

In the summer of 1990, after the Iraqi invasion of Kuwait, the United States and its coalition allies rapidly deployed large military forces to Saudi Arabia and adjacent countries, initially to prevent invasion of Saudi Arabia (Operation Desert Shield). Later that year, in November, additional large forces were deployed. In January and February 1991, the coalition conducted combined air, ground, and naval operations to eject Iraqi forces from Kuwait in Operation Desert Storm (Watson et al., 1991). The military offensive operations were rapid and successful.

Nearly 700,000 U.S. personnel served in the theater of operations. The U.S. forces had substantially fewer casualties and less illness than had been expected, despite a challenging environment (Quin, 1982) and an opponent with large, modern, and well-equipped forces experienced in combat in the region (Cordesman and Wagner, 1990; Helmkamp, 1994). Iraq's demonstrated ability to use chemical warfare and indications of its interest in biological warfare were major concerns for senior U.S. commanders (Clancy and Franks, 1997). These concerns influenced planning operations and led to very substantial defensive efforts, with extensive training, deployment of detectors, use of protective equipment, and the urgent deployment of pretreatments and immunizations.

After the termination of hostilities, coalition forces were rapidly reduced as efforts were being made to destroy Iraqi military materiel in occupied areas before withdrawal. Later, as part of international agreements, United Nations (UN) teams had access to Iraq to observe or conduct the destruction of weapons of mass destruction and the facilities associated with them, including Scud missiles and chemical facilities.

After the withdrawal of U.S. forces, it gradually became apparent that a considerable number of U.S. personnel who had served in the theater were ill with varied symptoms that in some cases did not readily fit common disease patterns. Later, some coalition countries reported similar symptoms in their personnel. In general, such reports were rare, and some countries reported none.

A later compilation from a registry of U.S. Gulf service personnel showed the following common problems, in descending order of frequency (Defense Science Board [DSB], 1994):

- skin rashes, fatigue
- muscle and joint pain
- headache
- loss of memory
- shortness of breath
- diarrhea
- cough
- choking sensation, sneezing, chest pain.

Reviews, including that of the DSB (1994), did not find chemical and biological agent exposures to be a plausible explanation for the many cases of illnesses in Gulf War veterans being reported. The information available at the time indicated that exposure to agents was not possible because of the great distances between U.S. forces and targets in Iraq where agents might have been released. Likewise, no clinical reports suggested exposures, and it was considered unlikely that long-term effects would arise from exposures that did not produce symptoms. More suspicion was directed toward stress as a basis for the illnesses.

The later disclosure that postwar demolition operations had caused some release of nerve agents proximate to U.S. forces at Khamisiyah led to some modification of views. The Institute of Medicine (IOM) felt that further animal research and human epidemiology studies were indicated to evaluate long-term neurotoxic effects of low-level exposures (IOM, 1997), and the Presidential Advisory Committee (PAC) on Gulf War Illnesses also considered that agent exposure could not be totally excluded as playing some role, although the calculated exposures were low.

Two main registries currently deal with illnesses in Gulf War veterans:

- the Comprehensive Clinical Evaluation Program (CCEP), involving active and reserve component military personnel, administered by the Department of Defense (DoD)
- a registry of former service members, operated by the Department of Veterans Affairs (Joseph, 1997; Hallman et al., 1998).

The concerns about health problems of those who served in the Gulf region have produced a number of reviews, study efforts, and comprehensive examination efforts (IOM, 1996; National Institutes of Health [NIH], 1994; DSB, 1994).

In 1994, there was a further IOM review of the CCEP, and the Veterans Administration (VA), the U.S. Department of Health and Human Services (DHHS), and the DoD jointly established the Gulf Veterans Coordinating Board. In 1995, the President established an advisory committee on Gulf veterans' illnesses. Many possible causes of veterans' problems have been considered, and a number of research programs were inspired by the problem (PAC, 1996a, 1996b, 1997).

