,000)	CCEP Participants (N = 18,075)	Registry Participants (N = 52,216)
<b>Gender</b>			
Male	93	88	90
Female	7	2	10
<b>Race</b>			
White	70	57	64
Black	23	32	23
Hispanic	5	6	10
Other/unknown	2	5	3
<b>Branch</b>			
Air Force	12	10	7
Army	50	81	72
Marines	15	4	12
Navy	23	1	1
Other/unknown	NA	1	1
<b>Status (in 1991)</b>			
Active Duty	83.3	83	54
Reserve	10.4	13*	20*
National Guard	6.3	NA	19*
Age (years) Mean (in 1991)	26	30	29

*Note:* NA = Not available; \*denotes Reserve/National Guard combined.

*Source:* PAC, Final Report, 1996.



request a medical evaluation due to a lack of health problems or a lack of individual association between any health problem and service in the Gulf. Some have raised the concern over whether or not participation will adversely impact one's career. An analysis of demographic risk factors for participation in the two registries identified service branch and type were strongly associated with registry participation with Army and National Guard personnel most likely to participate.<sup>58</sup>

Service in the Gulf during the fighting, age, enlisted rank, and construction work were also associated with participation. Other variables associated with participation included female sex and hospitalization during the 12-month period before the war. The significance of the overrepresentation of these demographic groups in the registries remains unknown. Nonetheless, participation rates in the registries have sometimes been presented as a surrogate for the rate of illness in a unit, as in a comparison of CCEP participation as a function of proximity to oil well fires or Khamisayah, the location of the chemical agents' release. Participation in CCEP does not automatically imply illness. Participation in CCEP may be a measure of the tendency to seek health evaluation. While these registries serve a purpose of responding to troops desiring evaluation and creating a centralized repository for information, conclusions drawn from the data are limited in generalizability to the entire cohort of deployed troops. Information or findings relative to a sample of a population is generalizable back to the population from which it came to the degree that any member of the population has a random chance of being included in the sample. To the degree that inclusion in the sample is not random, selection bias limits the ability to generalize the observations and conclusions about the sample to the entire population from which it came. Other limitations to the ability to generalize from this data are that symptoms and exposures were self-reported, and control groups were not utilized. The registries serve as an important source of entry into the medical system for veterans who need clinical services, and provide a source of hypothesis regarding the nature and extent of health problems experienced by PPGW veterans who enrolled.<sup>6</sup> They do not necessarily reflect new conditions or conditions related to Gulf service.

## VII. OUTCOMES IN SUBPOPULATIONS IN REGISTRIES

Participants in both the DVA Persian Gulf Health Registry and the CCEP registry represent a broad cross-section of service members who deployed to the Gulf, although the demographics of participants as a group differ from the deployed population in some respects as discussed above. At the time the comprehensive reports were published, 18,075 individuals had participated in CCEP, and 52,216 individuals had been evaluated through the PGHR.<sup>56-60</sup> The Presidential Advisory Committee (PAC) combined the data from both sources in their evaluation of the findings of the registries.<sup>59</sup> As stated, not all registry participants are ill; 10% of CCEP participants are asymptomatic, while 12% of PGHR participants report no symptoms. Symptomatic participants in both registries reported a broad range of symptoms spanning a variety of organ systems. The most common symptoms reported in CCEP participants were joint pain, fatigue, headache, and skin rash. Most commonly reported symptoms for the PGHR were almost identical.

The CCEP report included prevalence data from three studies of outpatient practice in the U.S. for common symptoms.<sup>56</sup> The prevalence of fatigue reported in the general population ranged from 25–58%, whereas in the combined registry data, fatigue was listed as 1 of the top 7 symptoms in 47% of participants. Joint pain prevalence in the general population ranged from 32–59%; 49% of registry participants reported fatigue to be one of their top seven complaints. Headaches reported in the general population ranged from 24–38% as compared to 39% of registry participants. Finally, sleep disturbances were reported in the general population with a prevalence of 15–35% as compared with 32% in the registry participants. While this data indicates that the types of symptoms reported by registry participants are not uncommon, it is noted that community outpatient surveys include populations estimated to be 20–25 years older, and the percentage of women is higher than in the PPGW registries.<sup>56</sup> Table 9.9 lists the ten most frequent symptoms in the combined registries as well as the percentage of participants reporting the symptom in the top seven and top three of their complaints.

