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PRINCIPAL INVESTIGATOR: Richard N. Miller

CONTRACTING ORGANIZATION: National Academy of Sciences
Washington, DC 20418

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This is an epidemiologic study of morbidity and mortality outcomes associated with potential exposure to low levels of chemical warfare agents at the Khamisiyah ammunition depot in southeastern Iraq. Health outcomes of troops putatively exposed during rocket demolition in 1991 will be compared to those of a similar group of unexposed military personnel for a minimum five-year follow-up period. Exposure levels will be estimated based on environmental and climatological modeling of the chemical footprint, in combination with troop location data during the time of the demolition. Specific objectives of the study are (1) to compare morbidity and mortality outcome rates among Army personnel putatively exposed to chemical warfare agents and those not exposed using both self-reported health information and passive records-based methods; and (2) to compare temporal trends in health perception and health care use before and after notification of potential chemical warfare agent exposure among the putatively exposed and unexposed groups.

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FOREWORD

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INTRODUCTION

SUBJECT: This is an epidemiologic study of morbidity and mortality outcomes associated with potential exposure to low levels of chemical warfare agents at the Khamisiyah ammunition depot in southeastern Iraq. Health outcomes of troops putatively exposed during rocket demolition in 1991 will be compared to those of a similar group of unexposed military personnel for a minimum five-year follow-up period. Exposure levels will be estimated based on environmental and climatological modeling of the chemical footprint, in combination with troop location data during the time of the demolition.

OBJECTIVES: Specific objectives of the study are (1) to compare morbidity and mortality outcome rates among Army personnel putatively exposed to chemical warfare agents and those not exposed using both self-reported health information and passive records-based methods; and (2) to compare temporal trends in health perception and health care use before and after notification of potential chemical warfare agent exposure among the putatively exposed and non-exposed groups.

SCOPE: The cohort for this study will be selected in collaboration with the Office of the Special Assistant for Gulf War Illnesses (OSAGWI), the Deployment Environmental Surveillance Program of the US Army Center for Health Promotion and Preventive Medicine (CHPPM), and the Environmental Epidemiology Service of the Department of Veterans Affairs (VA). Eligibility for entry into the cohort will be based on having served in the Persian Gulf Theater of Operations. Individuals identified as having been within and outside the modeled chemical footprint will be eligible for inclusion. The cohort will be defined not only in terms of potential chemical exposure, but also in terms of whether or not individuals were notified of potential exposure to chemical agents, and whether or not individuals participated in the VA National Health Survey of Persian Gulf War Veterans.

EXPECTED PRODUCTS (MILESTONES): Findings and conclusions will be published jointly with DoD and VA investigators in a peer-reviewed professional journal.

STATUS/RESULTS TO DATE: none reported.

BODY

BACKGROUND: On March 4 and 11, 1991, combat engineer and demolition units of the US Army XVIII Corps (Airborne) (ABN) destroyed two large caches of rockets-one in a bunker, the other in a nearby pit-at the 50 square kilometer (km) Khamisiyah ammunition storage depot, approximately 350 km southeast of Baghdad, Iraq. No alarms sounded which would have indicated release of chemical agents during this period or in the ensuing two months when additional facilities at the depot were destroyed. However, in October 1991 and March 1992, and again in May 1996, representatives from the United Nations Special Commission (UNSCOM) verified the existence of sarin and cyclosarin in both intact and damaged rockets in the bunker and pit. While US intelligence became aware of the UNSCOM findings in late 1991, no actions were taken to identify US troops who might have been in the area during the demolition for two reasons. First, no alarms indicated that any release of chemical agent had occurred and second, the veracity of Iraqi claims of the existence of rockets with chemical warheads was deemed suspect because of their lack of consistent cooperation with UNSCOM personnel. However, as concern about Persian Gulf War Syndrome grew in 1994 and 1995 (and upon definitive verification by UNSCOM in 1996 of the presence of chemical agents at Khamisiyah), the Department of Defense (DoD) released a statement on June 21, 1996 confirming the possibility that US troops had been exposed to chemical warfare agents during the demolition at Khamisiyah.

RESEARCH ACCOMPLISHMENTS: This will be a nonconcurrent prospective cohort study. Potential exposure occurred in March 1991 and individuals will be followed for outcomes from that time forward to the present (or until morbidity and mortality databases allow) for a minimum follow-up period of five years. The Medical Follow-up Agency (MFUA) staff will ascertain morbidity and mortality outcomes in a sample of active duty and former active duty soldiers using both self-assessment of health status and passive records-based methods. Personnel both known to have been within the modeled chemical footprint and known not to have been within the footprint will be included in the study so that outcome comparisons can be made among individuals with varying likelihood of potential exposure to chemical warfare agents.