The long list of potential exposures that have been of concern includes fuels, smoking, chemical and biological agents, solvents and petrochemicals, tent heater fumes, non-U.S. and contaminated food and water, oil-field fires, chemical-resistant paints, pesticides, immunizations, infectious diseases, microwaves, antimalarial drugs, depleted uranium, and stress (DSB, 1994; PAC, 1996a; Kroenke et al., 1998).<sup>1</sup>

To date, it has not been possible to develop a coherent case definition of a "Gulf War syndrome" (NIH, 1994; Joseph, 1997; Gibbons et al., 1998; Kroenke et al., 1998; Marshall and Gass, 1998). The term "illnesses in Gulf War veterans" has been used to describe the varied signs, symptoms, and findings in ill Gulf-service personnel.

The CCEP recorded data on 18,495 registered individuals, taken from structured histories, including self-reported exposures. A recent review used the CCEP data to provide a temporal picture of the onset of common symptoms (Kroenke et al., 1998). Table 1.1 shows the overall symptom frequency for the registry.

Figure 1.1 shows the timing of the onset of the symptoms. Fewer than 5 percent of veterans reported symptoms occurring before the war, 25 to 30 percent during the war, 25 percent in the year following the war and nearly 50 percent beginning 2 or more years after the war.

Kroenke et al. (1998) analyzed the exposures to various factors that registrants in the CCEP had self-reported. Although the reports have not yet been validated, 1,145 soldiers (6 percent) thought they were exposed to nerve agents, and 422 soldiers (2 percent) reported exposures to mustards. The authors found no association between individual symptoms and self-reported exposures.

Several more focused studies concentrated on units or regions (Haley and Kurt, 1997; Haley, Kurt, and Horn, 1997; Haley, Horn, et al., 1997; Stretch et al., 1995; Penman et al., 1996; Marshall and Gass, 1998; Cowan et al., 1998; Morris, 1998).

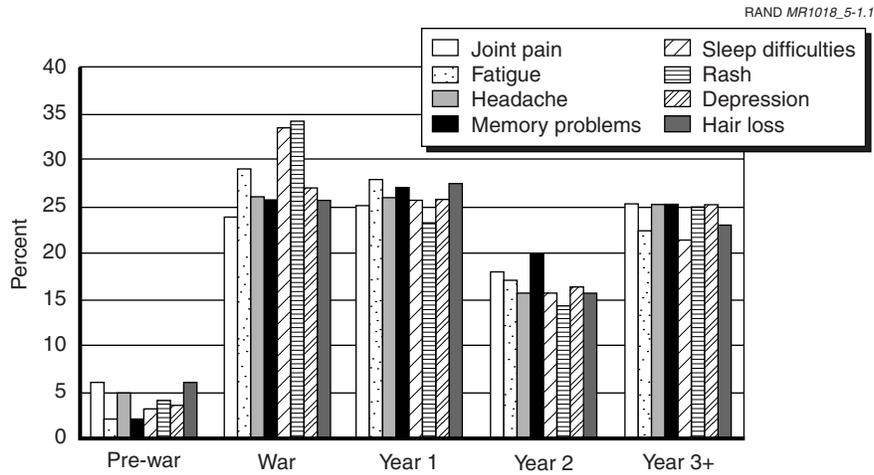
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<sup>1</sup>In addition to this report, the following of these are the subjects of RAND reviews: infectious diseases (Hilborne and Golomb, 2000), pyridostigmine bromide (Golomb, 1999), immunizations (Golomb, 2000), stress (Marshall, Davis, and Sherbourne, 1999), oil well fires (Spektor, 1998), depleted uranium (Harley et al., 1999), and pesticides (Cecchine et al., 2000).

**Table 1.1**  
**Symptom Frequency for 18,495 Gulf War Veterans Evaluated**  
**in the Comprehensive Clinical Evaluation Program**

Symptom	Any Complaint (%)	Chief Complaint (%)
Joint pain	50.0	12.1
Fatigue	46.9	10.6
Headache	39.7	7.9
Memory/fatigue problems	34.0	4.1
Sleep disturbance	33.0	2.7
Rash	30.2	6.3
Concentration difficulty	26.4	0.5
Depressed mood	22.3	1.0
Muscle pain	21.2	1.1
Dyspnea	18.4	2.7
Diarrhea	18.2	1.8
Abdominal pain	16.3	1.6
Hair loss	11.8	0.5
Bleeding gums	8.2	0.1
Weight loss	6.4	0.1

SOURCE: Kroenke, Koslowe, and Roy (1998); as compiled in 1994. Reprinted with permission.