For diagnosed conditions, the distribution of major diagnostic categories was similar in the two registries (Table 9.10).<sup>56,57</sup> Approximately 10% of registry participants are healthy. The most common primary diagnostic categories are psychological conditions, musculoskeletal system diseases, and symptoms, signs and ill-defined conditions (SSIDC). These three categories represent greater than 50% of the diagnoses made. Apart from these categories, diagnoses do not center in any single organ system.

In the PGHR population, relative rank-order of major diagnostic categories was the same for men and women, with the exception of digestive system disease ranking

**TABLE 9.9**  
**Frequency of the Ten Most Common Symptoms Reported by DoD CCEP Participants (N = 18,075) and the DVA Registry Participants (N = 52,216)**

Reported Symptoms	Chief Complaint	Any of Top Seven Symptoms	Any of the Top Three Symptoms
No symptoms	10%	10%	10%
Joint pain	11%	49%	17% <sup>a</sup>
Fatigue	10%	47%	20%
Headache	7%	39%	18%
Memory loss	4%	34%	14%
Sleep disturbance	2%	32%	6%
Rash/dermatitis	7%	31%	18%
Difficulty concentrating	<1%	27%	NA
Depression	1%	23%	NA
Muscle pain	1%	21%	<sup>a</sup>

*Note:* NA = Not available.

<sup>a</sup>In the VA registry, muscle and joint pain combined are 17%.

*Source:* PAC, Final Report, 1996.

**TABLE 9.10**  
**Frequency Distribution of Major Diagnostic Categories (ICD-9-CM) in**  
**Participants in DoD CCEP Participants (N = 18,075) and the DVA Registry**  
**Participants (N = 47,624)**

ICD-9-CM Diagnostic Code	Primary Diagnosis	Any of the Top Seven Diagnosis	Any of the Top Three Diagnosis
Psychological conditions	18%	36%	15%
Muscular system disease	18%	47%	25%
Symptoms, signs, ill-defined conditions	17%	43%	20%
Healthy	10%	10%	NA
Respiratory system diseases	7%	18%	14%
Digestive system diseases	6%	20%	11%
Skin diseases	6%	20%	14%
Nervous system diseases	6%	18%	8%
Infectious diseases	3%	9%	7%
Circulatory system diseases	2%	8%	7%
Endocrine disorders	2%	8%	NA
Genitourinary system diseases	1%	5%	3%
Injury and poisoning	1%	3%	5%
Neoplasms	<1%	3%	<1%
Blood and blood organ diseases	<1%	3%	NA

*Note:* NA, not available.

*Source:* PAC, 1996.

sixth in women and fifth in men. Infectious disease was diagnosed more commonly in men, and genitourinary disease was more common in women. One hypothesis is that the relative lack of gynecological care in the Gulf resulted in increased diagnoses on return.<sup>60</sup> Overall, for all participants, 69% of women reported their health to be all right, good, or very good, compared with 73% of men. For the CCEP population, the rank-listing of major diagnoses for men is the same as in Table 10. For women in the CCEP, the top three categories retained their rank order. Nervous system were the fourth most frequent diagnosis, followed by healthy, respiratory conditions, skin disorders, digestive system disorders, genitourinary diseases, endocrine disorders, infectious diseases, blood diseases, and circulatory diseases, with the remaining categories unchanged in order. To provide a point of comparison, as was done with data on the prevalence of symptoms in the general U.S. population, the CCEP report provided data on the frequency of primary diagnoses for the CCEP as compared to the National Ambulatory Medical Care Survey (NAMCS) for individuals aged 20–40 years.<sup>56</sup> The NAMCS population, although random, is said to differ from the CCEP population in that individuals captured in the NAMCS represent those seeking care for unknown conditions, as well as routine examinations in the absence of any adverse condition (Table 9.11).