The objectives of the study are:

1a. To compare mortality outcome rates among Army personnel potentially exposed and those not exposed using passive records-based methods.

1b. To compare morbidity outcome rates among Army personnel potentially exposed and those not exposed using both passive records-based methods and self-reported data from the VA National Gulf War Health Survey of returning veterans.

2. To compare temporal trends in health perception and health care use before and after notification of possible chemical warfare agent exposure among Army personnel potentially exposed and those not exposed.

The cohort for this study will be selected in collaboration with the Office of the Special Assistant to the Deputy Secretary of Defense for Persian Gulf War Illness (OSAGWI); the Deployment Environmental Surveillance Program, U.S. Army Center for Health Promotion and Preventive Medicine (DESP/USACHPPM); and the Department of Veterans Affairs (VA), Environmental Epidemiology Service. Eligibility for entry into the cohort will primarily be based on having served in the Persian Gulf Theatre of Operations. Modeling procedures were undertaken by a joint CIA-DoD task force to simulate the release and dispersion of chemical agents so that both exposed (likely to have been within the hypothetical chemical exposure footprint) and unexposed (not within the footprint) individuals could be identified.

In addition to eligibility based on potential exposure to chemical agents, the cohort will also be comprised of individuals who were notified of a potential exposure several years later and individuals who were not notified. Since the determination of which individuals were potentially exposed has changed from initial efforts due to the development of more sophisticated modeling techniques and better information on troop locations, it is likely that a proportion of those notified and not notified were incorrectly done so. That is, some individuals who were notified need not have been and some who were not notified should have been.

Finally, scientists from the Environmental Epidemiology Service of the Department of Veterans Affairs performed a health survey on 15,000 Gulf War veterans seeking information on their health and health care seeking behaviors. Phase I of the survey was performed prior to troop notification of potential chemical agent exposure at Khamisiyah.

As a result individuals in each of the following groups will actually comprise the study cohort:

1. Potential Chemical Exposure, Notified of Exposure
2. Potential Chemical Exposure, Not Notified of Exposure
3. No Chemical Exposure, Notified of Exposure
4. No Chemical Exposure, Not Notified of Exposure

Objective 1a/b: To compare mortality/morbidity outcome rates by

i. Exposed groups **(1+2)** vs. Unexposed groups **(3+4)**
ii. Exposed and Notified group **(1)** vs. Unexposed and Notified group **(3)**
iii. Exposed and Not Notified group **(2)** vs. Unexposed and Not Notified group **(4)**

Objective 2: To compare temporal trends in health perception and health care use among troops before and after notification of possible chemical agent exposure in

i. Exposed and Notified group **(1)** vs. Exposed and Not Notified group **(2)**
ii. Unexposed and Notified group **(3)** vs. Unexposed and Not Notified group **(4)**

PROSPECTIVE SAMPLE SIZES TO MEET OBJECTIVES:

Objective 1a: Mortality Rate comparisons
50,000 exposed:100,000 unexposed

Objective 1b: Morbidity Rate comparisons

854 exposed:8,366 unexposed (the population of Army personnel who participated in the VA National Gulf War Health Survey).

Objective 2: Health perception and care trends before and after notification. Arandom sample of 200 individuals from each of the four exposure categories will be selected from the 9,220 Army personnel who participated in the VA survey. These individuals will be re-surveyed using the same instrument they were given in Phase 1, prior to notification of potential chemical agent exposure.

Potentially Exposed and Notified	200
Potentially Exposed and Not Notified	200
Not Exposed and Notified	200
Not Exposed and Not Notified	200

OUTCOMES:

i. *Mortality.* A 9-track tape with identifier data on 50,000 potentially exposed veterans and 100,000 unexposed veterans will be created and submitted to the VA according to specifications for batch computer match with the Beneficiary Identification and Records Locator System (BIRLS). This will allow for ascertainment of vital status, as well as claims folder location for those individuals not already identified as deceased by our collaborator at the VA Environmental Epidemiology Service. Non-matching records resulting from the batch processing will be resubmitted through the interactive on-line system called Target at the MFUA office in the VA Regional office in DC. BIRLS has been estimated to be more than 90 percent complete for ascertainment of deaths among men in service during the World War II period. Data from an earlier pilot study showed that mortality reporting was 92.4%, and a more recent and much more comprehensive study of WWII veteran twins showed that BIRLS mortality ascertainment was 96% complete, when compared with the mortality files of the SSA. Despite these findings regarding the high rate of veteran mortality ascertainment using VA records, we will prepare a file containing records for all study subjects without records on BIRLS plus a sample of known decedents and subjects presumed alive and match it against the SSA death files. This same process was used in a methodological study of Vietnam era veteran deaths and resulted in 96% complete ascertainment. Records with fact and date of death from both the BIRLS and SSA matches will be sent to NDI+ for determination of underlying cause of death.