SOURCE: Reprinted with permission from Kroenke, Koslow, and Roy (1998).

**Figure 1.1—Onset of Symptoms**

Mortality and hospital studies have not shown differences in hospitalization rates or mortality between military personnel who deployed to the Gulf and a matched control military population that did not, but this has not eased concern about the problem (Gray et al., 1996; Kang and Bullman, 1996). Mortality from motor vehicle accidents was higher in Gulf returnees than in nondeployed control groups.

Some caution is advisable in drawing conclusions from these studies and the CCEP. Haley (1998a, 1998b) has hypothesized there may be some possible selection bias due to the “healthy warrior” effect: Illness might simply have been more prevalent in the control population, since sick persons were not deployed. He further hypothesized that hospitalization rates might not be reliable in that sick veterans might have disproportionately separated early from the service and might have received care from nonfederal health facilities, which were not included in the hospital case review. The hospital experience of veterans in nonfederal hospitals is now under study in California (Smith et al., 1998). Other researchers have questioned Haley’s theories (Gray, Knoke, et al., 1998; Kang and Bullman, 1998; Cowan, Gray, and DeFraités, 1998).

An important concern has been raised that U.S. personnel may have been exposed to military chemical warfare agents and toxins, and that such exposures play a role in the ongoing problems of some who served in the region. Previous reviews have considered this possibility but did not find significant exposures plausible, given assurances that no Iraqi attacks had occurred and that the Iraqi chemical targets struck during the air war were too remote to affect U.S. personnel. This conclusion was somewhat controversial, with congressional hearings producing reports of unusual events, positive detector alarms, and other anecdotes as contrary data (Riegle and D’Amato, 1994; Senate, 1994; House, 1997).<sup>2</sup>

The later discovery that U.S. forces, in the course of demolition work at the Iraqi depot of Khamisiyah, had unknowingly exploded bunkers and rockets containing nerve agents has required recognition that exposures were possible. Several efforts to model this event have identified a larger exposed personnel population than earlier such attempts suggested. The levels of agent were rather low for this population. Apart from the possibility of unauthorized or unintended small-scale Iraqi employment of agents, congressional hearings and the General Accounting Office (GAO) have raised the possibility that air war attacks on Iraqi facilities where chemical or biological agents were present might have

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<sup>2</sup>The Office of the Special Assistant to the Deputy Secretary of Defense for Gulf War Illnesses (OSAGWI) has been investigating thoroughly the events covered in testimony and others brought to attention using a case study approach. The office has posted completed studies on its Web site (<http://www.gulflink.osd.mil/>).

resulted in agent transport into areas where U.S. and coalition forces could have been exposed (Riegle and D'Amato, 1994; GAO, 1997; Senate, 1994; House, 1997).

Two small-scale events during and after the war have not been readily explained. Czech chemical defense troops supporting the Saudi army made low-level detections of nerve agent, subsequently identified as sarin, on January 19, 1991. No casualties resulted, but the origin of the small amount of sarin is unexplained (OSAGWI, 1998b<sup>3</sup>). After the war, a U.S. soldier engaged in destroying Iraqi equipment entered a bunker and then left. Hours later, he developed a typical mild mustard-type injury on his arm. Interpretation of detector readings from that event has been inconclusive and complicated by oil contamination on garments (OSAGWI, 1997d).

Before the war, it was known that Iraq had a substantial chemical and biological warfare program and had employed chemical agents against Kurdish dissidents and extensively against Iran during their long war (Cordesman and Wagner, 1990; Stockholm International Peace Research Institute [SIPRI], 1971; UN, 1984). Since the Gulf War, UN demilitarization efforts have yielded a clearer picture of Iraqi capabilities (Marshall, 1997; Zilinskas, 1997; United Nations Special Commission [UNSCOM], 1991, 1992, 1995).

The Special Assistant for Gulf War Illnesses asked RAND to review the scientific literature on the health effects of eight possible causes of illness among veterans of the Gulf War. This review of selected chemical and toxin agents is a part of the effort. The intention is to provide factual information about agents and issues of concern.