**TABLE 9.11****Frequency of Primary Diagnosis for CCEP and NAMCS, by Sex, for Subjects 20–40 Years of Age**

Primary Diagnosis	Men Aged 20–40 Percent Primary Diagnosis		Women Aged 20–40 Percent Primary Diagnosis	
	CCEP	NAMCS	CCEP	NAMCS
Psychological conditions	18	7	18	5
Muscular system disease	19	9	16	5
Symptoms, signs, ill-defined conditions	18	3	17	3
Healthy	10	11	9	27
Respiratory system diseases	7	11	6	10
Digestive system diseases	6	5	5	3
Skin diseases	6	9	6	7
Nervous system diseases	5	9	9	7
Infectious diseases	3	5	3	4
Circulatory system diseases	2	3	2	2
Endocrine disorders	2	2	3	3
Genitourinary system diseases	1	5	4	10
Injury and poisoning	1	17	1	7
Neoplasms	1	2	1	3
Blood and blood organ diseases	<1	<1	2	<1

Source: CCEP Report, DoD, 1996.

Comparing the frequencies of diagnoses between the two age-matched populations, men in the CCEP were two to five times more likely to receive a diagnosis in the categories of psychological conditions, signs, symptoms and ill-defined conditions, and musculoskeletal conditions. The proportion with a diagnosis of healthy did not differ substantially, and CCEP participants were less likely to receive a diagnosis in the respiratory, nervous, infectious disease, and skin categories. For women, CCEP participants were three or more times as likely to receive a diagnosis of psychological conditions, signs, symptoms and ill-defined conditions, and musculoskeletal conditions. They were much less likely to receive a diagnosis of healthy, or in the genitourinary group. While these differences are interesting, they are not readily interpretable with respect to risk factors or significant differences between the two populations. Similar symptom prevalence has been documented in Canadian and British forces, and preliminary results from a Danish study of troops deployed to the Gulf following the war for peacekeeping and humanitarian tasks indicate “a pattern of diseases and symptoms in some respects comparable to the findings in U.S. Gulf War veterans.”<sup>61,62</sup>

Both the CCEP and PGHR serve an important purpose as an access to care for concerned individuals and a centralized database of information on those seeking to register. Interpretation of the actual significance of the findings has been limited, as

the biases associated with a voluntary, self-referred registry without a comparison population have been noted. The Institute of Medicine committee evaluated the data from the initial 10,000 DoD participants and noted that the CCEP evaluations “were not, however, designed to answer epidemiological questions. Instead, it was designed as a medical evaluation and treatment program. Although useful to bound and explain the problem in a subgroup of veterans, the information is of limited value for determining the prevalence and incidence of illnesses in the full cohort of PGW veterans because they are not necessarily representative of the troops who did not participate, and they do not include comparison populations.”<sup>60</sup>

## **VIII. IS THERE A SINGLE PGW SYNDROME?**

### **THE PROBLEM WITH CASE DEFINITION**

Given that both large registries found a frequency of unexplained, as yet undiagnosed conditions in about 20–25% of participants, a basic question asked whether or not the symptoms represented a new and unique syndrome. Examinations of large numbers of individuals in a systematic fashion would seemingly provide a reasonable opportunity to diagnose a new definitive condition. A series of six expert panels evaluated the available scientific data but did not identify a single, coherent syndrome, although many illnesses reported by veterans might be attributable to Gulf War service.<sup>3–8</sup> The 1994 NIH Workshop Panel found that no single disease or syndrome is apparent, but rather found evidence for multiple illnesses with overlapping symptoms and causes.<sup>4</sup> Symptomatic veterans were found to be ill due to a wide diversity of health problems, but no specific previously unknown disease was identified, and no case definition related to unexplained symptoms emerged. The NIH panel concluded that “An evolving case definition might be more appropriately used in developing a research strategy.” The PAC noted that many veterans were interested in possible links between unexplained illness and symptom-based conditions such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS).<sup>7,8</sup> These conditions lack specific diagnostic tests, but are based on symptoms reported by patients, rather than physical abnormalities or laboratory tests. Chronic fatigue syndrome was defined by a 1994 Centers for Disease Control (CDC) and Prevention as new and unexplained fatigue of 6 months duration accompanied during the six months by persistent and recurrent symptoms. At least four of the following should also be present: memory impairment significant enough to impair function, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without redness or swelling, headaches, unrefreshing sleep or post-exertional malaise lasting more than 24 h. Chronic fatigue syndrome is considered a disease of exclusion in that many conditions must be ruled out before a diagnosis is made.<sup>63</sup>

