Long-Term Health Effects of Participation in Project SHAD (Shipboard Hazard and Defense)

William F. Page, Heather A. Young, and Harriet M. Crawford, authors, with Oversight from the Advisory Panel for the Study of Long-Term Health Effects of Participation in Project SHAD

ISBN: 0-309-66090-4, 142 pages, 8 1/2 x 11, (2007)

LONG-TERM HEALTH EFFECTS OF PARTICIPATION IN PROJECT SHAD

(SHIPBOARD HAZARD AND DEFENSE)

William F. Page, Heather A. Young, and Harriet M. Crawford, authors

with Oversight from the

Advisory Panel for the Study of Long-Term Health Effects of Participation in Project SHAD

Medical Follow-Up Agency
Board on Military and Veterans Health

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS **500 Fifth Street, N.W.** **Washington, DC 20001**

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the advisory panel that oversaw the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. V101(93)P-1637, T/0#26 between the National Academy of Sciences and the Department of Veterans Affairs. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-10210-0
International Standard Book Number-10: 0-309-10210-3

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

For more information about the Institute of Medicine, visit the IOM home page at: **www.iom.edu**.

Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museum in Berlin.

Suggested citation: IOM (Institute of Medicine). 2007. *Long-term health effects of participation in Project SHAD (Shipboard Hazard and Defense).* Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the Nation. Improving Health.

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

AUTHORS

WILLIAM F. PAGE (*Study Director*), Epidemiologist
HEATHER A. YOUNG, Statistician
HARRIET M. CRAWFORD, IT Project Manager

ADVISORY PANEL FOR THE STUDY OF LONG-TERM HEALTH EFFECTS OF PARTICIPATION IN PROJECT SHAD

Project Staff

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Norman Breslow, School of Public Health and Community Medicine, University of Washington
Carlos A. Camargo, Jr., Emergency Medicine Network Coordinating Center, Massachusetts General Hospital
Robert Hoover, Epidemiology and Biostatistics Program, National Cancer Institute
Matthew L. Puglisi, Business Development, Aptima, Inc.
Kenneth R. Still, Occupational Toxicology Associates, Hillsboro, Oregon

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Dr. Melvin Worth**, Scholar-in-Residence, Institute of Medicine. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the Institute of Medicine.

Preface

Our study of the long-term health effects of participation in Project SHAD (Shipboard Hazard and Defense) posed a number of challenges, including difficulties in identifying all the Project SHAD participants, assembling an appropriate control group, devising and administering a suitable survey instrument, and producing a sound analysis and accompanying report. We could not have achieved the results we did without a great deal of help.

Throughout this study, Institute of Medicine (IOM) staff have relied especially on the good guidance of our expert advisory panel. Its members included experts in biostatistics, epidemiology, survey research, infectious disease epidemiology, toxicology, and military veteran epidemiology. We could not have persevered through all of the difficult challenges we faced without their help and support. Nonetheless, although the expert panel provided sound guidance for which the study and this report are better, the authoring staff take full responsibility for the final product.

We are also grateful especially to the military veterans who provided us with information, support, and encouragement. Without their willingness to donate their time and effort in support of this project, this study would not have been possible.

William F. Page, Ph.D.
Heather A. Young, Ph.D.
Harriet M. Crawford, B.S.

Acknowledgments

The study of the health effects of participation in Project SHAD was a large enterprise, and the list of people who deserve recognition for their contribution is enormous. Members of the Medical Follow-Up Agency (MFUA) data operations staff who worked on this study include Dwayne Bell, Jihad Daghmash, John Larson, Robert Mathes, Al Mattei, and Noreen Stephenson. Richard Miller, former Director of MFUA, provided valuable guidance for this study.

The data collection efforts for the Project SHAD study involved many people outside of MFUA. We appreciate the efforts of Robert Bilgrad and staff at the National Death Index; Barbara Bauman and staff at the National Personnel Records Center in St. Louis, Missouri; the staff at the National Archives in College Park, MD (Archives II); and staff at many federal archives centers and Department of Veterans Affairs (VA) regional offices across the country, especially the VA regional office in the District of Columbia. We relied on a few consultants external to the staff for some technical work critical to the conduct of the study, including Victor Miller, James Quinn, and Ada Youk. We are particularly grateful to SRBI, Inc., who conducted the telephone interviews for our health survey, especially John Boyle, Stephen Dienstfrey, and Paul Schroeder.

The MFUA staff has benefited from the vigilance and enthusiasm of many interested veterans, including Jack Alderson, Robert Bates, Jim Druckemiller, Norman LaChapelle, and John Olsen. The latter two also served on the Project SHAD Task Force, chaired by Jack Devine, of the Vietnam Veterans of America (VVA), whom we also thank for their assistance. We are especially grateful to Rick Weidman and Bernard Edelman, VVA staff, for their help and support throughout the study.

The current members of the Advisory Panel for the Study of Long-Term Health Effects of Participation in Project SHAD (Shipboard Hazard and Defense)—chair Daniel H. Freeman, Jr., Dan G. Blazer, Donald S. Burke, Linda D. Cowan, Gregory C. Gray, and Peter S. Spencer—have helped to ensure the quality of the logic followed in the conduct of this study. We thank them and assume responsibility for whatever items of advice they offered that we did not take.

Mark Brown and Han Kang of the VA have provided us valuable help, and Michael Kilpatrick and his staff at the Department of Defense's Force Health Protection and Readiness Program (formerly Deployment Health) have been particularly helpful to us. We wish to single out Dee Morris and Roy Finno for their special assistance on this project.

Lara Andersen, Sue Barron, Andrea Cohen, James Jensen, Linda Kilroy, Bronwyn Schrecker, Christine Stencel and the many other staff at the Institute of Medicine and the National Academies all helped along the way. Special thanks to Medical Follow-up Agency Director, Frederick (Rick) Erdtmann, and administrative assistant, Pamela Ramey-McCray, who provided much appreciated support to the project.

We—William Page, Harriet Crawford, and Heather Young Durick—thank everyone on this list (and perhaps a few whose names we have unintentionally omitted) for producing with us this report.

Contents

Abbreviations and Acronyms **xvii**

Summary **1**

1 Study Rationale and Overview **3**
Origin and Background, 3
References, 6

2 Investigating the Potential Health Effects from Participation in Project SHAD **7**
Literature Review, 7
Public Meetings, 8
Review of Classified Material, 8
References, 9

3 An Overview of Project SHAD (Shipboard Hazard and Defense) **10**
References, 10

4 Records-Based Data Sources **13**
Introduction, 13
Data Sources Used to Identify Participants and Controls, 13
Data Sources Used to Locate and Follow-Up Participants and Controls, 14
References, 15

5 Participant Cohort **16**
Initial Identification, 16
Outreach Effort to Identify Additional Participants, 17
Gathering Further Identifier Data from Military Records, 17

6 Referent Cohort **19**
General Scheme, 19
Detailed Information, 19

7 Health Survey **24**
Background, 24
Content of the Health Survey, 24
Conduct of the Health Survey, 25
Using FedEx Delivery to Check the Quality of Survey Addresses, 25
Final Survey Response Rates, 27
Variation in Telephone Responses by Time, 29
Comparison of Mail Questionnaire Versus Telephone Interview Responses, 29
Department of Veterans Affairs Outpatient Visits by Participation Status and Response Status, 29
References, 31

8 Analysis Structure **33**
Overview, 33
Available Data, 33
Defining Exposure Groups, 35
Methods of Analysis, 36
References, 38

9 Mortality Results **39**
Vital Status Data and All-Cause Mortality, 39

10 Morbidity Results **45**
Overview: Survey Response, 45
Primary Outcome Variable: SF-36, 45
Other Scaled Data, 56
Other Medical Data, 56
References, 64

11 Discussion **68**
The Study's Strengths and Weaknesses, 68
References, 72

Appendixes
A Executive Summaries of Reports on Toxicological or Biological Agents 73
B Questionnaire 101
C Material Concerning Outreach Survey 119

Tables and Figures

TABLES

3-1 List of Project SHAD Tests, Ships, or Military Units Involved, and Agents, 11

6-1 The Process of Selecting Control Ships, 20
6-2 List of Participant and Control Units Showing Selected Characteristics, 21

7-1 Number and Percent of FedEx-Delivered Mailings by Source of Address, 26
7-2 Number and Percent of FedEx-Delivered Mailings by Mailing Group, 27
7-3 Percent Distribution of Various Demographic Characteristics by Participation Status, for All Study Subjects and for Survey Respondents, 28
7-4 Percent of Study Subjects with Social Security Number, by Analysis Group, 28
7-5 Response Proportions by Analysis Group, Participation Status, and Presence of Social Security Number, 29
7-6 Comparison of Mail Questionnaire Versus Telephone Interview Respondents for Selected Characteristics by Percentage Distribution, 30
7-7 Percent Distribution of Subjects with a VA Outpatient Visit, by Participation and Response Status, for Various Characteristics, 31

8-1 Variables Considered for Analysis and Their Sources, 34
8-2 Primary, Secondary, and Tertiary Outcome Variables, 35
8-3 SHAD Exposure Groups, 36

9-1 Vital Status and Availability of Death Data by Project SHAD Participant Status and Exposure Group, 40
9-2 Percentage of Study Subjects with SSN and BIRLS Record, by Exposure Group and Project SHAD Participation Status, 40
9-3 Proportional Hazards Analysis of Total Mortality, by Exposure Group, Including All Subjects, Regardless of Completeness of Mortality Follow-Up, 41

9-4 Proportional Hazards Analysis of Total Mortality, by Exposure Group, Including Only Subjects with SSNs, Presumably with Virtually Complete Mortality Follow-Up, 42
9-5 Survival Analysis Using Proportional Hazards Regression: Cause-Specific Mortality Comparing Participants to Controls (Adjusted for Age, Race, Pay Grade, and Branch in Group B Only), Including Only Subjects with SSNs, Presumably with Virtually Complete Mortality Follow-Up, 43
9-6 Mortality Analysis Using Standardized Mortality Ratios (SMRs): Observed Number of Deaths and SMRs for Participants and Controls with SSNs for Selected Causes of Death, 1979–2004, by Analysis Group, 44

10-1 Availability of Mail Questionnaire and Telephone Interview Data by Analysis Group and Participation Status, 46
10-2 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, by Analysis Group and Participation Status (Sample Sizes in Parentheses), with Results of *t*-Test Comparisons, 46
10-3 Mean SF-36 Subscale Scores, by Analysis Group and Participation Status, with Results of *t*-Test Comparisons, 49
10-4 Mean SF-36 Summary Scores, by Analysis Group and Various Other Factors, with Results of *F*-Test Comparisons, 50
10-5 Adjusted Mean SF-36 Summary Scores, by Analysis Group, with Results of *F*-Test Comparisons, 52
10-6 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores for Subjects in Group A (Standard Errors in Parentheses), by Agent, with Adjustment for Age, Race, Branch, Pay Grade, Smoking, Drinking, and Body Mass Index (Model 1) or These Factors Plus Number of Tests (Model 2), 54
10-7 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores (Standard Errors in Parentheses) for Subjects in Group A, by "Dose" of Agent, with Adjustment for Age, Race, Pay Grade, and Branch, 55
10-8 Mean Somatization Scores, Unadjusted and Adjusted, for Participants and Controls, by Analysis Group, 56
10-9 Mean Memory and Attention Scores, Unadjusted and Adjusted, for Participants and Controls, by Analysis Group, 57
10-10 Number of Medical Conditions for Participants and Controls, with Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs), by Analysis Group, 57
10-11 Summary of Cancer Types by Group and Participant Status,59
10-12 Ungrouped Medical Conditions by Analysis Group, Comparing Participants to Controls (Navy and Marine Only), 60
10-13 Reports of Other Neurodegenerative Diseases by Participant and Group Status,64
10-14 Numbers of Symptoms by Group Comparing Participants to Controls, with Adjusted Odds Ratios (ORs), 65
10-15 Proportion of Subjects Hospitalized Since Discharge from Active Duty Comparing Participants to Controls, with Adjusted Odds Ratios (ORs), 67
10-16 Birth Defects Among Those Who Fathered a Child Comparing Participants to Controls, with Adjusted Odds Ratios (ORs), 67

FIGURES

7-1 Mean summary SF-36 scores by month of telephone interview, 30

10-1 Average SF-36 physical component scores (PCS) by study group and participation status, 47
10-2 Average SF-36 mental component scores (MCS) by study group and participation status, 48

Abbreviations and Acronyms

BIRLS	Beneficiary Identification and Records Locator Subsystem
BUPERS	Bureau of Personnel (Navy)
DoD	Department of Defense
DTC	Deseret Test Center
ICD	International Classification of Diseases
IOM	Institute of Medicine
IRB	institutional review board
IRS	Internal Revenue Service
MCS	mental component summary score of the SF-36
MFUA	Medical Follow-Up Agency
MSN	military service number
NCHS	National Center for Health Statistics
NDI	National Death Index
NHIS	National Health Interview Survey
NIOSH	National Institute for Occupational Safety and Health
NIS	Neuropsychological Impairment Score
OPT	outpatient treatment file
PCS	physical component summary score of the SF-36
PTF	patient treatment file
SHAD	Shipboard Hazard and Defense
SMR	standardized mortality ratio

SSA	Social Security Administration
SSN	Social Security number
TARGET	online interface to BIRLS system
VA	Department of Veterans Affairs
VSO	veterans service organization
VVA	Vietnam Veterans of America

Summary

More than 5,800 military personnel, mostly Navy personnel and Marines, participated in a series of tests of U.S. warship vulnerability to biological and chemical warfare agents, Project SHAD (Shipboard Hazard and Defense), in the period 1962–1973. Only some of the involved military personnel were aware of these tests at the time. Many of these tests used simulants, substances with the physical properties of a chemical or biological warfare agent, thought at the time to have been harmless. After the tests were conducted, the results were reported in classified documents.

The existence of these tests did not come to light until many decades later. In September 2000, at the request of the Department of Veterans Affairs (VA), the Department of Defense (DoD) undertook the task to provide data related to Project SHAD to the VA and others. As a result of their investigations, the DoD publicly released information about the Project SHAD tests and assembled a list of Project SHAD participants. In September 2002, the Institute of Medicine (IOM) agreed to undertake a scientific study, funded by the VA, of potential long-term health effects of participation in Project SHAD.

Beginning with a list of Project SHAD participants provided by the DoD, IOM staff went back to military unit records to assemble as complete a list of Project SHAD participants as possible. IOM staff also assembled a list of comparable nonparticipant controls, and mounted a health survey of general content, with the assistance of SRBI of Silver Spring, Maryland, who conducted the telephone interviews. IOM staff met with Project SHAD personnel and with the representatives of various veteran service organizations (VSOs), eliciting their help with the design and conduct of the health survey. Mortality data were also collected from various records sources. Throughout the study, IOM staff drew upon the advice of an expert panel, headed by Dr. Daniel Freeman. The study was reviewed and approved by the National Academies Human Subjects Research Committee.

In reviewing the Project SHAD fact sheets, IOM staff realized that the Project SHAD participants could be broken down into four broad groups, based on their potential exposures. Group A consisted of more than 3,000 participants whose potential exposure was limited to one of two agents: *Bacillus globigii* (BG) or methylacetoacetate (MAA). Indeed, there was a natural pattern of exposures that enabled one to make independent statistical estimates of the health effects of BG and MAA. Group B consisted of some 850 participants whose only potential exposure was to trioctyl phosphate (TEHP or TOF). Group B was unusual in that there were a relatively large number of Marine participants, and it was also unusual in that there were individual dose estimates for a large proportion of these Marine participants. Group C consisted of around 720 participants who were in tests where active agents were used. Finally, Group D consisted of roughly 850 subjects potentially exposed to simulants who were not in

groups A, B, or C, that is, they were not solely exposed to BG, MAA, or TOF, nor were they potentially exposed to any active chemical or biological warfare agents. Control groups were assembled for each of the four exposure groups, and most analyses were exposure-group specific.

Of the nearly 12,500 Navy and Marine study subjects, roughly 9,600 were assumed to be alive (i.e., no evidence of death from available records sources) and eligible to be surveyed. We received mail questionnaire or telephone interview responses from 60.8 percent of Project SHAD participants and 46.6 percent of controls. The primary study outcome was the SF-36 assessment of general health, particularly the two summary scores, physical component summary (PCS) and mental component summary (MCS). We also asked for a history of medical conditions and present symptoms. Questionnaire items to determine somatization symptoms and neuropsychological problems were included, as well as items on postservice hospitalization and birth defects.

In general, there was no difference in all-cause mortality between Project SHAD participants and nonparticipant controls, although participants statistically had a significantly higher risk of death due to heart disease. However, the lack of cardiovascular risk factor data as well as any explanation as to biological plausibility makes this latter difference difficult to interpret. Participants also reported statistically significantly worse health than controls, but no consistent, specific, clinically significant patterns of ill health were found. Both PCS and MCS of the SF-36 were significantly lower among participants than controls, but these differences were mostly small in magnitude. Group C, the only group with potential exposure to active chemical or biological agents, reported the smallest SF-36 differences. There were small but statistically significant increases in self-reported memory and attention problems as well as somatization scores. Project SHAD participants reported higher levels of neurodegenerative medical conditions, but most of these were of an unspecified nature. Participants also reported nearly uniformly higher rates of symptoms, including a specific symptom (earlobe pain) without an apparent medical basis, thus raising the question of reporting bias. There were no significant differences in self-reported hospitalization, and in one group (group D), participants reported a higher rate of birth defects than controls; however, this significant difference can be attributed to an unusually low control rate rather than a high rate among participants.

While we have found no clear evidence of specific health effects that are associated with Project SHAD participation, we must remark that this does not constitute clear evidence of a lack of health effects. Although the sample seems large, some of the exposure groups are indeed rather moderate in size, and the lack of specific a priori hypotheses of health effects becomes a real limitation. If there were, for example, very specific, targeted effects on a particular organ system, but with a relatively low prevalence, our relatively coarse grouping of health outcomes might well have missed finding such a specific effect.

Although the focus of our study was on the potential health effects of participation in Project SHAD, we found some evidence of ill health among the group B Marines in this study, as compared to Navy group B participants. They had significantly higher mortality than Navy personnel, adjusting for age, participation status, race, and pay grade, as well as significantly lower PCS and MCS scores, with a large (more than 9-point) difference in MCS scores. Although these latter findings are not related to the original charge of the study, to examine the effects of Project SHAD participation per se, they may warrant some further investigations.

1

Study Rationale and Overview

The goal of our study was to determine the current health of participants in the Project SHAD (Shipboard Hazard and Defense) tests and compare their health with that of a comparable group of nonparticipant veterans from the same era. As a secondary goal, we hoped to be able to derive separate estimates of health effects for different kinds of participation, extending, if possible, to the estimation of separate effects for different agents used in Project SHAD. Data on current health status came primarily from a health survey, but mortality data were also collected and analyzed. A panel of expert advisors advised the Medical Follow-up Agency (MFUA) investigators in the conduct of this study. The contract for the study began on September 30, 2002, and ended on March 31, 2007.

ORIGIN AND BACKGROUND

Project SHAD was a series of tests conducted by the Department of Defense (DoD) in the 1960s to investigate the effectiveness of shipboard detection of and protection procedures against chemical and biological warfare agents (DoD, 2006). Within each test there were typically several separate trials involving exposure of vessels with various agents. In some cases, all the trials within a particular test used the same agent, but for some tests, different agents were used in different trials. Agents included chemical warfare agents sarin and VX; biological warfare agents *Pasteurella tularensis*, *Coxiella burnetti*, and staphylococcal enterotoxin B; chemical warfare simulants such as zinc cadmium sulfide; and biological warfare simulants such as *Bacillus globigii* and *Serratia marcescens* (see Appendix A for a complete list). Although the tests were originally classified, public and media interest has led the DoD to investigate these tests and to declassify and make publicly available relevant information from them. Further material describing the nature and conduct of the tests may be found on the study website (IOM, 2006) under "SHAD March meeting agenda."

Expert Panel and Meetings

A panel of outside experts was appointed to advise us on the conduct of the study (see front matter). The panel members had expertise in epidemiology, biostatistics, study design and analysis, environmental epidemiology, infectious disease, and toxicology. The panel, appointed in accordance with standard policies of the National Academies, advised the study staff on the soundness of the proposed study design, monitored the conduct of the study, and reviewed the analyses and report of study findings. Because the panel was solely advisory to study

staff and did not provide advice to the federal government, its activities were not subject to the Federal Advisory Committee Act (FACA).

Work Plan

Assembling the Participant and Control Cohorts

For each Project SHAD test, the DoD declassified and made public the following information: test name, military units involved, vessels involved, location, dates, and agents used. It is important to note that the declassified information gives only dates of the *test* and agents used, not the date of the individual *trials* and the agent(s) used at each trial. The DoD also assembled a list of individuals who were assigned to a test, whether or not they actually participated in any of the exposure trials within that test, and provided that list to the Department of Veterans Affairs (VA) and to us. We further refined these crew lists by abstracting and computerizing daily military unit records. We also asked the DoD to declassify and provide us the information necessary to determine trial participation.

We compared the health of Project SHAD veterans to that of a group of comparable nonparticipants. For each ship in Project SHAD, with the exception of the light tugs, the DoD provided us with potential control ships of similar type. We did additional research on these potential control ships and then selected a nonparticipating ship of the same type and manning, with contemporary service, and obtained its personnel rosters. A roster of nonparticipant controls was then produced by a process similar to that for participants.

Tracing Subjects

Because our primary health outcome data were collected by health survey, we first had to locate the study subjects and obtain their current addresses and telephone numbers. This tracing involved both the use of commercial tracing firms and the National Institute for Occupational Safety and Health (NIOSH) access to address information from Internal Revenue Service (IRS) files. To make use of these sources of relatively up-to-date addresses, however, correct Social Security numbers (SSNs) are needed to match files; SSN was not used as the military service number until the 1970s. After conducting a pilot study, we decided to obtain SSNs from the individual hard-copy military service records of both participants and nonparticipants to supplement the SSNs obtained from readily available computerized sources, such as Beneficiary Identification and Records Locator Subsystem (BIRLS) (see Chapter 5 for further detail).

Mortality Follow-Up

The BIRLS search that was done to obtain SSNs also provided a date of death, which was used to screen out decedents before the interviewing process began. We followed the BIRLS search by a search of the National Death Index (NDI) files (see Chapter 4) to identify deaths and to obtain cause of death information. When we had identified a death using the BIRLS file, we obtained cause of death data from the NDI if the death occurred in 1979 or later. For deaths prior to 1979, the VA agreed to provide causes of death using records available in VA claims folders for participants only.

Morbidity Follow-Up Using VA Records

We matched the participant and nonparticipant rosters against the VA's computerized files of inpatient (patient treatment file [PTF]) and outpatient (OPT) medical care. However, because veterans typically obtain only a small portion of their health care through the VA, the VA computerized morbidity data we obtained was useful only to compare survey respondents and nonrespondents and to validate self-reported morbidity information. Unfortunately, there was insufficient time for the latter analysis to be done.

Questionnaire Development

We used a health survey to determine the general health of participants and nonparticipants as well as to identify possible adverse health effects (should they exist) that might be expected following exposure to the agents used in Project SHAD. However, in many instances, little is known about the long-term health effects following a particular exposure, making it difficult to know exactly what conditions should be captured by the follow-up survey.

For that reason, we concentrated on the assessment of general health and also asked about a variety of medical conditions. There were several motivations for this. First, general health status provided a more accurate overall picture of the long-term health of these veterans than any single outcome measures. Second, because we did not know precisely which health outcomes might be associated with Project SHAD exposures, we needed to screen for a broad array of medical conditions. The questionnaire items on general health were the SF-36 (Ware et al., 2000), and current medical conditions were based on items taken from the National Health Interview Survey (NHIS) (NCHS, 2005), distributed by the Centers for Disease Control and Prevention (CDC). Not only do we have experience with the NHIS items from our earlier Edgewood study, but also the use of the SF-36 and NHIS items had the additional advantage of providing national data against which to compare the survey responses.

Regarding specific health outcomes that we might expect to be sequelae of Project SHAD exposures, we asked our expert panel to identify specific outcomes for inclusion in the survey. We also asked a local firm to briefly review the toxicological literature for each agent used in Project SHAD. The executive summaries of these reports are in Appendix A, and the full text of the reports are available on the study website (IOM, 2006). For the special case of anticholinesterase nerve agents (i.e., sarin and VX), we used some items developed for an earlier survey, including two subscales from the Neuropsychological Impairment Scale (NIS), a survey measure with high validity and test-retest stability, which measured memory and attention problems (O'Donnell et al., 1993).

The Data Collection Process

The primary sources of morbidity data were mail questionnaires and telephone interviews. After the mail questionnaire was developed and approved by our institutional review board (IRB), we subcontracted with SRBI, a company experienced in telephone interviewing, to modify the mail questionnaire for use in telephone interviewing and to administer the survey by telephone interview. We worked with the National Academies' Office of Contracts and Grants to develop a request for proposal, solicited bids, reviewed the bids for technical merit, and selected SRBI as our subcontractor. All data collection was approved by the National Academies' IRB. Further details of data collection are available in Chapter 7.

Sample Size Estimates

When we began the study, we did not know the exact number of Project SHAD participants, but assumed the number was close to 4,000. Thus we assumed that there were 4,000 participants and that we would enroll an equal number of nonparticipants. Further, we assumed a location percentage of 85 percent and a survey response of 75 percent among those located, yielding 2,550 participant responses and an equal number of nonparticipant responses. Applying a standard formula to calculate minimum detectable relative risk at a 2-sided significance level of 5 percent and with 80 percent power, we obtained the following results: for a condition with 1 percent prevalence, there was a minimum detectable relative risk of 1.97; for a 5 percent prevalence, a 1.40 relative risk; for a 10 percent prevalence, a 1.29 relative risk; and for a 20 percent prevalence, a 1.21 relative risk. Thus, we determined that we would have sufficient power to detect 2-fold differences in health conditions provided they have a prevalence of 1 percent or more. In the end, we obtained nearly 2,700 responses from roughly 4,400 participants and more than 2,400 responses from roughly 5,200 nonparticipant controls, figures that are generally in line with our original power calculations.

Analytic Methods

Outcome data included both nominal measures (e.g., prevalence of medical conditions) as well as continuous measures (e.g., scale measures for attention deficit). We used chi-square and *t*-tests for crude comparisons of these two types of measures, and logistic regression and general linear models analysis for adjusted comparisons. The adjusted comparisons took into account factors such as age, race, and pay grade. Cause-specific mortality was analyzed using standard mortality ratios and proportional hazards analysis, which allowed adjustments for factors such as age and race. Further details are available in Chapter 8.

REFERENCES

DoD (Department of Defense). 2006. *Project 112*. http://deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml (accessed November 28, 2006).

IOM (Institute of Medicine). 2006. *Long-term health effects of participation in Project SHAD*. http://www.iom.edu/CMS/3795/4909.aspx (accessed November 28, 2006).

NCHS (National Center for Health Statistics). 2005. NHIS questionnaire, sample adult, adult conditions. http://www.cdc.gov/nchs/about/major/nhis/ quest_data_related_1997_forward.htm (accessed November 28, 2006).

O'Donnell, W. E., C. B. DeSoto, and J. L. DeSoto. 1993. Validity and reliability of the revised Neuropsychological Impairment Scale (NIS). *Journal of Clinical Psychology* 49:372-382.

Ware, J. E., M. Kosinski, and J. E. Dewey. 2000. *How to score version 2 of the SF-36 health survey*. Lincoln, RI: QualityMetric Incorporated.

2

Investigating the Potential Health Effects from Participation in Project SHAD

To conduct a reasonable study of the effects of participation in Project SHAD (Shipboard Hazard and Defense), we needed to come to some understanding of potential health effects of such participation. The starting point for this effort was the information published by the Department of Defense (DoD) in its fact sheets. We then did our own literature review, including commissioning a series of papers on the potential health effects of various agents used in Project SHAD. In addition, at the second meeting of the expert panel (described below), we heard from various sources, including former Project SHAD participants. Further, at the strong urging of the expert panel, a review of Project SHAD classified documents was made by an expert panel member and a Medical Follow-Up Agency (MFUA) staff member with the proper clearances. Finally, MFUA study staff attended Project SHAD "reunion meetings" in Kansas City and Seattle to talk to former Project SHAD participants about the conduct of the study and to hear about their health concerns. Many health concerns centered around current medical conditions of shipmates, and we were given a health questionnaire that was being administered to Project SHAD participants. We included many of the items in this questionnaire in our own health questionnaire.

LITERATURE REVIEW

Normally, a literature review would include articles on the precise topic under question, here the health of former participants in Project SHAD. However, we were unable to identify any articles on this topic. Falling back to long-term health studies of veterans potentially exposed to the agents and simulants used during Project SHAD added little.

Two studies have been published on the long-term health of volunteers who participated in experimental studies of the effects of controlled exposure to various warfare agents. The earlier report looked at the experience of all identifiable study subjects, while the later report focused more specifically on subjects experimentally exposed to anticholinesterase agents, such as sarin. The first report concluded that there were no important health effects (BOTEHH, 1985), while the second report found only two statistically significant differences: volunteers exposed to anticholinesterase agents reported significantly fewer attention problems than subjects exposed to other chemical agents and reported significantly more sleep problems than subjects exposed to no chemical agents (Page, 2003).

Although there was little literature on health effects in military veterans, we felt that a more general review of relevant toxicological literature was in order. We thus contracted with the Center for Research Information

(CRI, Inc.), in Silver Spring, Maryland, to do a series of literature reviews. Appendix A contains the executive summaries of the literature review on the agents used in Project SHAD, and the full reports can be found on the study's website (IOM, 2006).

PUBLIC MEETINGS

In addition to examining the DoD fact sheets and commissioning a series of toxicological reviews, we wanted to hear from Project SHAD participants about the kinds of things they had done in Project SHAD, their possible exposures, and their thoughts about potential health effects. At the second meeting of the expert panel, held on March 21, 2003, we therefore invited a number of guests to testify in an open meeting. The expert panel and MFUA staff heard from three panels. The first panel contained Dr. Mark Brown of the Department of Veterans Affairs (VA) and Dr. Michael Kilpatrick and Ms. Dee Morris of the DoD. The second panel consisted of Dr. J. Clifton Spendlove, former Plans and Operations Officer of Project SHAD. The third panel consisted of veteran participants in Project SHAD as well as a representative from a veterans service organization: Mr. Rick Weidman, Vietnam Veterans of America; Mr. Jack Alderson, Project SHAD participant; Mr. Robert Bates, Project SHAD participant; Mr. Jim Druckemiller, Project SHAD participant; and Mr. Norman LaChapelle, Project SHAD participant. Material from these presentations is available on the study website (IOM, 2006).

REVIEW OF CLASSIFIED MATERIAL

To expedite making the information about Project SHAD public, the DoD investigation team requested declassification of only those portions of the documents it collected that were necessary to identify test participants and prepare the test fact sheets. This practice led to repeated veteran accusations that vital health-related information was not being made available. To counter this accusation, and at the expert panel's urging, the DoD made its classified Project SHAD collection available for review by the Institute of Medicine (IOM).

In February 2005, an expert panel member and a MFUA staff member with security clearances reviewed all the documents that the DoD had used for the Project SHAD investigation. They found little additional information to inform the study and requested that only two additional pages be declassified.

On February 10, 2006, two members of the SHAD team, one advisory panel member (Don Burke), and one staff member (Rick Erdtmann), visited the DoD deployment office, which serves as the repository for Project SHAD's classified documents. The documents were reviewed by the two visitors to clarify questions or concerns expressed by the Project SHAD advisory panel. Their report was handwritten and reviewed by members of the DoD security office staff prior to being physically removed from the premises. The staff indicated that the summary was unclassified in its entirety.

The following conclusions were reached:

- Reasons for maintaining classification of the Project SHAD documents were apparent.
- Test plans had scientific protocols well conceived to answer important questions with clear statements of test objectives using reasonable methods.
- Some test documentation was not available in the files.
- There was no human health data noted in the reports; some testing did involve use of human data to judge adequacy of protective masks or to estimate relative exposure levels.
- We saw no lists with individual names except for DTC-69-10, the VX simulant (trioctyl phosphate) where various clothes and respiratory devices were worn by participating marines.
- We saw no reference to human illness attributable to test agents in the reports.
- No new agents were identified in the reports from those previously provided.

- Levels of the test agents could not be assigned to individuals exposed with the following exceptions:
  - Two studies used nasopharangeal swabs to evaluate exposure levels or effectiveness of masks while using the *Bacillus globigii* simulant agent.
  - One study of trioctyl phosphate listed, by name, relative levels of exposure.
- Animal studies were used in live agent testing. Results could not be used to directly judge risk to test participants.
- There were no reports of environmental exposure suggesting untoward effects by test agents.
- There were no vaccines for participants mentioned in the reports.
- Nothing we saw in the reports would inform changes to the Project SHAD study design.

REFERENCES

BOTEHH (Board on Toxicology and Environmental Health Hazards), Committee on Toxicology. 1985. *Possible long-term health effects of short-term exposure to chemical agents.* Washington, DC: National Academy Press.

Page, W. F. 2003. Long-term health effects of exposure to sarin and other anticholinesterase chemical warfare agents. *Military Medicine* 168:239-245.

IOM (Institute of Medicine). 2006. *Long-term health effects of participation in Project SHAD*. http://www.iom.edu/CMS/3795/4909.aspx (accessed November 28, 2006).

3

An Overview of Project SHAD (Shipboard Hazard and Defense)

Project SHAD (Shipboard Hazard and Defense) was a series of tests conducted by the Department of Defense (DoD) in the 1960s and early 1970s to investigate the effectiveness of shipboard detection of and protection procedures against chemical and biological warfare agents (DoD, 2006). Within each test there were typically several separate trials involving exposure of vessels with various agents. In some cases, all the trials within a particular test used the same agent, but for some tests, different agents were used in different trials. Agents included chemical warfare agents sarin and VX; biological warfare agents *Pasteurella tularensis*, *Coxiella burnetti*, and staphylococcal enterotoxin B; chemical warfare simulants such as zinc cadmium sulfide; and biological warfare simulants such as *Bacillus globigii* and *Serratia marcescens*. Although the tests were originally classified, public and media interest has led the DoD to investigate these tests and to declassify and make publicly available relevant information from them.

Project SHAD involved mainly service members from the Navy and Marines, numbering more than 5,000. The tests were conducted in several areas of the Southwest Pacific, many around Hawaii, and in the Atlantic. The general procedure for testing ship vulnerabilities to biological and chemical agents and simulants varied slightly for the tests and trials. The most common method of disseminating the materials on the ships was by aircraft. Typically, aircraft would fly in front of the target ship and release the materials from spray tanks mounted on the wings. After the material was released, the ship would then steer through the release cloud and record information. The second most popular method for dispersing agents or simulants was to release the material from a turbine disseminator located at the bow of the target ship. Further material describing the nature and conduct of the tests may be found on the study website (IOM, 2006) under "SHAD March meeting agenda."

Table 3-1 shows a list of Project SHAD tests with military units involved and agents used taken from DoD fact sheets. Test 70-C does not appear on this list because it did not involve any agents, and we therefore did not include it in our study. In addition, although test Flower Drum II appears in the list of Project SHAD tests, according to DoD personnel, no individuals could be assigned to this particular test, and so it is not part of our study.

REFERENCES

DoD (Department of Defense). 2006. *Project 112*. http://deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml (accessed November 28, 2006).

IOM (Institute of Medicine). 2006. *Long-term health effects of participation in Project SHAD*. http://www.iom.edu/CMS/3795/4909.aspx (accessed November 28, 2006).

TABLE 3-1 List of Project SHAD Tests, Ships, or Military Units Involved, and Agents

Test Name	Ship or Military Unit	Agent/Simulant/Decontaminant
Eager Belle I	USS George Eastman	BG (*Bacillus globigii*)
Eager Belle II	USS George Eastman USS Granville S. Hall USS Carpenter USS Navarro USS Tioga County Marine Medium Helicopter Squadron	BG
Autumn Gold	USS Navarro USS Tioga County USS Carpenter USS Hoel USS Granville S. Hall Marine Air Group 13, 1st Marine Brigade	BG
Errand Boy	USS George Eastman	BG betapropiolactone
Flower Drum I	USS George Eastman USS Granville S. Hall	Sarin Sulfur dioxide Methylacetoacetate
Shady Grove	USS Granville S. Hall Army Light Tugs 2080, 2081, 2085, 2086, 2087 Marine Aviation Group 13 Patrol Squadron Four Patrol Squadron Six AEWBARONPAC Detachment	BG Fluorescent particles *Coxiella burnetii* *Pasteurella tularensis*
Copper Head	USS Power	BG Fluorescent particles betapropiolactone
Magic Sword	USS George Eastman	Mosquitoes Insecticide
Big Tom	USS Granville S. Hall USS Carbonero	BG Zinc cadmium sulfide
High Low	USS Berkeley USS Fechteler USS Okanogan USS Wexford County	Methylacetoacetate
Fearless Johnny	USS George Eastman USS Granville S. Hall Two light tugs VC-1 Patrol Squadron Six	VX Diethylphthlate with fluorescent dye DF-504
Purple Sage	USS Herbert J. Thomas	Methylacetoacetate
Scarlet Sage	USS Herbert J. Thomas	BG
Half Note	USS George Eastman USS Granville S. Hall USS Carbonero Army light tugs 2080, 2081, 2085, 2086, 2087	BG *Serratia marcescens* *Escherichia coli* Calcofluor Zinc cadmium sulfide

continued

TABLE 3-1 Continued

Test Name	Ship or Military Unit	Agent/Simulant/Decontaminant
Speckled Start	USS Granville S. Hall Five Army light tugs 4533rd Tactical Test Squadron, 33rd Tactical Fighter Wing	BG Staphylococcal enterotoxin B Uranine dye
Folded Arrow	USS Carbonero USS Granville S. Hall Five Army light tugs	BG betapropiolactone
69-10	USS Fort Snelling Landing Force Carib 1-69/ BLT 1/8 (attached and supporting personnel from 2nd Marine Division) VMA-324, MAG-321, 2nd Marine Aircraft Wing	Tri (2-ethylhexyl) phosphate (TOF or TEHP)
69-31	USS Herbert J. Thomas	BG Methylacetoacetate
69-32	USS Granville S. Hall Five Army light tugs VC-1, Blue Air Squadron Patrol Squadron Six, Fleet Airwing Two	*Serratia marcescens* *Escherichia coli* BG Calcofluor

4

Records-Based Data Sources

INTRODUCTION

In this chapter, the records-based data sources are briefly discussed, while a separate chapter (Chapter 7) describes the health survey. Records-based sources include the fact sheets published by the Department of Defense (DoD) that identified the Project SHAD (Shipboard Hazard and Defense) tests and described the military units of the participants in each test (DoD, 2006). A database assembled by the DoD contained records identifying each Project SHAD participant, with additional information from Department of Veterans Affairs (VA) records, such as Social Security number (SSN) or address. We received these records and further processed them to include data from the Defense Manpower Data Center, the VA's Beneficiary Identifier and Records Locator Subsystem (BIRLS), and the National Death Index (NDI), among other sources. We also obtained data from hard-copy sources, such as the individual's military personnel record, and included these data in the study's master file. A parallel effort assembled similar data for military veterans who were not participants in Project SHAD. This chapter will briefly describe the data sources used to assemble the study's data files. More detail on VA records resources is available in Boyko et al., 2000.

DATA SOURCES USED TO IDENTIFY PARTICIPANTS AND CONTROLS

DoD Fact Sheets

Basic information about the Project SHAD tests came from fact sheets prepared by the DoD and posted on a DoD website (DoD, 2006). These were updated as additional information came to light about the tests. The DoD website contains a list of all Project SHAD tests, together with links to the fact sheet for each Project SHAD test. The fact sheets for each Project SHAD test give information on the dates of the test, military units involved, agents used in the test, and so on. The listings of military units involved in each test provided the starting point for our research using military unit records.

Project SHAD Technical Reports

Although Project SHAD technical reports remain, in general, classified, we were sent selected declassified sections from some final reports. Of particular use were Tables 12 through 15 of Volume II of the final report for DTC Test 69-10, which contained estimates of contamination for certain individual participants. See Chapter 8 for further details.

Military Unit Records

DoD personnel assembled the initial roster of Project SHAD participants using military unit rosters, which we also consulted. For Navy personnel, the *quarterly unit rosters* for enlisted personnel, BuPers Report 1080-14, record every enlisted person on that ship on the given day that ends a quarter (e.g., March 31), showing name, service number, and rate (e.g., machinist mate); the listing is arranged by rate. Officers present on the ship on the given date of a quarterly report are listed separately on the Officer Distribution Control Report, which shows name, service number, and job title (e.g., commanding officer). We also obtained and reviewed the *daily personnel diaries* for each ship in each Project SHAD test, as well as for control ships. The daily personnel diaries list individuals who have come on or left the ship, along with a description of the reason for the movement on or off ship (e.g., absent of sailing). Marine participants were occasionally listed in Navy unit records, particularly the daily personnel diaries.

The Marine unit records are similar to those of the Navy. The *monthly personnel roster* is a list of Marines by name, military service number, and pay grade. We used these rosters as well as the company diaries, which document the movement of individuals, to assemble the Marine participant and control cohorts.

DATA SOURCES USED TO LOCATE AND FOLLOW-UP PARTICIPANTS AND CONTROLS

BIRLS

The VA's BIRLS file is a computer file that identifies beneficiaries and locates their VA claims records. We used BIRLS records as the first step in our mortality follow-up process, as this file contains the date of death for deceased veterans. A BIRLS record may also contain a military service number as well as an SSN, making it a potential cross-index of service numbers and SSNs. Although our primary method of obtaining BIRLS data was by matching a computer file with many records (typically tens of thousands), we also searched the BIRLS file by individual record, using TARGET access.