ii. Morbidity. A 9-track tape will be created containing the sample of potentially exposed soldiers, as well as demographically matched unexposed subjects. The tape will be submitted to the VA according to specifications for batch computer match with the VA Patient Treatment File (PTF) to obtain discharge diagnostic data for all hospitalizations during the period January 1991 through December 1998. All matching hospitalization records will be returned via the same medium. Records that are considered good matches will then be updated to MFUA files and processed for morbidity information.

iii. Health self-assessment. To assess the impact of notification of potential exposure to a chemical warfare agent on health self-perception among highly trained and motivated soldiers, we will compare the temporal change in the health self-assessment before and after notification. Health perception data prior to notification will be derived from the survey of a sample of Gulf War veterans performed by Dr. Han Kang and colleagues of the VA Environmental Epidemiology Service. When matched to the notification and potential chemical exposure data obtained from OSAGWI, the health perception data from Phase I and II of the VA PGW Veterans' Study will result in the categories of exposure listed above. The same contractor that performed the pre-notification survey (Phase I and II) will perform the post-notification survey on the same population, resulting in a "before-after" notification self-assessment of health care and health care behavior.

ANALYSIS: For morbidity data, an association between selected health outcomes and potential exposure to chemical warfare agents will be evaluated by multivariate techniques that provide for the estimate of relative risks with adjustment for covariates. For mortality data, analysis will include a formal comparison of all-cause and cause-specific standardized mortality ratios (SMRs) between exposed and non-exposed study subjects, as well as a proportional hazards analysis. The relatively close matching of non-exposed subjects by age, race, sex, and other variables permits the use of SMR analysis. The SMRs themselves will be calculated by dividing observed age-, race-, time-, and cause-specific deaths by comparable figures based on data for the U.S. general population. Most of these SMRs are expected to be below 100; that is, for the most part, death rates among workers and veterans are lower than among the general population, due to the so-called "healthy worker/soldier effect." The comparison to U.S. rates is also useful in those situations in which subset exposed and non-exposed death rates appear to be different, for it can identify whether such a difference is due to a higher than expected rate in one group or a lower than expected rate in the other (or both).

In addition, a proportional hazards analysis will be undertaken to compare subset exposed and non-exposed all-cause and cause-specific mortality, using the general list of causes specified in the previous studies of the subset. Use of the proportional hazards analysis will permit the computation of relative risk of mortality (subset exposed versus non-exposed), adjusted for age and other variables.

PROBLEMS: Minor administrative issues in defining both exposed and unexposed populations have resulted in delays in receiving this information from OSAGWI and CHPPM. These issues have been resolved and the computer files containing individuals potentially exposed (based upon meteorological and chemical dispersion modeling) and non-exposed have been received by MFUA and are currently being processed.

In addition, the National Research Council Protocol Oversight Committee, formed to advise MFUA staff on the conduct and analysis of this study, recommended that morbidity data should be collected not only from passive surveillance techniques (i.e., inpatient and outpatient military and VA medical databases), but also from the VA

National Gulf War Survey of returning veterans, a self-report instrument). A portion of the morbidity identified via the survey should also be validated through the VA inpatient and outpatient databases, the Patient Treatment File (PTF) and the Outpatient Clinic File (OPC).

RECOMMENDED CHANGES/FUTURE WORK: None

REPORTABLE OUTCOMES: None

CONCLUSIONS: Results from this study are not yet available. After overcoming some early stumbling blocks concerned with obtaining DoD data necessary to successfully complete the study, research is proceeding, albeit slightly behind schedule.

LIST OF PERSONNEL

Richard N. Miller, MD, MPH	Director, MFUA
Philip O. Renzullo, PhD, MPH	Senior Program Officer/Study Director
Kelle Straley-Eason, MPH	Research Associate
Harriet Crawford	Senior Analyst/Programmer
Jihad Daghmash	Analyst
Pamela Ramey-McCray	Administrative Assistant
Andrea Cohen	Financial Associate