The PAC noted that the DoD reported 42 of the first 10,020 registry participants met the CDC case definition, but that the VA has not reported the proportion of veterans with this diagnosis.<sup>59</sup>

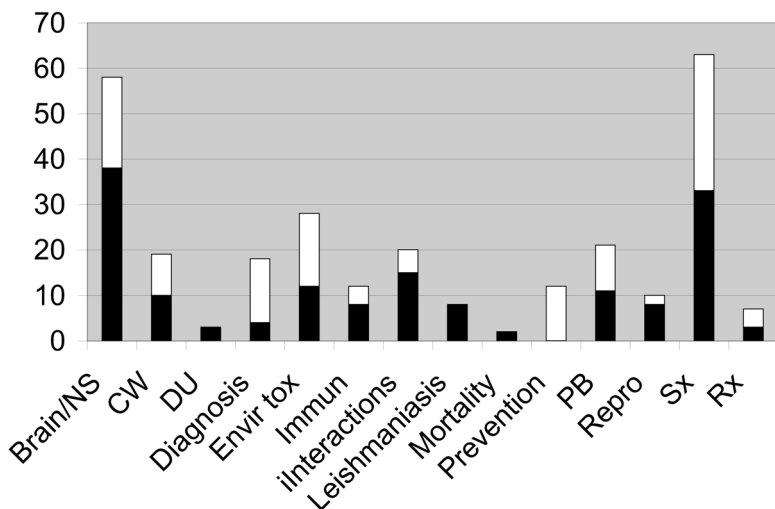
Fibromyalgia is defined by the American College of Rheumatology as chronic, widespread pain in all 4 quadrants of the body and pain in at least 11 of 18 tender point sites on digital palpation.<sup>64</sup>

Patients with FM also report sleep disturbance, fatigue, morning stiffness, anxiety, headache, and depression. Patients can be diagnosed with other conditions simultaneously, and no specific laboratory test exists. The DVA has not reported the prevalence of FM in its registry participants, but DoD noted that 1.5% of CCEP participants received a primary or secondary diagnosis of FM.<sup>56</sup> Multiple chemical sensitivity does not have a consensus case definition and thus, the frequency in the registry participants cannot be estimated. Hyams discussed symptom-based diagnoses in the context of the Gulf War.<sup>65</sup> Federal funds have been awarded to researchers in the area of CFS, FM, and MCS.

## IX. FUTURE RESEARCH DIRECTIONS

On August 31, 1993, in response to Section 707 of Public Law 102–585, President William J. Clinton named the Secretary of Veterans Affairs to coordinate research funded by the Executive Branch of the Federal Government into health consequences of service in the Gulf War. Section 104 of Public Law 105–368 (1998) expands the responsibilities. The DVA carries out the coordinating role through the auspices of the Research Working Group (RWG) of the Persian Gulf Veterans' Coordinating Board (PGVCB). The Secretaries of the Department of Defense, Health and Human Services and DVA chair the PGVCB and have representatives on the RWG, as does the Environmental Protection Agency.<sup>66</sup>