Registry and Individual Service Records

Each military veteran has an individual personnel folder, which contains, among other things, identifier and demographic data such as name, rank, military service number, and SSN. These records are housed at the National Personnel Records Center in St. Louis, Missouri, and are indexed by a computerized registry file. Access to individual military records was granted by the individual service branch that owned the records.

MSN/SSN File and Bidex/Tridex

When military service numbers (MSN) were replaced by SSNs as the military services' identification number starting in July 1969, a number of MSN/SSN cross-index files were created. The MSN/SSN file is such a file and contains several million records with name, MSN, and SSN. We used the MSN/SSN file to try to obtain SSNs for veterans for whom we had only an MSN. The Bidex and Tridex files are cross-index files with MSN and SSN and name, MSN, and SSN, respectively. However, both the computerized MSN/SSN file and the Bidex and Tridex files are only partial cross-indices, for reasons unknown to us.

National Death Index

The NDI is a computer file maintained by the National Center for Health Statistics. We used the NDI both to identify decedents and to provide causes of death. Because the NDI contains death information from 1979 on, other data sources must be used to obtain fact and cause of death prior to 1979.

Commercial Address Tracing Firms

A number of firms can obtain a current address by matching against their files using name and SSN. We made use of Intellius and Choice Point in this study.

The National Institute of Occupational Safety and Health and the IRS

Special legislative authority exists for the director of the National Institute of Occupational Safety and Health (NIOSH) to request mailing addresses from the Internal Revenue Service (IRS) to locate individuals who "may have been exposed to occupational hazards during active military, naval, or air service . . ." (Public Law 96-128, section 502). We used NIOSH/IRS addresses in some of our attempts to contact study subjects.

REFERENCES

Boyko, E. J., T. D. Koepsell, J. M. Gaziano, R. D. Horner, J. R. Feussner. 2000. US Department of Veterans Affairs medical care system as a resource to epidemiologists. *American Journal of Epidemiology* 151(3):307-314.

DoD (Department of Defense). 2006. *Project 112.* http://deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml (accessed November 28, 2006).

5

Participant Cohort

INITIAL IDENTIFICATION

Department of Defense (DoD) personnel assembled the initial roster of Project SHAD (Shipboard Hazard and Defense) participants using military unit rosters and continued to update this roster as new information was obtained. For Navy personnel, the DoD obtained the quarterly unit rosters of each ship in each Project SHAD test, using the rosters just before and after the actual test dates; e.g., the December 31, 1963, and March 31, 1964, quarterly rosters were selected for a February 1964 test. The quarterly unit rosters for enlisted personnel, BuPers Report 1080-14, record every enlisted person on that ship on the given day, showing name, service number, and rate; the listing is arranged by rate (e.g., machinist mate). Officers present on the ship on the given date of report are listed separately on the Officer Distribution Control Report, which shows name, service number, and job title (e.g., commanding officer).

It is important to note that the use of only quarterly rosters to identify participants may not provide a complete list of participants. In theory, using the previous example, a sailor could have joined the ship's complement on February 1, 1964, left on February 28, 1964, and would have been a participant who did not appear on either of the two closest quarterly rosters. For this reason, the DoD also obtained and reviewed the daily personnel diaries for each ship in each Project SHAD test. We also did this and keyed every individual entry, along with a description of the reason for movement on or off ship (e.g., absent of sailing). This allowed us to compare the daily personnel diaries with the quarterly unit rosters and determine a complete list of possible participants. In cases where we identified Navy personnel who were not on the DoD list, we provided these names, along with service numbers and unit documentation of their participation, to the DoD for validation. Upon DoD review, we either kept in our study the potential participants they validated or excluded the potential participants they did not validate. Marine participants were occasionally listed in Navy unit records, particularly the daily personnel diaries.

The process for Marine unit records was similar to that for Navy records. We used the monthly personnel roster to assemble the list of Marines by name, military service number, and pay grade. This was supplemented by company diaries that documented the movement of individuals. Again, we keyed all the entries on these two kinds of reports and compared our combined roster with the DoD roster. If we found any additional Marine participants, we sent their names, service numbers, and documentation to the DoD for review. Only the participants validated by the DoD were added to our study file. The Department of Veterans Affairs (VA) also added data from its own databases to the data it received from the DoD. The VA data included identifier data, claims data, address, and so

on. We received initial databases from the VA and the DoD as well as subsequent updates. The final number of participants in the study was 5,867.

OUTREACH EFFORT TO IDENTIFY ADDITIONAL PARTICIPANTS

Throughout the course of participant identification, we kept our advisory committee apprised of our progress. In the process, our advisory panel became convinced that neither we nor the DoD had a foolproof method for determining whether we had a complete participant list. They thus advised us to undertake an outreach effort to see if additional participants could be located.

After consulting with the panel and with various veteran service organizations (VSOs), we came up with a draft of a letter that was posted to our website and published in several VSO venues. The letter and a form on which a veteran could report his information were developed and reviewed by our panel and several VSOs. The letter invited Project SHAD participants who had not been contacted by the VA to contact the Medical Follow-Up Agency (MFUA). The form also asked for identifying information as well as participation information, including documentation of participation, if available. MFUA asked the responders for permission to forward their information to the DoD for confirmation, and a deadline of August 31, 2005, was set for responses. To our knowledge, both the American Legion and the Vietnam Veterans of America published our outreach material. The letter and data form were reviewed and approved by the National Academies' institutional review board (IRB) before being sent to VSOs. The letter and data form are in Appendix C, along with the list of VSOs to which this material was sent.

By the end of the response period, 14 letters had arrived in response to the outreach effort. Of these, 9 were already identified as Project SHAD participants, many of whom sent copies of the Project SHAD letter they had already received from the VA as documentation of participation; apparently, our instructions were unclear or were not followed in these cases. In 3 additional cases, we could not determine whether the responder was a participant in Project SHAD. Of the 3, 1 was a possible Eager Belle participant, but was not on the VA or DoD list and sent no documentation, and the other 2 listed tests or ships that were not known to be part of Project SHAD.

Two other respondents represented possible new participants not previously known to us. One of them served on the light tugs, and the other was a member of Project SHAD's technical staff. We had known that the list of participants with light tug service or technical staff service was not complete, so these responses were both expected and welcome. We forwarded the documentation sent by these two men to the DoD for confirmation, with the hope that the material they sent would lead to the identification of other new participants. Only the self-reported participants validated by the DoD were included in the study.

In light of the amount of effort made, the response we received was not overwhelming. Indeed, most of the respondents not only were known to us but had also been contacted by the VA. However, the responses from the two potential new participants were exactly the kind of contact we had sought, and they came from two of the groups whose enumeration we knew was likely to be incomplete. Although we cannot draw any definitive conclusion from the outreach effort, it seems reasonable to conclude that there were not a large number of Project SHAD participants of whom we were unaware.

GATHERING FURTHER IDENTIFIER DATA FROM MILITARY RECORDS

By and large, the unit records that formed the basis for identifying Project SHAD participants identified these participants by name, rank, and military service number. At the time of the initial Project SHAD tests, Social Security numbers (SSNs) had not yet been adopted as the military's identification number. The lack of SSNs for Project SHAD participants severely hampered follow-up efforts, including limiting the VA's ability to conduct an outreach program by sending letters to all known Project SHAD participants. Lacking SSNs, we were greatly handicapped in conducting a records-based mortality follow-up, and locating individuals to invite them to participate in a health study was practically impossible.

We tried to find a readily available source of SSNs for the Project SHAD participants, and undertook a special pilot study on this topic. From the file of Project SHAD participants provided by the VA, we randomly sampled N = 200 computerized records that did not contain a SSN. We subjected these records to searches of the microfiche

indices known as Bidex and Tridex and matched them against the Beneficiary Identification and Records Locator Subsystem (BIRLS) file using TARGET and against a computerized cross-index file of service numbers and SSNs (see Chapter 4 for a description of these data sources). We then ordered hard-copy Navy personnel records for all 200 and abstracted military service number and SSN information from them. We used these data to calculate SSN finding proportions by source.

When we drew the random sample, we did not appreciate the fact that it included 9 Army records, 16 Marine Corps records, and 1 Navy medical (rather than personnel) record. Removing these 26 records from consideration left N = 174 records in the random sample. Our request for 174 records netted only 142; the remainder were either charged out to someone else (N = 8) or the hard-copy record could not be found (N = 24). Thus our hard-copy record yield was 81.6 percent (142/174). All of the 142 hard-copy Navy records we obtained had SSN information. In 40 cases, the SSN was found only in the hard-copy record, while in the remaining 102 cases, the hard-copy record verified an SSN from another source.

Because we independently searched the other sources for all 200 records, we had SSN information from these sources even when no hard-copy record was obtained. Among the 8 "charge-outs" we had 4 SSNs from another source, and among the 24 "not found" we had 6 SSNs. Combining all sources, 87.4 percent ([142 + 4 + 6])/174) of records yielded an SSN from at least one source. In summary, using a variety of searches in our pilot study, we were able to find SSNs for nearly 90 percent of the sample subjects whose SSNs were absent from the original DoD or VA file.

When we completed our pilot study, we consulted with our expert advisory panel, and in the end, we all had to reluctantly conclude that a sufficient number of SSNs could only be obtained by ordering military personnel records and abstracting information from them, as well as conducting the easier (and less expensive) searches of microfiche and computerized files. However, this also afforded us an opportunity to collect dates of birth, another crucial piece of information not readily available in complete and accurate form from any other source, as well as demographic information, such as race or ethnicity.

The SSN information we gathered was seen as useful by both the DoD and the VA. However, when we investigated returning SSNs to the VA, we found out that IRB restrictions would not allow this. Instead, we returned the list of SSNs we found in the military records back to the DoD.

6

Referent Cohort

GENERAL SCHEME

We decided on a two-stage scheme for selecting nonparticipant controls. For study personnel on ships, we began first by selecting a matching control ship for each participant ship. We then obtained the two quarterly rosters closest to, and bracketing, the dates of the corresponding test. Using these two quarterly rosters, we compiled a roster of all Navy personnel on the control ship who became part of the referent population for the study. In contrast to the process for identifying participants, we did not obtain and key information from the daily personnel diaries for the control ships. Although up to five Army light tugs, manned by Navy personnel, participated in several Project SHAD (Shipboard Hazard and Defense) tests, their complete personnel rosters were never found by the Department of Defense (DoD) or by us. Because there were relatively few Navy participants on these light tugs and because we had more than sufficient controls selected from other ships in the same tests, we did not select specific control ships for the Army light tugs.

Because we did not sample individuals from the control ships but instead took all persons on a selected ship (i.e., a census), our selection of controls is not strictly speaking a cluster sample. There is, nonetheless, an unmeasured component of variability associated with the sampling of ships. To properly estimate this component of variability would have required a much larger sample of ships than we had.

The process for Marine control units was similar in that each Marine participant unit was matched with a control unit. Finally, because there were so few identified Army, Air Force, and Coast Guard participants and controls (N = 160), we omitted them from most of the analyses.

DETAILED INFORMATION

Stage 1: Selecting Ships

DoD personnel provided us a list of potential control ships for each participant ship and test, choosing potential control ships of the same type and class. We then developed formal control ship selection criteria that were sent to our expert advisory panel and to members of the Vietnam Veterans of America's (VVA's) Project SHAD Task Force for comment. The final control ship selection criteria are shown in Table 6-1. In general terms, we selected control ships to be the same type and class as the corresponding participant ship. We further selected control ships

TABLE 6-1 The Process of Selecting Control Ships

Step	Procedure
Review the DoD control ships list.	Verify similarity of ship type (the control ship should be of the same type and class as the test ship, or a similar type and class). Determine size of the complement (the complement of the control ship should be at least as large as that of the test ship, or larger). Determine operating area (the control ship should have operated in the same ocean area as the test ship [in most cases, the Pacific Ocean]). Determine operational status (the control ship should have been in an operational status during the test period, meaning it should not have been in an extended overhaul or dry dock status). Determine home port (the control ship should have had the same home port).
Designate potential control ships.	Remove from consideration ships that do not meet all the criteria (except for home port).[a]
Rank candidates.	Assign a rank to each potential control ship depending on the similarity of control ship to participant ship (ties are allowed).
Select the control ship.[b]	Take the control ship with the highest rank; if there are ties, select randomly.

[a]Deviations from these criteria were avoided when possible, but could be necessitated by factors that prevailed at the time of the tests; e.g., there may have been no similar type ship in the DoD list of potential control ships, all DoD-listed potential control ships may have been in a nonoperational status during the exact period of a test, or the potential control ships may not have had the same home port as the test ship.

[b]A test ship that served in multiple tests may have more than one control ship selected because of changes in a potential control ship's fulfillment of one or more of the above criteria; e.g., it may have been operational during the period of one test, but in dry dock during another test.

with a complement, operating area, and home port similar to that of a Project SHAD vessel. When there were multiple possible control ships, we ranked them in order of desirability and selected the closest match. To assist in characterizing potential control ships, we hired Jim Quinn, Commander, USN retired, as a consultant. For the few Marine units, we selected a similar unit in operation at the same time. In general, we tried to select the identical unit in a parallel battalion or division. The final list of control units is shown in Table 6-2.

Stage 2: Selecting Individual Subjects

Once a control ship had been selected, we used a similar process as was used for participant ships; that is, we obtained the quarterly BuPers reports for the corresponding time periods. However, we did not make use of personnel diaries. We keyed the entries from unit records and produced a list of control subjects, identified by name, military service number, and rate or job title (for officers). The process for Marine control units was similar to that for Marine participants, except that, again, we did not use personnel diaries. In some cases, we selected Marine nonparticipants from the same unit as the participants. We do not think that omitting potential controls who would have been identified solely from personnel diaries is a substantial omission; only 5 percent of Navy participants were identified solely from personnel diaries.

In preparing a participant roster for their own purposes, the DoD supplemented the unit record information on participants with other data from other sources, for example, Social Security numbers (SSNs) from individual personnel records, addresses from other sources, and so on. Because the DoD did not assemble a control roster, we had to begin *ab initio* from unit records to assemble the control roster for our study, and our controls never had initial identifying information beyond name, service number, and rate. Although we undertook a similar process as the DoD, we began our identification of controls later, and thus our control subjects were typically less well identified than participants and harder to trace, locate, and contact.

TABLE 6-2 List of Participant and Control Units Showing Selected Characteristics

Participant Unit			Control Units		
Test Name and Unit Name	Ship Type	Operating Area	Unit Name	Ship Type	Operating Area
Autumn Gold					
1. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Radar picket ship	Picket Station 1 (Canada), Treasure Island, Portland
2. USS Navarro (APA-215)	Attack transport	Pearl Harbor	2. USS Talladega (APA-208)	Attack transport	Long Beach
3. USS Tioga County (LST-1158)	Tank landing ship	Pearl Harbor	3. USS Vernon County (LST-1161)	Tank landing ship	Japan, Philippines
4. USS Carpenter (DD-825)	Destroyer	Pearl Harbor	4. USS John R. Craig (DD-885)	Destroyer	San Diego
5. USS Hoel (DDG-13)	Guided missile destroyer	Pearl Harbor	5. USS Towers (DDG-9)	Guided missile destroyer	San Diego
VMA 214, Marine Air Group 13	—	—	VMA 332, Marine Air Group 14	—	—
Big Tom					
1. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	1. USS Oxford (AGTR-1)	Auxiliary ship	Subic Bay, Philippines
2. USS Carbonero (SS-337)	Submarine	—	2. USS Raton (SS-270)	Submarine	San Clemente, San Diego
Copper Head					
1. USS Power (DD-839)	Destroyer	—	1. USS Gyatt (DD-712)	Destroyer	Norfolk, Portsmouth
DTC Test 69-10					
1. USS Fort Snelling (LSD-30)	Dock landing ship	—	1. USS Spiegel Grove (LSD-32)	Dock landing ship	Little Creek, VA; Onslow Beach, SC; Morehead City, NC; Vieques
Landing Force Carib 1-69/BLT 1/8	—	—	1st Battalion, 6th Marines, 2nd Marine Division	—	—
VMA 324, MAG-32	—	—	VMA 324, MAG-32	—	—
DTC Test 69-31					
1. USS Herbert J. Thomas (DD-833)	Destroyer	Pearl Harbor	1. USS Agerholm (DD-826)	Destroyer	San Diego
DTC Test 69-32					
1. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	1. USS Jamestown (AGTR-3)	Auxiliary ship	South China Sea, Thailand, Vietnam, Subic Bay, Special Operations
Eager Belle I					
1. USS George Eastman (YAG-39)	Auxiliary ship	Pearl Harbor and maneuvers	1. USS Interceptor (AGR-8)	Radar picket ship	Picket Station 1, Picket Station 9, San Francisco
Eager Belle II					
1. USS George Eastman (YAG-39)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Radar picket ship	San Francisco Picket Stations 1, 3, 9

continued

TABLE 6-2 Continued

Participant Unit			Control Units		
Test Name and Unit Name	Ship Type	Operating Area	Unit Name	Ship Type	Operating Area
2. USS Tioga County (LST-1185)	Tank landing ship	Pearl Harbor	2. USS Vernon County (LST-1161)	Tank landing ship	Yokosuka, Kobe, Taiwan, Po Hong Do, Okinawa
3. USS Carpenter (DD-825)	Destroyer	Pearl Harbor	3. USS Agerholm (DD-826)	Destroyer	Subic Bay, Hong Kong, Manila, Yokosuka, Okinawa
USS Granville S. Hall (YAG-40)	Auxiliary ship	—	USS Interdictor (AGR-13)	Radar picket ship	—
USS Navarro (APA-215)	Attack transport	—	USS Noble (APA-218)	Attack transport	—
Marine Medium Helicopter Squadron 161	—	—	Marine Medium Helicopter Squadron 161	—	—
Errand Boy					
1. USS George Eastman (YAG-39)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Radar picket ship	San Francisco, Picket Station 7
Fearless Johnny		—			
1. USS George Eastman (YAG-39)	Auxiliary ship		1. USS Oxford (AGTR-1)	Auxiliary ship	Hong Kong, Subic Bay
2. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	2. USS Georgetown (AGTR-2)	Auxiliary ship	Hong Kong, Subic Bay
Flower Drum I					
1. USS George Eastman (YAG-39)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Radar picket ship	San Francisco, San Diego, Radar Picket Stations 1, 5, 7
USS Granville S. Hall (YAG-40)	Auxiliary ship	—	USS Interdictor (AGR-13)	Radar picket ship	—
Folded Arrow					
1. USS Granville S. Hall (YAG-40)	Auxiliary Ship	Pearl Harbor	1. USS Oxford (AGTR-1)	Auxiliary ship	Subic Bay, South China Sea
2. USS Carbonero (SS-337)	Submarine	Pearl Harbor	2. USS Tunny (SS-282)	Submarine	Subic Bay, Special Ops
Half Note		—			
1. USS George Eastman (YAG-39)	Auxiliary Ship		1. USS Oxford (AGTR-1)	Auxiliary ship	Taiwan, Hong Kong, Special Operations
2. USS Granville S. Hall (YAG-40)	Auxiliary Ship	Pearl Harbor	2. USS Jamestown (AGTR-3)	Auxiliary ship	Malaysia, Taiwan, Special Operations
3. USS Carbonero (SS-337)	Submarine	—	3. USS Tunny (SS-282)	Submarine	Pearl Harbor, Subic Bay
4. Light tug 2085	—	—	4. None selected	—	—

TABLE 6-2 Continued

Participant Unit			Control Units		
Test Name and Unit Name	Ship Type	Operating Area	Unit Name	Ship Type	Operating Area
High Low		—			
1. USS Berkeley (DDG-15)	Destroyer		1. USS Lynde McCormick (DDG-8)	Destroyer	Hong Kong, Yokosuka, San Diego
2. USS Fechteler (DD-870/DDR-870)	Destroyer	—	2. USS John R. Craig (DD-885)	Destroyer	San Diego
3. USS Okanogan (APA-220)	Attack transport	—	3. USS Montrose (APA-212)	Attack transport	San Diego, Pearl Harbor, San Clemente
4. USS Wexford County (LST-1168)	Tank landing ship	—	4. USS Washoe County (LST-1165)	Tank landing ship	Numazu, Yokosuka, Okinawa
Magic Sword					
1. USS George Eastman (YAG-39)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Auxiliary ship	Durban, Subic Bay
Purple Sage		—			
1. USS Herbert J. Thomas (DD-833)	Destroyer		1. USS Agerholm (DD-826)	Destroyer	San Diego
Scarlet Sage		—			
1. USS Herbert J. Thomas (DD-833)	Destroyer		1. USS Agerholm (DD-826)	Destroyer	San Diego, Long Beach
Shady Grove					
1. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	1. USS Interceptor (AGR-8)	Auxiliary ship	Bremerton, Wash; Panama Canal Zone; Guantanamo Bay, Cuba; Portsmouth, VA
2. VMA 214, MAG13	—	—	2. VMA214, MAG 13	—	—
3. MWSG 13, Marine Air Group 13*	—	—	3. MWSG, MAG 13	—	—
4. MABS 13, Marine Air Group 13*	—	—	4. MABS 13, MAG 13	—	—
5. HMM 161, Marine Air Group 13	—	—	5. HMM 161, MAG 13	—	—
6. Light tugs 2080, 2081, 2085, 2086, 2087	—	—	6. None selected	—	—
Speckled Start					
1. USS Granville S. Hall (YAG-40)	Auxiliary ship	Pearl Harbor	1. USS Oxford (ATGR-1)	Auxiliary ship	Subic Bay, South China Sea

*Original participant files contained personnel in these units who were subsequently removed from the study.

7

Health Survey

BACKGROUND

Because the subjects in our study were primarily ages 55–64, their health was characterized best by a morbidity survey. Although mortality data were collected and analyzed, there was little expectation that much could be learned from these data, given the relatively young age of the study subjects. In addition, although the Department of Veterans Affairs (VA) system could provide data on inpatient and outpatient care, these data would be limited to the minority of veterans who were users of the VA health-care system. Thus, we were compelled to mount a health survey.

Although the health survey would not be subject to the same biases as would a records-based morbidity follow-up using only VA records, there are inherent limitations to this approach as well. Two important limitations can result in biased findings. First, a low response rate could produce biased prevalence estimates of specific conditions, as well as introduce bias into comparisons between participant and control groups depending on the nature of the nonresponse. Whether or not bias is introduced by low response rates depends on whether the nonresponse is differential or nondifferential with respect to participation. Differential nonresponse occurs when respondents differ in some systematic way from respondents within the participation group, and it will introduce bias into estimates of prevalence and of associations of participation with outcome. Second, respondents may not accurately report their current health for a variety of reasons, resulting in misclassification of outcome status. We will discuss the possible effects of these biases later in this report.

CONTENT OF THE HEALTH SURVEY

In many health surveys, the focus of the survey is easily determined. This was not the case in our study: although the agents used in the Project SHAD (Ship Hazard and Defense) tests were well characterized, potential long-term health effects are not. In an attempt to characterize potential long-term health effects, we consulted the Department of Defense (DoD) fact sheets (DoD, 2006) for each test and examined the VA's guidance to physicians who were examining Project SHAD participants (VHA, 2002). We also took a careful look at published research on a group of experimental volunteers, some of whom had been exposed to a similar list of agents (Page, 2003), and asked members of our expert panel what sorts of items should be included in the health survey. We also consulted with former participants in Project SHAD who had developed an illness checklist, as well as the Vietnam Veterans

of America's (VVA's) SHAD Task Force, who provided us a list of questionnaire items regarding participation. Finally, at the urging of our expert panel, we commissioned a series of reports that reviewed the toxicological literature on the agents used in the Project SHAD tests. The executive summaries of these reports are included in Appendix A, and the full reports can be found on the study's website (IOM, 2006).

Because we identified few predetermined health end points, we decided to use the SF-36 as our primary measure of health (Ware et al., 2000). The SF-36 has been used in a large number of studies and is a standard health survey instrument. The fact that the SF-36 is widely used also means that national normative data are available. In addition to the SF-36, we included standard items on self-reported medical conditions and symptoms (NCHS, 2005), including largely the same items as in the health survey of the Millennium Cohort Study (Millennium Cohort Study, 2006). To these items we added a scale for neurological problems and cognitive difficulties (O'Donnell et al., 1993), as well as questions on history of hospitalization, reproductive history, smoking, and alcohol use. The last part of the questionnaire includes items for Project SHAD participants only, asking about symptoms experienced during the tests, use of protective gear during the tests, decontamination experience, and so on. The entire questionnaire can be found in Appendix B.

The questionnaire was reviewed and approved by the National Academies' Human Subjects Committee (institutional review board [IRB]), along with an accompanying cover letter and two endorsement letters, one signed by DoD and VA personnel and one signed by representatives of various veterans service organizations (VSOs). One of the stipulations of the National Academies' IRB was that three different contact letters and informed consent documents would be mailed to study subjects. Notwithstanding our concerns that different contact letters might lead to response bias, the IRB was especially concerned that our request for information might be the initial contact with study subjects who did not know, until we contacted them, that they had been participants in Project SHAD. Thus, the initial contact letters were written so that a study subject would be informed of his possible exposures. The three different sets of documents were worded so that study subjects would know whether, according to the records we reviewed, they had been (1) possibly exposed to active chemical or biological agents during their participation in Project SHAD; (2) possibly exposed to simulants (agents thought to be harmless) during their participation in Project SHAD; or (3) not exposed to active agents or simulants (i.e., nonparticipants). The three sets of contact letters and informed consent forms, together with the endorsement letters, may also be found in Appendix B.

CONDUCT OF THE HEALTH SURVEY

After some discussion with our expert panel, we decided on a dual mode (mail questionnaire and telephone interview) for our health survey. There were some potential advantages to using a web-based questionnaire, but after consultation with some VSOs, we deemed it unlikely that participation rates would be high enough to justify the required additional effort. We decided to begin with an initial mailing of the questionnaire, followed by telephone interviewing of nonrespondents. The reason for this strategy was to obtain a quick, inexpensive response through the mail, and then follow that with a slower accumulation of data through telephone interviews. The initial mailing of the health survey took place December 2005.

As we prepared for the initial mailing, we selected a contractor for the telephone interviewing, Schulman, Ronca, and Bucuvalis (SRBI), of Silver Spring, Maryland. After five months of telephone interviewing, there were still several thousand nonrespondents for whom we had address information. We therefore decided to do a second mailing of the questionnaire in July 2006. This allowed us to update addresses from multiple sources, as well.

USING FEDEX DELIVERY TO CHECK THE QUALITY OF SURVEY ADDRESSES

After several months of data collection, there was still a high proportion of study subjects who had not responded to either a mail questionnaire or an attempted telephone interview. We were concerned that perhaps we had not correctly located these individuals, and thus we decided to undertake a pilot study to test the quality of our address information.

A stratified sample of N = 400 subjects was chosen from all nonrespondent subjects not known to be dead. The sample was stratified into three groups: group 1 (N = 100) consisted of subjects possibly exposed to active

TABLE 7-1 Number and Percent of FedEx-Delivered Mailings by Source of Address

Source of Address	Delivered	Wrong Address	Not Deliverable[a]	Refused	Total[b]
DoD June 2006	76 (64.4%)	16 (13.6%)	19 (16.1%)	7 (5.9%)	118 (100%)
IRS	139 (78.1%)	8 (4.5%)	26 (14.6%)	5 (2.8%)	178 (100%)
Commercial tracing	56 (94.9%)	1 (1.7%)	0 (0%)	2 (3.4%)	59 (100%)
Post office	7 (100%)	0 (0%)	0 (0%)	0 (0%)	7 (100%)
Addresses updated during telephone number search	29 (85.3%)	1 (2.9%)	4 (11.8%)	0 (0%)	34 (100%)
Total	307 (77.5%)	26 (6.6%)	49 (12.4%)	14 (3.5%)	396 (100%)

[a]Includes post office box or rural route addresses.
[b]Excludes 1 decedent, 2 pending, and 1 unknown status subject.

chemical or biological agents; group 2 (N = 100) consisted of subjects possibly exposed only to simulants (agents thought to be harmless but having physical properties that make them resemble certain active agents); and group 3 (N = 200) consisted of subjects who were not participants in Project SHAD.

A FedEx delivery of the mail questionnaire, cover letter, endorsement letters from different VSOs, and the DoD and VA, together with an informed consent form, was attempted for all 400 subjects using the latest address on file. FedEx evening and weekend delivery with required signature was chosen to minimize subject burden while still obtaining documentation of actual delivery. We were interested in finding the percentage of "good" addresses, that is, addresses for which a FedEx delivery could successfully be made. We were also interested in how the percentage of good addresses varied by source of address and by group. Response proportions are shown as simple percentages.

Table 7-1 shows the number and percent of FedEx-delivered packages by source of address, while Table 7-2 shows a breakdown by study group. Overall, just over three-quarters of the mailings were successfully delivered by FedEx, with 12.2 percent not deliverable (a category that includes post office box or rural route addresses), 6.6 percent bad addresses, and 3.5 percent refused. Thus, the total percentage of good addresses could be as high as 81.0 percent, if we presume (possibly in error) that subjects who refused delivery were at the correct address, but did not want to receive the package or participate in the study.

Table 7-1 shows that post office and commercial tracing addresses were most often successfully delivered, with rates of 100 percent and 94.9 percent, respectively. DoD addresses, although thought to be up to date, were successfully delivered only 64.4 percent of the time, with the highest percentages of wrong (13.6 percent) and undeliverable (16.1 percent) addresses. Both the addresses updated during a telephone number search and those supplied by the Internal Revenue Service (IRS) were close to 80 percent successful. Differences between delivery rates for the five sources were statistically significant; a chi-square test, 4 df, gave a value of 25.13, $P = .00005$.

Table 7-2 shows that successful FedEx delivery rates were somewhat higher for groups 1 and 3 (possible exposure to active agents and controls), with correspondingly higher rates of wrong addresses, undeliverable addresses, and refusals in group 2 (possible exposure to simulants). Differences between delivery rates among the three groups were not statistically different; a chi-square test, 2 df, gave a value of 5.01, $P = .082$. Finally, out of the total of 400 attempted deliveries, there were a total of 50 questionnaire responses sent by returned mail and 30 subsequently completed telephone interviews. This gives an overall response rate of 20 percent to the FedEx mailing.

There are two major points that are clear from the pilot study that used FedEx to test the quality of addresses for nonrespondents. First, the addresses we had for nonrespondents were overwhelmingly correct ones, based on a FedEx delivery rate of nearly 80 percent. Second, because we now know that our addresses are overwhelmingly

TABLE 7-2 Number and Percent of FedEx-Delivered Mailings by Mailing Group[a]

Mailing Group[a]	Delivered	Wrong Address	Not Deliverable[b]	Refused	Total[c]
Participants; possible active agents	75 (78.1%)	6 (6.3%)	14 (14.6%)	1 (1.0%)	96 (100%)
Participants; no active agents	70 (70%)	13 (13%)	9 (9%)	8 (8%)	100 (100%)
Controls	162 (81.4%)	7 (3.5%)	25 (12.6%)	5 (2.5%)	199 (100%)
Total	307 (77.7%)	26 (6.6%)	48 (12.2%)	14 (3.5%)	395 (100%)

[a]"Participants; possible active agents" consisted of subjects possibly exposed to active chemical or biological agents; "Participants; no active agents" consisted of subjects possibly exposed only to simulants (agents thought to be harmless but having physical properties that make them resemble certain active agents); and "Controls" consisted of subjects who were not participants in Project SHAD.

[b]Includes post office box or rural route addresses.

[c]Excludes 1 decedent, 2 pending, and 2 unknown status subject.

correct, the 80 percent nonresponse rate for this pilot study can be attributed to a subject's choice not to return a questionnaire, other than our inability to locate him and put a questionnaire in his hands.

Aside from these two major points, we saw that commercial address tracing produces addresses with an apparently higher rate of delivery than provided by either the IRS or the DoD. We also saw no substantial difference in FedEx delivery rates among the groups, although we can not explain the reason for the nonstatistically lower rate of FedEx deliveries to group 2 participants.

FINAL SURVEY RESPONSE RATES

Table 7-3 shows the distribution of several demographic characteristics for all participants and controls, as well as respondent participants and controls. Compared with Project SHAD participants, controls had fewer nonwhites and fewer officers. Compared with respondent participants, respondent controls had fewer Marines and fewer officers.

Of all the identifier data we collected, Social Security number (SSN) was by far the most important. Indeed, because address tracing depends in large part on having SSN for subjects, it turned out that no subjects without an SSN were respondents. Table 7-4 shows the percentage of subjects with SSN by analysis group (defined in Chapter 8). With the exception of group B controls, in all other analysis groups, whether participants or controls, the percentage of subjects with SSN was around 95 percent; for group B controls, it was only 84 percent. This no doubt limited our ability to locate subjects in this group and contributed to a lower response rate (see next paragraph).

Table 7-5 shows response proportions by analysis group, Project SHAD participation status, and the presence of an SSN. Response was higher among subjects with an SSN, but not very much higher, since relatively few subjects did not have an SSN. Response proportions were lower in group B than in the other analysis groups, particularly among controls, and participants had generally higher response proportions than controls. Limiting the comparison to subjects with SSNs, participants had a 63.6 percent response proportion, and controls had a proportion of 50.4 percent.

Due to difficulties in identifying and processing Marine control units, although Marine control subjects eventually went through the same follow-up procedures as all other study subjects, there was less time for follow-up of these subjects. This may have contributed to lower response rates. For example, in group B, Marine controls had an unusually low response rate of 16.1 percent, and 22.8 percent of them did not have an SSN. Excluding Marines from the group B controls gives a revised response rate of 59.1 percent, and limiting this further to subjects with SSNs gives a revised response rate of 61.4 percent.

TABLE 7-3 Percent Distribution of Various Demographic Characteristics by Participation Status, for All Study Subjects and for Survey Respondents

Characteristic	All Project SHAD Participants (N = 5,741)	All Controls (N = 6,757)	Project SHAD Participant Respondents (N = 2,684)	Control Respondents (N = 2,433)
Age at survey				
54–64	68.5%	69.7%	73.1%	76.0%
65–74	21.5%	20.3%	22.2%	18.5%
75+	9.8%	9.8%	4.8%	5.4%
Missing	0.2%	0.2%	0.2%	0.2%
Race				
Nonwhite	9.6%	6.1%	8.4%	6.8%
White	90.4%	93.9%	91.6%	93.2%
Branch				
Navy	89.7%	90.8%	90.4%	96.8%
Marines	10.3%	9.2%	9.6%	3.2%
Pay grade				
E1–E3	51.1%	55.0%	53.0%	57.7%
E4–E8	39.3%	38.9%	38.9%	40.1%
Officer[a]	9.6%	6.1%	8.2%	2.2%
Ever smoked cigarettes?	—	—	79.1%	82.5%
Currently drink alcohol?	—	—	58.2%	57.1%
Average BMI (Body Mass Index[b])	—	—	28.7	28.6

[a]Includes warrant officers.
[b]Body Mass Index = weight (in kilograms)/height (in meters) squared.

TABLE 7-4 Percent of Study Subjects with Social Security Number, by Analysis Group

Analysis Group[a]	Participants[b] (N = 4,403)	Controls[b] (N = 5,219)
Group A	96.4%	93.4%
Group B	93.3%	83.9%
Group C	94.4%	93.4%
Group D	96.3%	95.4%
Total	95.6%	92.4%

[a]Group A = participants potentially exposed only to *Bacillus globigii* (BG) simulant agent or methyl acetoacetate (MAA); group B = participants potentially exposed only to trioctyl phosphate (TOF); group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.
[b]Excludes decedents and subjects not in the Navy or Marines.

Finally, we used logistic regression to analyze response rates. After 106 observations were excluded for missing data, the final model included 9,516 subjects with data on age, participant status, race, pay grade, and branch. Neither age nor race had a statistically significant association with response, but the remaining variables were all statistically associated with response rate. Compared with officers, both E1–E3 and E4–E8 pay grades had significantly higher odds of responding, while Marines subjects had significantly lower odds of responding than Navy subjects. Controls also had lower odds of responding than participants. All significant odds ratios were roughly 2-to-1 (or 0.5 to 1).

TABLE 7-5 Response Proportions by Analysis Group, Participation Status, and Presence of Social Security Number

Analysis Group[a]	All Project SHAD Participants[b] (N = 4,403)	All Controls[b] (N = 5,219)	Project SHAD Participants with SSN (N = 4,210)	Controls with SSN (N = 4,822)
Group A	62.0%	48.9%	64.3%	52.4%
Group B	54.1%	31.2%	58.0%	37.2%
Group C	61.5%	45.5%	65.2%	48.7%
Group D	62.8%	52.9%	65.2%	55.4%
Total	60.8%	46.6%	63.6%	50.4%

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]Excludes decedents and subjects not in the Navy or Marines.

VARIATION IN TELEPHONE RESPONSES BY TIME

Because cumulative response rates necessarily grow with increasing time in the field, we spent nearly 12 months collecting morbidity data. Eventually, however, data collection had to be halted, and we were curious about the potential effects of setting a data collection cutoff date. Because we had read access to telephone interview data by interview date, we looked at SF-36 summary score responses over time (see Chapter 10 for further discussion of the SF-36 summary scales).

Figure 7-1 shows the mean values of the physical component score and the mental component score by month of telephone interview; sample sizes are shown in parenthesis below month of interview. Neither average physical component score nor mental component score show any substantial trends over time, which is welcome news.

COMPARISON OF MAIL QUESTIONNAIRE VERSUS TELEPHONE INTERVIEW RESPONSES

Although we attempted to translate the mail questionnaire as closely as possible into a telephone interview format, we were aware that there could be differences in responses between the two data collection modes. Differences between the mail and telephone interview data could come from two obvious sources: inherent differences in responding to the mail and telephone versions of the questionnaire or inherent differences in the subjects who chose to respond to either of the two questionnaire versions.

Table 7-6 shows a comparison of selected characteristics for mail questionnaire respondents versus telephone interview respondents. The group of telephone interview respondents were younger than mail questionnaire respondents, contained fewer officers, and more Marines. Mail questionnaire and telephone interview respondents reported the same SF-36 physical component scores, but telephone interviewees reported higher mental component scores than their mail questionnaire counterparts. Other researchers have reported similar findings (McHorney et al., 1994).

DEPARTMENT OF VETERANS AFFAIRS OUTPATIENT VISITS BY PARTICIPATION STATUS AND RESPONSE STATUS

Although there are difficulties associated with the use of VA data for follow-up, as noted in Chapter 1, we did use VA outpatient data to compare participants and control respondents and nonrespondents. Table 7-7 shows the percentage distribution of subjects with a VA outpatient visit for participants and controls by survey response status. Because there are potential differences in eligibility for VA care between not only participants and controls, but also respondents and nonrespondents, we can make few definitive statements about these data. Generally speaking, more respondents than nonrespondents tended to have VA outpatient visits, and more participants than

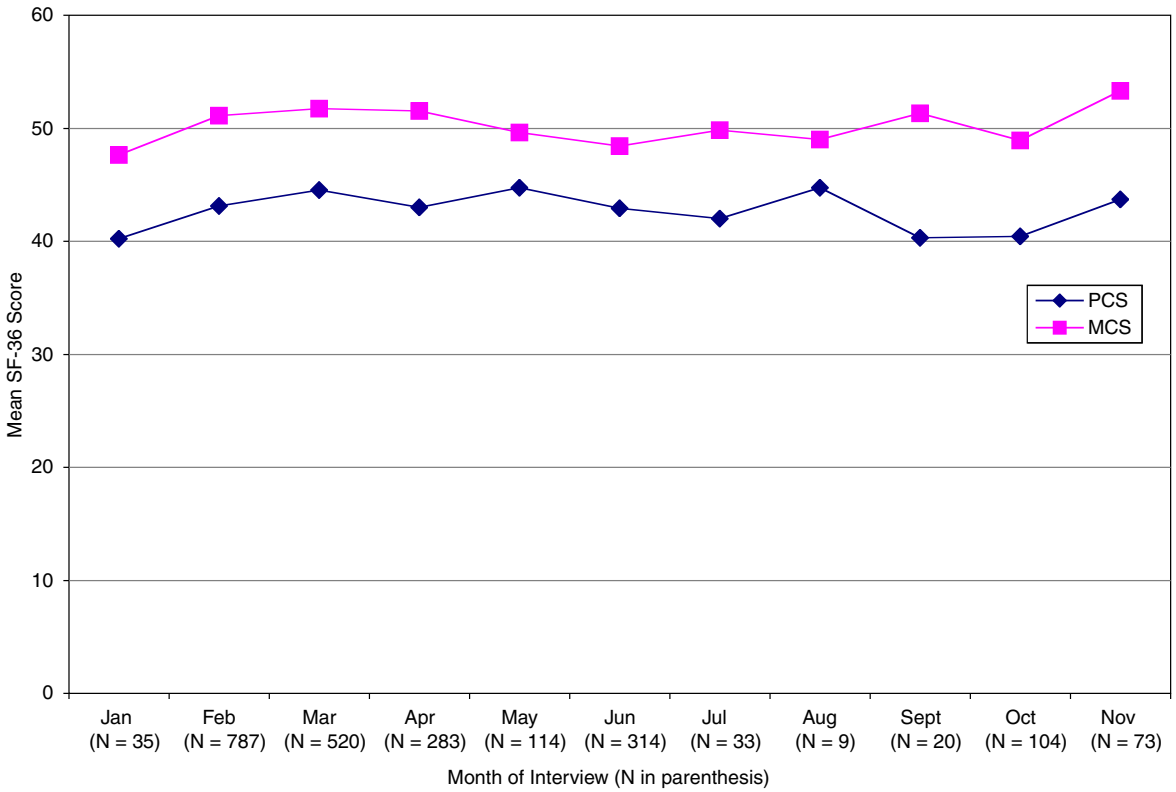


FIGURE 7-1 Mean summary SF-36 scores by month of telephone interview.