## APPROACH

RAND was initially asked to review chemical and biological warfare agents that Iraq was thought to possess:

- sarin (GB)
- cyclosarin (GF)
- thiosarin
- mustard (presumably H or distilled mustard [HD])
- phosgene oxime (CX).

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<sup>3</sup>OSAGWI has made a large number of Gulf War-related documents available on line in addition to its own products. For simplicity, all are listed under OSAGWI in the Bibliography.

After studying reports of the Iran-Iraq War and unclassified post-Gulf War information, RAND added additional agents (with the concurrence of OSAGWI) but gave priority to the initial list. The author had no advice or assistance from U.S. intelligence organizations in the selection of agents for study. It was also noted there was no immediately available information on thiosarin, although there were a few references to thiosoman (SIPRI, 1973). Also noted was that there was little information on human exposures to phosgene oxime, and less on long-term or low-dose effects. The additional agents were

- tabun (GA), an agent Iraq used against Iran (UN, 1984)
- soman (GD), a very toxic nerve agent suspected to be in Iraqi stocks
- VX, an extremely toxic nerve agent attributed to Iraq (OSAGWI, 1990)
- lewisite (L), a blister agent that a Fox vehicle reportedly detected during the Gulf War (Riegle and D'Amato, 1994), which Iraq had previously been suspected of using (OSAGWI, 1997c)
- toxins, specifically trichothecene mycotoxins, which were suspected to have been used in the Iran-Iraq War (Heyndrickx, 1984; Marshall, 1997; Zilinskas, 1997)
- ricin (W), a plant toxin that Iraq acknowledged having in stock (UNSCOM, 1991, 1992, 1995; Zilinskas, 1997)
- aflatoxin, a fungal mycotoxin that Iraq admitted having in Scud warheads and bombs (UNSCOM, 1991, 1992, 1995; Marshall, 1997; Zilinskas, 1997; Sidell, Takafuji, and Franz, 1997).<sup>4</sup>

As the review process continued, much new information became available as a result of research inspired by Gulf War illnesses. Some references could not be retrieved. Some older U.S. government documents are no longer available from the Defense Technical Information Center (DTIC). Moreover, it has not, to date, been possible to obtain some older foreign references (Speigleberg, 1963). In addition to the many panel and study group reports (IOM, 1996; DSB, 1994; NIH, 1994; PAC, 1996b; Riegel and D'Amato, 1994), clinical and operational reports of medical experiences during the Gulf War were considered.<sup>5</sup> The U.S. Army Medical Research Institute of Chemical Defense staff and library were

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<sup>4</sup>Botulinum toxin, which is remarkably toxic, with little chance of unrecognized exposures, is being considered in a companion piece (Hilborne and Golomb, 2000).

<sup>5</sup>Most of these were found in the journal *Military Medicine*, which gave a background picture of illnesses both in U.S. forces and Iraqi prisoners; see Joseph (1997), Garland (1993), Koshes and Rothberg (1995), Cook (1994), Newmark and Clayton (1995), Hines (1993), McDiarmid et al. (1995), Hyams et al. (1996), Paparello et al. (1993), Wintermeyer et al. (1994, 1996), West (1993), Longmire (1991), Keenan (1991), Pierce (1997), Wittich (1996), Wasserman et al. (1997).

very helpful in making available references that were otherwise difficult to obtain.

Discussions with staff members of the Armed Forces Institute of Pathology and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) provided helpful background information, as did informal discussions with Department of Veterans Affairs clinicians concerned with agents and illnesses in Gulf War veterans.<sup>6</sup>

The descending priority of retrieval and review was as follows:

1. **Documented human experience** (especially lower-dose, chronic, and longer-term effects). There is documented information about human exposure to most agents. The following situations can yield such information:
  - *Military and civilian casualties* can occur during operational use of agents.
  - *Accidental and occupational exposures* can give a great deal of information about clinical responses, and in some cases have had sustained follow-up. The quantitative amount and duration of exposure are, however, unknown, although rough estimates are sometimes possible. Epidemiological information, when available, is reported.
  - *Intentional exposure as part of research* has yielded a considerable amount of information from older studies, especially with nerve agents and mustards, and in some cases there have been long-term follow-up studies. (The situation is similar with respect to human experience with organophosphate pesticides.)
2. **Relevant nonhuman primate data.** Nonhuman primates are widely considered the best models for predicting human responses to chemicals and toxins. They are often used to validate studies using nonprimate animal models. As will be discussed later, there are substantial problems in extrapolating quantitative data from rodents, dogs, cats, and hens to humans. Indeed, even within a class, responses can be surprising. For example, Husain et al. (Husain, Kumar, et al., 1993; Husain, Vijayaraghavan, et al., 1993) found that chronic sarin exposure did not produce delayed neuropathy in rats but did so in mice. Even nonhuman primates are incomplete models for humans, e.g., they do not develop blisters from mustard agents.
3. **Other animal research**, especially low-dose chronic regimes.

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<sup>6</sup>The comprehensive *Textbook of Military Medicine* (Sidell, Takafuji, and Franz, 1997) only became available late in the preparation of this report.

4. **Mechanisms of action**, especially those that might produce long-term effects.
5. **Variations in sensitivity and response**, and interactions with the environment and other chemicals.
6. **Studies and experience** as above with analogous chemicals (chiefly organophosphate pesticides).

A prominent theme in many Gulf War discussions is the speculation that some illnesses may result from the combined effects of several drugs and chemicals (Senate, 1994; House, 1997; Haley and Kurt, 1997; Haley, Kurt, and Horn, 1997; Haley, Horn, et al., 1997). Although there has been disagreement about design and conclusions of this hypothesis (Haley et al., 1998a), there is perhaps some experimental support for these concerns (Abou-Donia et al., 1996). These animal studies of high sublethal doses of several chemicals (not agents) have been criticized for using routes of exposure that might not replicate human exposure in the animals used. There is no convincingly predictive, quantitative science available to predict multiple chemical interactions in living organisms. Industrial and environmental exposures are commonly multiple, but the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA) generally regulate chemicals singly. The pharmaceutical industry has an analogous problem because it is not always possible to forecast drug interactions, which is one of the reasons for postmarketing surveillance.

## HOW THE REVIEW IS ORGANIZED

The report consists of a brief overview of chemical and biological warfare in Chapter Two, followed by three chapters that discuss the following specific classes of agents:

- skin-damaging agents: lewisite, mustards, and phosgene oxime (Chapter Three)
- toxins: ricin, trichothecenes, and aflatoxin (Chapter Four)
- nerve agents: tabun, sarin, soman, cyclosarin, VX, and thiosarin (Chapter Five).

Chapter Six provides conclusions and recommendations, while additional information can be found in the appendixes. A glossary defines specialized terminology found in the report.

It will be apparent that, despite an extensive amount of information on the many agents, there is a lack of data in specific exposure domains of interest, such as the reported low concentration of 0.01296 mg-min/m<sup>3</sup> for sarin down-

wind from Khamisiyah (Central Intelligence Agency [CIA], 1997). This level is below what is discussed in most clinical reports and studies.<sup>7</sup>

This report discusses “exposures” and exposure levels. Defining adverse exposure or “no-effect” levels is not straightforward; neither is being certain of the biological effects of chemicals and toxins at low levels. In some cases, natural protective defense mechanisms make low-level exposures innocuous. The American Thoracic Society made a considerable effort to define adverse respiratory health effects rigorously, including standards to judge studies, noting that some “no effect” studies lacked statistical power, giving false negative findings.<sup>8</sup> Some perceived health problems may be false-positive findings.

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<sup>7</sup>The time-weighted average of exposures for 8 hours that the Surgeon General has approved for workers is 0.0001 mg/m<sup>3</sup> (Watson et al., 1998; DHHS, 1988; MMWR, 1998), a domain below expected physiological responses and below permissible levels for many less-toxic pesticides. (DHHS, 1988, contains the exposure recommendations.)

<sup>8</sup>“Guidelines as to What Constitutes an Adverse Respiratory Health Effect, with Special Reference to Epidemiologic Studies of Air Pollution” (1985).