The RWG has developed a strategic plan for research, to include a plan for research on the health effects of exposure to low levels of organophosphorous nerve agents. It also established a programmatic review of peer-reviewed, completed research proposals leading to funding recommendations for more than \$100 million in research projects. The strategic plan for the conduct of research on Gulf War veterans' illnesses aims to: (1) determine the nature and prevalence of symptoms, diseases, and other conditions among Gulf War veterans; (2) identify risk factors for symptoms, diseases, and other conditions; and (3) identify diagnostic tools, treatment methods, and prevention/intervention strategies. The plan contains about 20 research questions in broad areas of exposure and outcome posed by Gulf War veterans' illnesses. In 1996, new factual and conceptual knowledge about exposures and outcomes during and after the Gulf War led to a revised set of short-term and long-term research recommendations. Short-term recommendations include epidemiological follow-up on Gulf War veterans' mortality experience at appropriate time intervals and longitudinal follow-up studies of Gulf War veterans' health status. Also to be addressed is peer-review of the atmospheric exposure models for pollutants such as the oil well fires and chemical warfare agent releases at Khamisiyah, Iraq. Long-term research recommendations include research on risk factors for stress-related disorders, excess mortality due to accidents, biomarkers of chemical warfare agents, a strategic plan for investigation of the health effects of low-level chemical warfare agent exposures, and a test for *L. tropica* infection.<sup>67</sup> Since 1994, the Federal Government has sponsored 145 research projects and committed \$133.5 million in resources. Non-governmental researchers conduct more than half of these studies. Through 1998, 40 projects have been completed, 103 are ongoing, and 2 are pending



**FIGURE 9.2** Cumulative number of research projects funded, by focus area.

start-up. Since 1994, the proportion of research projects funded in epidemiology has remained constant, while funding for products related to the toxicology of chemical weapons has markedly increased. Beginning in 1998, new research on treatment has received increased funding, and \$10 million has been invested in two clinical trials. The first is a large multi-center trial to address the effectiveness of behavioral and cognitive therapy and exercise on symptomatic veterans. The other is multi-center trial of the effectiveness of doxycycline in reducing symptomatic complaints. This research was prompted by a growing number of veterans receiving this treatment without evidence of infection or known efficacy for this purpose. The cumulative numbers of research projects across various areas of research focus are shown in Figure 9.2.

## **X. ASSOCIATION VS. CAUSATION IN ENVIRONMENTAL EPIDEMIOLOGY**

While research into the outcomes in PGW veterans continues, a corollary effort is to utilize the lessons learned from the Gulf to improve data collection on future deployments. Currently, the DoD has asked the National Academy of Sciences and the Institute of Medicine to recommend ways in which the DoD can enhance or improve its protection of the health of deployed U.S. military forces in the future.<sup>68</sup> Specific issues to be addressed include: assessing health risks during deployments in hostile environments through the use of an analytical framework; assessing technology and methods for detection and tracking of exposures to a subset of harmful agents; and assessing past, current, and potential future approaches for developing, evaluating and fielding protective equipment, clothing, and technologies related to decontamination.

Given that a major limitation of all epidemiological studies to date has been the lack of detailed exposure data, every committee reviewing the Persian Gulf has recommended that broad-based exposure and outcome data collection be conducted on all future deployments. The IOM recommended "A single, uniform, continuous and retrievable electronic medical record for each service person. The uniform record should include each relevant health item (including baseline personal risk factors, every inpatient and outpatient medical contact and all health-related interventions."<sup>6</sup> It was also recommended that such a record allow linkage to exposure and other data sets and incorporate medical information from the DVA, civilian, and other health-care facilities. Presumably, this would enable the tracking of outcomes or events resulting in medical interface on all individuals with service time for their entire lives. If realized and perfected, this would address the concerns regarding complete capture of all medical outcomes (as opposed to self-referral for entry into a registry or symptom-based cluster evaluations), and would also address incomplete follow-up for individuals who leave the service, and capture of events that occur outside DoD/DVA health care facilities. If functional and amenable to epidemiological analysis, this would represent a close to perfect data set with respect to outcome capture. With respect to exposure information, the other critical component of the exposure-outcome association question, recommendations have been made as well.<sup>6,7</sup> "The DoD should ensure that military medical preparedness for deployments includes detailed attempts to monitor natural and man-made environmental exposures and to prepare for rapid response, early investigation and accurate data collection, when possible, on physical and natural environmental exposures that are known or possible in the specific theater of operations."<sup>6</sup>