TABLE 7-6 Comparison of Mail Questionnaire Versus Telephone Interview Respondents for Selected Characteristics by Percentage Distribution

Characteristic	Mail Questionnaire Respondents	Telephone Interview Respondents
Project SHAD participation		
Participant	52.6%	51.1%
Control	47.4%	48.9%
Current age		
55–64	70.9%*	78.7%*
65–74	23.2%*	17.4%*
75 +	5.9%*	3.9%*
Pay grade		
E1–E4	51.6%*	59.1%*
E5–E8	42.2%*	36.8%*
Officer/Warrant Officer	6.3%*	4.2%*
Branch		
Marine	4.3%*	8.6%*
Navy	95.7%*	91.4%*
SF-36 mean summary score		
PCS	43.3	43.2
MCS	49.4*	50.5*
Ever smoked cigarettes?	81.5%	79.9%
Currently drink alcohol?	60.3%*	54.7%*
Average BMI (body mass index)	28.7	28.6

NOTE: Respondents with both mail and telephone data were excluded for comparison purposes. Missing values were excluded.
*Statistically significant difference, $P < .05$.

TABLE 7-7 Percent Distribution of Subjects with a VA Outpatient Visit, by Participation and Response Status, for Various Characteristics

Characteristic	Project SHAD Participant Respondents (N = 2,684)	Project SHAD Participant Nonrespondents (N = 3,057)	Control Respondents (N = 2,433)	Control Nonrespondents (N = 4,324)
Exposure Group[a]				
A	39.3%	22.7%	31.4%	19.7%
B	45.1%	27.9%	30.0%	25.6%
C	46.6%	22.0%	33.4%	21.6%
D	36.7%	38.6%	30.3%	20.9%
Selected Diagnoses				
Infectious disease	8.6%	5.6%	7.4%	5.3%
Cancer	12.1%	7.8%	9.1%	6.9%
Endocrine disease	27.8%	13.8%	22.0%	13.2%
Mental disorder	18.9%	11.6%	15.4%	11.2%
Circulatory disease	28.1%	16.1%	22.9%	14.6%
Respiratory disease	17.0%	10.2%	13.3%	9.4%
Digestive disease	19.0%	11.4%	14.7%	10.4%
Genitourinary disease	14.6%	7.7%	12.0%	7.4%
Skin disease	14.7%	8.2%	11.5%	7.5%
Musculoskeletal disease	21.6%	12.4%	18.7%	11.9%
Ill-defined disease	23.9%	14.1%	18.5%	13.7%
Injury	9.9%	6.8%	9.0%	6.2%
Branch				
Navy	39.4%	21.8%	31.2%	20.2%
Marines	52.9%	34.5%	35.1%	26.9%
Paycode				
E1–E3	41.8%	26.7%	31.1%	22.8%
E4–E8	40.0%	20.8%	31.5%	21.8%
Officer[b]	36.1%	16.4%	35.2%	6.7%
Total	40.6%	23.3%	31.4%	21.1%

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]Includes warrant officers.

controls had VA outpatient visits. With one exception (group D participants), these tendencies were true regardless of exposure group, outpatient diagnosis, branch, or paycode.

REFERENCES

DoD (Department of Defense). 2006. *Project 112*. http://deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml (accessed November 28, 2006).

IOM (Institute of Medicine). 2006. *Long-term health effects of participation in Project SHAD*. http://www.iom.edu/CMS/3795/4909.aspx (accessed November 28, 2006).

McHorney, C. A., M. Kosinski, and J. E. Ware, Jr. 1994. Comparisons of the cost and quality of norms for the SF-36 health survey collected by mail versus telephone interview: Results from a national survey. *Medical Care* 32:551-567.

NCHS (National Center for Health Statistics). 2005. NHIS questionnaire, sample adult, adult conditions. http://www.cdc.gov/nchs/about/major/nhis/ quest_data_related_1997_forward.htm (accessed November 28, 2006).

O'Donnell, W. E., C. B. DeSoto, and J. L. DeSoto. 1993. Validity and reliability of the revised Neuropsychological Impairment Scale (NIS). *Journal of Clinical Psychology* 49:372-382.

Page, W. F. 2003. Long-term health effects of exposure to sarin and other anticholinesterase chemical warfare agents. *Military Medicine* 168:239-245.

Millennium Cohort Study. http://www.millenniumcohort.org/index.php (accessed November 27, 2006).
VHA (Veterans Health Administration). 2002. Clinical evaluation of veterans involved in Project 112 and related Project SHAD tests (VHA Directive 2002-079). http://www1.va.gov/shad/docs/Project_112-SHAD_Directive_2002-079.pdf (accessed November 28, 2006).
Ware, J. E., M. Kosinski, and J. E. Dewey. 2000. *How to score version 2 of the SF-36 health survey*. Lincoln, RI: QualityMetric Incorporated.

8

Analysis Structure

OVERVIEW

The analysis plan for the Project SHAD (Shipboard Hazard and Defense) study was structured to check data validity, test hypotheses, and interactively explore data to follow leads arising from data analysis. The study was designed to address: (1) whether mortality (both cause-specific and overall) differed between Project SHAD participants and nonparticipants; (2) whether morbidity differed between Project SHAD participants and nonparticipants; and (3) whether mortality and morbidity differed among specific Project SHAD exposure groups.

The basic comparison involves the mortality and morbidity experiences of Project SHAD participants relative to that of referent cohort members. A number of measures from the study questionnaire were used to ascertain morbidity while fact of death and cause-specific mortality data were identified from the National Death Index (NDI), the Social Security Administration (SSA) Death Master File, and the Department of Veterans Affairs (VA) Beneficiary Identification and Records Locator Subsystem (BIRLS) file (see Chapter 4 regarding these sources).

AVAILABLE DATA

Data available for the analyses consist of measures or indicators of (1) presumed exposure; (2) demographic, lifestyle, and military service characteristics that might confound an association between exposure and outcome; (3) morbidity outcomes; and (4) mortality outcome. Table 8-1 presents the variables that were included in the analysis dataset. It should be noted that variables were not all of the same quality with regard to completeness and validity.

The variables included in the basic analyses are participant status, SHAD participant exposure group, age, race, branch of service, pay grade, smoking, drinking, body mass index (BMI; weight in kilograms divided by height squared, in meters), vital status, date of death, cause of death, and SF-36 score. Analyses also explore relationships using variables such as SF-36 subscale scores, Neuropsychological Impairment Scale (NIS) scores, Structured Clinical Interview for DSM-IV (SCID) somatization scores, and history of chronic medical conditions or symptoms. (The definitions and rationale for the use of these outcome variables are described in Chapter 7.)

As there were a large number of morbidity outcome variables collected in the questionnaire, the morbidity variables were categorized into primary, secondary, and tertiary outcomes. These categories were developed based on consultation with the advisory panel. Table 8-2 shows the list of primary, secondary, and tertiary outcome

TABLE 8-1 Variables Considered for Analysis and Their Sources

Variable	Sample value	Source
Participant status	Participant	Military records
Race	White, nonwhite	Military records
Current marital status	Single	Questionnaire
Education	Bachelor degree	Questionnaire
Height	5'7"	Questionnaire
Current weight	175 lbs	Questionnaire
Date of birth	1/2/1945	Military record/questionnaire
General health status	Excellent	Questionnaire
SF-36 score*		Questionnaire
SCID Somatization Scale score*		Questionnaire
Neuropsychological Impairment Scale score*		Questionnaire
History of 45 chronic medical conditions*	Yes	Questionnaire
History of 12 general health problems*	Yes	Questionnaire
History of 19 symptoms within past year*	Yes	Questionnaire
Hospitalization while in Navy	Yes	Questionnaire
Number of hospitalizations while in Navy	3	Questionnaire
Hospitalizations since discharge from active duty	Yes	Questionnaire
Number of hospitalizations since discharge from active duty	2	Questionnaire
Length of time since last hospitalization	More than 5 years ago	Questionnaire
Biological father of any pregnancy	Yes	Questionnaire
Number of live birth pregnancies	2	Questionnaire
Number of children with birth defects	0	Questionnaire
Ever smoked	Yes	Questionnaire
Current smoker	Yes	Questionnaire
Age stopped smoking	40	Questionnaire
Years of smoking	5	Questionnaire
Cigarettes smoked/day	7	Questionnaire
Current drinker	No	Questionnaire
Frequency of drinking	3–4 times per week	Questionnaire
Problems with alcohol (series of 3 questions)	Yes	Questionnaire
Ever drinker	Yes	Questionnaire
Age stopped drinking	35	Questionnaire
Date of entry into military	2/1965	Military record/questionnaire
Date of discharge/separation	10/1974	Military record/questionnaire
Military handling of herbicides, insecticides, or hazardous chemicals	Yes	Questionnaire
Perception of physical and mental risk of testing*	Yes (high risk)	Questionnaire
Days involved in Project SHAD	5	Questionnaire
Physical or mental problems during or after testing*	Yes	Questionnaire
Perception of likelihood of long-term physical or mental effects*	Somewhat unlikely	Questionnaire
Number of SHAD trials	3	Military records
Specific information about test and post-test activities	Yes	Questionnaire/military records
Name of ship	USS George Eastman	DoD fact sheet
Type of agent used in test	Trioctyl phosphate	DoD fact sheet
Number of days or dates on ships	35 or 7/1–8/5/1972	Military unit records
Vital status	Alive	National Death Index/SSA/VA records
Date of death	8/15/2000	National Death Index/SSA/VA records
Cause of death	ICD-9 code	National Death Index
Branch of service	Navy	Military records
Pay grade	E1	Military records

*See Appendix B for specific questionnaire items.

TABLE 8-2 Primary, Secondary, and Tertiary Outcome Variables

Primary outcomes	Description
SF-36 summary score	Physical and mental summary scores
Vital status	Alive/dead and date of death
Cause of death	Based on ICD groupings
Secondary outcomes	
SF-36 subscale scores	Physical functioning, role physical, bodily pain, general health perception, vitality, social functioning, role emotional, and mental health
Neuropsychological Impairment Scale	Memory and attention subscale
SCID Somatization Scale	Measure of somatization
Medical condition groupings (created from 45 chronic medical conditions)	Cardiovascular, visual, respiratory, renal, endocrine, liver, autoimmune, gastrointestinal, neurological, psychological, and cancer
Tertiary outcomes	
History of 45 chronic medical conditions	See questionnaire in Appendix B
History of 19 symptoms within past year	See questionnaire in Appendix B
Number of children with birth defects	See questionnaire in Appendix B
Total number of postdischarge hospitalizations	See questionnaire in Appendix B

variables. Although there are a large number of health outcomes, we did not make adjustment for multiple statistical comparisons.

The primary exposure classification was defined as participant versus nonparticipant, but we also defined four exposure groups based on information in the Department of Defense (DoD) fact sheets and information on an individual's test participation history (see below for details).

Data on the following potential confounders were also collected via questionnaire and from military records: smoking, drinking, age, general health status, perception of tests, branch of service, race, length of service, marital status, education, pay grade, and current BMI.

DEFINING EXPOSURE GROUPS

In addition to participant versus nonparticipant comparisons, it was desirable to define specific exposure groups within the Project SHAD participants to answer the question of whether outcomes differed by specific patterns of exposure. We also looked at whether health outcomes differed by individual ship. In defining the exposure groups, we took advantage of the fact that Project SHAD exposures fell into four natural groups. First, a large number of Project SHAD participants were exposed only to *Bacillus globigii* (BG) or methylacetoacetate (MAA), including those only in Autumn Gold, Eager Belle, Scarlet Sage, and Purple Sage. This exposure group we named group A and took additional advantage of the fact that there was a natural factorial design based on presence (+) or absence (–) of the two exposures. The four exposure groups were BG+/MAA+; BG+/MAA–;BG–/MAA+; and BG–/MAA–. Similarly, participants who were in only DTC test 69-10 were exposed only to trioctyl phosphate (TOF or TEHP) and were named group B. Removing the participants in groups A and B from further consideration, the remaining participants fell into two remaining groups: group C included participants who were at any test using active agents; and group D included participants who were at tests where no active agents were used. Thus, group D subjects might have been exposed to any one of the following agents or decontaminants: BG, betapropriolactone, calcofluor, DF-504, diethylphthlate with fluorescent dye, *Echerichia coli*, fluorescent particles, MAA, *Serratia marcescens*, trioctyl phosphate, uranine dye, or zinc cadmium sulfide. Table 8-3 shows the four exposure groups, numbers of participants, and number of controls.

Individual Exposure Data

During Project SHAD test DTC 69-10, Marine troops were subjected to a simulated chemical weapons assault with the purpose of determining the "operational effects of a persistent, toxic, chemical agent spray attack on U.S.

TABLE 8-3 SHAD Exposure Groups

Group Name	Type of Exposure*	Number of Participants	Number of Controls
Group A	Only BG or MAA	3,392	3,615
Group B	Only TOF	856	870
Group C	Nerve agent or biological agent (with or without possible simulant exposure)	749	1,093
Group D	No active agents	870	1,212
Total	—	5,867	6,790

NOTE: In Project SHAD, test Magic Sword uninfected mosquitoes were released from a ship to see if they would make it to a nearby island. These participants were not exposed to any agents.

*BG = *Bacillus globigii*; MAA = methylacetoacetate; TOF = trioctyl phosphate; nerve agents = sarin or VX; biological agents = *Coxiella burnetti, Pasteurella tularensis*, staphyloccocal enterotoxin B; no active agents = remainder of participants after Groups A, B, and C have been removed that were exposed to some other type of agent.

amphibious forces" (DoD, 2006). During this test, sampling was conducted on exposed personnel and their clothing to determine the extent of exposure to the simulant agent TOF. DTC test 69-10 was conducted at Vieques Island, east of Puerto Rico, on May 3, 4, 5, and 7, 1969.

We received a redacted version of the DTC test 69-10 final report from the DoD. Tables 12 through 15 of that report showed estimates of contamination on landing force personnel for trials on the days May 3, 4, 5, and 7, respectively. Each table showed the military unit (down to platoon level) and listed individuals, along with their estimated magnitude of contamination, on an ordinal scale: VH (very heavy), H (heavy), M (medium), L (light), VL (very light), T (trace), and N (negligible). In these tables, individuals were identified by last name or last name and initial or initials. Presumably, initials were shown when there were duplicates of last names.

Using data from the Marine unit roster, we attempted to identify all the individuals with DTC test 69-10 exposure data, determine their military service number, and link their exposure data with their responses on the health survey. There were 706 daily exposure records (including multiple records per individual), of which 672 (95 percent) were successfully linked to an individual on our study roster. When multiple exposures were taken into account, there were 428 individuals who had ordinal contamination data from one or more trials. Because the DoD was unable to provide quantitative data regarding the contamination levels, we analyzed the TOF exposure data by arbitrarily assigning the following exposure values: T (trace) and N (negligible) = 0.5 ; VL (very light) = 1.0; L (light) = 2.0; M (medium) = 3.0; H (heavy) = 4.0; and VH (very heavy) = 5.0. We further assigned a dose of zero to Marine controls in DTC test 69-10.

METHODS OF ANALYSIS

Mortality Analyses

The research group defined two analytic approaches for the mortality outcome. The first uses standardized mortality ratios (SMRs), calculated for each cohort (participant and referent) separately using standard rates adjusted for age, race, sex, and calendar year of death. The second involves proportional hazards modeling using a wider range of available covariates.

SMRs are a commonly used tool to compare death rates among a cohort of interest to those in a larger, reference population, customarily the U.S. general population. The deaths that actually occur in the cohort of interest are labeled as "observed" deaths; one also calculates the "expected" number of deaths that would have occurred had the numbers of the cohort died at the same rate as the U.S. population with the same age, race, and sex distribution. The ratio of observed to expected deaths is an SMR, which is equal to 1.0 if the number of deaths observed in the cohort of interest is the same as the number of deaths expected to have occurred if the cohort members had died at the same rate as the rest of the U.S. population.

SMRs show whether the mortality of the cohort of interest is higher or lower than that of the U.S. population. One typically sees SMRs for veterans' cohorts that are less than 1.0. Reasons given for this refer to the requirement that military servicemen pass an entrance physical and also pass periodic physical fitness exams while in military service, both effectively screening in favor of healthier individuals versus their general civilian counterparts. Not only is this healthiness thought to produce lower death rates among active duty military personnel, but lower mortality rates apparently persist even after discharge from active duty (Seltzer and Jablon, 1974, 1977). Such effects seen among occupational groups have been labeled as the "healthy worker effect," and by analogy, lower SMRs among military veterans can be attributed to a "healthy soldier effect." Despite this limitation, SMRs provide a way to compare the mortality of the cohort of interest to that of the general population. Also, because SMRs are based on standard distributions of deaths, they can be compared across studies. We used OCMAP Plus software to compute SMRs (Marsh et al., 1998). SMR results were also stratified by exposure group, ship/unit, officer or enlisted, and branch as sample size permitted. All-cause and cause-specific mortality were investigated.

Crude mortality was also examined using Kaplan-Meier survival curves to assess mortality differences between analysis groups. Cox proportional hazard regression analysis was used to assess mortality differences while adjusting for potential confounders. We implemented these analyses using the SAS PHREG procedure (SAS Institute, Inc., 1999). In this approach, the risk of death—in statistical terms, the hazard—is modeled in a regression that includes a baseline hazard as well as coefficients that represent the additional hazards associated with various factors such as participation in Project SHAD. The coefficient associated with a factor represents a hazard ratio (HR), which can be interpreted as a relative risk of death that remains constant over the follow-up period. In our analyses, coefficients were included for participation, age at time of first participation, race (white versus nonwhite), service branch (Navy versus Marines), and pay grade. Hazard ratios are considered statistically significant if their associated 95 percent confidence interval (CI) excludes the value 1.0. For those participants who were missing a date of birth (roughly 7%) the following procedure was used to impute a date of birth. The day of birth was randomly assigned as 1 to 28 with each day having a uniform chance of being assigned. The month of birth was randomly assigned as 1 to 12 with each month having a uniform chance of being assigned. The year of birth was randomly assigned based on the following probabilities: 1939 = 4 percent; 1940 = 5 percent; 1941 = 8 percent; 1942 = 14 percent; 1943 = 15 percent; 1944 = 15 percent; 1945 = 12 percent; 1946 = 10 percent; 1947 = 8 percent; 1948 = 5 percent; and 1949 = 4 percent. For those participants who were missing a value for race (roughly 29%), the value was set to white.

The *International Classification of Diseases, Tenth Revision* (ICD-10) and the *International Classification of Diseases, Ninth Revision* (ICD-9) were used to identify deaths due to malignant neoplasm (ICD-10 codes C00–C97 and ICD-9 codes 140–208), cardiovascular disease (ICD-10 codes I00–I99 and ICD-9 codes 390–459), respiratory disease (ICD-10 codes J00–J99 and ICD-9 codes 460–519), endocrine and metabolic diseases (ICD-10 codes E00–E90 and ICD-9 codes 240–279), infectious diseases (ICD-10 codes A00–B99 and ICD-9 codes 001–139), and injury/external causes (ICD-10 codes S00–T90 and V01–X85 and ICD-9 codes 800–959 and E codes 800–999). For all-cause survival analysis, persons who were not matched to a death record were considered alive through the follow-up period and administratively censored as of the end of the study period. For cause-specific analyses, follow-up for those who died from other causes was censored at the age of death. Although the main mortality analysis included an overall comparison of total and cause-specific mortality for Project SHAD participants versus nonparticipants, similar analyses were done for each of the four exposure groups as defined above.

Morbidity Analyses

The main morbidity analysis focused on differences between Project SHAD participants and nonparticipant controls for the primary outcome of the SF-36 score, physical and mental summary scores. Differences in secondary and tertiary outcomes as described above were also examined. With regard to morbidity outcomes, crude comparison of differences in mean scale measurements were made using analysis of variance and Student's *t*-test as appropriate to compare the outlined exposure and control groups. Comparison of differences in mean scale measurements with adjustment for potential confounders of age, race, branch, pay grade, smoking, drinking, and BMI was accomplished using a general linear models analysis. SF-36 scales were also analyzed to examine differ-

ences in dose groupings of BG and MAA. In addition, a subgroup analysis of SF-36 scores among the DTC test 69-10 Marines was conducted to look for exposure-response relationships. The mean NIS and SCID Somatization Scale scores were analyzed as outlined above for the SF-36 scales and subscales. The NIS scores were also used to create a dichotomous outcome for memory and attention problems. Crude comparisons of prevalence of these outcomes, as well as comparisons of the prevalence of medical conditions and symptoms, were conducted using odds ratios and 95 percent CI. Comparison of prevalence rates adjusted for the potential confounders of age, race, pay grade, smoking, drinking, and BMI was done using logistic regression analysis. Medical conditions were analyzed as individual items and also in the following 11 major groupings: cardiovascular, visual, respiratory, renal, endocrine, liver, autoimmune, gastrointestinal, neurological, psychological, and cancer.

REFERENCES

DoD (Department of Defense). 2006. *Project 112.* http://deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml (accessed November 28, 2006).

Marsh, G.M., A.O. Youk, R.A. Stone, S. Sefcik, and C. Alcorn. 1998. OCMAP-PLUS: A program for the comprehensive analysis of occupational cohort data. *Journal of Occupational and Environmental Medicine* 40:351-362.

SAS Institute, Inc. 1999. *SAS/STAT Software version 8*. Cary, NC.

Seltzer, C.C., and S. Jablon. 1974. Effects of selection on mortality. *American Journal of Epidemiology* 100:367-372.

Seltzer, C.C., and S. Jablon. 1977. Army rank and subsequent mortality by cause: 23-year follow-up. *American Journal of Epidemiology* 105:559-566.

9

Mortality Results

VITAL STATUS DATA AND ALL-CAUSE MORTALITY

Table 9-1 shows vital status percentages and the availability of cause-of-death information by analysis group. There are no large differences in the percentage assumed alive between Project SHAD (Shipboard Hazard and Defense) participants and controls within exposure group, and with the exception of group B, the proportion assumed alive is roughly three-quarters for both participants and controls. Subjects with only date of death or fact of death include those whose death occurred before 1979 (for whom we were unable to obtain causes) and represent 4–5 percent of participants or controls across all groups.

Table 9-2 shows the availability of follow-up information by exposure group and Project SHAD participation status. Mortality follow-up was done by matching both the Beneficiary Identification and Records Locator Subsystem (BIRLS) file, using military service number as well as Social Security number (SSN), and the National Death Index (NDI) file, using only SSNs. Because we consider mortality follow-up that relied on NDI to be virtually complete, only study subjects with SSN can be considered well followed, evidenced by the fact that the crude death rate among subjects with SSNs (22.7 percent) was roughly eight-fold higher than among subjects without SSNs (2.8 percent). Table 9-2 shows that in all but group B controls, the percentage of not-well-followed subjects (i.e., the sum of the first two columns) is less than 6 percent. Subsequent mortality analyses will therefore be done using all subjects and then only subjects with SSNs; although the latter omits some known deaths identified by BIRLS without SSNs, it does mean that all such subjects will have been searched for in the National Death Index. The results of these two analyses of all-cause mortality are shown in Tables 9-3 and 9-4, respectively.

Table 9-3 shows the results of proportional hazards analyses of total mortality by exposure group with all subjects included, regardless of completeness of mortality follow-up. All analyses were adjusted for age, race, and pay grade, but only in group B were there sufficient Marines to adjust also for service branch. There were no statistically significant differences in all-cause mortality between Project SHAD participants and controls, although in group B the hazard ratio (HR) was 1.25 (95 percent confidence interval [CI] 0.99–1.60). The effect of age was statistically significant in all groups, while race was significant only in group B, in which nonwhites had significantly higher mortality than whites; in all other groups, all-cause mortality was lower among nonwhites. Officers had significantly lower mortality than enlisted personnel in all groups, except for group C, and Marines in group B had significantly higher mortality than Navy personnel in group B.

TABLE 9-1 Vital Status and Availability of Death Data by Project SHAD Participant Status and Exposure Group

Vital Status and Death Data Availability	Group A Participant	Group A Control	Group B Participant	Group B Control	Group C Participant	Group C Control	Group D Participant	Group D Control
Assumed alive	2,537 (76.5%)	2,762 (76.7%)	712 (83.4%)	749 (86.3%)	560 (77.7%)	844 (77.6%)	666 (78.6%)	960 (80.0%)
Date or fact of death only	149 (4.5%)	163 (4.5%)	32 (3.7%)	34 (3.9%)	35 (4.9%)	53 (4.9%)	35 (4.1%)	50 (4.2%)
Cause of death	632 (19.1%)	677 (18.8%)	110 (12.9%)	85 (9.8%)	126 (17.5%)	190 (17.5%)	146 (17.2%)	190 (15.8%)
Total subjects	3,318 (100%)	3,602 (100%)	854 (100%)	868 (100%)	721 (100%)	1,087 (100%)	847 (100%)	1,200 (100%)

NOTE: Group A = participants potentially exposed only to *Bacillus globigii* (BG) simulant agent or methylacetoacetate (MAA); group B = participants potentially exposed only to trioctyl phosphate (TOF); group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

TABLE 9-2 Percentage of Study Subjects with SSN and BIRLS Record, by Exposure Group and Project SHAD Participation Status

Exposure Group and Participation Status*	No SSN and No BIRLS Record Found	Only BIRLS Record Found	SSN Only	Both SSN and BIRLS Record Found
Group A participants (N = 3,318)	2.0%	0.8%	14.2%	83.0%
Group A controls (N = 3,602)	3.1%	2.1%	15.5%	79.4%
Group B participants (N = 854)	4.8%	0.8%	10.2%	84.2%
Group B controls (N = 868)	10.9%	3.0%	20.9%	65.2%
Group C participants (N = 721)	3.1%	2.1%	13.6%	81.3%
Group C controls (N = 1,087)	2.6%	2.9%	15.6%	79.0%
Group D participants (N = 847)	2.0%	0.8%	13.8%	83.4%
Group D controls (N = 1,200)	2.4%	1.2%	12.0%	84.4%

*Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

Table 9-4 shows the results of the same proportional hazards analysis of all-cause mortality, including only those with SSN in whom mortality follow-up was assumed to be most complete. With the exception of group B, the results of this analysis are much the same as shown in Table 9-3. In group B, the hazard ratios associated with race and pay grade are no longer statistically significant.

Table 9-5 shows the results of proportional hazards ratio analyses of selected cause-specific mortality end points for only subjects with SSNs. Group A participants had a statistically significantly higher hazard ratio than

TABLE 9-3 Proportional Hazards Analysis of Total Mortality, by Exposure Group, Including All Subjects, Regardless of Completeness of Mortality Follow-Up

Exposure Group[a] and Risk Factor[b]	Hazard Ratio (95% CI)
Group A	
Participant versus control	1.01 (0.92–1.11)
Age (per year)	**1.10 (1.09–1.11)**
Race (nonwhite versus white)	0.91 (0.78–1.07)
Pay grade (officer versus enlisted	**0.50 (0.41–0.62)**
Group B	
Participant versus control	1.26 (0.99–1.60)
Age (per year)	**1.08 (1.05–1.10)**
Race (nonwhite versus white)	**1.44 (1.05–1.97)**
Pay grade (officer versus enlisted)	**0.59 (0.38–0.90)**
Branch (Marine versus Navy)	**1.49 (1.13–1.95)**
Group C	
Participant versus control	0.90 (0.74–1.09)
Age (per year)	**1.10 (1.09–1.12)**
Race (nonwhite versus white)	0.69 (0.47–1.00)
Pay grade (officer versus enlisted)	0.73 (0.52–1.02)
Group D	
Participant versus control	1.06 (0.88–1.28)
Age (per year)	**1.09 (1.08–1.11)**
Race (nonwhite versus white)	0.92 (0.62–1.37)
Pay grade (officer versus enlisted)	**0.50 (0.33–0.76)**
Total	
Participant versus control	1.02 (0.95–1.10)
Age (per year)	**1.09 (1.09–1.10)**
Race (nonwhite versus white)	0.96 (0.85–1.09)
Pay grade (officer versus enlisted)	**0.56 (0.48–0.65)**

NOTE: Statistically significant hazard ratios are in bold.

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]Each factor is adjusted for all others in the list.

controls for death because of cardiovascular disease. Group B participants had statistically significantly higher hazard ratios for cancer and cardiovascular deaths. Although group B participants had higher death rates than controls for many of the selected mortality outcomes in Table 9-5, most differences were not statistically significant, due to the relatively small number of deaths. Finally, comparing all Project SHAD participants versus all controls, heart disease deaths showed a statistically significant increase.

Standardized Mortality Ratios

As explained in Chapter 8, standardized mortality ratios (SMRs) are used to compare the number of observed deaths in a cohort with the number of expected deaths in the U.S. general population of the same age, race, and sex. An SMR value of 100 indicates that the number of observed deaths equals the number expected. Table 9-6 shows SMRs for subjects with SSNs by analysis group for various causes of death. Because we did not have

TABLE 9-4 Proportional Hazards Analysis of Total Mortality, by Exposure Group, Including Only Subjects with SSNs, Presumably with Virtually Complete Mortality Follow-Up

Exposure Group[a] and Risk Factor[b]	Hazard Ratio (95% CI)
Group A	
Participant versus control	1.00 (0.91–1.10)
Age (per year)	**1.09 (1.09–1.10)**
Race (nonwhite versus white)	0.91 (0.77–1.07)
Pay grade (officer versus enlisted)	**0.55 (0.44–0.68)**
Group B	
Participant versus control	1.15 (0.90–1.46)
Age (per year)	**1.08 (1.05–1.10)**
Race (nonwhite versus white)	1.29 (0.94–1.76)
Pay grade (officer versus enlisted)	0.66 (0.43–1.02)
Branch (Marine versus Navy)	**1.57 (1.19–2.07)**
Group C	
Participant versus control	0.87 (0.71–1.06)
Age (per year)	**1.10 (1.09–1.12)**
Race (nonwhite versus white)	**0.69 (0.47–1.00)**
Pay grade (officer versus enlisted)	0.81 (0.57–1.14)
Group D	
Participant versus control	1.06 (0.88–1.28)
Age (per year)	**1.09 (1.08–1.10)**
Race (nonwhite versus white)	0.90 (0.60–1.34)
Pay grade (officer versus enlisted)	**0.51 (0.34–0.78)**
Total	
Participant versus control	1.01 (0.93–1.08)
Age (per year)	**1.09 (1.09–1.10)**
Race (nonwhite versus white)	0.95 (0.84–1.08)
Pay grade (officer versus enlisted)	**0.61 (0.52–0.71)**

NOTE: Statistically significant hazard ratios are in bold.

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]Each factor is adjusted for all others in the list.

causes for deaths prior to 1979, the follow-up period for calculation of SMRs begins in 1979. The causes of death in Table 9-6 mirror those in Table 9-5, except that diabetes has replaced endocrine disease.

All-cause SMRs are all close to 100, save for group A controls and group B participants, indicating that overall mortality in these analysis groups is close to that of the U.S. population. However, all-cause SMRs for all participants and all controls combined are slightly, but statistically significantly, greater than 100. Although the cancer mortality SMR is slightly above 100 in almost all groups, it is statistically significant only for all controls and group A controls. Most of the excess cancer deaths were due to lung cancer, which might be attributable to smoking, and several participant and control group SMRs for nonmalignant respiratory disease are above 100, but not statistically significantly different from 100. SMRs for heart disease deaths are all close to 100, with the exception of group B participants. Deaths due to external causes tended to have low SMRs, and were statistically significantly lower among all participants.

TABLE 9-5 Survival Analysis Using Proportional Hazards Regression: Cause-Specific Mortality Comparing Participants to Controls (Adjusted for Age, Race, Pay Grade, and Branch in Group B Only), Including Only Subjects with SSNs, Presumably with Virtually Complete Mortality Follow-Up

	Participants	Controls	Adjusted HR*	95% CI
Group A	(# with death information: 3,318)	(# with death information: 3,602)		
	# died	# died		
Cancer	221	251	0.97	0.81–1.16
Heart disease	220	192	**1.24**	**1.02–1.51**
Respiratory disease	23	18	1.39	0.75–2.58
Endocrine/metabolic disease	58	62	0.99	0.69–1.42
Infectious disease	43	53	0.84	0.56–1.27
Injury/external causes	41	60	0.76	0.51–1.13
Group B	(# with death information: 854)	(# with death information: 868)		
	# died	# died		
Cancer	36	21	**1.92**	**1.12–3.31**
Heart disease	48	28	**1.71**	**1.06–2.75**
Respiratory disease	2	2	1.31	0.18–9.43
Endocrine/metabolic disease	10	4	2.31	0.71–7.51
Infectious disease	11	11	1.04	0.45–2.41
Injury/external causes	6	10	0.65	0.23–1.81
Group C	(# with death information: 721)	(# with death information: 1,087)		
	# died	# died		
Cancer	49	62	1.10	0.75–1.61
Heart disease	36	57	0.89	0.59–1.36
Respiratory disease	7	10	0.89	0.34–2.38
Endocrine/metabolic disease	12	23	0.74	0.37–1.49
Infectious disease	10	10	1.61	0.53–3.07
Injury/external causes	9	12	1.27	0.66–3.64
Group D	(# with death information: 848)	(# with death information: 1,200)		
	# died	# died		
Cancer	47	64	1.04	0.71–1.52
Heart disease	47	70	0.96	0.67–1.40
Respiratory disease	6	4	2.08	0.58–7.43
Endocrine/metabolic disease	11	12	1.26	0.55–2.85
Infectious disease	10	15	1.00	0.45–2.23
Injury/external causes	11	15	1.16	0.52–2.55
Total	(# with death information: 5,741)	(# with death information: 6,757)		
	# died	# died		
Cancer	353	398	1.06	0.95–1.10
Heart disease	351	347	**1.20**	**1.03–1.39**
Respiratory disease	38	34	1.32	0.83–2.10
Endocrine/metabolic disease	91	101	1.03	0.78–1.38
Infectious disease	74	89	0.97	0.71–1.32
Injury/external causes	67	97	0.86	0.63–1.17

*Adjusted for age, race, pay grade, and branch.

TABLE 9-6 Mortality Analysis Using Standardized Mortality Ratios (SMRs): Observed Number of Deaths and SMRs for Participants and Controls with SSNs for Selected Causes of Death, 1979–2004, by Analysis Group

	Participants: Number of deaths	SMR* (95% CI)	Controls: Number of deaths	SMR* (95% CI)
Group A				
All causes	677	105 (97–113)	721	**108 (100–116)**
Cancer	201	106 (92–122)	233	**119 (104–135)**
Heart disease	198	100 (86–114)	190	92 (80–106)
Respiratory disease	47	118 (87–157)	41	99 (71–134)
Diabetes	16	93 (53–151)	20	115 (70–177)
Injury/external causes	52	82 (62–108)	77	117 (92–146)
Group B				
All causes	126	**126 (105–150)**	98	106 (86–129)
Cancer	29	121 (81–174)	25	112 (72–165)
Heart disease	40	**156 (112–213)**	25	105 (68–155)
Respiratory disease	8	179 (77–353)	2	48 (6–174)
Diabetes	3	118 (24–346)	0	—
Injury/external causes	9	**50 (23–96)**	11	66 (33–117)
Group C				
All causes	137	101 (85–120)	205	109 (95–125)
Cancer	48	122 (90–161)	56	103 (78–133)
Heart disease	36	87 (61–120)	45	79 (58–106)
Respiratory disease	9	106 (49–202)	17	152 (89–244)
Diabetes	3	84 (17–245)	9	182 (83–345)
Injury/external causes	9	66 (30–126)	14	70 (38–117)
Group D				
All causes	158	107 (91–125)	210	102 (89–117)
Cancer	46	108 (79–144)	61	102 (78–131)
Heart disease	48	107 (79–142)	65	105 (81–133)
Respiratory disease	10	113 (54–207)	15	122 (69–202)
Diabetes	4	104 (28–265)	2	38 (5–136)
Injury/external causes	12	74 (38–130)	19	83 (50–130)
Total				
All causes	1,098	**107 (100–113)**	1,234	**107 (101–113)**
Cancer	324	110 (98–122)	375	**113 (102–125)**
Heart disease	322	104 (93–116)	325	93 (83–104)
Respiratory disease	74	120 (94–150)	75	109 (85–136)
Diabetes	26	96 (62–140)	31	104 (70–147)
Injury/external causes	82	**74 (59–92)**	121	97 (80–115)

NOTE: Statistically significant differences are in bold.

*SMRs are comparisons to national death rates, adjusted for age, race, sex, and calendar year of death (see text for details).

10

Morbidity Results

OVERVIEW: SURVEY RESPONSE

The data in this section of the report come from mail questionnaires and telephone interviews, as described in Chapter 7. The total number of subjects is 12,499, which excludes a total of 159 Army, Air Force, and Coast Guard participants and controls. As explained in Chapter 5, the primary reason for excluding the non-Navy, non-Marine subjects was their small number and our inability to assemble reasonable control groups. A total of 5,106 respondents is included in the analyses in this chapter.

Table 10-1 shows the total numbers of subjects and response rates for mail questionnaires and telephone interviews by analysis group. Response rates were calculated based on number of subjects presumed alive through 2005, and in all groups, participants have substantially higher response rates within each analysis group. Except for group B controls, participant response rates are all over 60 percent, while control response rates are 45–53 percent. In addition, mail questionnaire response rates were usually higher than telephone interview response rates. Overall, the response rate was 53.1 percent.

PRIMARY OUTCOME VARIABLE: SF-36

Unadjusted SF-36 Summary Scores by Analysis Group

Table 10-2 shows the two primary morbidity outcome measures from the SF-36, the physical component summary (PCS) and mental component summary (MCS) scores, by analysis group and participation status. Participants show uniformly lower scores (worse health) than controls in total as well as across all four analysis groups, with most of the differences in SF-36 scores being relatively small, in the range of 1 to 2 points. The exception is MCS scores in groups B and D, which show differences of around 5 points, considered moderate in size. Moreover, all differences between participant and control PCS and MCS scores were statistically significant, except for MCS and PCS scores in analysis group C, which contained the subjects potentially exposed to active agents. PCS and MCS scores in our survey were generally lower than comparable national norms for males aged 55–64 and 65–74: national PCS scores were 48.16 and 45.13, respectively; national MCS scores were 52.53 and 53.66, respectively.

It is important, especially when sample sizes are large, to interpret the clinical importance of these differences as well. According to the customary rule of thumb, based on Cohen's criteria, differences of 0.2 to 0.49 standard

TABLE 10-1 Availability of Mail Questionnaire and Telephone Interview Data by Analysis Group and Participation Status

Analysis Group and Participation Status*	Mail Questionnaire Only	Telephone Interview Only	Any Response (includes both)	Total Subjects Presumed Alive
Group A, participants	834	637	1,545	2,494
	(33.4%)	(25.5%)	(62.0%)	(100%)
Group A, controls	725	552	1,325	2,710
	(26.8%)	(20.4%)	(48.9%)	(100%)
Group B, participants	192	175	380	702
	(27.4%)	(24.9%)	(54.1%)	(100%)
Group B, controls	85	137	230	738
	(11.5%)	(18.6%)	(31.2%)	(100%)
Group C, participants	174	130	339	551
	(31.9%)	(23.6%)	(61.5%)	(100%)
Group C, controls	209	159	377	829
	(25.2%)	(19.2%)	(45.5%)	(100%)
Group D, participants	218	178	412	656
	(33.2%)	(27.1%)	(62.8%)	(100%)
Group D, controls	261	225	498	942
	(27.7%)	(23.9%)	(54.7%)	(100%)
Total number of responding subjects	2,700	2,193	5,106	9,622
	(28.1%)	(22.8%)	(53.1%)	(100%)

*Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

TABLE 10-2 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores, by Analysis Group and Participation Status (Sample Sizes in Parentheses), with Results of *t*-Test Comparisons

Analysis Group[a]	PCS Participant (sample size)	PCS Control (sample size)	*t*-Test[b]	MCS Participant (sample size)	MCS Control (sample size)	*t*-Test
Group A	42.36	44.20	**4.09**	49.32	51.22	**3.92**
	(N = 1,438)	(N = 1,220)	**2,656 df**	(N = 1,438)	(N = 1,220)	**2,656 df**
			***P* < .0001**			***P* < .0001**
Group B	42.64	44.93	**2.41**	44.54	49.78	**4.21**
	(N = 357)	(N = 220)	**575 df**	(N = 357)	(N = 220)	**575 df**
			***P* = .0163**			***P* < .0001**
Group C	42.14	42.82	0.75	48.83	50.06	1.24
	(N = 315)	(N = 345)	658 df	(N = 315)	(N = 345)	658 df
			P = .4558			*P* = .2158
Group D	42.80	44.59	**2.22**	47.90	52.31	**5.30**
	(N = 388)	(N = 460)	**846 df**	(N = 388)	(N = 460)	**846 df**
			***P* = .0269**			***P* < .0001**
All Subjects	42.44	44.14	**5.06**	48.74	51.48	**7.40**
	(N = 2,498)	(N = 2,245)	**4,741 df**	(N = 2,498)	(N = 245)	**4,741 df**
			***P* < .0001**			***P* < .0001**
National norms for males						
age 55–64		48.16			52.53	
age 65–74		45.13			53.66	

NOTE: Statistically significant items are in bold.