One difficulty with this recommendation is that no specific level of threat has been identified, and the range of possible exposures is broad. For some hazards, guidance for acceptable levels for occupational exposure exist but may not be applicable for extended work shifts or continuous exposure possible in a deployed setting. Screening levels derived for application in risk assessment to represent "No adverse effect levels" for the general population are not suitable because they are meant to protect sensitive members of the population for lifetime exposures and utilize very conservative assumptions at each step of the derivation. Exceedances of such screening levels may be suitable as a basis for determining whether or not a remedial action should be considered, but do not serve as a threshold useful to predict the frequency or magnitude of a health effect. Health effects, if they occur at all, might be subtle and not discernable without specific, tailored, outcome-based medical surveillance, apart from waiting for and tallying specific outcomes. With respect to cancer outcomes, values are derived based on a non-threshold model that may not be appropriate for all hazards. Exceeding a screening level derived to address a cancer endpoint based on a theoretical model may result in anxiety, and consideration of latency would leave the issue unresolved for many years. In actuality, monitoring on recent deployments has been troubled by a time lag between measurement and available results such that information cannot be utilized in any preventive sense to reduce exposure, but may raise questions with respect to significance and prognostic interpretation for those



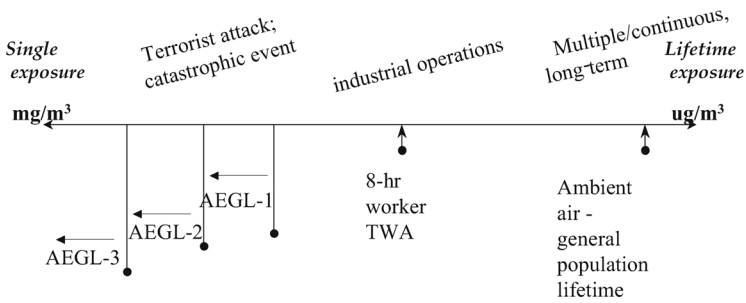
exposed. This raises questions regarding the value of such information for any purpose other than after-the-fact epidemiological analysis, which is not useful for the commander in the field who has the responsibility to complete the mission managing competing risks. Commanders are currently trained to manage risk in accordance with FM 100-14, Risk Management, which applies a probability/severity of health outcome matrix to hazards<sup>69</sup> (Figure 9.3). Obvious catastrophic events such as a release of highly toxic materials would have severe health risks, although the probability of such a release can only be estimated (Figure 9.4). However, since the most profound preventive action is avoidance, troop locations can be selected with regard to proximity and plume direction from industrial facilities. With respect to exposure to low ambient levels of chemicals, health effects may be delayed or produce little obvious and measurable impact on the immediate mission, but the probability of occurrence is high. Even if monitoring information were available immediately, uncertainties relating to actual health impact would make decision making difficult. One approach adopted by the U.S. Army Center for Health Promotion and Preventive Medicine provides concentrations of chemicals of interest representing high, medium, and low risk for short-term exposure.<sup>70</sup> A companion document is under development to address the more problematic long-term exposures.<sup>71</sup> These documents can be viewed at <http://chppmwww.apgea.army.mil/hracp/pages/caw/index.html>. A major consideration relates to the degree of conservatism to apply to the available toxicological reference values to fit the scenario of long-term exposure of a healthy population on a continuous basis. Appreciated, but not well quantifiable, are issues relating to mixtures of compounds and potentially additive or synergistic effects, interaction with other biologicals such as vaccines and medications, and the effects of stress, reduced sleep, and other considerations in a deployed setting.

RISK ASSESSMENT MATRIX

<i>SEVERITY</i>	<i>PROBABILITY</i>				
	Frequent	Likely	Occasional	Seldom	Unlikely
Catastrophic	E	E	H	H	M
Critical	E	H	H	M	L
Marginal	H	M	M	L	L
Negligible	M	L	L	L	L
E- Extremely High Risk					
H - High Risk					
M- Moderate Risk					
L- Low Risk					
Figure 2-4, FM 100-14, Risk Management					

FIGURE 9.3 Risk assessment matrix.