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]*t*-test value based on pooled variance estimate.

deviations are considered "small," differences of 0.5 to 0.79 standard deviations are considered "moderate," and differences greater than 0.8 standard deviations are considered "large." Because our normed scores all have a mean of 50 and a standard deviation of 10, this means that differences in mean SF-36 scores of 2 to 4.9 points are interpreted as "small," 5 to 7.9 points as "moderate," and 8 or more points as "large."

Figures 10-1 and 10-2 show bar graphs of the PCS and MCS scores by analysis group and participation status. Most of the differences in the PCS scores were considered small, around 2 points, with a smaller difference of less than 1 point in group C. For MCS scores, groups A and C showed small, 2-point differences, while the group B and D differences were moderate.

The next step was to examine the data for the SF-36 subscales, shown in Table 10-3. Overall, there were no striking differences in the SF-36 subscales. Group A showed small but consistent differences in all the SF-36 subscales, while group B differences were moderate in size, ranging up to 5 points; in all subscales, participants showed smaller values than controls. Group D differences were similar, but slightly smaller, than those of group B. Virtually all the SF-36 subscale differences in groups A, B, and D were statistically significant. In contrast, group C differences were relatively small, and none of them were statistically significant.

SF-36 Summary Scales by Potential Confounding Variables

Table 10-4 shows adjusted mean SF-36 summary scale values by analysis group for various potential confounding factors, with branch included only for group B, where there were sufficient numbers of Marines. Age was significantly associated with PCS and MCS scores in the majority of analysis groups, while race differences

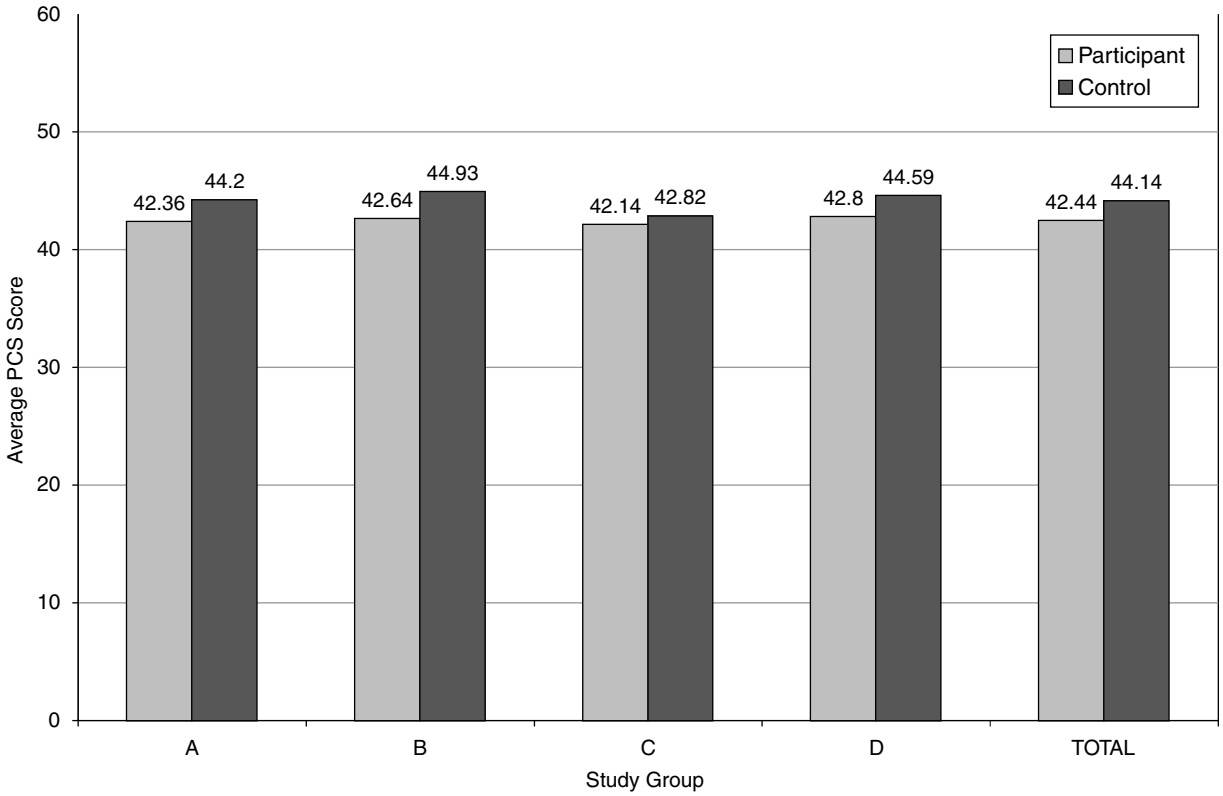


FIGURE 10-1 Average SF-36 physical component scores (PCS) by study group and participation status.

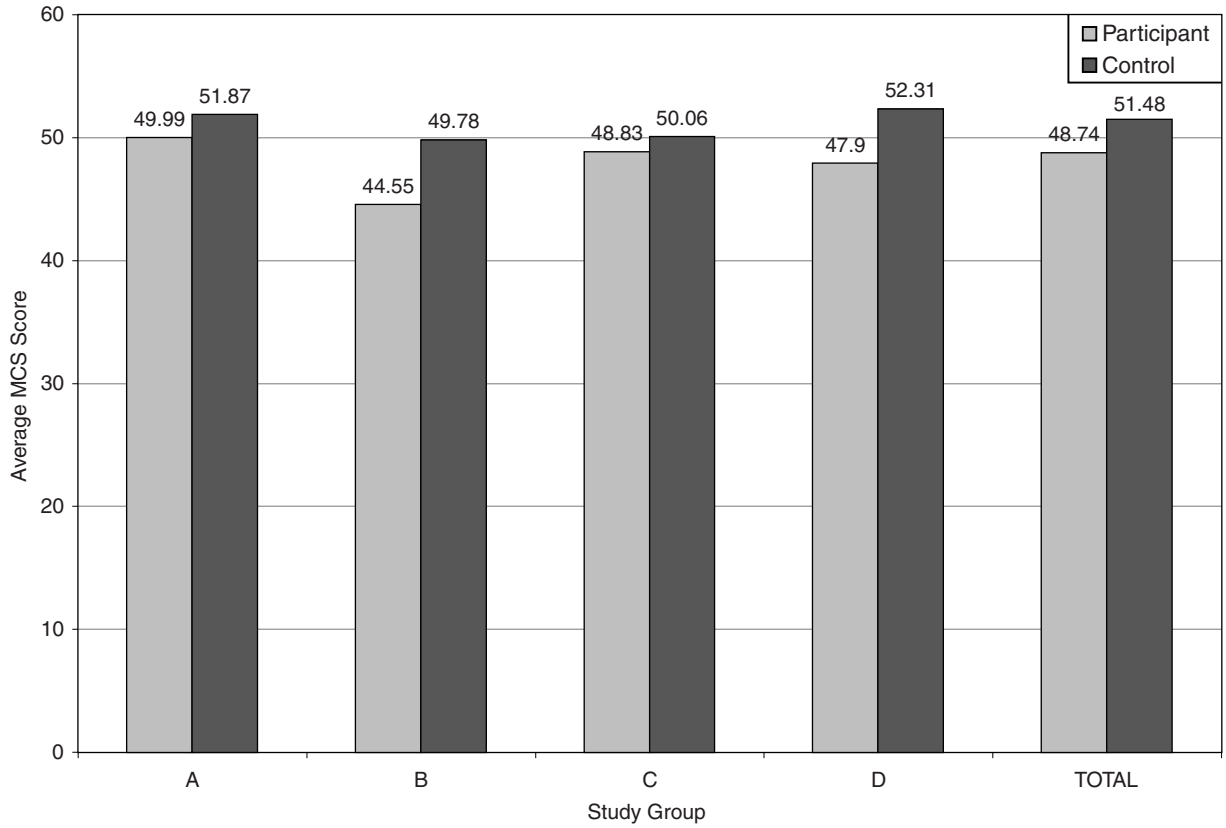


FIGURE 10-2 Average SF-36 mental component scores (MCS) by study group and participation status.

were statistically significant only for group A's PCS and MCS scores and group B's PCS score. Pay grade differences were all statistically significant except for group B; some of the differences by pay grade in Table 10-4 are moderate to large in size. Smoking, drinking, and body mass index (BMI) all had statistically significant effects on PCS and MCS in more than one analysis group, although BMI was not statistically associated with MCS in any group. In summary, age, race, pay grade, branch, smoking, drinking, and BMI were all significantly associated with either PCS or MCS scores in at least one of the analysis groups. Therefore, further general linear model analyses will compare SF-36 summary scores within analysis groups, having adjusted for age, race, pay grade, branch, smoking, drinking, and BMI. Because statistical adjustment for source of data (mail questionnaire versus telephone interview) and for age-squared did not result in any meaningful change in estimates, we did not adjust for either of these covariates, in the interests of parsimony.

Analysis of Adjusted SF-36 Summary Scores by Analysis Group

Having established that age, race, pay grade, and branch are all potential confounding variables, our general linear model analyses compared SF-36 summary scores adjusted for all these variables simultaneously. Table 10-5 shows the results of our general linear models comparisons.

Although participants have uniformly smaller adjusted mean SF-36 summary scores than controls, there were differences between PCS and MCS scores. Adjusted mean PCS scores all showed small differences between participants and controls, roughly two points, with the group C difference not reaching statistical significance.

TABLE 10-3 Mean SF-36 Subscale Scores, by Analysis Group and Participation Status, with Results of *t*-Test Comparisons

Analysis Group[a] and SF-36 Subscale[b]	Participant	Control	*t*-Test[c]
Group A			
PF	42.30	43.78	3.14, 2,794 df, $P = .0017$
RP	43.79	45.74	4.17, 2,842 df, $P < .0001$
BP	45.88	47.59	4.05, 2,845 df, $P < .0001$
GH	42.73	45.40	5.79, 2,840 df, $P < .0001$
VT	48.56	50.97	5.34, 2,811 df, $P < .0001$
SF	46.25	48.09	3.99, 2,831 df, $P < .0001$
RE	46.41	48.63	4.72, 2,850 df, $P < .0001$
MH	48.95	51.07	4.67, 2,814 df, $P < .0001$
Group B			
PF	42.48	45.32	2.80, 597 df, $P = .0053$
RP	42.99	46.56	3.37, 601 df, $P = .0008$
BP	43.70	46.81	3.20, 603 df, $P = .0015$
GH	40.49	44.50	3.72, 605 df, $P = .0002$
VT	46.05	50.04	3.83, 601 df, $P = .0001$
SF	42.05	46.89	4.24, 605 df, $P < .0001$
RE	42.72	47.72	4.14, 602 df, $P < .0001$
MH	44.31	49.33	4.28, 598 df, $P < .0001$
Group C			
PF	42.30	42.32	0.03, 698 df, $P = .9764$
RP	43.48	44.06	0.61, 702 df, $P = .5423$
BP	45.53	45.86	0.39, 705 df, $P = .6935$
GH	41.92	43.36	1.61, 701 df, $P = .1071$
VT	47.40	48.73	1.44, 703 df, $P = .1492$
SF	45.93	45.48	-0.47, 706 df, $P = .6378$
RE	45.78	46.34	0.56, 702 df, $P = .5781$
MH	48.49	49.47	1.04, 706 df, $P = .2999$
Group D			
PF	42.69	44.29	1.91, 884 df, $P = .0565$
RP	43.87	46.35	3.02, 899 df, $P = .0026$
BP	45.12	47.90	3.77, 901 df, $P = .0002$
GH	42.20	45.09	3.52, 901 df, $P = .0004$
VT	47.41	50.73	4.07, 890 df, $P < .0001$
SF	44.90	48.36	4.29, 895 df, $P < .0001$
RE	45.45	49.36	4.80, 901 df, $P < .0001$
MH	47.18	50.64	4.17, 893 df, $P < .0001$

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; and MH = mental health.

[c]*t*-test value based on pooled variance estimate.

TABLE 10-4 Mean SF-36 Summary Scores, by Analysis Group and Various Other Factors, with Results of *F*-Test Comparisons

Analysis Group and Factor*	Mean Value PCS	*F*-Test	Mean Value MCS	*F*-Test
Group A				
Age	—	**28.70, 1 df**	—	**12.05, 1 df**
		***P* < 0.0001**		***P* = 0.0005**
Race				
White	45.40	**7.64, 1 df**	50.33	3.75, 1 df
Nonwhite	43.00	***P* = 0.0078**	48.46	*P* = 0.0529
Pay grade				
E1–E3	41.58	**13.13, 2 df**	47.71	**5.74, 2 df**
E4–E8	42.65	***P* < 0.0001**	49.05	***P* = 0.0032**
Officer	48.36		51.43	
Branch				
Marine	48.06	**2.58, 1 df**	47.29	3.43, 1 df
Navy	44.72	**P = 0.1080**	51.51	*P* = 0.0643
Smoking				
Yes	44.67	**36.81, 1 df**	48.61	**6.38, 1 df**
No	48.11	***P* < 0.0001**	50.18	***P* = 0.0116**
Drinking				
Yes	47.98	**51.12, 1 df**	50.54	**21.97, 1 df**
No	44.80	***P* < 0.0001**	48.25	***P* < 0.0001**
Body Mass Index	—	**78.73, 1 df**	—	1.30, 1 df
		***P* < 0.0001**		*P* = 0.2540
Group B				
Age	—	0.20, 1 df	—	2.64, 1 df
		P = 0.6510		*P* = 0.1048
Race				
White	44.38	**4.01, 1 df**	47.28	1.93, 1 df
Nonwhite	41.55	***P* = 0.0457**	44.70	*P* = 0.1652
Pay grade				
E1–E3	43.51	2.98, 2 df	46.00	0.56, 2 df
E4–E8	44.57	*P* = 0.0514	46.96	*P* = 0.5721
Officer	40.82		45.01	
Branch				
Marines	42.53	0.77, 1 df	42.74	**24.96, 1 df**
Navy	43.40	*P* = 0.3809	49.24	***P* < 0.0001**
Smoking				
Yes	40.94	**14.51, 1 df**	45.25	1.14, 1 df
No	44.99	***P* = 0.0002**	46.73	*P* = 0.2866
Drinking				
Yes	45.11	**22.12, 1 df**	47.08	3.29, 1 df
No	40.82	***P* < 0.0001**	44.90	*P* = 0.0702
Body Mass Index	—	**11.25, 1 df**	—	0.14, 1 df
		***P* = 0.0008**		*P* = 0.7120

TABLE 10-4 Continued

Analysis Group and Factor*	Mean Value PCS	*F*-Test	Mean Value MCS	*F*-Test
Group C				
Age	—	**6.05, 1 df**	—	0.03, 1 df
		***P* = 0.0142**		*P* = 0.8725
Race				
White	48.63	0.42, 1 df	53.87	0.02, 1 df
Nonwhite	47.67	*P* = 0.5185	54.10	*P* = 0.8888
Pay grade				
E1–E3	46.10	**4.07, 2 df**	51.48	3.01, 2 df
E4–E8	46.25	***P* = 0.0176**	53.39	*P* = 0.0501
Officer	52.11		57.07	
Branch				
Marine	51.79	0.84, 1 df	56.41	0.29, 1 df
Navy	44.52	*P* = 0.8597	51.55	*P* = 0.5894
Smoking				
Yes	46.67	**6.76, 1 df**	52.71	**3.91, 1 df**
No	49.63	***P* = 0.0095**	55.26	***P* = 0.0486**
Drinking				
Yes	50.10	**17.16, 1 df**	55.27	**6.28, 1 df**
No	46.28	***P* < 0.0001**	52.70	***P* = 0.0125**
Body Mass Index	—	**27.28, 1 df**	—	0.74, 1 df
		***P* < 0.0001**		*P* = 0.3914
Group D				
Age	—	**7.47, 1 df**	—	**8.38, 1 df**
		***P* = 0.0064**		***P* = 0.0039**
Race				
White	45.98	0.35, 1 df	51.95	2.32, 1 df
Nonwhite	47.17	*P* = 0.5519	48.72	*P* = 0.1282
Pay grade				
E1–E3	45.04	**4.25, 2 df**	48.67	2.17, 2 df
E4–E8	44.45	***P* = 0.0146**	49.06	*P* = 0.1146
Officer	50.24		53.28	
Branch	—		—	
Marine		—		—
Navy				
Smoking				
Yes	44.63	**16.92, 1 df**	48.93	**7.75, 1 df**
No	48.52	***P* < 0.0001**	51.73	***P* = 0.0055**
Drinking				
Yes	48.37	**17.94, 1 df**	52.01	**15.12, 1 df**
No	44.78	***P* < 0.0001**	48.66	***P* < 0.0001**
Body Mass Index	—	**40.37, 1 df**	—	0.12, 1 df
		***P* < 0.0001**		*P* = 0.7244

NOTE: Statistically significant items are in bold.

*Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

TABLE 10-5 Adjusted Mean SF-36 Summary Scores, by Analysis Group, with Results of *F*-Test Comparisons

Analysis Group and Factor*	Adjusted Mean PCS Score	*F*-Test	Adjusted Mean MCS Score	*F*-Test
Group A				
Participants	45.32	**23.54, 1 df, *P* < .0001**	48.36	**18.50, 1 df, *P* < .0001**
Controls	47.45		50.43	
Age	—	**28.70, 1 df, *P* < .0001**	—	**12.05, 1 df, *P* = .0005**
Race	—	**7.64, 1 df, *P* = .0058**	—	3.75, 1 df, *P* = 0.0529
Pay grade	—	**13.13, 2 df, *P* < .0001**	—	**5.74, 2 df, *P* = .0032**
Branch	—	2.58, 1 df, *P* = .1080	—	3.43, 1 df, *P* = .0643
Smoking	—	**36.81, 1 df, *P* < 0.0001**	—	**6.38, 1 df, P = 0.0116**
Drinking	—	**51.12, 1 df, *P* < 0.0001**	—	**21.97, 1 df, *P* < 0.0001**
Body mass index	—	**78.73, 1 df, *P* < 0.0001**	—	1.30, 1 df, p = 0.2540
Group B				
Participants	42.12	3.06, 1 df, *P* = .0808	43.92	**10.73, 1 df, *P* = .0011**
Controls	43.81		48.07	
Age	—	0.20, 1 df, *P* = .6510	—	2.64, 1 df, *P* = .1048
Race	—	**4.01, 1 df, *P* = .0457**	—	1.93, 1 df, *P* = .1652
Pay grade	—	2.98, 2 df, *P* = .0514	—	0.56, 2 df, *P* = .5721
Branch	—	0.77, 1 df, *P* = .3809	—	**24.96, 1 df, *P* < .0001**
Smoking	—	**14.51, 1 df, *P* = 0.0002**	—	1.14, 1 df, *P* = 0.2866
Drinking	—	**22.12, 1 df, *P* < 0.0001**	—	3.29, 1 df, *P* = 0.0702
Body mass index	—	**11.25, 1 df, *P* = 0.0008**	—	0.14, 1 df, *P* = 0.7120
Group C				
Participants	47.51	2.06, 1 df, *P* = .1517	53.03	3.59, 1 df, *P* = .0587
Controls	48.79		54.94	
Age	—	**6.05, 1 df, *P* = .0142**	—	0.03, 1 df, *P* = .8725
Race	—	0.42, 1 df, *P* = .5185	—	0.02, 1 df, *P* = .8888
Pay grade	—	**4.07, 2 df, *P* = .0176**	—	3.01, 2 df, *P* = 0.0501
Branch	—	0.84, 1 df, *P* = .8597	—	0.29, 1 df, *P* = .5894
Smoking	—	**6.76, 1 df, *P* = 0.0095**	—	**3.91, 1 df, *P* = 0.0486**
Drinking	—	**17.16, 1 df, *P* < 0.0001**	—	**6.28, 1 df, *P* = 0.0125**
Body mass index	—	**27.28, 1 df, P < 0.0001**	—	0.74, 1 df, *P* = 0.3914
Group D				
Participants	45.50	**7.56, 1 df, *P* = .0061**	47.70	**40.26, 1 df, *P* < .0001**
Controls	47.88		52.97	
Age	—	**7.47, 1 df, *P* = .0064**	—	**8.38, 1 df, *P* = 0.0039**
Race	—	0.35, 1 df, *P* = .3519	—	2.32, 1 df, *P* = 0.1282
Pay grade	—	**4.25, 2 df, *P* = .0146**	—	2.17, 2 df, *P* = 0.1146
Branch	—	—	—	—
Smoking	—	**16.92, 1 df, *P* < 0.0001**	—	**7.75, 1 df, *P* = 0.0055**
Drinking	—	**17.94, 1 df, *P* < 0.0001**	—	**15.12, 1 df, *P* < 0.0001**
Body mass index	—	**40.37, 1 df, *P* < 0.0001**	—	0.12, 1 df, *P* = 0.7244

NOTE: Mean SF-36 summary scores adjusted for age, race, pay grade, branch, smoking, drinking, and body mass index. Statistically significant items are in bold.

*Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

Differences between participants and controls for adjusted mean MCS scores were small in groups A and C (group A's difference was statistically significant), whereas groups B and D showed larger differences (both statistically significant). The statistical significance of age, race, pay grade, and branch varied by group and by summary score, especially the effect of branch in group B's MCS score. We note that although group C participants were the only subjects potentially exposed to active agents, neither adjusted mean PCS or MCS scores differed from those of group C controls.

Analysis of Group A "Factorial Design"

The subjects in group A were exposed only to *Bacillus globigii* (BG) simulant agent or methylacetoacetate (MAA), which allows a natural factorial design that allows for independent estimates of the effects of BG and MAA. Table 10-6 shows the results of a general linear model analysis of PCS and MCS mean scores, based on 2,661 subjects. The first analysis is a main effects model with separate effects for BG and MAA exposure, adjusted for age at participation, race, pay grade, branch, smoking, drinking, and body mass index. The second analysis was identical to the first, except that an additional adjustment was made for number of tests, a categorical variable with level 0 for controls and levels 1, 2, or 3 for participants.

In model 1, without adjustment for number of tests, potential exposure to BG or to MAA resulted in a statistically significant lowering of the PCS scores of around one point. MCS scores in model 1 were not statistically significantly different for BG exposure, but they were for MAA exposure, the difference being around 2.5 points. We also fit the same model with an interaction term added, which was not statistically significant (data not shown). In model 2, the effects of possible BG and MAA exposure were all attenuated and none were statistically significant. In model 2, the number of tests is a statistically significant factor for PCS and for MCS. For neither PCS nor MCS score is there a monotone decline in score with an increasing number of tests; that is, there is not a clear dose-response effect with number of tests.

Models 1 and 2 looked at the effects of simple BG or MAA exposure as either a yes or no. In Table 10-7 we report an analysis that attempts to assign "doses" of BG and MAA. Specifically, in this model, we defined the dose for BG and MAA as the number of tests at which a particular subject might have been exposed to these agents. For example, participation in Autumn Gold yields a BG dose of 1 and an MAA dose of 0, since only BG was used in that test. Eager Belle I, Eager Belle II, and Scarlet Sage also used only BG. Tests High Low and Purple Sage used only MAA, but DTC test 69-31 used both BG and MAA. The range of observed dose for BG ranged from 0 (controls) to 3, while the range of observed dose for MAA ranged from 0 to 2.

General linear model analyses of PCS and MCS scores were run using BG and MAA dose data as independent variables, adjusted for age, race, pay grade, and branch. Table 10-7 shows that both PCS and MCS scores have a statistically significant difference by BG and MAA dose, although neither exposure relationship shows a clear gradient. The maximum effect size is around 3–4 points for BG and MAA dose effects.

However, it is mostly the highest exposure group for both PCS and MCS that is not strictly monotone, and this is the group whose effect estimates have the largest standard error. Thus, we did analyses for linear trends. We found statistically significant coefficients for linear trend for both BG and MAA for both PCS and MCS scores, evidence that PCS and MCS scores were statistically significantly lower with each additional test in which there was potential exposure to either BG or MAA.

Analysis of Individual Exposure Data from DTC Test 69-10

As explained in detail in Chapter 8, during Project SHAD (Shipboard Hazard and Defense) test DTC 69-10, Marine troops were subjected to a simulated chemical weapons assault with the purpose of determining the "operational effects of a persistent, toxic, chemical agent spray attack on U.S. amphibious forces." During this test, sampling was conducted on exposed personnel and their clothing to determine the extent of exposure to the simulant agent, trioctyl phosphate (TOF). DTC test 69-10 was conducted at Vieques island, east of Puerto Rico, on May 3, 4, 5, and 7, 1969. Using material from a redacted version of the DTC test 69-10 final report, we assigned individual exposure levels based on individual estimates of magnitude of contamination on an ordinal

TABLE 10-6 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores for Subjects in Group A (Standard Errors in Parentheses), by Agent, with Adjustment for Age, Race, Branch, Pay Grade, Smoking, Drinking, and Body Mass Index (Model 1) or These Factors Plus Number of Tests (Model 2)

Model Factor and Level	Adjusted Mean PCS Value	*F*-Test Value and Probability	Adjusted Mean MCS Value	*F*-Test Value and Probability
Model 1				
BG				
No	45.84 (1.25)	**10.38, 1 df, *P* = .0013**	48.80 (1.37)	2.77, 1 df, *P* = .0964
Yes	44.37 (1.21)		47.97 (1.33)	
MAA				
No	45.92 (1.20)	**11.38, 1 df, *P* = .0008**	49.58 (1.32)	**20.11, 1 df, *P* < .0001**
Yes	44.28 (1.26)		47.19 (1.39)	
Age	—	**29.06, 1 df, *P* < .0001**	—	**6.62, 1 df, *P* = .0101**
Race	—	**7.89, 1 df, *P* = .0050**	—	3.76, 1 df, *P* = .0526
Pay grade	—	**12.88, 2 df, *P* < .0001**	—	**6.66, 2 df, *P* = .0013**
Branch	—	1.02, 1 df, *P* = .3123	—	**4.38, 1 df, *P* = .0364**
Smoking	—	**35.53, 1 df, *P* < .0001**	—	**5.86, 1 df, *P* = .0155**
Drinking	—	**51.54, 1 df, *P* < .0001**	—	**21.61, 1 df, *P* < .0001**
BMI*	—	**76.35, 1 df, *P* < .0001**	—	1.47, 1 df, *P* = .2251
Model 2				
BG				
No	44.45 (1.40)	0.85, 1 df, *P* = .3565	47.78 (1.54)	1.23, 1 df, *P* = .2666
Yes	45.33 (1.35)		48.94 (1.48)	
MAA				
No	45.36 (1.30)	1.37, 1 df, *P* = .2422	49.17 (1.43)	3.35, 1 df, *P* = .0674
Yes	44.42 (1.40)		47.55 (1.54)	
Age	—	**32.52, 1 df, *P* < .0001**	—	**5.52, 1 df, *P* = .0189**
Race	—	**7.69, 1 df, *P* = .0056**	—	3.58, 1 df, *P* = .0584
Pay grade	—	**14.78, 2 df, *P* < .0001**	—	**7.63, 2 df, *P* = .0005**
Branch	—	0.54, 1 df, *P* = .4605	—	**4.87, 1 df, *P* = .0274**
Smoking	—	**34.91, 1 df, *P* < .0001**	—	**5.77, 1 df, *P* = .0164**
Drinking	—	**49.80, 1 df, *P* < .0001**	—	**20.67, 1 df, *P* < .0001**
BMI*	—	**77.63, 1 df, *P* < .0001**	—	1.60, 1 df, *P* = .2067
Number of tests				
0	46.59 (1.53)	**5.57, 3 df, *P* = .0008**	49.86 (1.68)	**2.74, 3 df, *P* = .0419**
1	45.38 (1.21)		48.54 (1.33)	
2	42.56 (1.37)		46.51 (1.50)	
3	45.03 (2.10)		48.53 (2.31)	

NOTE: Statistically significant items are in bold.
*BMI = body mass index.

scale: VH (very heavy), H (heavy), M (medium), L (light), VL (very light), T (trace) and N (negligible). When multiple exposures were taken into account, there were 428 individuals who had ordinal contamination data from one or more trials. Because we were unable to obtain quantitative data regarding the contamination levels, we analyzed the TOF exposure data by arbitrarily assigning the following exposure values: T (trace) and N (negligible) = 0.5; VL (very light) = 1.0; L (light) = 2.0; M (medium) = 3.0; H (heavy) = 4.0; and VH (very heavy) = 5.0. We further assigned a dose of zero to Marine controls in DTC test 69-10.

A total of 260 Marine subjects in group B provided data for an analysis of SF-36 summary outcomes. After adjusting for age, race, and pay grade, SF-36 PCS did not differ significantly by assigned TOF exposure levels (*F* statistic = 0.01, 1 df, *P* = .9309) nor did mental component scores (*F* statistic = 0.44, 1 df, *P* = .5094). When we dichotomized exposure into two groups, with "high" defined as 4.0 or more and "low" defined as less than 4.0, we

TABLE 10-7 Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores (Standard Errors in Parentheses) for Subjects in Group A, by "Dose" of Agent, with Adjustment for Age, Race, Pay Grade, and Branch

Model Factor and Dose[a]	Adjusted Mean PCS Value	*F*-Test Value and Probability	Adjusted Mean MCS Value	*F*-Test Value and Probability
BG				
0	46.30 (1.46)	**6.93, 3 df, *P* = .0001**	48.58 (1.61)	**4.12, 3 df, *P* = .0063**
1	45.77 (1.43)		48.75 (1.57)	
2	43.30 (1.47)		46.15 (1.62)	
3	45.25 (2.93)		49.87 (3.22)	
MAA				
0	45.27 (1.36)	**9.24, 2 df, *P* < .0001**	49.48 (1.49)	**12.91, 2 df, *P* < .0001**
1	43.11 (1.45)		46.62 (1.59)	
2	47.08 (2.61)		48.91 (2.87)	
Age	—	**31.59, 1 df, *P* < .0001**	—	**5.35, 1 df, *P* = .0208**
Race	—	**7.70, 1 df, *P* = .0056**	—	3.60, 1 df, *P* = .0579
Pay grade	—	**14.42, 2 df, *P* < .0001**	—	**7.82, 2 df, *P* = .0004**
Branch	—	0.29, 1 df, *P* = .5907	—	**6.28, 1 df, *P* = .0123**
Smoking	—	**35.42, 1 df, *P* < .0001**	—	**5.73, 1 df, *P* = .0167**
Drinking	—	**48.88, 1 df, *P* < .0001**	—	**19.96, 1 df, *P* < .0001**
BMI[b]	—	**76.61, 1 df, *P* < .0001**	—	1.45, 1 df, *P* = .2286

NOTE: Statistically significant items are in bold.
[a]Dose is the number of tests in which a subject was potentially exposed to an agent.
[b]BMI = body mass index.

found similar results. The SF-36 summary scores did not differ statistically significantly for either PCS (*F* statistic = 0.00, 1 df, *P* = .9937) or MCS (*F* statistic = 0.40, 1 df, *P* = .5278).

SF-36 Summary

In summary, we detected many statistically significant differences in SF-36 scores, although relatively few were of even moderate size. In most cases, differences in adjusted SF-36 summary scores are all around two points, with age and pay grade generally the most important covariates, although group C differences were smaller and not statistically significant. In comparison to national norms, both participants and controls had lower PCS and MCS scores (worse health), but controls had PCS and MCS scores that were nearer the national norms. In comparison, veterans aged 50–64 in the Veterans Health Study, who were receiving outpatient care from the Department of Veterans Affairs (VA), had an average PCS score of 37.2 and an average MCS score of 47.0 (Payne et al., 2005), both of which are substantially lower than the participant or control scores in our study.

An analysis of the independent effects of BG and MAA exposure in group A found that neither agent was associated with a large change in SF-36 summary score, although both agents had a statistically significant effect on both PCS and MCS adjusted mean scores. We did not see a clear dose-response relationship between the number of tests in group A and either PCS or MCS, but there was a statistically significant linear trend. An analysis of the only individual exposure data available, from DTC test 69-10, showed no statistically significant association of recorded exposure level, either on an ordinal scale or dichotomized, with either PCS or MCS.

OTHER SCALED DATA

Somatization Scale

Twelve items, taken from the Structured Clinical Interview for DSM-IV (SCID) somatization scale, were included in the Project SHAD health survey questionnaire. The number of "yes" responses was totaled to produce a score ranging from 0 to 12. If 3 or more items were missing, the score was considered missing. Table 10-8 shows unadjusted and adjusted (for age, race, pay grade, branch, smoking, drinking, and BMI) somatization scores for participants and controls by analysis group; all mean differences were statistically significant. Somatization scores were uniformly higher for participants, with differences typically less than one point.

Memory and Attention Subscales of the Neuropsychological Scale

The subscales on memory and attention problems, taken from the Neuropsychological Impairment Scale (O'Donnell et al., 1993), were included in the Project SHAD health survey questionnaire. Each questionnaire item (e.g., "I have a hard time remembering people's names") is scored from 1 to 5 ("not at all" to "extremely") and the individual items scores are summed. The responses on the memory subscale range from 0 to 32, and the attention subscale responses range from 0 to 36. We also analyzed data based on a dichotomous outcome, with a score of 14 or more on either scale considered as "high."

Table 10-9 shows unadjusted and adjusted (for age, race, pay grade, branch, smoking, drinking, and BMI) memory and attention scores for participants and controls by analysis group. Except for group C, all mean differences were statistically significant; in group C only the adjusted memory scale scores were significantly different. Both memory and attention scores were uniformly higher for participants (indicating greater problems), with differences in unadjusted mean scores ranging from one to almost four points. The largest differences were found in group B.

OTHER MEDICAL DATA

Medical Conditions

Table 10-10 shows self-reported medical conditions by analysis group. The original 45 medical conditions (including open-ended items such as "Any other heart condition [please specify]") have been grouped into 11 broader categories for analysis. Adjusted (for age, race, pay grade, smoking, drinking, and BMI) odds ratios (OR) are shown, with statistically significant odds ratios shown in bold.

TABLE 10-8 Mean Somatization Scores, Unadjusted and Adjusted, for Participants and Controls, by Analysis Group

	Unadjusted		Adjusted[a]	
	Participants	Controls	Participants	Controls
Group A[c]	2.83[b]	2.15	2.38[b]	1.63
Group B[c]	3.49[b]	2.59	3.62[b]	2.90
Group C[c]	3.02[b]	2.59	2.18[b]	1.62
Group D[c]	2.90[b]	2.27	2.76[b]	1.98

[a]Adjusted for age, race, pay grade, branch, smoking, drinking, and body mass index.

[b]Statistically significant difference.

[c]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

TABLE 10-9 Mean Memory and Attention Scores, Unadjusted and Adjusted, for Participants and Controls, by Analysis Group[a]

	Unadjusted		Adjusted[c]	
	Participants	Controls	Participants	Controls
Group A				
Memory	8.33[b]	6.83	8.27[b]	6.64
Attention	9.09[b]	7.10	9.30[b]	7.17
Group B				
Memory	10.08[b]	7.56	10.12[b]	8.32
Attention	11.66[b]	7.93	11.41[b]	8.25
Group C				
Memory	8.46	7.59	5.74[b]	4.56
Attention	9.23	8.37	5.52	4.35
Group D				
Memory	8.53[b]	6.89	8.30[b]	6.51
Attention	9.62[b]	7.38	9.69[b]	7.23

[a]Group A = participants potentially exposed only to BG or MAA; group B = participants potentially exposed only to TOF; group C = participants potentially exposed to any active chemical or biological agent; group D = participants potentially exposed only to simulants and not in groups A or B.

[b]Statistically significant difference.

[c]Adjusted for age, race, pay grade, branch, smoking, drinking, and body mass index.

TABLE 10-10 Number of Medical Conditions for Participants and Controls, with Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs), by Analysis Group

	Participants	Controls	Adjusted OR*	95% CI
Group A	**N = 1,548**	**N = 1,326**		
Cardiovascular	**1,106**	**892**	**1.31**	**1.05–1.62**
Visual	541	418	1.21	0.98–1.50
Respiratory	**648**	**460**	**1.49**	**1.22–1.83**
Renal	**245**	**158**	**1.49**	**1.09–1.96**
Endocrine	**556**	**421**	**1.26**	**1.01–1.56**
Liver	124	89	1.11	0.76–1.62
Autoimmune	323	253	1.09	0.85–1.40
Gastrointestinal	256	179	1.28	0.97–1.68
Neurological	**468**	**567**	**1.54**	**1.26–1.88**
Psychological	**375**	**259**	**1.59**	**1.25–2.04**
Cancer	**263**	**185**	**1.43**	**1.08–1.89**
Group B	**N = 384**	**N = 230**		
Cardiovascular	278	154	1.47	0.83–2.60
Visual	115	55	1.02	0.57–1.84
Respiratory	177	81	1.57	0.90–2.74
Renal	63	20	1.74	0.79–3.80
Endocrine	112	68	0.96	0.53–1.76
Liver	38	20	0.66	0.24–1.81
Autoimmune	**102**	**43**	**2.14**	**1.05–4.35**
Gastrointestinal	74	28	1.75	0.82–3.74
Neurological	**214**	**87**	**2.01**	**1.16–3.47**
Psychological	**161**	**63**	**2.84**	**1.50–5.37**
Cancer	56	24	1.27	0.52–3.09

continued

TABLE 10-10 Continued

	Participants	Controls	Adjusted OR*	95% CI
Group C	**N = 337**	**N = 376**		
Cardiovascular	251	264	1.16	0.73–1.86
Visual	120	118	1.43	0.93–2.20
Respiratory	159	139	1.27	0.85–1.92
Renal	59	52	1.17	0.68–2.00
Endocrine	128	133	0.78	0.50–1.20
Liver	16	32	0.47	0.20–1.07
Autoimmune	68	73	1.23	0.75–2.01
Gastrointestinal	**72**	**66**	**1.97**	**1.17–3.32**
Neurological	175	166	1.16	0.77–1.75
Psychological	90	89	1.12	0.70–1.79
Cancer	69	60	1.35	0.79–2.32
Group D	**N = 411**	**N = 498**		
Cardiovascular	286	333	1.06	0.71–1.59
Visual	131	144	1.18	0.80–1.74
Respiratory	169	178	1.30	0.90–1.88
Renal	63	56	1.65	0.98–2.72
Endocrine	131	157	1.08	0.73–1.62
Liver	28	38	1.09	0.57–2.06
Autoimmune	83	98	0.97	0.61–1.54
Gastrointestinal	59	68	1.07	0.65–1.75
Neurological	184	221	1.04	0.72–1.50
Psychological	**121**	**94**	**2.04**	**1.34–3.09**
Cancer	71	59	1.40	0.86–2.28

NOTE: Cardiovascular: hypertension, coronary heart disease, heart attack, angina, other heart condition, stroke; Visual: cataract/lens problems, conjunctivitis; Respiratory: sinusitis, chronic bronchitis, emphysema, asthma; Renal: kidney failure, bladder infection; Endocrine: pancreatitis, diabetes, gallstones, thyroid condition; Liver: hepatitis B, hepatitis C, any other hepatitis, cirrhosis; Autoimmune: rheumatoid arthritis, lupus, multiple sclerosis; Gastrointestinal: Crohn's disease, stomach/peptic ulcer, ulcerative colitis; Neurologic: neuropathy, seizures, Parkinson's, amyotrophic lateral sclerosis, other neurodegenerative disease, migraines, hearing loss; Psychologic: depression, schizophrenia/psychosis, manic depressive disorder, post-traumatic stress disorder. Sleep apnea, anemia, chronic fatigue syndrome, and dermatitis/eczema/psoriasis did not fit into any categories. Statistically significant odds ratios in bold.

*Adjusted for age, race, pay grade, smoking, drinking, and body mass index.

Based on adjusted OR estimates, in group A there were significantly more cardiovascular, respiratory, renal, endocrine, gastrointestinal, neurological, and psychological medical conditions reported by participants than controls; in group B, significantly more respiratory, renal, autoimmune, gastrointestinal, neurological, and psychological conditions reported by participants; for group C, significantly more respiratory and neurological conditions; and in group D, significantly more psychological conditions. Most adjusted ORs were under 2.0. Respiratory conditions were reported at significantly higher rates among participants in all analysis groups but group D, and psychological conditions in all but group C.

Table 10-11 shows a distribution of self-reported cancer by type. Skin cancer and prostate cancer are generally reported with the highest prevalences.

Table 10-12 shows adjusted ORs for medical conditions as they appeared in the questionnaire, rather than grouped into broader categories. The sparser data make for larger confidence intervals (CIs) and some slightly higher ORs. All groups reported higher rates of neurodegenerative conditions, with relatively large and statistically significant ORs in groups A, B, and C. Table 10-13 shows a breakdown of these self-reported neurodegenerative

TABLE 10-11 Summary of Cancer Types by Group and Participant Status

	Participant	Control
Group A	(N = 263)	(N = 185)
Skin	15.2% (40)	12.4% (23)
Prostate	12.5% (33)	19.5% (36)
Colon	4.2% (11)	2.7% (5)
Lung	2.3% (6)	3.8% (7)
Other	6.1% (16) (includes 3 kidney, 4 leukemia, 2 bladder, 2 multiple myeloma, 2 NHL, 1 liver, 2 testicular)	7.0% (13) (includes 1 esophageal, 3 kidney, 2 leukemia, 2 NHL, 2 bone, 1 bladder, 1 lip, 1 throat)
Unspecified	59.6% (157)	66.1% (101)
Group B	(N = 56)	(N = 24)
Skin	17.9% (10)	37.5% (9)
Prostate	8.9% (5)	4.2% (1)
Colon	3.6% (2)	8.3% (2)
Lung	5.4% (1)	8.3% (2)
Other	7.5% (3) (includes 1 kidney, 1 bladder, 1 testicular)	25.0% (6) (includes 3 bladder, 1 liver, 1 throat, 1 testicular)
Unspecified	62.5% (35)	16.7% (4)
Group C	(N = 69)	(N = 60)
Skin	34.7% (24)	13.3% (8)
Prostate	7.2% (5)	16.7% (10)
Colon	1.4% (1)	3.3% (2)
Lung	0% (0)	3.3% (2)
Other	7.2% (5) (includes 2 bladder, 1 NHL, 1 kidney, 1 thyroid)	11.7% (7) (includes 3 bladder, 2 throat, 1 lymphoma, 1 leukemia)
Unspecified	49.3% (34)	51.7% (31)
Group D	(N = 71)	(N = 59)
Skin	16.9% (12)	13.6% (8)
Prostate	14.1% (10)	8.5% (5)
Colon	0% (0)	5.1% (3)
Lung	2.8% (2)	3.4% (2)
Other	2.8% (2) (includes 1 NHL, 1 bladder)	8.5% (5) (includes 2 throat, 1 kidney, 1 leukemia, 1 testicular)
Unspecified	63.4% (45)	61.0% (36)

NOTE: NHL = non-Hodgkin's lymphoma.

conditions. Most of the entries were unspecified, some overlap the categories in Table 10-12 (e.g., neuropathy), and the inclusion of conditions such as arthritis calls into doubt the utility of these data for further analyses.

Table 10-14 shows self-reported symptoms, rather than medical conditions, for participants and controls, along with adjusted ORs. In contrast to the data on medical conditions, nearly every symptom is reported at higher prevalence among participants than nonparticipants, even though not all differences are statistically significant. Among these is included "earlobe pain," an item without a clear medical basis, included to obtain data on possible overreporting of medical problems.

TABLE 10-12 Ungrouped Medical Conditions by Analysis Group, Comparing Participants to Controls (Navy and Marine Only)

Analysis Group and Medical Condition	Participants (N = 1,548)	Controls (N = 1,326)	Adjusted OR for Age, Race, Pay Grade, Smoking, Drinking, and BMI	95% CI
Group A	**N**	**N**		
Hypertension	949	766	1.24	1.00–1.53
Coronary heart disease	**338**	**242**	**1.30**	**1.01–1.68**
Heart attack	265	186	1.23	0.93–1.62
Angina	**374**	**261**	**1.31**	**1.02–1.67**
Other heart condition	157	112	1.59	0.61–4.13
Cataracts/eye lens	497	397	1.14	0.92–1.42
Conjunctivitis	**85**	**36**	**2.85**	**1.54–5.25**
Sinusitis	**455**	**290**	**1.63**	**1.30–2.04**
Chronic bronchitis	**230**	**156**	**1.56**	**1.15–2.12**
Emphysema	106	139	1.28	0.89–1.83
Asthma	157	115	1.20	0.85–1.69
Kidney failure	16	13	0.78	0.22–2.75
Bladder infection	**235**	**148**	**1.48**	**1.09–1.99**
Pancreatitis	33	28	1.17	0.59–2.31
Diabetes	363	279	1.24	0.96–1.59
Gallstones	163	110	1.15	0.82–1.61
Hepatitis B	37	25	0.88	0.41–1.86
Hepatitis C	26	23	0.91	0.42–1.97
Any other hepatitis	46	37	0.85	0.50–1.47
Cirrhosis	33	23	1.54	0.73–3.26
Rheumatoid arthritis	303	244	1.06	0.82–1.37
Lupus	14	10	0.96	0.32–2.88
Multiple sclerosis	5	4	0.91	0.06–14.63
Crohn's disease	13	9	1.43	0.46–4.1
Stomach/peptic ulcer	214	154	1.24	0.92–1.67
Ulcerative colitis	51	44	0.94	0.53–1.66
Hearing loss	**567**	**405**	**1.31**	**1.06–1.61**
Migraines	**171**	**112**	**1.86**	**1.28–2.71**
Stroke	107	71	1.27	0.82–1.96
Neuropathy	**320**	**203**	**1.69**	**1.30–2.20**
Seizures	32	34	1.05	0.53–2.09
Sleep apnea	319	222	1.31	1.00–1.70
Anemia	75	52	1.29	0.79–2.11
Thyroid condition	98	82	1.12	0.76–1.66
Cancer	**263**	**185**	**1.43**	**1.08–1.89**
Chronic fatigue syndrome	**100**	**41**	**2.55**	**1.51–4.30**
Depression	**350**	**234**	**1.68**	**1.30–2.16**
Schizophrenia	19	11	4.34	0.95–19.89
Manic depressive disorder	42	29	1.42	0.70–2.88
PTSD	105	88	0.99	0.65–1.50
Dermatitis, eczema, psoriasis	**269**	**135**	**1.83**	**1.36–2.45**
Parkinson's	9	5	2.39	0.48–12.02
ALS	2	1	1.70	0.15–18.89
Other neurodegenerative disease	**61**	**18**	**3.77**	**1.81–7.84**

TABLE 10-12 Continued

Analysis Group and Medical Condition	Participants (N = 384)	Controls (N = 230)	Adjusted OR for Age, Race, Pay Grade, Smoking, Drinking, and BMI	95% CI
Group B	N	N		
Hypertension	241	138	1.12	0.64–1.96
Coronary heart disease	74	37	1.28	0.59–2.79
Heart attack	57	25	1.29	0.56–2.97
Angina	**108**	**48**	**2.12**	**1.06–4.16**
Other heart condition	42	29	2.07	0.06–72.76
Cataracts/eye lens	101	46	1.01	0.55–1.87
Conjunctivitis	23	10	1.64	0.49–5.50
Sinusitis	121	53	1.86	1.00–3.44
Chronic bronchitis	68	32	1.68	0.70–4.04
Emphysema	41	14	1.21	0.43–3.42
Asthma	46	22	0.98	0.45–2.14
Kidney failure	6	0	—	
Bladder infection	61	20	1.66	0.78–3.65
Pancreatitis	12	3	3.43	0.35–34.09
Diabetes	88	50	0.87	0.45–11.66
Gallstones	27	20	1.22	0.43–3.72
Hepatitis B	15	4	1.77	0.19–16.33
Hepatitis C	14	8	0.62	0.17–2.34
Any other hepatitis	11	5	0.86	0.15–5.06
Cirrhosis	5	6	0.66	0.05–8.16
Rheumatoid arthritis	**99**	**41**	**2.28**	**1.09–4.74**
Lupus	4	1	—	
Multiple sclerosis	2	0	—	
Crohn's disease	2	1	0.92	0.08–11.04
Stomach/peptic ulcer	62	25	1.93	0.81–4.56
Ulcerative colitis	17	2	2.63	0.53–13.03
Hearing loss	**154**	**55**	**2.08**	**1.14–3.79**
Migraines	**70**	**25**	**3.15**	**1.16–8.58**
Stroke	23	12	1.05	0.30–3.67
Neuropathy	88	34	1.46	0.70–3.3
Seizures	18	6	1.14	0.28–4.69
Sleep apnea	91	52	0.98	0.51–1.86
Anemia	20	12	2.83	0.56–14.26
Thyroid condition	19	9	2.55	0.55–11.87
Cancer	56	24	1.27	0.52–3.09
Chronic fatigue syndrome	**31**	**12**	**9.27**	**1.12–76.80**
Depression	**136**	**56**	**2.55**	**1.33–4.91**
Schizophrenia	12	4	**1.68**	0.33–8.66
Manic depressive disorder	24	8	3.20	0.67–15.41
PTSD	**91**	**28**	**5.87**	**1.99–17.33**
Dermatitis, eczema, psoriasis	52	28	1.85	0.71–4.82
Parkinson's	6	0	—	
ALS	1	0	—	
Other neurodegenerative disease	18	4	2.85	0.31–25.93

continued

TABLE 10-12 Continued

Analysis Group and Medical Condition	Participants (N = 337)	Controls (N = 376)	Adjusted OR for Age, Race, Pay Grade, Smoking, Drinking, and BMI	95% CI
Group C	N	N		
Hypertension	211	232	1.06	0.69–1.65
Coronary heart disease	67	82	0.91	0.55–1.50
Heart attack	50	66	0.85	0.49–1.46
Angina	71	90	0.93	0.58–1.51
Other heart condition	36	38	0.64	0.06–6.61
Cataracts/eye lens	106	104	1.20	0.77–1.86
Conjunctivitis	23	19	2.52	0.98–6.47
Sinusitis	115	86	1.46	0.93–2.28
Chronic bronchitis	57	45	1.18	0.62–2.24
Emphysema	35	36	1.21	0.61–2.38
Asthma	42	32	1.44	0.74–2.82
Kidney failure	5	3	1.59	0.09–27.74
Bladder infection	56	50	1.14	0.66–1.97
Pancreatitis	13	8	1.81	0.49–6.69
Diabetes	80	90	0.68	0.41–1.13
Gallstones	41	39	0.82	0.43–1.55
Hepatitis B	5	11	0.33	0.08–1.36
Hepatitis C	4	10	0.40	0.08–2.05
Any other hepatitis	6	9	0.97	0.29–3.29
Cirrhosis	4	6	0.28	0.03–2.61
Rheumatoid arthritis	66	69	1.30	0.78–2.15
Lupus	1	4	0.35	0.04–3.45
Multiple sclerosis	0	0	—	
Crohn's disease	4	3	1.68	0.28–10.26
Stomach/peptic ulcer	**57**	**60**	**1.79**	**1.04–3.08**
Ulcerative colitis	**19**	**7**	**4.99**	**1.29–19.30**
Hearing loss	119	121	0.99	0.64–1.53
Migraines	45	41	1.21	0.66–2.24
Stroke	18	21	1.46	0.60–3.53
Neuropathy	70	62	1.31	0.79–2.19
Seizures	14	9	2.02	0.57–7.15
Sleep apnea	74	73	0.97	0.57–1.65
Anemia	28	21	1.69	0.76–3.77
Thyroid condition	25	23	1.17	0.52–2.65
Cancer	69	60	1.35	0.79–2.32
Chronic fatigue syndrome	26	25	1.65	0.78–3.60
Depression	86	84	1.19	0.74–1.91
Schizophrenia	2	9	0.16	0.02–1.77
Manic depressive disorder	8	9	0.72	0.14–3.58
PTSD	17	27	0.54	0.20–1.48
Dermatitis, eczema, psoriasis	66	49	1.71	0.96–3.03
Parkinson's	6	8	0.79	0.23–2.72
ALS	0	1	—	
Other neurodegenerative disease	17	6	3.25	0.84–12.59

TABLE 10-12 Continued

Analysis Group and Medical Condition	Participants (N = 411)	Controls (N = 498)	Adjusted OR for Age, Race, Pay Grade, Smoking, Drinking, and BMI	95% CI
Group D	N	N		
Hypertension	254	290	0.92	0.62–1.35
Coronary heart disease	80	86	1.21	0.73–2.01
Heart attack	61	63	1.34	0.78–2.31
Angina	91	94	1.45	0.92–2.27
Other heart condition	48	41	0.95	0.12–7.86
Cataracts/eye lens	118	135	1.16	0.78–1.72
Conjunctivitis	22	22	0.96	0.42–2.22
Sinusitis	114	119	1.02	0.68–1.52
Chronic bronchitis	**66**	**54**	**1.91**	**1.08–3.38**
Emphysema	42	42	1.21	0.65–2.26
Asthma	41	52	1.33	0.75–2.37
Kidney failure	3	2	1.77	0.29–10.83
Bladder infection	61	54	1.68	0.99–2.87
Pancreatitis	6	20	0.28	0.07–1.02
Diabetes	85	108	1.17	0.75–1.83
Gallstones	27	35	0.79	0.39–1.61
Hepatitis B	9	19	0.73	0.27–1.96
Hepatitis C	5	9	1.00	0.26–3.86
Any other hepatitis	8	10	1.48	0.44–4.44
Cirrhosis	8	5	1.85	0.48–7.08
Rheumatoid arthritis	80	92	0.99	0.62–1.58
Lupus	4	2	4.14	0.42–41.20
Multiple sclerosis	4	5	1.67	0.36–7.70
Crohn's disease	3	1	2.25	0.20–25.20
Stomach/peptic ulcer	51	59	1.00	0.59–1.71
Ulcerative colitis	16	14	1.81	0.71–4.63
Hearing loss	122	147	1.01	0.68–1.51
Migraines	59	53	1.70	0.98–2.94
Stroke	24	32	0.67	0.28–1.58
Neuropathy	81	80	1.25	0.79–1.98
Seizures	10	11	2.05	0.59–7.18
Sleep apnea	101	92	1.43	0.91–2.24
Anemia	26	30	0.83	0.41–1.69
Thyroid condition	40	31	1.84	0.95–3.53
Cancer	71	59	1.40	0.86–2.28
Chronic fatigue syndrome	**29**	**21**	**2.46**	**1.19–5.10**
Depression	**115**	**88**	**1.91**	**1.25–2.93**
Schizophrenia	8	2	8.04	0.95–68.01
Manic depressive disorder	18	10	2.49	0.81–7.64
PTSD	**32**	**30**	**2.06**	**1.04–3.09**
Dermatitis, eczema, psoriasis	79	70	1.52	0.93–2.47
Parkinson's	2	2	—	
ALS	0	0	—	
Other neurodegenerative disease	17	14	2.74	1.00–7.53

NOTE: PTSD = post-traumatic stress disorder; ALS = amyotrophic lateral sclerosis (Lou Gehrig disease). Statistically significant odds ratios in bold.

TABLE 10-13 Reports of Other Neurodegenerative Diseases by Participant and Group Status

	Participant	Control
Group A	(N = 61) 46 unspecified, 8 spinal problems/degenerative discs, 1 meningitis, 1 myasthenia gravis, 1 dementia, 1 erectile dysfunction, 1 diverticulitis, 1 gout, 1 polio	(N = 18) 13 unspecified, 2 spinal/degenerative discs, 1 arthritis, 1 dementia, 1 neuropathy
Group B	(N = 18) 8 unspecified, 7 spinal problems/degenerative discs, 2 arthritis, 1 diverticulitis	(N = 4) 1 unspecified, 2 osteoporosis, 1 anxiety
Group C	(N = 17) 12 unspecified, 3 tremors, 1 hearing loss, 1 attention deficit disorder	(N = 6) 4 unspecified, 1 dementia, 1 neuropathy
Group D	(N = 17) 15 unspecified, 1 arthritis, 1 anxiety	(N = 14) 8 unspecified, 2 neuropathy, 1 myasthenia gravis, 1 Guillan-Barre syndrome, 1 brain tumor, 1 spinal problem

Hospitalizations Since Discharge from Active Duty

Table 10-15 shows self-reported data on hospitalizations since discharge from active duty. Roughly two-thirds of participants and controls reported a hospitalization, across all analysis groups; there were no statistically significant differences. Data on the mean number of hospitalizations (those not reporting a hospitalization were assigned zero number of hospitalizations) showed nearly equal rates between participants and controls across analysis groups, with no statistically significant differences.

Birth Defects

Table 10-16 shows data on self-reported birth defects. To calculate these rates, we divided the number of subjects who reported children with birth defects by the number of "eligible fathers." Eligible fathers are defined as men who answered "yes" to the following question, "Have you ever been the biological father of any pregnancy, regardless of whether there was a live birth outcome from that pregnancy?" and also answered one or more to the following question, "How many of the pregnancies ended in live births, even if the infant died shortly after birth?"

Table 10-16 shows that roughly 10–16 percent of participants reported birth defects among their children born live. The corresponding rate among participant subjects was larger in group D, while the mean number of children born with birth defects showed no statistically significant differences.

REFERENCES

O'Donnell, W. E., C. B. DeSoto, and J. L. DeSoto. 1993. Validity and reliability of the revised Neuropsychological Impairment Scale (NIS). *Journal of Clinical Psychology* 49:372-382.

Payne, S. M., A. Lee, J. A. Clark, W. H. Rogers, D. R. Miller, K. M. Skinner, X. S. Ren, and L. E. Kazis. 2005. Utilization of medical services by Veterans Health Study (VHS) respondents. *Journal of Ambulatory Care Management* 28:125-140.

TABLE 10-14 Numbers of Symptoms by Group Comparing Participants to Controls, with Adjusted Odds Ratios (ORs)

	Participants	Controls	Adjusted OR*	95% CI
Group A	(N = 1,548)	(N = 1,326)		
Severe headache	**201**	**115**	**1.73**	**1.25–2.38**
Diarrhea	**284**	**143**	**1.90**	**1.43–2.52**
Rash/skin ulcer	**282**	**137**	**2.00**	**1.51–2.63**
Sore throat	**309**	**168**	**1.58**	**1.21–2.06**
Frequent bladder infections	61	32	1.55	0.84–2.85
Cough	**511**	**323**	**1.62**	**1.30–2.01**
Fever	150	90	1.42	1.00–2.01
Unexplained hair loss	71	32	1.77	1.00–3.15
Earlobe pain	53	35	1.15	0.65–2.01
Sleepy all the time	**321**	**207**	**1.52**	**1.16–1.98**
Night sweats	**373**	**253**	**1.34**	**1.05–1.70**
Chest pain	**325**	**191**	**1.79**	**1.38–2.34**
Unusual muscle pains	**483**	**286**	**1.77**	**1.41–2.21**
Shortness of breath	**592**	**414**	**1.53**	**1.24–1.89**
Trouble sleeping	**625**	**416**	**1.50**	**1.22–1.84**
Unusual fatigue	**444**	**309**	**1.42**	**1.13–1.78**
Forgetfulness	**561**	**399**	**1.71**	**1.38–2.12**
Confusion	**214**	**130**	**1.71**	**1.25–2.35**
Group B	(N = 384)	(N = 230)		
Severe headache	88	27	1.63	0.77–3.44
Diarrhea	**91**	**28**	**2.41**	**1.10–5.28**
Rash/skin ulcer	74	33	1.35	0.67–2.69
Sore throat	85	39	1.36	0.70–2.62
Frequent bladder infections	3	20	3.06	0.36–26.05
Cough	132	58	1.50	0.85–2.64
Fever	51	19	2.76	0.99–7.73
Unexplained hair loss	27	12	3.40	0.69–16.80
Earlobe pain	17	13	1.01	0.32–3.17
Sleepy all the time	**124**	**37**	**3.73**	**1.71–8.41**
Night sweats	**149**	**52**	**3.10**	**1.58–6.07**
Chest pain	106	46	1.59	0.83–3.06
Unusual muscle pains	160	61	1.35	0.77–2.37
Shortness of breath	154	73	1.65	0.94–2.91
Trouble sleeping	**199**	**89**	**1.86**	**1.08–3..18**
Unusual fatigue	**164**	**52**	**2.87**	**1.55–5.30**
Forgetfulness	**176**	**71**	**2.45**	**1.34–4.74**
Confusion	**96**	**31**	**3.79**	**1.61–8.94**

continued

TABLE 10-14 Continued

	Participants	Controls	Adjusted OR*	95% CI
Group C	(N = 337)	(N = 376)		
Severe headache	46	49	1.14	0.63–2.07
Diarrhea	68	66	1.28	0.76–2.15
Rash/skin ulcer	**73**	**48**	**2.20**	**1.29–3.76**
Sore throat	76	64	1.32	0.79–2.20
Frequent bladder infections	15	20	0.75	0.29–1.95
Cough	115	105	1.24	0.80–1.92
Fever	29	27	1.77	0.82–3.82
Unexplained hair loss	13	15	1.97	0.62–6.26
Earlobe pain	11	11	0.90	0.77–3.03
Sleepy all the time	81	78	1.07	0.66–1.76
Night sweats	74	87	1.07	0.66–1.72
Chest pain	71	79	1.02	0.62–1.68
Unusual muscle pains	**132**	**90**	**2.51**	**1.62–3.90**
Shortness of breath	135	143	1.15	0.76–1.75
Trouble sleeping	152	141	1.48	0.98–2.22
Unusual fatigue	**119**	**102**	**1.88**	**1.21–2.92**
Forgetfulness	**136**	**123**	**1.73**	**1.13–2.64**
Confusion	53	56	1.35	0.73–2.50
Group D	(N = 411)	(N = 498)		
Severe headache	**63**	**50**	**1.81**	**1.07–3.07**
Diarrhea	63	78	1.10	0.69–1.77
Rash/skin ulcer	**84**	**58**	**2.16**	**1.37–3.42**
Sore throat	**74**	**58**	**1.70**	**1.05–2.78**
Frequent bladder infections	16	14	1.74	0.67–4.47
Cough	**133**	**132**	**1.51**	**1.03–2.22**
Fever	36	34	1.28	0.71–2.34
Unexplained hair loss	**15**	**11**	**3.89**	**1.22–12.38**
Earlobe pain	14	13	1.48	0.57–3.87
Sleepy all the time	**98**	**73**	**2.03**	**1.28–3.23**
Night sweats	95	95	1.36	0.89–2.08
Chest pain	**82**	**74**	**1.61**	**1.01–2.55**
Unusual muscle pains	**133**	**110**	**1.85**	**1.25–2.75**
Shortness of breath	**169**	**143**	**1.81**	**1.23–2.66**
Trouble sleeping	**172**	**164**	**1.70**	**1.16–2.48**
Unusual fatigue	**135**	**116**	**1.72**	**1.16–2.54**
Forgetfulness	**148**	**143**	**1.68**	**1.15–2.46**
Confusion	**68**	**50**	**2.10**	**1.23–3.56**

Note: Statistically significant odds ratios in bold.
*Adjusted for age, race, and pay grade.

TABLE 10-15 Proportion of Subjects Hospitalized Since Discharge from Active Duty Comparing Participants to Controls, with Adjusted Odds Ratios (ORs)

	Participants	Controls	Adjusted OR*	95% CI
Group A	68.0% (484)	66.0% (396)	1.10	0.87–1.39
Group B	65.3% (124)	62.5% (91)	1.04	0.64–1.69
Group C	71.2% (116)	67.9% (114)	1.20	0.74–1.95
Group D	69.3% (133)	64.4% (152)	1.19	0.78–1.81
Mean # of Hospitalizations	Participants	Controls	Adjusted Means (95% CI) Participants	Adjusted Means (95% CI) Controls
Group A	3.18	3.23	2.82 (2.17–3.47)	2.86 (2.17–3.55)
Group B	3.69	3.23	3.17 (2.24–4.10)	3.45 (2.30–4.59)
Group C	3.69	3.61	3.95 (2.40–5.49)	4.12 (2.47–5.77)
Group D	2.81	3.40	2.97 (1.62–4.35)	2.35 (0.86–3.84)

NOTE: Percentages are based on those who answered question—not total number.
*Adjusted for age, race, and pay grade.

TABLE 10-16 Birth Defects Among Those Who Fathered a Child Comparing Participants to Controls, with Adjusted Odds Ratios (ORs)

	Participants	Controls	Adjusted OR*	95% CI
Group A	10.8% (59)	13.0% (61)	0.82	0.56–1.21
Group B	14.8% (19)	16.5% (19)	1.11	0.55–2.27
Group C	16.1% (20)	9.3 (12)	1.02	0.96–1.09
Group D	**13.3% (20)**	**5.6% (10)**	**2.42**	**1.07–5.48**
Mean # of Birth Defects	Participants	Controls	Adjusted Means (95% CI) Participants	Adjusted Means (95% CI) Controls
Group A	0.14	0.15	0.10 (0.03–0.18)	0.12 (0.04–0.200
Group B	0.19	0.25	0.19 (0.06–0.31)	0.21 (0.05–0.37)
Group C	0.18	0.14	0.19 (0.04–0.35)	0.16 (-0.01–0.32)
Group D	0.18	0.08	0.28 (0.10–0.45)	0.18 (-0.01–0.37)

NOTE: Percentages and means are based on those who answered and had fathered a child. Statistically significant odds ratios in bold.
*Adjusted for age, race, and pay grade.

11

Discussion

THE STUDY'S STRENGTHS AND WEAKNESSES

Strengths

The quality of a study of this magnitude and complexity is not easily characterized. The strengths of this study include a relatively large initial cohort of participants and an equally large cohort of nonparticipant controls. After much effort, most of the members of these two cohorts were identified well enough to permit a relatively complete follow-up. With less than 6 percent of subjects lacking Social Security numbers (SSN), except for group B, we can be fairly confident that the combination of Department of Veterans Affairs (VA) and National Death Index (NDI) mortality follow-up is quite complete (Sohn et al., 2006).

Eventually, we were also able to obtain addresses and telephone numbers on a large majority of potential health survey respondents. We had a reasonably broad health survey instrument that included the SF-36 assessment of general health, allowing comparisons to national, normed data. The entire mail questionnaire, accompanying material, and telephone interview script (such as veteran service organizations' [VSO] endorsement letter) were reviewed and approved by the National Academies' Committee to Review Studies of Human Subjects committee.

Shortcomings: Response Rates

On the other side of the ledger are the study's shortcomings. Primary among these is the low response rate to the health survey, only about 53 percent. Of additional concern is the fact that the response rate of participants (61 percent) was higher than that of controls (47 percent). Part of the reason for these low response rates was our inability to contact potential respondents. This is not a problem for our study alone. A very large survey of recently separated military veterans estimated that roughly 15 percent were not contactable (Ryan et al., In press), and we were further handicapped because we were trying to locate and trace a cohort of veterans who had been out of service for decades. On the other hand, our pilot study using FedEx delivery seemed to indicate that lack of response was probably not due to a bad address.

Although we saw few differences between survey respondents and nonrespondents when we examined available demographic data, the lack of evidence of differences is not very strong evidence of a lack of differences. With an overall response rate of 53 percent, we can not be confident that we have a complete picture of the health

of the Project SHAD (Shipboard Hazard and Defense) participants or their controls. Yet the link between nonresponse rates and nonresponse bias is far from simple. A recent study of the link between nonresponse rates and nonresponse bias looked at 30 articles that reported 235 separate estimates of nonresponse rates (Groves, 2006). The mean nonresponse rate was 35 percent, fairly close to the rate among the Project SHAD participants in our study. Further analyses showed that a survey's nonresponse rate was not in itself a good predictor of nonresponse bias, but that "nonresponse biases should be expected to vary across estimates within the same survey. The biases are heavily influenced by the covariance between response propensities and particular survey variables" (Groves, 2006). Thus, we cannot conclude very much about nonresponse bias based on our survey nonresponse rate of 39 percent for Project SHAD participants and 53 percent for controls.

One further complication that might have affected the nonresponse rate was the use of three different contact letters, depending on potential Project SHAD exposure, a requirement of the National Academies' institutional review board (IRB). Although there is a clear argument for the use of three different contact letters, so that survey subjects who were previously unaware of their potential Project SHAD exposures were made aware of them, we can not be sure that the use of three different letters did not unwittingly contribute to differential responses. Certainly, the response rate for controls was lower than for participants, and this might have been due partly to the contact letter.

Shortcomings: Survey Content

We were further handicapped in our health survey by a lack of well-defined end points for study. Although we commissioned a series of literature reports on the potential health effects of the various agents, we did not identify a clear, unambiguous list of potential health end points whose presence might be attributable to earlier exposure to some Project SHAD agent, either active agent or simulant. We also made a survey of the classified material on Project SHAD, convincing ourselves that nothing essential had been overlooked. In the end, we mounted a fairly comprehensive survey of general health and of a wide variety of medical diagnoses and symptoms. A downside to the large number of questionnaire items is that there are a large number of outcomes to examine statistically, creating a problem with multiple comparisons. That is, the more statistical tests one performs, the greater the chance of observing so-called statistically significant differences that are actually due to chance. We dealt with this problem in part by using a number of summary measures, in effect reducing the number of statistical comparisons. Nonetheless, the large number of statistical comparisons increases the odds for chance findings, and following what we believe is current good epidemiologic practice, we did not adjust for multiple comparisons.

We had the additional complication of a multimode health survey, consisting of a mail questionnaire and a telephone interview. We also saw some substantial differences between mail questionnaire and telephone interview respondents, including a statistically significant difference in SF-36 mental component summary (MCS) score. In a national survey of health status, investigators compared mail and telephone survey respondents, finding that self-reported health measures, including SF-36 scales, were worse for mail than for telephone respondents (McHorney et al., 1994), a finding that mirrors our own.

Many investigators have studied the shortcomings of self-reported health data, typically by comparing self-reported data to similar data from another source, such as medical records. A recent study of a rural Canadian population found that health survey information agreed well with medical chart information for diabetes, heart problems, hypertension, and breathing problems (Voaklander et al., 2006). Poor agreement was observed for diagnoses of depression, back problems, eye problems, stroke, walking problems, and bone and joint problems. These findings were similar to those in other studies. A Mayo Clinic study found good agreement between health questionnaire responses and medical records for diabetes, hypertension, myocardial infarction, and stroke, but not for heart failure (Okura et al., 2004). In this study, factors associated with higher agreement included age under 65 years and education greater than 12 years. We should note that because we used self-reported data from both Project SHAD participants and controls, we expect that the shortcoming of self-reported data would apply to both cohorts and would thus not materially affect our comparisons.

Finally, because there was concern about an overreporting of symptoms, we included an item on earlobe pain, a symptom not thought to have a physiologic basis. We found rates ranging from 3–6 percent, with higher (but not

statistically significant) rates among participants. A study of Gulf War veterans (Knoke et al., 2000) found a rate of self-reported earlobe pain of 1.2 percent among deployed Gulf War veterans and a rate of 0.2 percent among nondeployed Gulf War–era veterans, both lower than our reported rates.

Summary and Interpretation of Results

Mortality

We found no statistically significant difference in all-cause mortality between participants and controls in any of the four analysis groups, nor for the total comparison. Indeed, hazard ratios for all-cause mortality were less than 1.0 in group C and very close to 1.0 in groups A and D. However, heart disease mortality was significantly elevated overall and in groups A and B. The lack of a biological basis for this finding, together with the lack of data on cardiovascular risk factors, makes this finding difficult to interpret. There was a significant elevation of cancer mortality among group B participants as well, with the same difficulties in interpretation. Generally, hazard ratios associated with Project SHAD participation were not so large as for other significant factors, such as pay grade, but Marines in group B had significantly higher mortality than did Navy subjects. All-cause standardized mortality ratios (SMRs) were significantly greater than 100 for all participants and all controls combined, but were close to 100 for all participant and control analysis groups save for group B participants, indicating that mortality was close to that expected in the U.S. general population. Cancer SMRs were statistically significantly higher for group A controls and all controls, with most of this excess due to lung cancer; SMRs for non-cancer respiratory disease were not significantly different from 100 in these two groups. SMRs for injuries and external causes of death were also significantly low among all participants. We must note that causes of death were not available for deaths prior to 1979, and so our cause-specific mortality analyses are incomplete.

Morbidity: SF-36

In general, although many differences in SF-36 summary scores between participants and controls were statistically significant, most were generally small, around 1 to 2 points. Interestingly, the smallest differences were seen in group C, the only group with potential exposure to active agents. SF-36 summary scores in our study were smaller than age- and sex-specific national norms, indicating that our subjects reported themselves to be less well than did comparable U.S. males. In contrast, veterans aged 50–64 in the Veterans Health Study, who were receiving VA outpatient care, had an average physical component summary (PCS) score of 37.2 and an average MCS score of 47.0 (Payne et al., 2005), both of which are substantially lower than the participant or control scores in our study.

We made two attempts to look at level of exposure, one in group A and one in group B. Group A participants made up the largest of the groups and contained only men with potential exposure to either *Bacillus globigii* (BG) simulant agent or methylacetoacetate (MAA). The conduct of the tests made it possible to estimate independently the health effects associated with BG and with MAA. Once again, we found small but statistically significant differences, but when we attempted to analyze the effect of the number of tests as a proxy for exposure, there was no clear gradient. We further looked at the individual numbers of tests at which a participant might have been exposed to either BG or MAA and again found no clear exposure gradient. However, we did find statistically significant coefficients for linear trend for both BG and MAA for both PCS and MCS scores, evidence that PCS and MCS scores were statistically significantly lower with each additional test in which there was potential exposure to either BG or MAA. On the other hand, when estimating the effects of BG and MAA exposure controlling for the total number of Project SHAD tests, the statistically significant effects of BG and MAA all disappeared, whereas the differences in SF-36 summary scores by total number of tests was statistically significant. It appears that for group A participants, the number of Project SHAD tests is a more important factor than putative exposure to either agent.

Only for a subsample of group B participants did we have individual exposure data that were recorded (ordinal) levels of contamination by trioctyl phosphate (TOF), a simulant with low toxic potential. We were unable to

obtain precise, numeric exposure estimates and so analyzed these data by arbitrarily assigning numeric doses to the ordinal levels measured (e.g., trace = 0.5, very light = 1.0, and so on). We found no evidence that our ordinal exposure levels were associated with either SF-36 summary health measures.

Morbidity: Other Outcomes

Project SHAD participants across all groups had higher somatization scores than did controls, based on a total of 12 items, with adjusted participant scores ranging from 2.2 to 3.8 and control scores ranging from 1.7 to 3.0. In a study of military volunteers at Edgewood Arsenal (many from the Vietnam era) exposed to anticholinesterase agents (Page, 2003), the average somatization score for a 20-item scale was 5.15, with military volunteers exposed to other agents having a score 5.00, and volunteers unexposed to chemical agents having an average score of 5.33. If we prorate the Edgewood results to estimate a 12-item score, their prorated scores would have averaged around 3.0. Thus, the somatization scores we observed among Project SHAD participants were close to those in the earlier study.

We also saw statistically significantly higher adjusted memory and attention problem scores among participants in all but group C, with adjusted participant scores ranging from 8.0 to 11.6 and control scores ranging from 4.5 to 7.2. In the same study of military volunteers at Edgewood Arsenal exposed to anticholinesterase agents (Page, 2003), the average memory and attention scores were 7.2 and 7.7, respectively. The average scores for military volunteers exposed to other agents were 7.5 and 8.3, respectively, while volunteers unexposed to chemical agents had an average score of 7.2 and 7.7. Compared to these Edgewood results, the scores for Project SHAD participants were slightly higher, while those for controls were roughly the same, with the exception of the group B participants. In the Edgewood study, differences attributable to experimental exposure between the anticholinesterase and control subjects ranged from –0.60 to +0.31, while differences attributable to nonexperimental exposure were substantially larger, 0.92 and 1.12. The differences we observed between Project SHAD participants and controls are more in line with the nonexperimental differences seen in the Edgewood study.

Project SHAD participants reported higher prevalence rates of medical conditions than did controls, although not all these differences were statistically significant. Respiratory conditions were significantly higher in all groups but D, and psychological conditions in all groups but C. All participant groups reported higher rates of neurodegenerative disease, with some moderately high adjusted odds ratios, but most of these conditions were unspecified, making interpretation difficult. Project SHAD participants similarly reported higher prevalence levels for symptoms of many kinds. This includes higher rates of earlobe pain, an item without a clear medical basis. There were no statistically significant differences in self-reported hospitalization rates between participants and controls, and rates of self-reported birth defects were similar for participants and controls except for group D, with a 2.4 odds ratio. We note, however, that the self-reported rate of birth defects among group D participants was similar to the rate in other groups of participants, and thus the higher odds ratio is attributable to a markedly lower self-reported rate among group D controls. We did not have sufficient data to do an agent-specific analysis in group D.

Conclusions

In conclusion, we saw no difference in all-cause mortality between Project SHAD participants and nonparticipant controls, and although participants had a statistically significantly higher risk of death due to heart disease, that lack of cardiovascular risk factor data as well as biological plausibility makes this latter difference difficult to interpret. We found overall deaths rates that were higher in both all participants and all controls than the U.S. population, as well as a higher cancer death rate among all controls, mostly attributable to lung cancer. We also found overall worse reported health in participants, but no consistent, specific, clinically significant patterns of ill health. Both PCS and MCS scores of the SF-36 were lower among participants than controls, but these differences were small in magnitude. Group C, the only group with potential exposure to active chemical or biological agents, reported the smallest differences. We also saw small but statistically significant increases in self-reported memory and attention problems as well as somatization scores. Project SHAD participants reported higher levels

of neurodegenerative medical conditions, but most of these were of an unspecified nature, and participants also reported nearly uniformly higher rates of symptoms, including a symptom without an apparent medical basis, thus raising the question of reporting bias. There were no significant differences in self-reported hospitalization, and in one group (group D), participants reported a higher rate of birth defects than controls; however, this significant difference can be attributed to an unusually low control rate rather than a high rate among participants.

While we have found no clear evidence of specific health effects that are associated with Project SHAD participation, we must remark that this does not constitute clear evidence of a lack of health effects. Although the sample seems large, some of the exposure groups are indeed rather moderate in size, and the lack of specific a priori hypotheses of health effects becomes a real limitation. If there were, for example, very specific, targeted effects on a particular organ system, but with a relatively low prevalence, our relatively coarse grouping of health outcomes might well have missed finding such a specific effect.

Were future research to be conducted, several items could be of potential interest. First, some way to reduce nonresponse bias should be considered. The collection of clinical, rather than self-report data, might also be contemplated. Included in this might be a records-based study of birth defects in these subjects; because many Project SHAD ships operated out of Pearl Harbor, data from the Hawaii Birth Defects Program might prove useful. Also of potential interest would be the collection and analysis of cause of death data for early (pre-1979) deaths. Other, similar possibilities would include linkages with population-based cancer registries, the VA's inpatient database (PTF), and with the Medicare database for subjects 65 years of age or older. These same data sources would provide information to validate self-reported health outcomes. Another way to deal with nonresponse bias would be to mount a separate survey of nonrespondents.

A better method of dealing with exposure data is always welcome in this kind of study, but the lack of exposure-related difference in our group A and group B analyses shows that this may not yield important results. Finally, further analyses of already collected data could be undertaken, especially if some ancillary risk factor data were added, such as service in Vietnam and combat service in Vietnam. These kinds of analyses might also be focused on the group B Marines in this study, who had significantly higher mortality than Navy personnel, adjusting for age, participation status, race, and pay grade. Marines in group B also had significantly lower PCS and MCS scores, with a large (more than 9-point) difference in MCS scores. Although these latter findings are not related to the original charge of the study, to examine the effects of Project SHAD participation per se, they may warrant some further investigations.

REFERENCES

Groves, R. M. 2006. Nonresponse rates and nonresponse bias in household surveys, *Public Opinion Quarterly* 70:646-675.

Knocke, J. D., T. C. Smith, G. C. Gray, K. S. Kaiser, and A. W. Hawksworth. 2000. Factor analysis of self-reported symptoms: Does it identify a Gulf War syndrome? *American Journal of Epidemiology* 152:379-388.

McHorney, C. A., M. Kosinski, and J. E. Ware, Jr. 1994. Comparisons of the cost and quality of norms for the SF-36 health survey collected by mail versus telephone interview: Results from a national survey. *Medical Care* 32:551-567.

Okura, Y., L. H. Urban, D. W. Mahomey, S. J. Jacobsen, and R. J. Rodeheffer. 2004. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *Journal of Clinical Epidemiology* 57:1096-1103.

Page, W. F. 2003. Long-term health effects of exposure to sarin and other anticholinesterase chemical warfare agents. *Military Medicine* 168:239-245.

Payne, S. M., A. Lee, J. A. Clark, W. H. Rogers, D. R. Miller, K. M. Skinner, X. S. Ren, and L. E. Kazis. 2005. Utilization of medical services by Veterans Health Study (VHS) respondents. *Journal of Ambulatory Care Management* 28:125-140.

Ryan, M. A. K., T. C. Smith, B. Smith, P. D. Amoroso, E. J. Boyko, G. C. Gray, G. D. Gackstetter, J. R. Riddle, T. S. Wells, G. R. Gumbs, T. E. Corbeil, and T. I. Hooper. (In press). Enrollment in the Millennium Cohort begins a 21-year contribution to understanding the impact of military service. *Journal of Clinical Epidemiology*.

Sohn, M., N. Arnold, C. Maynard, and D. M. Hynes. 2006. *Population Health Metrics* 4:2.

Voaklander, D., H. Thommasen, and A. Michalos. 2006. The relationship between health survey and medical chart review results in a rural population. *Social Indicators Research* 77:287-305.

Appendix A

Executive Summaries of Reports on Toxicological or Biological Agents

1. *Bacillus globigii* (BG)
2. Betapropiolactone (beta-propiolactone; BPL)
3. Bis Hydrogen Phosphite (BHP)
4. Calcofluor
5. *Coxiella burnetii* (CB; Q fever)
6. Diethylphthalate (DEP or D)
7. *Escherichia coli* [*E. coli*]
8. Methyl Acetoacetate (MAA)
9. Phosphorus-32 [^{32}P]
10. Sarin
11. *Serratia marcescens* (SM)
12. Staphylococcal Enterotoxin Type B (SEB)
13. Sulfur Dioxide (SO_2)
14. Trioctyl Phosphate (TEHP or TOF)
15. *Pasteurella tularensis* (*Francisella tularensis*)
16. Uranine
17. VX Nerve Agent (VX)
18. Zinc Cadmium Sulfide (ZnCdS)

References

Bacillus globigii

Bacillus globigii (BG) has been called *B. subtilis* var *niger*, *B. licheniformis* and, most recently, *B. atrophaeus*. It is a Gram-positive, spore-forming, facultative anaerobe commonly found in dust, soil, and water. It is widely used as a biological tracer and has been shown to produce substances that exhibit antimicrobial activity. In Project SHAD, *B.globigii* was used to simulate biological warfare agents, because it was then considered a contaminant with little health consequence to humans.