# Air Exposure Continuum



*NOTE: generalized schematic - not exact scale for any particular chemical*

**FIGURE 9.4** Air exposure concentration “continuum.”

Given that such exposure and outcome data systems come to fruition, will they eliminate or alleviate questions regarding exposure and outcome associations following future deployments? Questions such as addressing whether or not a specific deployed cohort is experiencing statistically significant excesses of certain adverse outcomes would conceivably be answerable. Questions relating to the association of such outcomes with specific exposure on a deployment may not. Given measurable and measured exposures to a known hazard in the range known to produce health effects in humans, the question should be easy to answer. Given measured concentrations of a broad variety of hazards with unclear, but possible health effects (“gray-zone” concentrations), much more sophisticated methods will be required to evaluate the association. Additionally, much more exposure data is needed. The Government Accounting Office, in its review of Gulf War Illness efforts, stated that “The need for accurate, dose-specific information is particularly critical when low-level or intermittent exposure to drugs, chemicals or air pollutants is possible. It is important not only to assess the presence or absence of exposure, but to characterize the intensity and duration of the exposure.”<sup>9</sup> This essentially calls for continuous monitoring on a broad range of low-level hazards on deployments, but, in actuality, comparable data would be needed on a control population, unless sufficient data is collected on a large enough population with frequent enough outcomes to assess for a trend in dose-response. Further, adequate information on confounding variables would be required. Identifying the confounding variables up-front may be somewhat difficult without knowledge of which exposures or outcomes will be a concern and subject to analysis. Will sufficient data ever be available following a deployment to evaluate an exposure/outcome relationship in terms of causation? To avoid an ecological fallacy, quite specific information is required at the individual level. Adequate baseline on conditions and/or symptoms pre-deployment is necessary to establish the critical chronological relationship (exposure must precede the disease to be considered causal). Current predeployment questionnaires are too simplistic, although the “seamless

medical record,” which has been proposed, may alleviate this problem. Causality is supported by the strength of the association, in that the greater the magnitude of the demonstrated association, the more likely the significance.<sup>70</sup> Low-level exposures, such as those evaluated with respect to hazardous waste and health effects have largely been determined to pose low-level risks with broad confidence intervals.<sup>11</sup> Causality is also supported if a dose-response trend can be demonstrated, that is, that those with the most intense and longest duration exposure have a greater chance of developing the outcome. Given enough data points of exposure magnitude and/or duration, and a sufficiently large population, this would be a possibility. Another criteria that supports causality relates to the specificity of the association. If the effect or outcome is specific and/or unusual, associated with the particular potential cause, the relationship between exposure and outcome is more likely to be causal. Whether or not this factor will be relevant depends to some degree on the potential exposures and mechanisms of toxicity. If an unusual outcome is identified, relating it to a particular exposure would be dependent upon the toxicological research associated with that outcome, or more specifically, potential exposures associated with that outcome. Another criterion that supports causation is consistency of the association. If many observers in many studies or settings have replicated the finding, then the role of chance as an explanation for the finding is minimized. Abundant data on particulates and respiratory effects exist, and so, for example, if a finding related to particulate levels and respiratory disease outcomes is noted, causality would be much less of a question. The remaining criterion for causality is biological plausibility. The connection between the potential cause and the possible effect must make biological sense. Documented exposures and documented outcomes may be associated statistically, but causality requires that some plausible mechanism link the two. Much of the basic research currently conducted aims to elucidate the mechanisms of neurotoxic damage to provide support for hypotheses related to exposures in the Gulf and neurological outcomes.<sup>66</sup>

“Recent military deployments, especially in Vietnam and the Persian Gulf, have demonstrated that concerns about the health consequences of participation in military action arise long after deployment has ended and that the evaluation of those concerns and the provision of health care to affected personnel may represent formidable challenges to both epidemiologists and to medical caregivers. Although some of these challenges can be attributed to the intrinsic difficulty of evaluating poorly understood clusters of events that were not among the expected consequences of combat or of environmental conditions, they also may be attributed in part to limitations of the systems used to collect and manage data regarding the health and service-related exposures of military personnel. No system of record keeping can be expected to provide the information needed to address every unanticipated research issue, including the health consequences of military service.”<sup>6</sup>

## ACKNOWLEDGMENTS

The author wishes to thank Dr. Robert DeFraités, Dr. John Brundage, Dr. K. Craig Hyams, and Dr. Donald MacCorquodale for their thoughtful review and comments on this chapter.

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