BG is now considered a pathogen for humans. Most infections are associated with the experience of invasive trauma (e.g., catheters, surgery) and/or a debilitated health state; thus it is often encountered as a nosocomial pathogen. BG is also a well-known cause of food poisoning, resulting in diarrhea and vomiting. Infections are rarely known to be fatal, although fatal food poisoning has been reported. Ocular infections, bacteremia, sepsis/septicemia, ventriculitis, and peritonitis are the reported types of infection, and they are usually treated with antibiotics. Cases of long-term persistence or recurrence, or of extended latency, have not been found.

Psychogenic effects specifically of BG exposure are not reported. General psychogenic effects of perceived exposure to biological and chemical weapons are found in the supplement under this contract entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents." Prevention of exposure is conscientious hospital and food hygiene. Treatment involves various regimens of antibiotics; the literature provides inconsistent reports on resistance and efficacy of various antimicrobial agents.

Betapropiolactone

Betapropiolactone (beta-propiolactone; BPL) bears the chemical formula C_3-H_4-O_2 and is identified by the Chemical Abstracts Service Registry Number 57-57-8. It normally appears as a colorless liquid with a pungent irritating odor. Beta-propiolactone is soluble in water and miscible with acetone, chloroform, and ethanol.

Beta-propiolactone has been used as a disinfectant. Capable of sporicidal action, it has been employed in the making of vaccines and in the sterilization of surgical instruments and tissue grafts. Other medical sterilization uses have included the sterilization of blood plasma, water, nutrient broth, and milk. Beta-propiolactone has also served as a versatile intermediate in organic synthesis (acrylic acid and esters). In Project SHAD, it was used as a decontaminant.

Beta-propiolactone is quickly hydrolyzed, metabolized, and excreted by mammals. The hydrolysis products excrete rapidly as well. The main metabolite of beta-propiolactone is lactic acid; its main hydrolysis product is hydracrylic acid. The alkylating action of beta-propiolactone reacts with polynucleotides and DNA to form carboxylethyl derivatives, and this process is regarded as responsible for the genotoxicity characteristic of the compound.

Beta-propiolactone is a significant irritant to several systems and has shown permanent effects on the eye, liver, and kidney. Since the 1960s awareness has grown of the compound's high tumorigenic, genotoxic, and carcinogenic toxicity in animals, which have been observed to occur even from single-dose administration. Human epidemiological, case-study, and in vivo experimental reports have not been found, however, except for reports of a series of Henry Ford Hospital volunteer experiments in the 1950s using beta-propiolactone as an anti-hepatitis blood plasma disinfectant and the testing in 1968 of beta-propiolactone as a disinfectant in reaginic sera administered for allergy studies. The Henry Ford studies reported that human acute and chronic risks from intravenous administration are negligible; the reaginic sera study found minor irritations, displayed vesicles, discoloration, and papules in the areas of human skin inoculation. Related animal studies at Henry Ford did find chronic cumulative toxicity in animals, manifested as weight loss and necrosis of kidney tubules and the liver.

In acute administration in animals, beta-propiolactone has proven an irritant to skin, eyes, and the respiratory and digestive systems. Dermal contact can elicit blisters and burns. Scarring, erythema, and hair loss have been found on mouse skin after 1–6 administrations of 0.8–100 mg of beta-propiolactone.

Ocular administration in rabbits has resulted in pain, miosis, and corneal opacity, which can become permanent. Respiratory exposure is associated with inflammation of the respiratory tract. Oral ingestion can cause stomach and mouth burns. Acute intravenous administration has resulted in liver necrosis and kidney tubular damage. Systemic

absorption may result in twitching and gasping, with convulsion and death at higher doses. Frequent urination, dysuria, and hematuria may also attend higher systemic doses.

Degradation products from the hydrolysis of beta-propiolactone have been tested. They have been found to be significantly less toxic than beta-propiolactone. A comparison of their LD_{50}s shows toxicity levels of the degradation products to be as much as 5–10 times less toxic than beta-propiolactone.

Beta-propiolactone is rated a confirmed animal carcinogen with unknown relevance to humans (Group A3) by the ACGIH (American Conference of Governmental Industrial Hygienists). The Threshold Limit Value (TLV) recommended by the ACGIH is 0.5 ppm (1.5 mg/m^3). The *NIOSH Pocket Guide to Chemical Hazards* considers beta-propiolactone to be a potential occupational carcinogen. The International Agency for Research on Cancer (IARC) regards beta-propiolactone as a possible human carcinogen (Group 2B) and cautions that a single-dose exposure is enough to pose a significant risk of cancer

Probably as a result of the fact that beta-propiolactone degrades rapidly in water and plasma, its tumorigenic effects appear to occur primarily around the initial site of exposure. Thus, in tested animals, benign and malignant skin tumors (papillomas, squamous cell carcinomas, keratocanthomas, melanomas; subcutaneous injection-site sarcomas, fibrosarcomas, adenocarcinomas, squamous cell carcinomas), nasal tumors, and forestomach tumors (squamous cell carcinomas) are the observed effects, related to dermal/subcutaneous, inhalational, and oral administration respectively. Meanwhile, beta-propiolactone has been ruled out as an agent causing central nervous system cancer in rats.

Single-dose administration has resulted in cancer induction in experimental animals. After single-dose administration of 100 mg beta-propiolactone on suckling mice 9–11 days after birth, lymphomas and hepatomas were induced. Single-dose exposures also have been genotoxic.

The genotoxicity of beta-propiolactone has been well studied. Genotoxicity testing indicates a wide range of effects, both in vivo and in vitro. Cell transformation and gene mutations have been observed in human cells in vitro. Bacterial testing has induced gene conversion, aneuploidy, and mutations. In *Drosophila*, beta-propiolactone produced translocations and sex-linked recessive lethal mutations. In vivo, gene mutations in the stomach and liver of mice and DNA strand breaks in rat bone marrow cells have been reported, along with covalent binding to mouse skin DNA and RNA.

The treatment for acute exposure to beta-propiolactone is the standard emergency treatment for a highly irritant chemical, including avoiding emesis and diluting the chemical in the stomach after oral consumption. A possibility for chemoprevention of cancer effects is sodium thiosulfate, which may inhibit beta-propiolactone's capacity for stomach tumorigenesis.

Psychogenic effects of exposure specifically to beta-propiolactone were not found in the literature. General psychogenic effects of perceived exposure to agents involved in chemical and biological warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

An online "glossary" of Project SHAD agents suggests that beta-propiolactone's carcinogenicity is subject to question due to the absence of adequate controls in experiments. That appears to derive from a comment by the National Toxicology Program (2002) referring to one prior study's finding of beta-propiolactone induction of keratocanthomas and melanoma in one species. Controls, however, are reported in many studies, and the studies have been generally evaluated as adequate; beta-propiolactone's animal carcinogenicity is regarded as confirmed by the IARC; the chemical is regularly used to induce animal cancer in controlled tests.

Bis Hydrogen Phosphite

Bis hydrogen phosphite (BHP), more commonly termed bis(2-ethylhexyl) hydrogen phosphite in the scientific literature, bears the chemical formula C_{16}-H_{35}-O_3-P. It is identified by the Chemical Abstracts Service Registry Number 3658-48-8. Bis hydrogen phosphite appears as a colorless liquid with a faint odor. It is commonly used as a lubricant additive to prevent corrosion. In Project SHAD, it served as a chemical warfare agent simulant.

No published human studies of any kind, or experimental studies of carcinogenicity, genotoxicity, and reproductive toxicity of bis hydrogen phosphite are known. (There is a 1986 study suggesting that compounds with a 2-ethylhexyl moiety may have a tendency to cause liver cancer in female mice but it did not specifically address

bis hydrogen phosphite.) Nevertheless, the Toxicology Division of the U.S. Army Chemical Warfare Laboratories performed several animal studies in acute and subacute exposure to bis hydrogen phosphite in the late 1950s. The tests also evaluated cholinesterase inhibition through a red blood cell assay.

The study concluded overall that acute oral and ocular exposure was "relatively innocuous" as also was a cumulative oral exposure of 70 days (Joffe et al., 1958). It found, however, a significant degree of toxic reaction to inhalational, cutaneous, and intraperitoneal and intravenous exposure. The study nevertheless dismissed concerns regarding the latter two pathways because of the unlikely administration of the chemical through those routes into humans.

Inhalational exposure of rats and guinea pigs to saturated vapor and mist suggested that both one-time and cumulative exposure could cause significant respiratory distress and tissue injury. Dermal exposure caused a coagulative necrosis on the epidermis and dermis, with repeated exposure inhibiting regeneration. Human skin exposure, reported from accidental hand contact with bis hydrogen phosphite, also induced cases of dermatitis. An assay aimed at cholinesterase inhibition was also performed, testing for any inhibition in exposed rabbits and dogs. No effect was found.

Psychogenic effects specifically of bis hydrogen phosphite are not reported. General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

There is no reported antidote to any of the effects of bis hydrogen phosphite. The Registry of Toxic Effects of Chemical Substances (RTECS) categorizes bis hydrogen phosphite as a "primary irritant," for which standard medical emergency procedures should be performed, e.g., removal from the area of contact; monitoring and ventilating the victim; irrigating or washing the locus of contact, etc., as appropriate (RTECS, 2004).

Bis hydrogen phosphite is barely treated in secondary sources. Where it is, the discussion may be overly dismissive of risk. One Project SHAD information site declares flatly and conclusively that the substance is not carcinogenic. Actually, published studies of human carcinogenicity are unknown, as are animal studies on the same subject. Nor are there found published genotoxicity studies. A commercial distributor advertises for sale bis hydrogen phosphite as "harmless" despite its irritant qualities and absent long-term data (Pfaltz & Bauer Co., 1997). The Hazardous Substances Data Bank (HSDB) does not even report the main animal toxicology studies that have been published.

Calcofluor

Calcofluor is a member of the class of fluorescent whitening agent. Its chemical formula is $C_{40}H_{42}N_{12}O_{10}S_2.2Na$, and its Chemical Abstracts Service Registry Number is 4193-55-9. Calcofluor has a binding affinity specifically to both cellulose and chitin.

Calcofluor is used as a brightening agent for white-colored objects, such as paper, detergents, and textiles. Calcofluor's chitin-binding specificity makes it a good laboratory stain to detect, identify, and quantitate fungi. Another use for Calcofluor is as a groundwater tracer. In Project SHAD, Calcofluor was used as a fluorescent tracer, along with *Bacillus globigii*.

The toxicity of Calcofluor is low. Oral and dermal toxicity studies show Calcoflour to have relatively low toxicity to fish, mammals, and humans. There is moderate irritation to the eye, as evidenced in rabbit testing. The acute toxicity potential, as indicated by the Lethal Dose/Concentration levels for several species, appears very low.

Mice were found to have no abnormalities in body weight, food consumption, survival, appearance, behavior, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, microscopic pathology, or increases in neoplasms after chronic administration of oral Calcofluor. Topical application of Calcofluor to mice, rats, and rabbits elicited no irritation or sensitization. Human volunteers experienced no skin reactions and no mucous membrane reactions at concentrations of up to 1% (Burg et al., 1977).

Calcofluor has not been found to be carcinogenic or mutagenic to humans. Phototoxicity studies were also performed, with no adverse reactions found. Psychogenic effects specifically of exposure to Calcofluor have not been found in the literature. General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Discrepancies in nomenclature and identification exist. Alternate names (e.g., Fluorescent Brightener 28) appear in the literature but are not consistently applied to the same compound.

Coxiella burnetii

Coxiella burnetii (CB), the etiologic agent of Q fever, is a pleomorphic, Gram-negative, obligate intracellular coccobacillus, typically 0.2–0.4 μm wide and 0.4-1.0 μm long. In the 1950s, CB was investigated as a potential biowarfare agent and a stock of the microbe was maintained as part of the United States' biological warfare arsenal until the arsenal was destroyed in the early 1970s.

The term "Q fever" was first proposed in 1937, by Edward Holbrook Derrick, the Director of the Laboratory of Microbiology and Pathology of the Queensland Health Department, to describe an outbreak of febrile illness among abattoir workers in Queensland, Australia. Derrick provided infectious material to F. Macfarlane Burnet (who would later win a Nobel Prize in Medicine for work in immunology) who with Mavis Freeman was able to reproduce the disease in guinea pigs, mice, and monkeys as well as visualize an intracellular organism that appeared rickettsial in nature (Burnet and Freeman, 1937). Independently, in 1936 Herald Cox, working at the Rocky Mountain Labs in Hamilton Montana was able to transmit a febrile illness to guinea pigs from ticks collected at Nine Mile, Montana. Cox also demonstrated that the organism displayed properties consistent with a virus or rickettsia and was able to propagate the infectious agent in embryonated eggs. The agent isolated by both groups was shown to be the same microorganism after R. Eugene Dyer, the Director of NIH, became infected with the organism while working at the Rocky Mountain Laboratory. Dyer received material from Burnet and demonstrated that animals infected with Burnet's Q-fever strain were protected from challenge by strains isolated for his own blood (Maurin and Raoult, 1999).

CB is incapable of axenic growth but can be grown in vitro in a number of cell lines including macrophage-like cells, fibroblasts, and Vero cells. Monocytes-macrophages, however, are the only cells CB appears to target in vivo. CB entry into monocytes-macrophages is mediated through interactions between the bacteria's lipopolysaccharide (LPS) and an integrin complex consisting of alpha(v)beta(3) integrin and CR3, a complement receptor. CB initially enters phagosomes that then fuse rapidly with lysosomes to form large acidic vacuoles. CB appears to require acidic vacuoles for replication. The replication of CB is very slow for a bacterium with a doubling time of approximately 20 hours (Maurin and Raoult, 1999).

CB has a complex intracellular lifecycle leading to the formation of both small-cell and large-cell variants. Small-cell variants (SCV; spore-like), the extracellular form of CB, are metabolically inactive and resistant to both chemical and physical inactivation. The bacterium will remain infectious in natural environments for several weeks (Scott and Williams, 1990; McCaul, 1991). In addition to a spore-like transformation, CB undergoes phase variation akin to the smooth-to-rough transition of other Gram-negative bacteria. During acute Q fever the predominant antibody response is to phase II antigens and during chronic Q fever the predominant response is to phase I antigens. There are no morphological differences between phase I and phase II bacteria, but there are differences in the composition of LPS, buoyant density, and affinity for basic dyes.

Q fever is a zoonosis with a large reservoir that includes domestic and wild mammals, birds, and ticks. Ruminants, such as goats, sheep, and cattle are the most frequent source of human exposure, but domestic dogs and cats can be a source in urban environments. Many animals appear to be chronically infected but asymptomatic. Chronically infected animals constantly shed CB in their feces, urine, and milk with substantial shedding occurring during parturition. Human transmission occurs principally from aerosols of shedded bacteria, but ingestion of high doses of CB can also result in infection. Q fever is geographically diverse in spread, with epidemics seen throughout the world with the exception of New Zealand (Greenslade et al., 2003). Persons who work with animals, particularly goats or sheep or animal products, are at highest risk of infection. There is an increasing awareness that the prevalence of Q fever is underreported and underestimated (Besalgic et al., 2002, 2003).

The study of natural human exposures indicate that approximately 60% of patients infected with CB seroconvert without any clinical manifestations and only 2% are hospitalized after primary infection (Scheld et al., 2001). There are three major clinical manifestations seen in acute Q fever: a self-limited or isolated febrile illness, pneumonia, and hepatitis, and more than one of these manifestations can be seen during a single exposure. The

incubation time between exposure and acute clinical manifestations can range from 13–32 days. Both the incubation time and type of manifestation appear to be related to dose, route of exposure, and strain (Williams, 1991).

Self-limited febrile illness caused by CB usually consists of a high fever accompanied by a severe headache. Fever typically increases to a plateau of 39 to 40° C over 2–4 days and then rapidly disappears after 5–14 days. Almost all patients who present with Q-fever pneumonia also have fevers and headaches. Fatigue, myalgic and arthralgic pain, chest pains, dry cough, and moderate gastroenteric disturbances are also seen. Q-fever hepatitis is often only detected by increases in liver enzymes. Hepatitis is also frequently accompanied by fever and increases in several cytokines, less frequently by abdominal pain, anorexia, nausea, vomiting, and diarrhea, and occasionally by progressive jaundice. Myocarditis, pericarditis, meningoencephalitis, bone marrow necrosis, hemophagocytosis, hemolytic anemia, transient hypoplastic anemia, erythema nodosum, and skin rash can also be manifestations of acute Q fever. Autoantibodies are also frequently seen during acute Q fever. The route of exposure may also influence the clinical presentation with pneumonia being more common following aerosol exposure and hepatitis being more common following ingestion (Maurin and Raoult, 1999).

Although complications such as pyrurria, spleen rupture, rapid fatal pneumonia, encephalitis, acute renal failure, acute respiratory distress, multiple organ failure, and congestive heart failure are occasionally seen, mortality from acute infection is nevertheless low (approximately 1%) (Kazar, 1999; Raoult et al., 2000). Pregnancy can also be compromised; CB causes placentitis with resultant spontaneous abortion, premature birth, and low birth weight commonly seen (Maurin and Raoult, 1999; Raoult et al., 2000; Hellmeyer et al., 2002). Several studies have also indicated that chronic fatigue syndrome is more frequently in acute Q-fever patients 5 years post-infection than in case controls (Ayres et al., 1991).

T-cell immunity appears to be largely responsible for the control of CB infections although it is not clear if eradication is achieved in most cases. CB is able to survive within macrophages withstanding low pH and reactive oxygen intermediates. Persistence, recurrence, or reemergence of CB is a constant worry following acute infection. A significant decrease in CD4+ T-cells has been associated with chronic Q-fever endocarditis (Sabatier et al., 1997). A recent large study in France indicates that chronic Q fever will evolve in 1.5% of patients with acute Q fever. Q-fever endocarditis is the most frequent manifestation of chronic Q fever. Vascular and osteoarticular infection, chronic hepatitis and pericarditis, adenopathies, hepatomegaly, splenomegaly, clubbing of digits, purpuric rash, and arterial embolisms are also seen in chronic Q fever. The shift to chronic Q fever is favored in patients with heart valve disease and/or immunosuppression. The death rate for Q-fever endocarditis can be as high as 60% but is substantially reduced if diagnosed and treated early (Maurin and Raoult, 1999; Raoult et al., 2000).

Diagnosis is usually performed by serology after a culture-negative presentation of a fever when other possible Q-fever symptoms, exposure risks (e.g., animal contact), and biomarkers are present. Commercial kits that detect antibodies to different phases of CB are available using complement fixation, immunofluorescence, or ELISA formats. Electron microscopy and DNA detection schemes are used in research laboratories. Several of the immunodominant epitopes of CB have now been identified and cloned (Zhang et al., 2004).

Doxycycline administered at 200 mg daily over 14 days is the standard therapy for acute Q fever. Fluoroquinolones, macrolides, and co-trimoxazole are also effective alternatives. CB is resistant to both β-lactams and aminoglycosides. The treatment of chronic Q fever is more problematic. Doxycycline/fluoroquinolones combination therapy over an extended period of time was shown to be effective, but relapse rates of over 50% prompted a need for a new therapy. Chloroquine, which raises the pH of acidic vesicles, was chosen to be combined with doxycycline. An 18-month regimen of 100 mg b.i.d. of doxycycline and 200 mg t.i.d. of chloroquine is the currently recommended for the treatment of chronic Q fever (Maurin and Raoult, 1999).

A safe, efficacious vaccine against Q fever has been developed in Australia. A formalin inactivated preparation of CB commonly referred to as Q-Vax, prepared from the phase I form of *C. burnetii* Henzerling strain, appears to provide 100% protection from natural exposure over a period of 5 years (Ackland et al., 1994).

This health effects report details the microbiology, epidemiology, clinical course, and treatment of *Coxiella burnetii* Q-fever infection. (Given the diffuse and evolving state of study of Q fever, it is likely, however, that the last word on CB infection is far from being written.) A presentation of some of the deficiencies in the secondary health effects literature, including federal government advisories on Project SHAD agents, will also be provided. A supplementary table listing CB health effects also follows. A bibliography containing abstracts and some anno-

tation concludes this review. A review of possible psychogenic effects arising from the subjective perception of exposure to biological or chemical warfare agents will supplement this report.

Diethylphthalate

Diethylphthalate (more commonly rendered in the scientific literature as two words "diethyl phthalate") is a phthalic acid ester with the chemical formula $C_{12}H_{14}O_4$ and commonly identified by Chemical Abstracts Service Registry Number 84-66-2. It ordinarily appears as a bitter-tasting colorless or water-white liquid with no odor, or a slight aromatic odor. It is slightly soluble in water, while also soluble in alcohol, ether, benzene, and acetone. Diethylphthalate is miscible with vegetable oils, esters, and aromatic hydrocarbons. It is manufactured by refluxing one equivalent of phthalic anhydride with a greater than two-fold excess of ethanol in the presence of 1% of concentrated sulfuric acid. It is also classed as a phthalic anhydride ester (PAE).

Diethylphthalate is a widely encountered compound in daily life. Automobile parts, toothbrushes, tools, and food packaging are ordinary products in which one can frequently find diethylphthalate. Aspirin, insecticides, and cosmetics can also contain it. The most common industrial use for diethylphthalate is as a "plasticizer"—an agent for making plastics more flexible. In Project SHAD, diethylphthalate was used as a simulant for VX Nerve Agent. Because of its common use in so many household and personal consumer products, exposure through many pathways (oral, dermal, respiratory) has been studied.

The Threshold Limit Value for diethylphthalate of the American Conference of Governmental Industrial Hygienists (ACGIH) is 5 mg/m^3 based on an 8-hour workday time-weighted average. The pharmacology and kinetics of diethylphthalate exposure indicate slow absorption by the skin, the metabolic conversion of absorbed diethyphthalate into ethanol and the monoester monoethyl phthalate, followed by rapid excretion, mostly in the urine.

The effects of diethylphthalate are fairly extensively studied. The chemical shares with other phthalates the characteristic of being among the least toxic of substances in industrial use. In vivo human studies or case reports of serious direct physiological insult as a result of diethylphthalate exposure are not to be found, with the exception of mucous membrane/pulmonary irritation, or a general anesthetic effect at very high concentrations/doses, along with unusual sensitive skin reactions in exceptional sensitized individual cases. An in vitro study on a human skin model did produce a strong cytotoxic reaction, but this has not been duplicated in vivo.

Animal studies provide powerful corroboration of diethylphthalate's low toxicity. Only very high acute oral doses have produced lethality in animals. Otherwise, nontoxic systemic effects usually seen in animal testing are decreased weight gain with alterations in liver and kidney size, likely attributable to hypertrophy. Animal studies indicate that diethylphthalate is only mildly or moderately irritating when applied to the skin or the eye.

Evidence of carinogenicity is at best equivocal. In rodent studies a carcinoma/adenoma positive dose-response versus control results was found in only one sex of one species, and the response did not differ significantly from a historical mean for the species and gender. Evidence of genotoxicity is also weak, with only in vitro sister-chromatid exchanges (SCEs) a confirmed effect, but these occurred only in the presence of an S9 fraction from a sensitive species in which a correlation between SCEs and carcinogenicity is regarded as tenuous. Both the Environmental Protection Agency (EPA) and ACGIH regard diethylphthalate to be a substance without evidence of cancer risk [EPA class D; ACGIH class A4]; human case reports or epidemiological study of carcinogenesis from diethylphthalate have not been found.

Some concern may exist for toxicity in the reproductive/developmental area. Skeletal abnormalities in rodent offspring have been seen after maternal administration of high doses. Chicken embryos die at a faster rate after direct injection of diethylphthalate. A lowering of testosterone levels in rodents has been seen following diethylphthalate exposure, though no fertility or testicular damage was seen. A lowering of human sperm motility was observed after direct in vitro administration of diethylphthalate. Concerns have been raised on risks to pregnant human females and offspring in light of the detected presence of significant amounts of diethylphthalate in the blood of pregnant women in urban areas.

One comprehensive and relatively recent (2001) review of diethylphthalate toxicity concludes that there are ultimately "no toxic endpoints of concern" for the substance in regard to acute toxicity, eye irritation, dermal irrita-

tion, dermal sensitization, phototoxicity, photoallergenicity, percutaneous absorption, subchronic toxicity, teratogenicity, reproductive toxicity, genetic toxicity, chronic toxicity, carcinogenicity, and potential human exposure.

Psychogenic effects specifically of diethylphthalate exposure have not been found in the literature, but the general effects of a perceived exposure to chemical warfare agents are treated in the supplement provided under this contract entitled "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Secondary literature tends to be comprehensive. It appears that the similarity in names and characteristics of the PAE class may cause confusion in reportage of effects, however.

Escherichia coli

Escherichia coli (*E. coli*) is a Gram-negative, rod-shaped, facultatively anaerobic bacterium of the *Enterobacteriacae* family whose members are sometimes referred to simply as enteric bacteria. Discovered in 1884 by Theodor Escherich, *E. coli* and its strains are probably the most widely studied of microorganisms. The species is well known as part of the normal human intestinal microflora, where its presence is typically harmless or benignly symbiotic. It has abundant uses in the laboratory, lately finding a new role as a useful cloning host in recombinant DNA technology. In Project SHAD, it was released atmospherically as a simulant to study biological decay rates; the strain is unspecified.

Many strains of *E. coli*, along with nonintestinal exposure to "commensal" bacteria from the intestines, can be harmful, even deadly, however. The microbiology and molecular pathology of the microbe's virulence is an ongoing subject of intensive study. The effects of one factor in *E. coli* virulence, the endotoxin liposaccharide (LPS), is an area of particular note as it has, in some studies, shown the potential for long-term effects related to autoimmunity and fever regulation.

Currently, classification of the various infectious strains of *E. coli* is based on a mixture of several considerations—areas of colonization, clinical effects, serotype, and determinants of virulence.

For strains of *E. coli* with intraintestinal pathogenicity, the following are the most noted classes of strains and the pathogenic activity with which they are associated:

Enterotoxigenic *E. coli* (ETEC) —contaminates foods and water, causing diarrhea

Enterohemorrhagic (EHEC) strain—synthesizes verotoxin (VT) (shiga-like toxin), which damage the intestinal lining, causing hemorrhagic colitis with its uniquely severe bloody diarrhea (CFSAN, 2003)

Enteroinvasive *E. coli* (EIEC)—creates manifestations similar to the dysentery caused by *Shigella*, but does not synthesize shiga toxin

Enteropathogenic *E. coli* (EPEC)—damages intestines by adhering to and altering the cellular structure of the lining

Enteroaggregative *E. coli* (EAggEC)—also adheres to the intestinal lining and produces a toxin

Enteroadherent *E. coli* (EAEC)—colonizes and adheres to the small intestine and causes "traveler's diarrhea"

The relatively new strain *E. coli* O157:H7 has been of special interest over the past two decades. The Centers for Disease Control and Prevention (CDC) devotes a special notice to that strain. Strains that are pathogenic outside the intestinal tracts are called extra intestinal or uropathogenic *E. coli*.

E. coli is also a common nosocomial infection risk.

Definitive diagnosis is by culturing the body fluid of the infected area.

The effects of *E. coli* are well-characterized. Acute food poisoning, manifested as nausea and diarrhea, is the most commonly noted effect. "Traveler's diarrhea" and the Mexican water-borne "Montezuma's revenge" diarrhea are two very familiar examples. These conditions are usually self-limiting and last a few days.

Areas of greater concern in terms of seriousness and duration of effects include infections of the urinary tract and the abdomen and related complications. The spectrum of urinary tract infections (UTIs) ranges from asymptomatic bacteriuria to cystitis to acute and chronic pyelonephritis and renal abscess. The kidney infection pyelonephritis may lead to temporary or chronic renal insufficiency.

Although urinary tract infections are more commonly seen in women (where they can be chronic but not serious to overall life and health), they can also occur in men. They are often nosocomial, related to the use of

catheters and other invasive/manipulative procedures. Acute and chronic prostatitis, the latter being difficult to treat, are possible manifestations and consequences of *E. coli* UTIs.

Pathogenic *E. coli* may progress into other systems from the area of colonization. This spread can happen through the blood as bacteremia, and then proceed into sepsis and septic shock. Blood dissemination can lead to infection in other areas of the host. In UTIs, *E. coli* have been known to proceed to the kidney and induce pyelonephritis. This kidney infection can lead to acute or chronic renal challenge. Severe, complicated pyelonephritis is mainly seen among alcoholic, diabetic, and immunocompromised patients.

E. coli pneumonia is usually encountered also as a secondary infection of UTI. Rarely is it known to have arisen from direct exposure, though there have been cases of community-acquired *E. coli* pneumonia.

The nervous system may be directly invaded. Meningitis in neonates is a well-observed effect of *E. coli* activity; meningitis in adults is, however, far rarer and usually connected with neuroinvasive procedures. (One case study, nevertheless, reports aspergillar sinusitis being associated with recurrent *E. coli* meningitis episodes.)

The appearance of strain O157:H7 (EHEC) since about 1982 has given rise to a new concern over *E. coli* exposure: namely the complications hemolytic uremic syndrome (HUS) and thrombocytopenic purpura (TTP). Strain O157:H7 infection usually involves a gastrointestinal episode of severe diarrhea with blood in the stool. But in about 10% of these cases, in a matter of days or weeks, endothelial damage further induces microvascular lesions with platelet-fibrin hyaline microthrombi that occlude arterioles and capillaries. The aggregation of the platelets then causes consumptive thrombocytopenia.

In the HUS manifestation, the health effects are primarily limited to the kidneys with some possible central nervous system effects. TTP's effects are primarily of the central nervous system type; they typically include seizures arising from hypertensive encephalopathy. End stage failure and death are possible consequences of HUS; the overall death rate from HUS is 5–15%. Untreated TTP can have a mortality rate of 95%. Symptoms may include thrombocytopenia, fever, renal insufficiency, neurological deficit, microangiopathic hemolytic anemia (MAHA), headache, fatigue/malaise, altered mental status, and hemiplegia.

A lesser chronic complication of EHEC strain infection is the risk of irritable bowel syndrome after uncomplicated gastrointestinal infection.

Intra-abdominal effects tend to follow puncturing of the peritoneum. These effects, which often are polymicrobial, can lead to abscesses, which are usually accompanied by a low-grade fever and may proceed to septic shock, pylephlebitis of the portal vein, and liver abscess, as well as cholecystitis and cholangitis. Partial obstructions in the biliary system can be a greater risk for infection than full obstructions. Peritonitis is a common consequence of *E. coli* penetration of the peritoneum.

Other noted *E. coli* infection effects include endophthalmitis (usually associated with diabetic patients suffering from UTI or pyelonephritis), osteomyelitis, endocarditis, septic arthritis, and skin, soft tissue, and surgical wound injuries.

Special attention is called to lipopolysaccharide (LPS) endotoxin activity and possible associations it may have with long-term effects on the immune and immune regulatory systems. (LPS forms part of the outer cell wall of Gram-negative bacteria, including nonpathogenic laboratory strains like K-12.) Animal tests suggest that neonate exposure can lead to a diminution of fever response to a subsequent adult challenge from LPS. LPS has also been shown to have possible associations with the initiation of autoimmune joint disorders and in the induction of autoimmune diabetes.

Studies or reports of clinical psychogenic health effects resulting specifically from exposure to *E. coli* have not been found. General psychogenic effects of perceived exposure to agents of biological (and chemical) warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Preventive measures center on proper hygiene. No standardized treatment for *E. coli* infections exist; treatment is site and severity specific. Infection management usually includes intravenous hydration. The employment of antimicrobials in strain O157:H7 infection are not recommended because they may worsen the condition. Under development is the use of neutralizing human antitoxin antibodies, which appear to have a protective role in HUS.

Methyl Acetoacetate

Methyl acetoacetate bears the chemical formula $C_5H_8O_3$ (structured $CH_3COCH_2COOCH_3$) and has a molecular weight of 116.11. Its Chemical Abstracts Service Registry Number is 105-45-3. Its common alternative name is "Acetoacetic acid, methyl ester." Its density/specific gravity is 1.0762. At room temperature, the chemical is a colorless liquid with an agreeable odor. Its most common use is in the fragrance industry. Methyl acetoacetate was used as a simulant for sarin in at least two tests over the course of Project SHAD.

Methyl acetoacetate is generally regarded as being a mild to moderate irritant to the skin and mucous membrane, but with the capability (sometimes overlooked in secondary sources) of severe corrosive effect on the eye if directly contacted. The ocular exposure effect has been demonstrated in one earlier rabbit study. Secondary sources indicate gastrointestinal difficulties (nausea, vomiting, diarrhea) if it is swallowed, based upon the general characteristics of irritant toxic chemicals. Other effects extrapolated from general effects of irritant substances include swelling, redness, and pain at any dermal site of exposure, but also particularly on mucous membranes. Mouth, nose, and eyes are especially susceptible. Irritants also commonly cause cough, tachypnea, and wheezing after inhalation exposure.

There do not appear to have been any published studies of chronic exposure. Recently, however, two Japanese research laboratories have examined methyl acetoacetate's toxicity with greater thoroughness and a more updated focus on mutagenicity and carcinogenicity. They obtained results generally consistent with earlier studies on the questions of acute exposure. They also found no indication of mutagenicity or carcinogenicity. One mutagenicity test did yield a tentative finding of genotoxicity, but this was explained, after failure to replicate the effect in confirmation testing, to be the result of methyl acetoacetate's alteration of the test medium's pH. Methyl acetoacetate is also nowhere reported as a carcinogen.

One noticeable aspect of the literature on methyl acetoacetate has been the presence of significant discrepancies or omissions in the major secondary sources when compared with the primary studies or earlier secondary studies. These include (1) listing the wrong animal species used in a study, (2) providing dose figures not stated in the study being reported on, (3) offering a possibly misleading description of the animal lethality of one inhalation test, (4) omitting note of the substantial ocular toxicity of methyl acetoacetate, and (5) failing to update with later studies, including especially the recent Japanese laboratory studies. Issues of this type exist in the sources on methyl acetoacetate toxicity recommended by the Department of Defense and extend to such standard or authoritative sources as Toxnet's HSDB (Hazardous Substances Data Bank), *Patty's Toxicology*, RTECS (during its existence as a publicly-owned resource), and the *Merck Index*.

Phosphorus-32

Phosphorus-32 [^{32}P] was first synthesized in the 1930s. It has a physical half-life of 14.3 days and emits a relatively high-energy β particle. It was the first synthetic radionuclide to be used for human therapy. The isotope has found wide use as a tracer element in both biological and chemical studies.

^{32}P is one of only six radionuclides classified as a human carcinogen. The classification is primarily due to its ability to cause leukemia in polycythemia (PV) patients. Sodium [^{32}P] phosphate is currently a treatment of choice for PV and essential thrombocythaemia (ET) in the elderly; it is also used to treat bone pain from metastatic disease. Chromic [^{32}P] phosphate and other forms of ^{32}P have been used to treat a number of conditions. Sodium [^{32}P] phosphate tends to concentrate in the bone, liver, and spleen and has a whole-body biological half-life of 39.2 days.

Overdoses of sodium [^{32}P] phosphate result in haematological disorders such as aplasia, agranulocytosis, and severe thrombocytopenia. ^{32}P has been shown to cause cancer when locally deposited in animals. Sodium [^{32}P] phosphate has also been shown to cause low sperm counts and thyroid and blood disorders in animals. There is still controversy on whether a dose-response exists for the induction of leukemia and whether ^{32}P would cause leukemia in the general population.

Leukemia is typically seen 5–15 years after exposure. Single exposures can result in chronic effects. Occasional side effects of intraperitoneal instillation of chromic [^{32}P] phosphate have included bone marrow depression, pleuritis, nausea, and abdominal cramping.

Acute high-exposure responses are nonstochastic. These acute effects usually appear quickly and can result in burns and radiation sickness. The symptoms of radiation sickness can include nausea, weakness, hair loss, skin burns, and diminished organ function. At higher levels and exposure durations, system collapse, intestinal lining destruction, bleeding, and death can occur. Eye lens damage from external exposure also can occur, as indicated by the 15 rem yearly limit on eye radiation exposure.

Sarin

In 1936 German chemist Gerhard Schrader discovered that an organophosphate compound, ethyl dimethylphosphoramidocyanidate (later called tabun), was a potent insecticide. Dr. Schrader reported his discovery to German authorities, who then set up a laboratory for Schrader to further pursue toxic nerve agents for military purposes. In 1938, Schrader along with some associates, synthesized 1-methylethyl methylphosphonofluoridate. It was named sarin, after the chemists Schrader, Ambrose, Rüdige, and van der Linde, who were responsible for its synthesis.

Sarin is a chemical warfare nerve agent, which is described by the chemical formula $C_4H_{10}FO_2P$ and is identified by Chemical Abstracts Service Registry Number 107-44-8. Under normal conditions it is a colorless and odorless liquid. It is miscible in both polar and nonpolar solvents, and it hydrolyzes slowly in water at neutral or slightly acidic pH. Sarin is significantly less stable to hydrolysis than VX. Sarin's hydrolysis products are considerably less toxic than the original agent.

The synthesis of sarin's chemical class, the organophosphates, dates back to 1820. Widespread poisoning by organophosphates was first seen in the United States in early 1930, when many people developed a strange paralytic illness traced to a Prohibition-era alcohol substitute, called Jamaican Ginger or Jake, which had been adulterated with tri-ortho-cresyl phosphate (TOCP). TOCP was the first chemical proven to show a delayed type of neurotoxicity.

The use of chemical warfare agents is ancient, but their most extensive use occurred during World War I when chlorine and mustard gas inflicted over 1 million casualties.

Nazi Germany later produced large amounts of the organophosphate agent tabun along with far lesser amounts of sarin (1,000 lb) throughout World War II, but they were not known to be used. In 1950, the U.S. Army's Chemical Corp began the construction of plants for the full-scale production of sarin but ceased in 1957 because stockpile requirements were met.

The only confirmed military use of nerve agents in history was by Iraq, which used tabun and sarin aerial bombs to repel Iranian troops. In the latter part of the war, Iraq's extensive use of chemical warfare agents is believed to have brought an end to the conflict. Reports claim that between 5,500 to 10,000 Iranian troops were killed by nerve agents and mustard gas, and up to 100,000 soldiers were exposed. In March of 1988, Iraq used a combination of chemical weapons, including mustard gas, tabun, sarin, VX, and possibly even cyanide to kill as many as 5,000 people in the Kurdish town of Halabja. Iraq is believed to have produced between 790 to 810 tons of sarin, which degraded or were destroyed after the Gulf War.

The first known terrorist use of a nerve agent involved sarin and occurred in Matsumoto City, Japan, on the evening of June 27, 1994. About 12 liters of sarin were released using a heater and a fan from the window of a delivery truck. The attack was undertaken to kill four judges involved in a dispute with the Aum Shinrikyo cult. There were 471 victims of sarin poisoning; 54 were hospitalized and 253 were treated at outpatient facilities. Seven died.

On March 20, 1995, Aum Shinrikyo launched an even bolder attack on the subway system in Tokyo. At 8:00 a.m., at the height of rush hour, sarin was released. Twelve subway passengers were killed. About 980 persons suffered mild to moderate exposure, and 500 persons were hospitalized. Over 5,000 people, many of whom were not actually exposed, sought medical attention.

The largest experimental use of sarin on humans appears to have occurred at Porton Down in the United Kingdom in the 1950s. The purpose of the studies was to obtain precise information on the toxic properties of these agents. Certain experiments went terribly wrong. One man died 45 minutes after 200 mg of sarin were dripped onto a uniform patch on his forearm.

The United States also ran a number of tests using sarin that may have resulted in human exposure. The tests were part of Project 112 of the Deseret Test Center; Project SHAD (Shipboard Hazard and Defense) was part of this program. The tests monitored the environmental effects of sarin, the dispersal pattern of bomblets, shipboard detection of agents, and protective measures. Several of the tests did involve exposure of personnel to nerve agents and to potential biowarfare agents. The Department of Defense (DoD) has identified about 5,000–6,000 persons who may have been exposed to one or several of these agents.

Very little data on Soviet chemical weapons testing has emerged. Several reports indicate that there was exposure of the population in Russia to nerve agents. One paper had a short summary reporting 209 acute poisonings involving sarin, soman, or VX in Russian production facilities. Several long-term health effects were described including memory loss, asthenia, sleep disorders, and cardiovascular effects.

The most widespread use of nerve agents occurred during and shortly after the Iran-Iraq war, but unfortunately there is very little accessible scientific literature addressing either the short-term or long-term medical consequences of this use. Iraq used nerve agents and mustard gas against its Kurdish population from April 1987 to October 1988, to quell rebellion and punish the population. It is estimated that approximately 250,000 civilians where exposed to these agents and over 5,000 were killed. Unfortunately, there has been very little study of this population. The exposures to nerve agents in Japan remain the most extensively studied sarin incidents.

The acute toxicity of sarin is believed to be rooted in its inhibition of acetylcholinesterases (AChE's). The inhibition of AChE's leads to a rise in the concentration of acetylcholine and the hyperstimulation of both nicotinic and muscarinic acetylcholine nerve receptors. Sarin has been shown to react with a number of other receptors and enzymes as well. At very low concentrations (0.3–1.0 nM), sarin reacts with muscarinic m2 receptors on presynaptic gamma-aminobutyric acid (GABA)-ergic neurons. The reduction in the action-potential mediated release of GABA can account for the occurrence of seizures in individuals exposed to sarin. Sarin also binds tightly to muscarinic m2 receptors in the heart and may play a role in cardiotoxicity.

There have been several reports on the ability of sarin to inhibit the enzyme neurotoxic esterase or neuropathy targeted esterase (NTE). The inhibition of NTE has been reported to be responsible for the onset of organophosphate-induced delayed neuropathy (OPIDN). The pathway through which inhibition of NTE leads to OPIDN has not yet been elucidated, although it is known neuropathy only occurs when over 70% of NTE activity is inhibited following acute exposure and 50% following repeated exposures. It should be noted that subclinical neuropathy was reported 30 days after sarin exposure in Japan, and a subsequent study also picked up electromyographic evidence of neuropathy 6 months after exposure.

The acute effects of sarin are believed to be primarly due to (–)-isomer of sarin. The (+)-isomer appears to be eliminated rapidly from the body following administration. Animal studies indicate that (–)-sarin is rapidly distributed throughout the body, within minutes, but eliminated very slowly with a half-life of several hours. The primary metabolite of sarin, isopropyl methylphosphonic acid, was found in large amounts in the serum and urine of victims in Japan. The concentration of the metabolite and the amount of time from exposure can be used to estimate the level of exposure. These studies indicated that several of the survivors were exposed to supra-lethal levels of sarin.

There are currently no real-time clinical tests for sarin exposure, but there have been a number of forensic assays developed that can confirm exposure. Most of these tests involve isolating RBC AChE and/or serum butyrylcholinesterase from blood and releasing and detecting any organophosphates that are released. There has also been a great deal of work on the environmental detection of sarin and other nerve agents. The Department of Defense has developed several detectors to monitor air for the presence of nerve agents. The mainstay of the Army chemical detection is the M8A1 alarm, which constantly samples the air for higher-molecular-weight molecules. The detector ionizes gases and mass filters away the low molecular ions generated from air.

The health effects of sarin are dependent on the route of administration, dose received, and the speed at which treatment is given. Casualties can go from being fully functioning to comatose with severe respiratory distress in a matter of seconds following exposure. Aggressive, rapid therapy can substantially minimize adverse health effects seen in patients exposed to nerve agents.

Acute effects seen at low concentrations include miosis, ocular pain, blurred or dimmed vision, tearing, rhinorrhea, broncospasm, slight dyspnea, respiratory secretions, salvation, and diaphoreses. At intermediate concen-

trations, moderate dyspnea, nausea, vomiting, and diarrhea are seen. At high concentrations, convulsions, loss of consciousness, muscle fasciculations, flaccid paralysis, copious secretions, apnea, and death may occur.

Toxic factors and exposure limits established by the U.S. Department of Health and Human Services (DHHS) include the vapor concentration per period of exposure during which 50% lethality is seen for humans (LCt_{50}). That level is 100 mg/m^3/min; the no death dose equals 10 mg/m^3/min; the no neuromuscular (NNM) effect dose equals 4 mg/m^3/min. The concentration which induces miosis in 50% of victims (ECt_{50} [miosis]) equals 2–4 mg/m^3/min. The no observable effect level (NOEL) equals 0.5 mg/m^3/min; the maximal single concentration for 1 hour equals 0.001 mg/m^3; the maximal single concentration for 8 hours equals 0.0003 mg/m^3; the safety factor of 0.1 is used for the general population, and the limit levels are 0.0001 mg/m^3 for 1 hour, 0.00003 mg/m^3 for 8 hours, and 0.000003 mg/m^3 for 72 hours.

There has been no evidence in humans of reproductive or developmental toxicity. In animals, there has been no evidence of sarin-related adverse effects with respect to reproductive performance, fetal toxicity, and teratogenesis. There is no evidence of carcinogenicity in human. In chronic inhalation studies in mice, rats, and dogs, sarin did not appear to be carcinogenic. No significant pulmonary tumors were observed in strain A mice after 3/19 and 3/20 animals after 52 weeks of exposure to 0.001 and 0.0001 mg/m^3, respectively.

There is relatively little information available regarding the human genotoxicity of sarin. In bioassays using bacteria and mammalian cell cultures with and without metabolic activation, sarin did not show any evidence of genotoxic or mutagenic activity. There was no increase in mutations using the Ames test. But several studies of the victims of the Tokyo subway attack indicate that the sister-chromatid exchange (SCE) of lymphocytes was higher in persons exposed to sarin, and there was a positive correlation between the extent of serum cholinesterase inhibition and the level of SCE. The SCE effect appeared to last up to 3 years after exposure.

Miosis (pinpoint pupils) is characteristic of sarin exposure. It usually occurs within seconds or minutes of exposure. It can last up to 9 weeks resulting in dim vision. Blurred vision and eye pain can accompany sarin exposure. There is very little data on the effect of sarin on hearing.

Rhinorrhea, typically intense, is often seen shortly after sarin exposure. Tightness in the chest is a common symptom after exposure to small amounts of sarin and usually dissipates within hours of exposure. As the amount of exposure increases, dyspnea and pulmonary distress increase and often someone severely poisoned will go into respiratory failure and die. No data indicate that respiratory effects persist long after exposure.

Several animal studies that indicate there is a potential for some immunotoxicity or immunodulatory effects upon sarin exposure. Reductions of T-cell mediated immune reaction, a substantial increase in NK cell and macrophage activity, and a substantial decrease in CD4 T-cell activity have been seen in testing. A single exposure was observed to have the same effect as multiple exposures.

Bradycardia is frequently seen following moderate- or high-level sarin exposure. There have been reports of persistent arhythmias following exposure. In cases of severe poisoning, cardiomyopathy may also be seen.

Neuromuscular effects are common as acetylchloline is a primary neurotransmitter at the neuromuscular junction. Increased acetylcholine initially leads to stimulation, followed by fatigue and muscle paralysis. In the Tokyo attack, asthenia or muscle weakness was seen in most patients upon admission to the hospital. Following liquid exposure muscle fasciculations at the site of exposure are often seen after excessive sweating. Long-term shoulder stiffness may be a result of exposure. Myopathy has also been seen in rats in the absence of treatment following a moderate dose of sarin.

Although inducing convulsions and the resultant neuropathology, sarin in the Japanese incidents was found not to have caused persistent neurological disorders in most patients. One exception was a patient who suffered from akinetic mutism for at least 2 years following exposure. Studies in rats have shown that there is wide variability in neurotoxicity following repeated sublethal doses of sarin. There is a lack of tolerance with repeated doses and a cumulative effect on toxicity.

Headaches are a very common symptom of sarin exposure. Loss of memory can happen; a case of amnesia is reported following exposure in Japan. Long-term changes in electroencephalograms (EEGs) in workers following accidental sarin exposure have been observed. Increases in REM sleep have been found.

The initial diagnosis of sarin exposure is based on signs, symptoms, and historical factors. The first step in the diagnosis is to confirm presence of both nicotinic and muscarinic effects. A convenient mnemonic for the signs

and symptoms of nerve agent poisoning is dumbbels, which stands for **D**iaphoresis (and diarrhea); **U**rination; **M**iosis; **B**radycardia; **B**ronchospasm (and bronchorrhea); **E**mesis; **L**acrimation (with rhinorrhea and salivation); and **S**eizures (as well as muscle fasciculation and weakness).

Symptoms depend on the site and extent of exposure. Following dermal contact symptoms can be delayed 18 hours but symptoms from inhalation can occur within seconds. Percutaneous absorption of liquid sarin also occurs readily and typically leads to localized sweating, followed by muscular fasciculations and weakness (Lee, 2003; NRC, 1997). Useful markers of nerve agent exposure include serum butyrylcholinesterase and red blood cell AChE activity. Significantly reduced levels of these are indicative of nerve agent exposure. Analysis of patients from the Tokyo subway event indicates that miosis may be a better indicator of potential systemic toxicity than red blood cell (RBC) AChE levels.

Psychogenic effects were reported from the Japanese incidents. Post-traumatic stress disorder (PTSD) was seen in a number of sarin victims. Several studies have shown persistent decreases in serum cholinesterase activity in patients with PTSD that evolved over 6 months with no correlation with the serum cholinesterase activity taken right after exposure. Fatigue, asthenia, insomnia, blurred vision, and general anxiety were the common manifestations. A survey of general effects of perceived exposure to chemical and biological warfare agents is contained in the supplement under this contract, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

There are essentially five components of treatment for sarin exposure. The first component is prophylaxis. This is typically accomplished by the administration of pyridostigmine, a carbamate that reacts reversibly with AChE, protecting the enzyme from inactivation. The second component of treatment is decontamination and evacuation. The third component of treatment is the use of anticholinergic agents to block the effect of increased acetylcholine at synapses. Atropine is commonly used for this purpose. The fourth component is the use of oximes to regenerate AChE enzymes. The fifth component of treatment is the use of anticonvulsants. Diazepam has been the mainstay of anticonvulsant therapy for nerve agent poisoning. In addition to these treatments, there has also been interest in using adenosine agonists such as N6-cyclopentyladenosine (CPA) to attempt to decrease the amount of acetylcholine released at synapses. CPA has shown promise in reducing the potential cardiovascular toxicity following sarin exposure.

Future study of sarin would benefit from greater availability and evaluation of sarin-exposure and testing data from the Iran-Iraq war and the former Soviet Union.

Serratia marcescens

Serratia marcescens (formerly *Bacillus prodigiosus, -is, -um*) is a facultative anaerobic, motile Gram-negative, rod-shaped bacterium. It belongs to the *klebsiella-enterobacter-serratia* division of the family *Enteroacteriaceae.* A saprophyte, it can be normally found in water, soil, sewage, foodstuffs, and animals like rabbits, horses, deer, and water buffalo. In Project SHAD, it was disseminated in an aerosolized form in order to evaluate the effect of solar radiation on its viability.

Serratia marcescens has a historical background that may be described as literally colorful. Many strains yield a red pigment, called prodigiosin. Prior to the scientific age, the organism appears to have been the causative agent for a celebrated appearance of red fluid on communion bread in a Catholic Mass. Regarded as the miraculous appearance of blood, it became a factor in the adoption of the theological doctrine of the transubstantion of communion bread and wine into the body and blood of Christ. This episode and others like it may also have led to incidents of anti-Jewish violence as the appearance of what was taken for blood on communion hosts was sometimes attributed to the fasle anti-Semitic accusation of Jewish ritual desecration of Christian communion.

The microbe was first identified in modern times by an Italian pharmacist, Bartolomeo Bizio, in 1819. Human conflict appears not to have escaped the history of *S. marcescens* even then. The genus name that Bizio gave it, *Serratia,* was from the name of an Italian physicist Bizio believed did not get adequate credit for the invention of the commercial steamboat.

The secreted red pigment allowed *S. marcescens* to become a popular marker for tracing bacterial activity. At one point it was literally exhaled and expectorated into a cleared British House of Commons chamber to investi-

gate the spread of illness among members of Parliament. In 1920, it was also sprayed on the mouths and hands of African-American soldiers to test bacterial contagion in the washing of Army "mess-kits."

In the early 1950s, *S. marcescens* was part of a test for the atmospheric distribution of bacterial pathogens. The U.S. Army released bacteria off the coast of California. Years later, reports of an outbreak of nosocomial *S. marcescens* infections contemporar to the release in an area hospital (Stanford University) were discovered. Army tests were suspected to have been the cause, but this was later deemed unlikely after typing of the strains showed they were not the same. Production of the microbe by the military stopped with the termination of the biological weapons program in the late 1960s.

S. marcescens was still being used in medical training as a tracer in the early 1970s despite a growing awareness of another aspect—its pathogenic potential. About the same time, use as a tracer in human systems appears to have been stopped because of the awareness of the pathogenicity of *S. marcescens.* In Project SHAD, it was used as late as 1973 but not reported to be used on human subjects.

S. marcescens is most commonly encountered as an opportunistic pathogen in nosocomial settings. It is typically associated with the use of invasive devices or procedures (e.g., surgical wounds, hemodialysis) and with patients whose health is generally compromised. Other associations are poor hygiene in health-care facilities and prior unsuccessful treatment of the patient with antibiotics. Heroin addicts are sometimes found to have endocarditis traceable to the pathogen.

Frequent or noted conditions associated with *S. marcescens* infection include compromised/suppressed immunity, recent surgery, diabetes, cancer, burns, alcoholism, and recent corticosteroid therapy. Chronic Obstructive Pulmonary Disease (COPD) is a possible co-factor, or at least one common associated disorder. Being bed-ridden, receiving oral care, and receiving mechanical ventilation and manipulative airway procedures have all been found to be risk factors. Age, both elderly and neonatal, may also be a risk factor.

One notable feature of *S. marcescens* infection is the microbe's powerful, enduring, and adaptable resistance to antimicrobial agents.

Among the devices and reservoirs of *S. marcescens* pathogenesis are intravenous solutions, surfaces of blood packs, bristles on shaving brushes, double distilled water, moistening fluids for umbilical cords, sponges, fiberoptic bronchoscopes, adhesive tape, eyedrops, defibrillators, EDTA blood-collecting fluid, urine bottles, sinks, liquid soap dispensers, polyethylene containers, shower caps, plastic bottle caps, saline solutions, and various disinfectant solutions. Flowers, food, sinks, and soil can contain *S. marcescens*. Mouthwash and plastic nebulizers are additional known reservoirs. The human gastrointestinal tract may be a reservoir but probably not for adults. Contaminated blood is a rare source of human infection by *S. marcescens*, however.

One type of therapeutic device notably associated with *S. marcescens* infection is soft contact lenses. The pathogen is able to survive on them and can cause conjunctivitis, infective keratisis with frequent permanent effects on the eye, and corneal opacity. The transmission to the lens is usually via contaminated lens fluids. Other common devices associated with the pathogen are indwelling catheters.

A broad variety of infectious conditions have been traced to *S. marcescens* exposure.

The effects of *S. marcescens* infections can involve just about every physiological system. Urinary tract infections (usually associated with indwelling catheters), septicemia, bacteremia, osteoarthritis, septic arthritis, otitis media, empyema, lymphadenitis, soft tissue/skin infections (e.g., necrotizing fasciitis), ocular infections (microbial keratitis, endogenous ophthalmitis), endocarditis, meningitis, peritonitis, and various respiratory conditions like necrotizing pneumonia have been implicated.

Where infection does occur, identification and typing can be done through culturing of body fluids and the use of standard commercial systems like the API 20E system and pulsed-field gel electrophoresis (PFGE).

S. marcescens infections can often be lethal. When not, they tend to follow an acute course and go into spontaneous remission as resistance to antibiotic therapy is strong. Chronic cases are not common but long-term local bone infections related to trauma are reported (one lasting 16 years), most of which ultimately resolve despite the failure of antimicrobial therapy. Ocular effects can be devastating, with enucleation required or blindness following infection. Long-term diminution of visual ability is also possible.

In some cases, long periods of incubation may be taking place as there are gaps of months to a few years between the possible onset of exposure and the manifestation of illness.

Psychogenic effects of exposure to the pathogen have not been specifically identified although the historic record from the period prior to scientific understanding of microbes and their action shows that reaction to its pigment appearing mysteriously has caused political and religious tensions.

Prevention of infection is the maintenance of a good hygienic regimen around debilitated persons to avoid the "person-to-equipment-to-person" transmission. Where instances of infection have taken place, isolation of those afflicted from other vulnerable persons is recommended. Treatment is difficult due to the pathogen's notorious resistance to microbial agents. Most therapy is to be supportive in nature, and most prevention is to be simple conscientious hygienic care. Amputation or other surgery of an infected area may be necessary.

Because of the broad scope of possible infections, it is hard for literature to encapsulate all the risks of *S. marcescens* exposure. Information from the Department of Defense on Project SHAD, while noting the microbe's pathogenic potential, does not directly point out that infection can be lethal.

Staphylococcal Enterotoxin Type B

Staphylococcal Enterotoxin Type B (SEB) is one of at least 17 enterotoxins produced by the common infectious pathogen, *Staphylococcus aureus*. SEB is a heat-stable, 28-kilodalton protein toxin. Unlike many other enterotoxins, SEB can cross epithelial and mucosal tissue intact. Its stability, toxic properties, and ability to be easily aerosolized make it an attractive biological weapon. SEB was part of the American biological weapon stockpile until the 1970s and was formally defined as a biological warfare agent in the 1972 Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.

Biologically, SEB acts as a superantigen, activating the immune system at picomolar concentrations. The toxin activates both T-lymphocytes and antigen presenting cells (APC) by crosslinking the class II Major Histocompatibilty Complex (MHC) on the APC to the Vβ chain of the T-cell receptor. These interactions result in the polyclonal activation of T-cells (predominantly a Th-1 response) along with and the release of various cytokines (interleukin-2 [IL-2], interferon-gamma, interleukin-6 [IL-6]), tumor necrosis factor–alpha (TNF-α), and chemokines (pulmonary and activation-regulated chemokine [PARC], MIP-1alpha, MIP-1beta, and MCP-1). Approximately 20% of all CD4+ T-cells can be activated by SEB as compared to 1 in 100,000 to 1,000,000 that are activated by a typical peptide antigen. Both CD4+ (helper) and CD8+ (cytotoxic) T-cells that express Vβ7 and Vβ8.1, 8.2, and 8.3 T-cell receptor chains (TCR) can be activated by SEB. In addition to activating T-cells, SEB exposure can induce anergy or unresponsiveness in memory T-cells and apoptosis in cells that initially proliferate. This can prevent the immune system from responding to pathogens and may be a mechanism by which *Staphylcoccus aureus* is able to evade the immune system.

The oral route of exposure is the best-known means of producing SEB-induced illness. Staphylococcal enterotoxins are common causes of classic food poisoning. The enterotoxic effects of SEB, the ability to produce nausea and emesis, appear to be distinct from its ability to stimulate T-cells. Nonetheless, the aerosol dispersion of SEB can be used as a weapon in military or bioterrorist actions. Because SEB intoxication is rarely fatal, its use is likely to be limited to inducing enemy incapacitation for a brief strategic period, rather than for inflicting large-scale mortality. The onset of action is usually 1–6 hours after exposure, and as little as 1 microgram of SEB can cause enterotoxic effects in adults.

Diagnosis can be difficult because by the time SEB's effects appear, the toxin has been cleared from the serum. Conclusive diagnosis of SEB intoxication is nevertheless most properly made through the use of enzyme-linked immunosorbent assays (ELISA) of tissues, body fluids, or environmental samples. Urine samples can be helpful for rapid diagnosis as the toxin may be discernibly present in less than 1 day of exposure. Nasal swabs similarly may yield positive results within 12–24 hours after exposure.

The clinical recognition of SEB intoxication can be difficult because of the general nature of the initial symptoms (e.g., fever, myalgia, nausea). Other toxins or agents causing nausea and vomiting must be ruled out, particularly the heat-stable toxin of *Bacillus cereus*. Intoxication with metals or nitrates can also yield similar symptoms. In the very early stages following SEB exposure when intense fever is prominent, distinguishing SEB intoxication from inhalation anthrax, tularemia, plague, or Q fever can be problematic in a biowarfare context.

The most commonly observed acute effects of SEB exposure are two syndromes that vary according to the main likely routes of exposure—oral and inhalational. (These, however, are not the only possible routes as SEB dermatitis from prolonged skin exposure has been demonstrated. SEB has been shown to contact and enter the body through *S. aureus* colonization of skin, wound infections, and feminine hygiene devices.)

The symptoms of oral ingestion of SEB are the well-observed effects of food poisoning. There is a sudden onset of nausea a few hours after food consumption, which is followed by vomiting, cramping abdominal pain, and watery unbloody diarrhea. Anorexia and dehydration are frequent. Fever is less common (about 25% occurrence) and pulmonary involvement is not associated with oral exposure. Tachycardia, hypotension, hyperperistalsis, and a diffuse nonlocalizing abdominal pain are also possible symptoms. The symptoms can be incapacitating but usually resolve quickly, even within 24 hours.

Inhalation exposures are more complex and last longer, generally 1 to 2 weeks. Symptoms usually manifest within a few hours of exposure. Symptoms of inhalation exposure typically commence with a fever that can run as high as 40°C. Myalgia, headache, chills, chest pain, rales, dyspnea, and a cough (usually nonproductive) tend to follow. Nausea and vomiting may also occur following exposure, but diarrhea has not been reported.

Death is uncommon in acute cases. Evidence from animal testing and human tissue suggests that ingested SEB may also be a causative factor in sudden infant death syndrome (SIDS). Relapse or recurrence is not reported for acute episodes except in rare cases of nonmenstrual toxic shock syndrome, where persistence of an *S. aureus* colony along with an absence of seroconversion explains the renewed effect of SEB a few days or weeks after an initial acute episode is resolved.

Though death is rare, severe and even fatal septic shock, including nonmenstrual toxic shock syndrome, are possible consequences of exposure to large dosages. High pulmonary doses may also cause chest pain, pulmonary edema, and an adult (or "acute") respiratory distress syndrome (ARDS). A common respiratory sign is patchy interstitial edema on radiologic examination.

In terms of long-term effects, SEB exposure has been increasingly implicated in the genesis and exacerbation of certain allergic diseases like atopic dermatitis, psoriasis vulgaris, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. SEB has also been implicated in the induction of autoimmune diseases such as Graves disease, arthritis, and even multiple sclerosis (MS). In a rare case, SEB exposure has been associated with a long-term elevation of liver function tests though the role of SEB exposure was deemed inconclusive.

Because there is no antitoxin, general supportive care—supplemental oxygen, hydration, pain control—for the term of the illness is the standard recourse for those afflicted by SEB. Protective masks are recommended as a measure to prevent against inhalation exposure. Decontamination is usually performed with a solution of sodium hypochlorite. A promising inactivated recombinant SEB vaccine is in development and has been tested on primates. Compounds known to inhibit TNF-α production, such as Pirfenidone, niacinamide, and pentoxifylline, have been shown to be effective in blocking both the immunological and toxic effects of SEB in cells and animals.

Psychogenic effects specific to SEB are not reported. (General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents.") Secondary literature is fairly comprehensive and consistent on the subject of SEB, but the association of SEB exposure with chronic allergic diseases, autoimmune disorders, and sudden infant death syndrome are not treated in general discussions of the toxin as a warfare agent.

Sulfur Dioxide

Sulfur dioxide (SO_2) has the Chemical Abstracts Service Registry Number 7446-09-5. Under normal conditions, it is a colorless gas with a pungent odor. Sulfur dioxide is a significant component of air pollution and also has a variety of industrial applications, from refining raw materials to preserving food. In Project SHAD, SO_2 was tested to determine if it could be used as a simulant for the nerve gas sarin.

As sulfur dioxide is normally a gas, most exposure is likely to be through the respiratory tract, where the chemical's ready solubility causes it to produce sulfurous acid (H_2SO_3), a severe irritant. Additionally, sulfur dioxide produces H+, bisulfate (HSO3–), and sulfite (SO3=), which affect the smooth muscles and nerves involved in bronchoconstriction. These reactive ions have been shown to affect sodium currents and potassium currents in neurons.

The lungs are particularly susceptible to both the chronic and acute effects of SO_2. Acute reactions to the compound, which typically occur at levels higher than the odor threshold and standard permissible levels, include irritation, bronchoconstriction, asthma-like symptoms, and respiratory distress. Asthmatics can be particularly susceptible to the pulmonary effects of SO_2. Permanent impairment of lung function, particularly in the form of reactive airways dysfunction syndrome (RADS), chronic pulmonary disease, or Chronic Obstructive Pulmonary Disease (COPD), can result from exposures to high enough levels; asthmatics may suffer enhanced sensitivity.

SO_2 may also cause damage to developing fetuses and to the reproductive system. The testes in particular appear to be especially vulnerable to permanent toxic effects, indicated from both animal and human data. Chronic exposures to elevated SO_2 levels are associated with increases in cerebrovascular and heart disease, pulmonary disorders, increased morbidity and mortality, and low birth weights.

At the cellular/molecular level, SO_2 decreases levels of antioxidant enzymes, increases membrane permeability, causes chromosome breakage, and is mutagenic or comutagenic.

There exists evidence of a possible correlation between elevated SO_2 levels and increases in cancer. While evidence suggests sulfur dioxide to be a co-carcinogen, there is insufficient evidence to show that it causes cancer directly. (The International Agency for Research on Cancer (IARC) finds SO_2 to be *not classifiable as to its carcinogenicity* to humans [IARC Group 3], citing inadequate or limited evidence of carcinogenicity from either human or animal studies.)

Psychogenic health effects of perceived exposure to sulfur dioxide have been speculated to have occurred during pollution scares. Respiratory and cardiovascular diseases were proportionately increased in one incident although it could not be ruled out that the increase was from other causes. Information on the general psychogenic issues and effects of perceived exposure to biological or chemical warfare agents is contained in the supplement report under this contract, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Recommended treatments for sulfur dioxide exposure include 2% sodium bicarbonate sprayed into the air as well as inhaled into the lungs to neutralize its effects. Other treatments for SO_2 exposure include s-carboxymethyl-cysteine for asthmatics; theophylline, zafirlukast (a leukotriene receptor antagonist), and albuterol for patients with a specific allergy.

Trioctyl Phosphate

Trioctyl phosphate (TEHP), more commonly known as Tris(2-ethylhexyl) phosphate, bears the chemical formula C_{24}-H_{51}-O_4-P and is identified by the Chemical Abstracts Service Registry Number 78-42-2. It normally appears as a colorless viscous liquid possessing a low vapor pressure. It is soluble in alcohol, acetone, and ether but insoluble in water.

Tricotyl phosphate is ordinarily used as a plasticizer or fire retardant. It is commonly employed as a component of vinyl stabilizers. More than 10 million pounds of TEHP is produced worldwide each year. In Project SHAD, TEHP was used as a simulant for the chemical warfare nerve agent VX.

A National Toxicology Program (NTP) set of studies on TEHP was performed in 1984 and serves as the main source for TEHP toxicology. Its overall profile was of a substance with little toxic risk, though with some areas of concern. Those areas related to positive carcinogenic indications from certain chronic animal tests, and to mild acute irriation effects. The report also included a subchronic dog and rhesus monkey study that suggests chronic lung injury is possible due to continuous inhalation exposure.

Mammalian acute toxicity of TEHP tends to be very low, with median lethal oral animal doses exceeding testing levels in rats and mice. Acute findings indicate TEHP induces mild temporary irritation on the skin, eye, and respiratory systems. Moderate erythema on shaved skin has been reported for rabbits. Effects on the eye are usually mild, with animal studies showing very mild irritant effects or a causing temporary and moderate conjunctivitis in rabbit (Draize) testing. Acute inhalation exposure is only harmful at high doses with continuous exposure. Wistar rats experienced no mortality at a concentration of 287–460 mg/m^3 for 30 minutes. Guinea pigs experienced about 30% mortality at the same concentration after 60 minutes, which increased to 80% after 2 hours.

Human studies and case reports are not found in the published literature, with the exception of an NTP skin test on human volunteers, which resulted in no signs of significant skin irritation. Chronic and subchronic studies in

animals did show a mild chronic inflammation in dog lungs after 3 months of regular exposure to up to 85 mg/m^3. Other than that effect, which was restricted to dogs, no dogs or rhesus monkeys (the other tested animal) showed any signs of toxic effect. Neurotoxicology testing indicates no inhibition of cholinesterase activity, and no signs of delayed neurotoxicity. Cytotoxicity and micronucleation was not found in a series of rat exposures to aerosolized trioctyl phosphate.

Trioctyl phosphate is not classified anywhere as a human carcinogen. There is also no evidence of genotoxicity. Bacterial tests (*Salmonella* tester strains TA 98, TA 100, TA 1535, TA 1537) showed no signs of mutagenicity regardless of the presence of S9 liver fraction. Tests for sister-chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells have also been negative for genotoxicity.

Hyperplasia in thyroid follicular cells has been observed in rodents in a 2-year study. Weight loss was also reported in rats and mice after long-term exposure, but it was not found to be harmful or to have resulted from toxic action.

Some evidence of possible carcinogenicity has been found in the increase of hepatocellular carcinomas in female-only B6C3F1 mice in one NTP 2-year gavage test. Equivocal evidence has also been found in the dose-related presence of pheochromocytomas appearing in some male rats. The evidence from the studies has been deemed insufficient to establish a significant risk of human carcinogenicity. Four factors were decisive in that assessment: the neoplastic tumors occured in only one sex of one species, hepatocellular carcinoma tumors are considered rare in general, genotoxicity evidence is absent, and the background incidence of pheochromocytomas in rats is too variable to establish the significance of the tumor's appearance in the non-control rodents.

(Some studies suggest that 2-ethylhexanol, a metabolite of TEHP, as well as an ingredient of its manufacture and a characteristic component of chemicals with the 2-ethylhexyl moiety, may constitute a factor in any TEHP carcinogenic potential.)

Psychogenic effects specifically of trioctyl phosphate are not known. General psychogenic effects of perceived exposure to agents of chemical and biological warfare are examined in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents." Treatment of exposure to trioctyl phosphate is the standard regimen of assistance to anyone exposed to a general or unknown toxic substance. Laboratory facilities involved in caregiving ought to monitor the affected person's complete blood count and perform urinalysis if necessary. Liver and kidney function tests are suggested for patients with significant exposure. In cases of respiratory tract irritation or respiratory depression, the caregiver should monitor arterial blood gases, and chest x-rays, and perform pulmonary function tests.

Secondary sources do not appear to contain significant errors or oversights in treating the toxicology of TEHP, although *Patty's Toxicology* contains no separate monograph on trioctyl phosphate. The Hazardous Substances Data Bank of Toxnet at the National Library of Medicine contains a scattering of not clearly organized or updated information. For example, at one point it cites in all capital letters an outdated assertion that there are no long-term toxicity studies of trioctyl phosphate.

Pasteurella tularensis

Pasteurella tularensis is currently known as *Francisella tularensis*, which is the term employed throughout this report. Its newer name derives from the one developed by U.S. Public Health Service physician and scientist Edward Francis who pioneered the study of the microbe and its associated affliction, tularemia. Francis's work on infectious pathology would result in his nomination for a Nobel Prize, as well as his failure to follow through on that nomination process due to his hospitalization from the effects of another infectious agent he acquired from his dogged field and laboratory research. Ultimately considered a possible pathogen for Cold War–era biowarfare, *Pasteurella tularensis* was eventually renamed *Francisella tularensis* to give Francis his due, an effort initiated and pursued by admiring scientists from America's Cold War enemy, the Soviet Union.

Francisella tularensis is a Gram-negative small pleomorphic facultative intracellular coccobacillus. It is a zoonosis, most associated with tick bites or being in contact with infected animal carcasses or meats. Transmission of the pathogen to humans in an aerosol or dust form is also possible and is the likely method for bioterrorism or biowarfare use. Culturing a sample of *F. tularensis* can be dangerous (biosafety level 3 is the usual laboratory

requirement), and so determination of the pathogen's presence is typically performed by serology. An agglutin titer greater than 1:160 is the standard determinant. Generally, however, those levels are not reached until close to the second week of infection. A skin test developed by the U.S. Army (Active E-rosette test) has a high degree of specificity but also can yield a positive result over 3 decades after infection and illness by *Francisella tularensis*.

The incubation period of tularemia normally falls within a 3–6-day range but shorter and longer periods have been observed. When not asymptomatic, the infection usually presents as an acute febrile illness, along with some or all of the following generalized symptoms: chills, headaches, weight loss, emesis, diarrhea, muscle aches, joint pains, dry cough, hepatitis, and jaundice in serious cases. The fever is often biphasic, peaking twice in the first month of debilitation. In general, the full course of the illness is 1 month of fever, 1 month of complete weakness, and 1.5 months of gradual but complete recovery.

More extended infections have been reported to have durations lasting for several months to a few years. Only one case exists in the literature, however, in which a person continued to manifest recurrences (fever and ulcerations) over a clearly observed period (by the National Institutes of Health) lasting over a decade, and with no complete recovery ever recorded. Another older report also exists of an acute and atypical case that involved a peripheral neuropathy in which the elderly patient could no longer dorsflex his foot, and this ability was not known to have subsequently returned.

No case has been found of a person who first manifested symptoms many months to years after initial infection. This is so despite the likelihood of a long-term persistence of some *Francisella tularensis* pathogens in previously diseased individuals. In light of this, it is not surprising that tularemia is normally considered a strictly acute disease granting extraordinary immunity, if one survives it. In pre-antibiotic times, death rates of about 20% were reported, associated particularly with pre-existent health debilitations, delays in seeking treatment, and septicemia. In more recent times, this rate has been reduced to less than 4% through therapeutic intervention.

Locally and systemically, tularemia manifests acutely in several syndromes, often related to the manner of contact and inoculation. These syndromes are the ulceroglandular, the glandular, the oculoglandular, the pneumonic, the oropharyngeal, and the typhoidal. The rare typhoidal form is more deadly than the others, and also the most likely to result from aerosol contact. Respiratory involvement and lymphadenitis is very common in all varieties, however, though patients may not always present overt respiratory troubles. In the most common syndome, the ulceroglandular (as well as the oculoglandular and glandular syndromes), local lymphadenopathies, skin eruptions, and ulcerations are the common manifestations of tularemia in addition to the generalized symptoms. The manifestations in those syndromes typically occur at the place of initial inoculation (e.g., the eye in the case of oculoglandular tularemia).

F. tularensis has an affinity for the skin, lymph system, lungs and, to a lesser extent, liver. Differential diagnoses include "ulcer node" syndrome, rat-bite fever, cat-scratch disease, mycobacterial infection, chancroid, chancre, nocardiesis, sporotrichosis, cutaneous anthrax, inhalational anthrax, *Erysipelothrix*, pneumonic plague, influenza, mycplasma pneumonia, staphylococcal/streptococcal lymphadenitis, Legionnaire's disease, Q fever, bacterial pneumonia, brucellosis, *Listeria*, syphilis, lymphogranuloma venereum, scrub typhus, and plague.

Reflecting tularemia's protean manifestations, cases have been known to also present atypical signs and effects involving systems beyond the more common ones described above. Some neuropathies (peripheral and central) are reported, and meningeal and meningoencephalitic involvements have occurred (especially among children). Pericarditis, typically among those with pre-existing cardiac impairments, is an unusual but nevertheless well-known complication of tularemia. Cardiac complications tend to resolve with recovery from tularemia infection. Recovery tends to be complete after the acute period of about 3.5 months, but cases of greater duration are known.

Abdominal involvement is rare, but liver and spleen enlargement, sometimes with systemic jaundice, does occur. Tularemic disorders of the gastrointestinal tract are relatively rare; enteritis and appendicitis are mentioned in the literature but not as significant effects. Psychogenic effects specific to *F. tularensis* exposure have not been reported. The general question of possible psychogenic effects arising from the awareness of exposure to chemical and biological warfare agents is contained in the supplement, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Treatment for tularemia is usually the early administration of aminoglycoside antibiotics. Streptomycin and gentamicin are the common therapeutic agents. A vaccine (LVS—"live vaccine strain") was developed at Ft. Detrick

in the 1960s but it has proved only of limited effectiveness, primarily against the typhoidal form of tularemia and a weaker strain of *F. tularensis.*

The secondary literature, including that of the Department of Defense, does not offer significant contradictions to each other or to the information in the literature on tularemia. They acknowledge that it is an acute disease with no significant demonstrated long-term or late developing effects, but nevertheless they note that it can be serious and life-threatening, especially if untreated.

Uranine

When Johann Strauss composed the classic waltz, the "Beautiful Blue Danube" in 1867, he could not have known that, only 10 years later, a famous part of the blue Danube—its "sinks" in the upper river region—would turn green. The color change would be temporary and artificial, however, as it was the result of one of the first uses of fluorescein, a fluorescent tracer dye. Soon thereafter its more water-soluble sodium salt would circulate under the industrial name Uranin or Uranine. The dye would go on to have enormous and still-continuing important medical and environmental uses.

Uranine dye is known in more scientific circles as sodium fluorescein (or fluorescein sodium), as well as disodium fluorescein. It has the chemical formula C_{20}-H_{12}-O_5-2Na and the Chemical Abstracts Service (CAS) Registry Number 518-47-8. The name fluorescein is often used carelessly and interchangeably with the various compounds derived from fluorescein, including sodium fluorescein/uranine. In this report, therefore, the term uranine is used to mean specifically the sodium salt of fluorescein (CAS #518-47-8). The term fluorescein is used to mean the acid compound, fluorescein, which is identified by the CAS #2321-07-5 and has the formula C_{20}-H_{12}-O_5.

Uranine is freely soluble in water and alcohol; after dissolution it emits a bright yellowish-green fluorescence, especially under blue light. This indicator dye tends to appear more green the more alkaline the medium. Its use in ocular therapy is long-established: first synthesized in 1871, by 1882 uranine was being used as an injected dye for examining ocular fluid dynamics in cases of glaucoma. In 1959, it saw its first use in its most widespread application, intravenous fluorescein angiography, considered a vital advance in the examination of the pathophysiology of retinal diseases. Uranine is also used in topical ocular diagnostic and therapeutic applications.

Uranine is useful as a dye to trace cerebrospinal fluid leaks during surgery. Outside of medical uses, uranine is also used to trace the flow of subterranean waters. It functions also as a dye in cosmetics. In Project SHAD, uranine dye was used as a tracer for the biological agent Stapphylococcal Enterotoxin Type B. Increasingly, it is used as a tracer for the activity of inhaled particulates.

Typically, injected uranine takes less than 20 seconds to circulate in the blood stream. When absorbed, uranine is rapidly metabolized thorough glucuronidation in the liver. 80% of the dose is usually metabolized within in 1 hour. The pharmacodynamics and toxicodynamics of fluorescein are not well understood.

Animal studies show very low toxicity. At very high doses, death occurs from CNS depression, and one study suggests sensitivity to light exposure.

There exists a great deal of clinical data on the effects of injected uranine. Systemically, the common responses to injection range from a nontoxic yellowing of the skin to acute severe reactions up to and including (in very rare circumstances) mortality. The adverse effects of fluorescein angiography are usually grouped into three broad categories: mild, moderate, and severe. Males appear to be more susceptible to adverse effects than females.

The main mild adverse effects are transient nausea, vomiting, local pruritus, extravasation, and some allergic reactions. Urticaria, lowered pulse rate. syncope, dyspnea, and local effects at the injection site and region (thrombophlebitis, subcutaneous granuloma, neuritis) are among the more moderate reactions. The more severe reactions include respiratory effects like laryngeal edema, pulmonary edema, bronchospasms, anaphylaxis along with certain cardiac effects like basilar artery ischemia, circulatory shock, myocardial infarction and cardiac arrest. Tonic-clonic seizure is a noted neurologic reaction. Death can occur, though very rarely, about one case being reported per year. The main risk factor in such reactions appears to be a prior adverse reaction to uranine treatment.

The main noted risk factor in a fluorescein angiography appears to be a prior adverse event.

Local administration affects certain systems in observed ways. Topical ocular administration has produced transient discoloration and conjunctival chemosis. This occurred only when accompanied by active inflammatory

disease. When uranine has been employed intrathecally as a tracer for cerebrospinal fluid leaks in surgery, suboccipital punctures have resulted in cases of grand mal seizure, which did not seem to occur when suboccipital punctures were stopped. Lumbar administration has yielded severe neurotoxic signs: temperature elevation, headache, nausea, vomiting, dizziness, nuchal pain, and grand mal seizures.

Increasing interest in inhalation drug therapy has resulted in the use of uranine in pulmonary exposure experiments. The kinetics of such exposure include very rapid absorption by the lung and without any significant metabolism inside the lung. No studies or reports of toxic effects from this type of exposure have been found. A recent correspondence from a leading investigator in the field reports that although there is an absence of existing studies on the toxicity of inhalation exposure to uranine, studies with aerosolized uranine have been ongoing for several years in European hospitals with no untoward clinical effects of any kind known.

The only known studies of carcinogenicity go back to two tests in Japan in the 1950s. Cancerous tumors at the application site were elicited after chronic application of large concentrations of uranine. These results have been deemed equivocal evidence only of tumorigenicity by the Registry of Toxic Effects of Chemical Substances (RTECS). A screen for the carcinogenic/mutagenic potential of compounds using DNA cell binding assay gave inconclusive results for uranine. Other results from a genetic toxicity screen to predict carcinogenicity, *Salmonella*/microsome mutagenesis, chromosome aberration, sister-chromatid exchange, and mouse lympoma mutagenesis assay were compared for consistency to assess DNA damage from chemicals. Uranine yielded either negative or equivocal results for tumorigenicity and genetic toxicity and positive activity both with and without exogenous metabolic activation for sister-chromatid exchange.

Neither uranine nor fluorescein has been found by the International Agency for Research on Cancer (IARC), or any other authoritative agency, to be carcinogenic. No human cancer effects reports or studies have been found.

Psychogenic reactions brought on by the manner of uranine administration have been suggested to explain some adverse effects. A variation in response to fluorescein angiographies by gender has been noted in that regard. Observed reactions like syncope, hypotension, and lowered pulse rate (vasovagal effects) have been suggested to arise from the nature of the treatment, which is the internal injection of a discoloring and glowing substance while cameras are brought to peer into the inner eye along with strange bodily effects (e.g., skin discoloration) that can occur. Other psychogenic issues, such as the general stressor reactions to perceived exposure to a contaminant in biological and chemical warfare testing, are treated in the supplement under this contract, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Standard prophylaxis is to have an emergency tray and oxygen supply handy when a uranine procedure is performed. It has been shown that persons with allergic sensitivities benefit from a prophylactic administration of antihistamines. Epinephrine followed by diphenhydramine hydrochloride may be necessary for patients who have a hypotensive reaction.

Secondary sources (outside the field of ophthalmology) do not contain a great deal of data on uranine except in the context of fluorescein angiography. The confusing and careless interchangeable use among fluorescein, sodium fluorescein, and the term uranine (dye) can render research problematic. The Hazardous Substances Data Bank conflates acid fluorescein with the disodium salt fluorescein (i.e., uranine) in the same entry. *Patty's Toxicology* contains only a brief reference to fluorescein angiography and no section on fluorescein or sodium fluorescein (uranine).

VX Nerve Agent

VX nerve agent (VX) is a chemical warfare nerve agent. Its chemical formula is $C_{11}H_{26}NO_2PS$. Its formal chemical name is O-Ethyl S-(2-diisopropylaminoethyl) methylphosphonothiolate. Due to the existence of several isomers, VX has several Chemical Abstracts Service Registry Numbers: 50782-69-9, 51848-47-6, 53800-40-1, and 70938-84-0.

VX is an organophosphate compound and it belongs to the specific class of compounds known as the phosphonothiocholines. The "V" in VX stands for "venom," a tribute to this compound class having high potency and a characteristic ability to penetrate the skin. At normal temperatures, it is an oily liquid of low volatility with viscosity similar to motor oil.

Ranaji Ghosh first synthesized VX in the early 1950s. The British government noted VX's potential as a warfare agent and shared its research with the U.S. Army Edgewood facility. Eventually large quantities of VX were produced through the 1960s at a Newport Indiana facility. Some stocks still remain there and on other bases and were slated for destruction in 2004. The Soviet Union developed a related compound called Russian VX [O-Isobutyl S-(2-diethylamino) methylphosphonothioate].

VX has been the subject of accidental releases and controlled releases, and has been used as a weapon. The largest reported accidental release occurred at Utah's Dugway Proving Grounds on March 13, 1968, when approximately 9 kg of VX drifted over adjacent grazing land, killing over 6,000 sheep. There was also an accidental release of a nerve agent (sources conflict on whether VX was involved) at a storage facility in Okinawa in 1969, which resulted in the hospitalization of 23 military personnel and 1 civilian. In Project SHAD at least two test releases on ships have been reported.

In addition to releases by the U.S. Army, VX was used by the Aum Shinrikyo cult in Japan to kill several dissident members and others opposed to the cult. It may have also been used by Iraq as part of a cocktail in the Iran–Iraq war and to quell Kurdish uprisings in the 1980s. U.S. troops were exposed to nerve agents during destruction and disposal operations in the Gulf War, though VX is not reported to be among those agents.

VX is a potent and selective inhibitor of acetylcholinesterases (AChE), which results in the accumulation of acetylcholine in the synapses of both central and peripheral nerves. VX, in contrast to other nerve agents inhibits AChE significantly more than plasma cholinesterases. VX exposure and action results in intense stimulation of nicotinic, muscarinic, and central nervous system (CNS) receptors. Toxic effects are generally seen when over 50% of the AChE enzyme is inhibited. Death typically occurs when over 90% of the AChE enzyme is inhibited. Death is usually due to inhibition of the enzyme in the brain and diaphragm.

The increased amounts of acetylcholine in the brain produced by VX exposure leads to the release of large amounts of excitory amino acids, which stimulate NMDA receptors and result in neuronal toxicity. Seizures typically occur when 25–75% of AChE is inhibited and always occur during exposure to supralethal doses. Convulsions without treatment can lead to permanent neurological damage.

In addition to the inhibition of acetylcholinesterase, VX has been shown to bind to and block postjunctional glutamate receptors, nicotinic acetylcholine receptor-ion channels, and muscarinic acetylcholine receptors. The role of receptor binding and inhibition in toxicity is not clear. Studies in mice in which the acetylcholinesterase gene has been knocked out indicate that other targets of organophosphates may play a major role in toxicity and lethality.

The toxic effects of VX can be grouped around the types of nerve receptors overstimulated by acetylcholine. The muscarinic effects are typically miosis, headaches, blurring of vision, rhinorrhea, bradycardia, anorexia, nausea, vomiting, diarrhea, increased sweating, and lacrimation. The nicotinic effects are typically fatigue, muscular twitching, cramps, and paralysis of muscles (including respiratory muscles). The acute CNS effects are typically generalized weakness, cyanosis, hypotension, convulsions, loss of consciousness, coma, and death. Longer-term CNS effects including anxiety, insomnia, tremor, headaches, drowsiness, difficulty in concentration, memory problems, confusion, slurred speech, and ataxia have been associated with organophosphate poisoning but not VX specifically.

There currently are no commercial test kits that diagnose VX exposure. Diagnosis is from signs and symptoms. Gas chromatography coupled with mass spectrometry (GC-MS) can detect metabolites of VX in both urine and serum. Several tests have been developed that attempt to identify nerve agent poisoning through the quantification of cholinesterase activity in blood. The monitoring of AChE activity is a reliable marker for systemic toxicity. Systemic toxic effects are seen in approximately 50% of subjects when 75% of red blood cell AChE is inhibited. A more recent test relies on the ability of potassium fluoride to reactivate enzymes such as butyryl-cholinesterase and release fluorinated compounds. This technique can be used to monitor low levels of exposures and unambiguously identify both nerve agents and pesticides.

VX is considered to be the most toxic of the nerve agents developed for chemical warfare. Course, symptoms, and relative toxicity, however, can vary considerably by exposure route and dose. The human dermal LD_{50} (Lethal Dose) is estimated to be as low as 0.04 mg/kg; human inhalation LCt_{50} (Lethal Concentration) is estimated to be 36 $mg \cdot min/m^3$. By inhalation, it is twice as lethal as sarin. It is also 10 times more toxic in inducing miosis. VX

is at least 100 times more toxic than sarin as a percutaneous agent due to its low volatility, its stability, and its lipophilicity.

The effects of exposure by inhalation usually occur within minutes. Miosis, rhinorrhea, and airway constriction are initially seen at low to moderate concentrations. Larger doses of VX result in loss of consciousness, seizures, cessation of cardiac and respiratory activity, and death in the absence of medical treatment. Neuropsychiatric effects including loss of memory and depression are also seen but are relatively short-lived following exposure to VX.

The onset of symptoms can take hours when sublethal doses are applied to the skin. A small drop may initially cause localized muscle twitching and sweating, followed by nausea, vomiting, diarrhea, and generalized weakness. These symptoms typically last for several hours. Systematic dermal studies in humans showed vomiting occurred in 33% and 67% of subjects when red blood cholinesterase activity was 30–39% and less than 20% of control activity. Other studies have shown that a dose of 5 mg/kg of VX resulted in systemic toxicity in roughly half of the subjects. Persons whose skin is exposed to higher doses of VX may show no symptoms for up to 30 minutes, but then rapidly suffer loss of consciousness, convulsions, difficulty breathing, profuse secretions from nose and mouth, generalized muscle twitching, paralysis, and death. At lethal and near-lethal levels of exposure loss of consciousness, convulsions, flaccid paralysis, and apnea are seen. At high doses there is also a more rapid onset of signs and symptoms. Clothing, site of skin exposure, and temperature can greatly affect the nature and toxicity of dermal exposure.

Animal studies have indicated VX can cause cardiac effects, although these effects have not been seen in human volunteer studies. Arrhythmias were seen both in rats and dogs at doses that did not result in convulsions. Electrophysiological studies using guinea pig heart tissue showed that VX exposure led to a positive inotropic effect, two contractile events in response to each stimulation, and the development of delayed after-depolarizations**.** VX cardiac toxicity has been attributed to the inhibition of the rat cardiac Na+,K(+)-ATPase alpha 1 isoform.

Few studies have addressed long-term toxicity or effects of nerve agents in general and VX in particular. Textbooks indicate that most if not all of the effects of nerve agents dissipate within months after exposure. A recent telephone survey of over 4,000 volunteers who had participated in programs that involved exposure to chemical agents between 1955 and 1975 at the Edgewood facility found fewer attention problems as the only statistically significant differences between those exposed to nerve agents and those exposed to other chemical agents but it also found greater sleep disturbances in volunteers who had been exposed to nerve agents. VX differs from other nerve agents in that it does not appear to undergo aging or stabilization but does undergo spontaneous reactivation.

Unlike many other organophosphates, VX also has not been shown to induce a syndrome called organophosphorus-induced delayed neuropathy (OPIDN). OPIDN results from the inhibition of the enzyme neuropathy target esterase (NTE; also termed neurotoxic esterase). VX has been reported to be at least 1,000 times less effective than sarin in inhibiting NTE. The failure of VX to inhibit neuropathy target esterase and cause organophosphorus-induced delayed neuropathy together with the inability to "age" when bound to AChE or other proteins indicates that VX may not cause much of the long-term toxicity associated with other organophosphates.

VX has tested negative in a number of assays for mutagenicity, with and without metabolic activation. Human studies in personnel working with VX on a daily basis found no increased incidence of cancer. The teratogenic potential of VX has also been evaluated in sheep, rats, and rabbits; all have all been negative for teratogenicity. VX has not been deemed a carcinogen by any authority.

In regard to long-term neurotoxicity, VX has not been shown to have delayed or persistent psychological effects or to result in any long-term EEG changes. OPIDN has not resulted from VX exposure. Convulsions without treatment can lead to permanent neuropathogical damage.

Brain damage has been seen in animals injected with VX. Microinjections of VX into the amygdala resulted in convulsions and resultant neuropathology. Much of the brain damage that has been observed is believed to be due from the induction of convulsions and not the direct toxic actions of VX. Studies on neuroblastoma cells have indicated that VX displays some toxicity presumably through binding to muscarinic receptors.

No studies have been found addressing purely psychogenic effects arising from an awareness of, or a perception of, exposure to VX specifically. But the use of another organophosphate agent (sarin) in terror attacks in Japan in the 1990s has led to some investigation and consideration of the possible psychogenic effects of exposure to a nerve agent. Discussion of those reports appear in the review prepared under this contract for the health effects

of sarin. Information on the general psychogenic effects of perceived exposure to biological or chemical warfare agents is contained in the supplement report under this contract, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

There have been several approaches towards the treatment of, and protection against, VX exposure. Barrier methods, including garments, respirators, and even protective creams have been developed that will protect against even high levels of VX exposure. The use of reversible inhibitors of AChE to protect against subsequent exposure to nerve agents has been pursued extensively by the U.S. military. Pyridostigmine bromide was used by a large number of troops during the Gulf War to protect against possible exposure to soman and other nerve agents. Several studies since then have implicated pyridostigmine as a potential contributory factor in the induction of Gulf War Syndrome, a multi-symptom illness found in a number of veterans who served in Iraq. Other reports have since questioned its utility in protecting against VX exposure.

Several other agents have also been proposed for prophylaxis against nerve agent exposure. Both physostigmine and hyoscine has been reported superior to pyridostigmine in preventing the death of animals following VX exposure. Huperzine has also been found to be a more effective prophylactic agent than pyridostigmine. In contrast to other prophylactic agents, huperzine does not inhibit butyryl-cholinesterase (plasma), which can then still act to scavenge nerve agents.

To prevent mortality and minimize morbidity, aggressive medical intervention should be pursued following nerve agent exposure. Thorough decontamination should occur immediately following suspected exposure. Casualties should be decontaminated as fast as possible but should not be moved into clean treatment areas until decontamination is complete. Bleach should be used extensively to decontaminate any area or material where exposure has occurred. Atropine sulfate, an anticholinergic agent, should be administered as soon as possible following decontamination. Oxygen or oxygen-rich air should be used for ventilation if available. Oximes, such as pralidoxime salts, should also be administered as soon as possible to regenerate AChE enzymes. Early intervention to prevent or treat convulsions is also an essential component in the treatment of nerve agent poisoning. Imidazenil, a partial selective allosteric modulator of GABA action, has been shown to be more effective than diazepam in protecting rats against organophosphate-induced convulsions and death.

Secondary literature on VX generally adequately covers its well-known lethality and toxicity. Researchers ought to be cautioned to note that VX, due to varied isomers, has multiple CAS Registry Numbers.

Zinc Cadmium Sulfide

Zinc cadmium sulfide (ZnCdS) is a brightly fluorescent, stable compound formed by sintering ZnS (zinc sulfide) and CdS (cadmium sulfide). ZnCdS has several CAS (Chemical Abstracts Service) Registry Numbers. It is used in pigments, and its fluorescence is employed as a visualization agent for applications such as histology and nanotechnology. It was used in Project SHAD as a tracer for chemical and biological warfare agents because it was regarded to be a harmless dye.

Very little is published about its health effects. What little there is suggests minimal toxicity. Older studies found that ZnCdS did not induce deaths in dogs or rats despite extraordinarily high oral doses. No epidemiological, clinical, or case studies demonstrating deleterious effects from exposures were found. Personnel who had been most exposed during tests of the compound in the United Kingdom did not show unusual or discernible health consequences.

The National Research Council (NRC) published a book-length report in 1997 on ZnCdS toxicity arising out of public concern over the exposure of civilian populations to the compound during U.S. Army biological warfare testing in the 1950s and 1960s. The NRC found little literature existing on the subject and concluded that toxic effects of the compound are highly unlikely as the substance is insoluble and very unlikely to become bioavailable. Nonetheless, the NRC proceeded on a "worst-case" assumption that if ZnCdS were to degrade into its original sintered components, the most harmful product would be CdS. The report then focused upon the toxicological effects of CdS. It concluded that the amount of cadmium that people were exposed to in the trials was too low to pose a significant health risk.

A follow-up study by the U.S. Army concluded that particulate ZnCdS remained intact in rats after pulmonary

exposure and supported the NRC supposition that the compound was poorly bioavailable. ZnCdS was found to pass through the alveolar walls via macrophage action, but Zn and Cd were found present in the kidneys only in small amounts, were barely present in the liver, with no significant increase found in the blood. Proportionate (though slow, over 14 weeks) removal of Zn and Cd from the lungs indicated that the compound did not fragment; low liver and no significant blood levels of ZnCdS further argued against bioavailability. Some lung clearance was mucociliary in nature.

Some minor local and transitory toxic effects were noted: lung and lymph node inflammations, accumulations of foreign bodies in the lung, and altered enzyme, protein, and cell count levels. The experimental doses tested (on a body weight relative basis) far exceeded (at least by a factor of 500) the highest level of human exposure in previous U.S. Army tests. No other health effects were reported.

Other literature and uses of ZnCdS indicates that it lodges in capillaries after administration into the bloodstream. This is perhaps a factor to consider if ZnCdS is capable of passing into the bloodstream through the alveolar epithelium or other means.

A review of cadmium toxicity as a "worst-case" scenario (rendered less likely in light of the finding of zinc cadmium sulfate's lack of degradation and lack of bioavailabilty in the rat) reveals concerns over cancer, particularly lung cancer, although the high level of human carcinogenic potential of conventionally assumed to be the case has lately been challenged. CdS, the main toxic component of ZnCdS, has been shown to be genotoxic, and recent studies show clastogenesis.

Possible effects of acute exposure to cadmium include acute chemical pneumonitis or metal fume fever. There is typically no inflammatory response to cadmium sulfide (in contrast to observed effects of ZnCdS in the rat lung). Renal toxicity has been noted and long-term exposure to cadmium, even at low doses, damages kidney tubules and results in renal dysfunction.

No psychogenic effects of exposure to ZnCdS are reported. General reactions to perceived exposure to agents in biological and chemical warfare uses can be found in the supplement under this contract, "Psychogenic Effects of Perceived Exposure to Biochemical Warfare Agents."

Secondary source literature is sparse and multiple CAS numbers and terminological variations complicate searching. The CAS number used by the NRC is used by NIOSH to identify a product called "Cadmium Sulfide, Solid Soln. With Zinc Sulfide Silver Chloride-Doped" while "Cadmium Zinc Sulfide" is identified as 12442-27-2. British documents prefer to render "sulfide" as "sulphide."

No published specific handling instructions for ZnCdS were found.

REFERENCES

Ackland, J. R., D. A. Worswick, and B. P. Marmion. 1994. Vaccine prophylaxis of Q fever. A follow-up study of the efficacy of Q-Vax (CSL) 1985-1990. *Medical Journal of Australia* 160:704-708.

Ayres, J. G., N. Flint, E. G. Smith, W. S. Tunnicliffe, T. J. Fletcher, K. Hammond, D. Ward, and B. P. Marmion. 1991. Post-infection fatigue syndrome following Q fever. *QJM: Monthly Journal of the Associations of Physicians* 91:105-123.

Beslagic, E., S. Hamzic, S. Zvizdic, T. Bajrovic, and R. Velic. 2002. Laboratory diagnosis of Q-fever with the indirect immunofluorescence test. *Medicinski Arhiv* 56(2):89-92.

Beslagic, E., S. Hamzic, S. Puvacic, and S. Cavaljuga-Hotic. 2003. Q-fever serologic diagnostics with inhabitants of Canton of Sarajevo 2001 year. *Medicinski Arhiv* 57(2):71-74.

Burg, A. W., M. W. Rohovsky, and C. J. Kensler. 1977. Current status of human safety and environmental aspects of fluorescent whitening agents used in detergents in the United States. *CRC Critical Reviews in Environmental Control* 7:91-120.

Burnet, F. M., and M. Freeman. 1937. Experimental studies on the virus of "Q" fever. *Medical Journal of Australia* 2:299-305.

CFSAN (Center for Food Safety and Applied Nutrition). 2004. *Escherichia coli O157:H7*. http://vm.cfsan.fda.gov/~mow/chap15.html (accessed January 23, 2007).

Greenslade, E., R. Beasley, L. Jennings, A. Woodward, and P. Weinstein. 2003. Has *Coxiella burnetii* (Q fever) been introduced into New Zealand? *Emerging Infectious Diseases* 9:138-140.

Hellmeyer, L., G. Schmitz-Ziegler, W. Slenczka, and S. Schmidt. 2002. Q fever in pregnancy: A case report and review of the literature. *Zeitschrift fur Geburtshilfe und Neonatologie* 206:193-198.

Joffe, M. H., L. E. Gongwer, and C. L. Punte. 1958. Studies on the acute and subacute toxicity of bis(2-ethylhexyl) hydrogen phosphite. *AMA Archives of Industrial Health* 18(6):464-469.

Kazar, J. 1999. Q-fever current concept. In *Rickettsia and rickettsial diseases at the turn of the third millenium*, D. Raoult and P. Brouqui (eds.). Paris, France: Elsevier. Pp. 304-319.

Lee, E. C. 2003. Clinical manifestations of sarin nerve gas exposure. *Journal of the American Medical Association* 290(5):659-662.

Maurin, M., and D. Raoult. 1999. Q fever. *Clinical Microbiology Review* 12(4):518-553.

McCaul, T. F. 1991. The developmental cycle of *Coxiella burnetii.* In *Q-fever: The biology of* Coxiella burnetii, J. C. Williams and H. A. Thompson (eds.). Boca Raton, FL: CRC Press, 223-258.

NRC (National Research Council). 1997. *Review of acute human-toxicity estimates for selected chemical-warfare agents.* Washington, DC: National Academy Press. http://www.nap.edu/readingroom/books/toxicity/ (accessed January 25, 2007).

National Toxicology Program. 2002. Beta-Propiolactone. *Report on Carcinogens* 10:207-208.

Pfaltz & Bauer Co. 1997. *Bis(2-ethylhexyl) hydrogen phosphite 94%*. http://www.pfaltzandbauer.com/cgi-bin/details.pl?type=chemname&order=item&chem=&category=&item=B13840/ (accessed January 23, 2007).

Raoult, D., H. Tissot-Dupont, C. Foucault, J. Gouvernet, P. E. Fournier, E. Bernit, A. Stein, M. Nesri, J. R. Harie, and P. J. Weiller. 2000. Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. *Medicine (Baltimore)* 79(2):109-123.

RTECS (Registry of Toxic Effects of Chemical Substances). 1997. Phosphonic acid, bis (2-ethylhexyl) ester. *RTECS # SZ6840000.* http://www.cdc.gov/niosh/rtecs/sz685ec0.html (accessed January 23, 2007).

Sabatier, F., F. Dignat-George, J. L. Mege, C. Brunet, D. Raoult, and J. Sampol. 1997. CD4+ T-cell lymphopenia in Q fever endocarditis. *Clinical and Diagnostic Laboratory Immunology* 4:89-92.

Scheld, W. M., W. A. Craig, and J. M. Hughes. 2001. Q fever: Queries remaining after decades of research. In *Emerging infections,* W. M. Scheld, W. A. Craig, Hughes (eds.). Washington, DC: ASM Press. Pp. 29-56.

Scott, G. H., and J. C. Williams. 1990. Susceptibility of *Coxiella burnetii* to chemical disinfectants. *Annals of the New York Academy of Science* 590:291-296.

Williams, J. C. 1991. Infectivity, virulence and pathogenicity of *Coxiella burnetii* for various hosts. In *Q-fever: The biology of* Coxiella burnetii, J. C. Williams and H. A. Thompson (eds.). Boca Raton, FL: CRC Press. Pp. 21-64.

Zhang, G., K. Kiss, R. Seshadri, L. R. Hendrix, and J. E. Samuel. 2004. Identification and cloning of immunodominant antigens of *Coxiella burnetii*. *Infection and Immunity* 72:844-852.

Appendix B

Questionnaire

Medical Follow-up Agency

March 16, 2006

Ref#:

THE INSTITUTE OF MEDICINE'S VIETNAM ERA SHIPBOARD HEALTH STUDY

Dear Sir:

You are asked to participate in a research study conducted at the Institute of Medicine William F. Page, Ph.D., Study Director. Your participation in this study is voluntary. You should read the information below and ask questions about anything you do not understand before deciding whether or not to participate.

The Institute of Medicine (IOM) is part of the National Academies, a private, nongovernmental research organization chartered by Congress during Abraham Lincoln's presidency. We have been asked to conduct a survey of the health status of Vietnam era military service personnel such as yourself, most of whom served in the Navy and also participated in Project SHAD (Shipboard Hazard and Defense) tests, between 1963 and 1970. The Department of Veterans Affairs has funded IOM to do this survey to determine the present health of Project SHAD participants and a comparable group of non-participants. It is important for us to hear from you because our records indicate that you were a participant in tests in which active chemical or biological warfare agents were used, and your response is the only way we can get accurate and complete information about the current health of these participants.

If you volunteer to participate in this study, we would like you to complete the enclosed mail survey, which contains some questions about your current and past physical and emotional health. If you would prefer, we can also have someone contact you and ask you these questions over the telephone. Either way, the survey should take no more than 20 minutes of your time. The data collection procedures are not expected to involve any health risk or discomfort to you. The principal risk for you is problems that could occur if the data you provide were disclosed inappropriately. However, our research group has collected similar information from participants in dozens of studies without any cases of inappropriate disclosure.

We will keep the information we collect confidential and not share it outside our agency. All the data we collect will be kept in locked file cabinets or password-protected computer files to prevent access by unauthorized persons. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

500 Fifth Street, NW
Washington, DC 20001

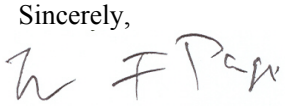
Phone: 202 334 2825
Fax: 202 334 2685

This study is not being done to improve your health or condition. Again, your participation in this research is voluntary. If you choose not to participate, that will not affect your relationship with the Department of Veterans Affairs or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice. You will not be paid for your participation.

I am enclosing a copy of the questionnaire to be filled out and returned using the postage-paid envelope. As a gift, I am including a pen with the National Academies logo which can be used to fill out the questionnaire, and is also yours to keep in appreciation for your assistance. There is an extra copy of the consent form to keep for your files. If we do not hear from you within the next several weeks, you may receive a telephone call about participation in the survey. If at that time you haven't sent in the consent form by mail, the interviewer will ask for your consent to be interviewed over the telephone before proceeding with any questions.

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights, or remedies because of your participation in this research study. If you have any questions about the study or regarding your rights as a research subject, you may call me toll-free at 1-800-556-9896. I hope that you will be able to participate in our health survey, and I thank you for your attention to this matter.

Sincerely,



William F. Page, Ph.D.
Study Director

Dear Veteran:

The Department of Veterans Affairs (VA) has asked the Institute of Medicine, part of the National Academies (a private, non-governmental research organization), to conduct a survey of the health status of veterans, some of who may have participated in Project Shipboard Hazard and Defense (SHAD) tests between 1963 and 1970. The VA has funded this survey and the Department of Defense (DoD) has provided information to identify study participants and to specify the kinds of health hazards Project SHAD participants may have encountered.

The goal of the study is to determine the present health of Project SHAD participants and a comparable group of non-participants. It is important for you to participate in this study so that accurate and complete information can be obtained. Both the VA and DoD have great interest in obtaining the best, most accurate picture possible of the potential adverse health effects that may have resulted from Project SHAD participation. The Institute of Medicine has been chosen to do this health survey because of their history of independent research regarding the health of military veterans.

I hope that you will agree to the Institute of Medicine's request to participate in this very important health survey, regardless of your participation status in Project SHAD. If you know that you were a participant, you should not have any misgivings about answering the questions in the survey. Much has been declassified about the SHAD tests, so answering these questions will not constitute a violation of your previous agreement not to disclose classified information. Also, whether or not you choose to participate, your relationship with the Departments of Defense and Veterans Affairs, and your right to health care or other services to which you are otherwise entitled will not be affected.

This is an important endeavor, and we appreciate your support.

Ellen P. Embrey
Deputy Assistant Secretary of Defense
Force Health Protection & Readiness
Department of Defense

Susan H. Mather
Chief Public Health and Environmental
Hazards Officer
Department of Veterans Affairs

October 24, 2005

William F. Page, Ph.D.
Senior Program Officer
Medical Follow-up Agency
Institute of Medicine
TNA 776
500 Fifth Street, N.W.
Washington, D.C. 20001

Dear Dr. Page:

We, the undersigned veterans service organizations and military service organizations, support fully the Institute of Medicine (IOM) study of the health effects of SHAD (Shipboard Hazard and Defense) testing in the 1960s and early 1970s. We believe that the data obtained from this study can go a long way towards answering many of the questions SHAD veterans have regarding health effects that may have been associated with their unwitting participation in SHAD tests while they were serving our nation.

We urge all veterans who receive a questionnaire from the IOM to take the time to fill it out and return it to the IOM. Their cooperation is essential if the study is to have the integrity and substance it needs for the IOM to make some definitive determinations about the health of SHAD veterans. Study results may compel the Department of Veterans Affairs (VA) to grant compensation and provide treatment for illnesses associated with exposure to the chemical and/or biological agents and decontaminants used in the SHAD project

Thank you for your cooperation.

Sincerely,

PETER S. GAYTAN
Director, Veterans Affairs and
Rehabilitation Division
The American Legion

THOMAS ZAMPIERI
Director of Government Relations
Blinded Veterans Association

JAMES B. KING
National Executive Director
AMVETS (American Veterans)

JOSEPH A. VIOLANTE
National Legislative Director
Disabled American Veterans

RICK JONES
Legislative Director
National Association for Uniformed Services

RICHARD B. FULLER
National Legislative Director
Paralyzed Veterans of America

VADM NORB RYAN, JR. (USN - RET.)
President
Military Officers Association of America

DENNIS CULLINAN
Legislative Director
Veterans of Foreign Wars of the United States

HERSHEL GOBER
National Legislative Director
Military Order of the Purple Heart of the U.S.A., Inc.

RICK WEIDMAN
Director of Government Relations
Vietnam Veterans of America, Inc.

THE INSTITUTE OF MEDICINE'S VIETNAM ERA SHIPBOARD HEALTH STUDY

Consent Form

What is this study about?

You are being asked to volunteer in a research study called "The Vietnam Era Shipboard Health Study." This purpose of the study is to assess the current health of veterans, many of whom were in the Navy during the Vietnam era. You are included in this study because, according to our records, you participated in tests in which chemical and biological agents were used. The results of the study will help in understanding if there were any long-term effects of those tests on the health of participants. This study is being conducted for the Department of Veterans Affairs by the National Academies, a respected, private, non-governmental research organization.

What will participation involve?

You are being asked to complete the attached questionnaire today. The questionnaire asks about your physical and mental health. The questions are similar to what a doctor or mental health professional might ask you on your first visit. Some questions are related to specific experiences of military service. Filling out the questionnaire will take about 20 minutes.

What are the risks involved in the study?

The data collection procedures are not expected to involve any health risk or discomfort to you. The principal risk for you is problems that could occur if the data you provide were disclosed inappropriately. However, this research group has collected similar information from participants in dozens of studies without any cases of inappropriate disclosure.

How will your data be protected?

All questionnaires will be kept in locked files. When your data are entered into computer files for analysis, your answers will be identified only by a special study identification number known to you and research team members. Your social security number and any other personal identification information will be removed from your questionnaire and data file upon return to the researchers. Even if someone outside the research team broke into the files, it would be impossible for them to identify your data. To minimize the risk of anyone breaking into the data files, those files will be maintained on computers protected by computer security measures. All members of the research team with access to the data files will be trained on computer security procedures specifically designed to protect sensitive data. Reports of the study findings will contain only group data, so that no individual study participant can be identified.

What are the benefits of participating in the study?

Your participation in this study will not directly benefit you; however, your participation will greatly assist us in better understanding the health and health care needs of present and future veterans involved in similar tests.

Will you be provided medical care based on your responses?

No. This is a population-based study and the data collected will not be used to make decisions about treatment that any individual should receive. If you feel that you might need medical care or counseling, you should make contact with the appropriate health care personnel.

Do you have to participate?

No, you do not. Your participation must be completely voluntary. If you decide to participate, you can stop at any time you wish or skip any question you choose. If you choose not to participate or if you later drop out of the study, you will not lose any rights or benefits to which you are otherwise entitled.

Who can provide additional information if you need it?

Questions about the research (science) aspects of the study, or questions about the ethical aspects of the study, your rights as a volunteer, or any problem related to the protection of research volunteers should be directed to Dr. William F. Page, toll-free telephone number 1-800-556-9896.

Voluntary Consent

I consent to participate in the study described above. My consent is completely voluntary and is based solely on the information provided in this consent form.

_____ _____

Volunteer's signature Date (mm/dd/yyyy)

_____

Volunteer's printed name (first, middle initial, last)

1. What is your current mailing address?

Address Line 1: ☐

Address Line 2: (optional) ☐

City (or FPO/APO): ☐

State/Province/Region: (or AA/AE/AP) ☐

Zip/Postal Code: ☐

Country: ☐

2. Please provide your daytime phone number with area code.

☐

3. What is today's date?

M M / D D / Y Y Y Y

4. What are the last four digits of your social security number?

☐☐☐☐

5. What is your **current** marital status? Choose the single best answer.

- ☐ Single, never married
- ☐ Now married
- ☐ Separated
- ☐ Divorced
- ☐ Widowed

6. What is the **highest level** of education that you have **completed**? Choose the single best answer.

- ☐ Less than high school completion/diploma
- ☐ High school degree/GED/equivalent
- ☐ Some college, no degree
- ☐ Associate's degree
- ☐ Bachelor's degree
- ☐ Master's, doctorate, or professional degree

7. What is your **main** racial background?

- ☐ White, non-Hispanic
- ☐ Black/African-American non-Hispanic
- ☐ Hispanic
- ☐ Asian/Pacific Islander
- ☐ American Indian/Alaskan Native
- ☐ Other

8. How tall are you?

☐ feet ☐☐ inches

9. Approximately how much do you currently weigh (in pounds)?

☐☐☐ pounds

10. What is your date of birth?

M M / D D / Y Y Y Y

GENERAL HEALTH STATUS

11. In general, would you say your health is....?

- ☐ Excellent.
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

12. Compared to ONE YEAR AGO, how would you rate your health in general NOW?

- ☐ MUCH BETTER than one year ago
- ☐ Somewhat BETTER than one year ago
- ☐ About the SAME as one year ago
- ☐ Somewhat WORSE than one year ago
- ☐ MUCH WORSE than one year ago

13. Does your health limit you in these activities? If so, how much?

	Yes, a little	Yes, a lot	No
a. The kinds or amounts of vigorous activities you can do like lifting heavy objects, running or participating in strenuous sports _ _ _ _ _ _ _ _ _ _	☐	☐	☐
b. The kinds or amounts of moderate activities that you can do, like moving a table, pushing a vacuum cleaner, bowling, or playing golf? _ _ _ _	☐	☐	☐
c. Lifting or carrying groceries? _	☐	☐	☐
d. Climbing several flights of stairs? _	☐	☐	☐
e. Climbing one flight of stairs? _	☐	☐	☐
f. Bending, kneeling or stooping? _	☐	☐	☐
g. Walking more than one mile? _	☐	☐	☐
h. Walking several blocks? _	☐	☐	☐
i. Walking one block? _	☐	☐	☐
j. Bathing or dressing yourself? _	☐	☐	☐

14. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A Little bit of the time	None of the time
a. Cut down the amount of time you spent on work or other activities? _ _ _ _ _ _ _ _ _	1	2	3	4	5
b. Accomplished less than you would like? _ _ _ _ _	1	2	3	4	5
c. Were limited in the kind of work or other activities? _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5
d. Had difficulty performing the work or other activities? (for example it took extra effort) _ _ _ _	1	2	3	4	5

15. During the past 4 weeks, have you had any of the following problemswith your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A Little bit of the time	None of the time
a. Cut down the amount of time you spent on work or other activities? _ _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5
b. Accomplished less than you would like? _ _ _ _ _	1	2	3	4	5
c. Didn't do work or other activities as carefully as usual? _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5

16. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

17. How much physical pain have you had during the past 4 weeks?

☐ None
☐ Very mild
☐ Mild
☐ Moderate
☐ Severe
☐ Very Severe

18. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all
☐ A little bit
☐ Moderately
☐ Quite a bit
☐ Extremely

19. These next questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A Little bit of the time	None of the time
a. Did you feel full of life? _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5
b. Have you been very nervous? _ _ _ _ _ _ _	1	2	3	4	5
c. Have you felt so down in the dumps that nothing could cheer you up? _ _ _ _ _	1	2	3	4	5
d. Have you felt calm and peaceful? _ _ _ _ _	1	2	3	4	5
e. Did you have a lot of energy? _ _ _ _ _ _ _	1	2	3	4	5
f. Have you felt downhearted and blue? _ _ _	1	2	3	4	5
g. Do you feel worn out? _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5
h. Have you been a happy person? _ _ _ _ _ _	1	2	3	4	5
i. Did you feel tired? _ _ _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5

20. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

21. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people. _ _ _ _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5
b. I am as healthy as anybody I know. _ _ _ _	1	2	3	4	5
c. I expect my health to get worse. _ _ _ _ _ _	1	2	3	4	5
d. My health is excellent. _ _ _ _ _ _ _ _ _ _ _	1	2	3	4	5

HEALTH PROBLEMS

22. In the past few years have you ever had ...?

	Yes	No	Don't Know
a. Pain when you urinate.	1	2	3
b. Trouble swallowing	1	2	3
c. Lost your voice for more than a few minutes	1	2	3
d. Completely deaf for a period of time	1	2	3
e. Fainting spells or been unconscious	1	2	3
f. Seizure or convulsions	1	2	3
g. Periods of weakness when you couldn't lift or move things that you normally could or paralysis	1	2	3
h. Tremors	1	2	3
i. Shortness of breath when not really exerting yourself	1	2	3
j. Heart racing, pounding or skipping	1	2	3
k. Chest pain	1	2	3
l. Dizziness	1	2	3

23. Please indicate if any of the following problems applies to you and to what extent.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
a. I have a hard time remembering people's names.	1	2	3	4	5
b. I forget the names of common things.	1	2	3	4	5
c. I have trouble remembering important things.	1	2	3	4	5
d. My mind tends to wander.	1	2	3	4	5
e. I have difficulty paying attention.	1	2	3	4	5
f I have trouble concentrating.	1	2	3	4	5
g. I am forgetful.	1	2	3	4	5
h. I have serious memory problems.	1	2	3	4	5
i. I have a hard time recognizing people's faces.	1	2	3	4	5
j. I forget what I am saying.	1	2	3	4	5
k. I have forgotten many things which happened in my childhood.	1	2	3	4	5
l. I have forgotten much of what I learned in school.	1	2	3	4	5
m. I forget where I put things.	1	2	3	4	5
n. My mind won't stay on one thing.	1	2	3	4	5
o. I often lose things.	1	2	3	4	5
p. I am easily distracted.	1	2	3	4	5
q. I am absent-minded.	1	2	3	4	5

MEDICAL CONDITIONS

24. Has your doctor or other health professional ever told you that you have...

a.	Hypertension (high blood pressure)	☐ Yes	☐ No
b.	Coronary heart disease	☐ Yes	☐ No
c.	Heart attack	☐ Yes	☐ No
d.	Angina (chest pain)	☐ Yes	☐ No
e.	Any other heart condition (please specify) [ ]	☐ Yes	☐ No
f.	Cataracts or eye lens problems	☐ Yes	☐ No
g.	Conjunctivitis	☐ Yes	☐ No
h.	Sinusitis	☐ Yes	☐ No
i.	Chronic bronchitis	☐ Yes	☐ No
j.	Emphysema	☐ Yes	☐ No
k.	Asthma	☐ Yes	☐ No
l.	Kidney failure requiring dialysis	☐ Yes	☐ No
m.	Bladder infection	☐ Yes	☐ No
n.	Pancreatitis	☐ Yes	☐ No
o.	Diabetes or sugar diabetes	☐ Yes	☐ No
p.	Gallstones	☐ Yes	☐ No
q.	Hepatitis B	☐ Yes	☐ No
r.	Hepatitis C	☐ Yes	☐ No
s.	Any other hepatitis	☐ Yes	☐ No
t.	Cirrhosis	☐ Yes	☐ No
u.	Rheumatoid arthritis	☐ Yes	☐ No
v.	Lupus	☐ Yes	☐ No
w.	Multiple sclerosis	☐ Yes	☐ No
x.	Crohn's disease	☐ Yes	☐ No
y.	Stomach, duodenal, or peptic ulcer	☐ Yes	☐ No
z.	Ulcerative colitis or proctitis	☐ Yes	☐ No
aa.	Significant hearing loss	☐ Yes	☐ No
bb.	Migraine headaches	☐ Yes	☐ No
cc.	Stroke	☐ Yes	☐ No
dd.	Neuropathy-caused reduced sensation in hands or feet	☐ Yes	☐ No
ee.	Seizures	☐ Yes	☐ No
ff.	Sleep apnea	☐ Yes	☐ No
gg.	Anemia	☐ Yes	☐ No
hh.	Thyroid condition other than cancer	☐ Yes	☐ No
ii.	Cancer (please specify) [ ]	☐ Yes	☐ No
jj.	Chronic fatigue syndrome	☐ Yes	☐ No

kk.	Depression	☐ Yes	☐ No
ll.	Schizophrenia or psychosis	☐ Yes	☐ No
mm.	Manic depressive disorder	☐ Yes	☐ No
nn.	Posttraumatic stress disorder	☐ Yes	☐ No
oo.	Dermatitis, eczema, or psoriasis	☐ Yes	☐ No
pp.	Parkinson's	☐ Yes	☐ No
qq.	Lou Gehrig's Disease (amyotrophic lateral sclerosis)	☐ Yes	☐ No
rr.	Other neuro-degenerative disease (please specify) ☐	☐ Yes	☐ No
ss.	Other (please specify ☐	☐ Yes	☐ No

SYMPTOM LIST

25. During the last 12 months have you had persistent or recurring problems with any of the following conditions?

a.	Severe headache	☐ Yes	☐ No
b.	Diarrhea	☐ Yes	☐ No
c.	Rash or skin ulcer	☐ Yes	☐ No
d.	Sore throat	☐ Yes	☐ No
e.	Frequent bladder infections	☐ Yes	☐ No
f.	Cough	☐ Yes	☐ No
g.	Fever	☐ Yes	☐ No
h.	Sudden unexplained hair loss	☐ Yes	☐ No
i.	Earlobe pain	☐ Yes	☐ No
j.	Sleepy all the time.	☐ Yes	☐ No
k.	Night sweats	☐ Yes	☐ No
l.	Chest pain	☐ Yes	☐ No
m.	Unusual muscle pains	☐ Yes	☐ No
n.	Shortness of breath	☐ Yes	☐ No
o.	Trouble sleeping	☐ Yes	☐ No
p.	Unusual fatigue	☐ Yes	☐ No
q.	Forgetfulness	☐ Yes	☐ No
r.	Confusion	☐ Yes	☐ No
s.	Other (please specify) ☐	☐ Yes	☐ No

HOSPITAL CARE

26. This question relates to your medical care while you were in the Navy. Not counting accidents, wounds or other injuries, were you a patient in a hospital overnight or longer while you were in the Navy?

☐ Yes ☐ No **(SKIP TO question 27)** ☐ Don't know **(SKIP TO question 27)**

26b. How many times were you hospitalized for an illness or medical condition while you were in the Navy? ☐

27. This question is about any overnight hospital stays you may have had since you were discharged from active duty. This could be in a VA or non-VA hospital. Please think carefully about the entire period from your discharge to the present time.

Not counting accidents or injuries, since your discharge from active duty, have you been a patient in a hospital overnight or longer?

- ☐ Yes
- ☐ No **(SKIP TO question 28)**
- ☐ Don't know **(SKIP TO question 28)**

27b. How many times were you hospitalized overnight or longer for an illness or medical condition (other than accidents or injuries) since you were discharged from active duty?

☐

27c. When was the most recent time that you were hospitalized overnight or longer for an illness or medical condition?

- ☐ Within the past 12 months
- ☐ Within the past 2 years
- ☐ Within the past 5 years.
- ☐ More than 5 years ago
- ☐ Don't know

REPRODUCTIVE HISTORY

28. Have you **ever** been the biological father of any pregnancy, regardless of whether there was a live birth outcome from that pregnancy?

- ☐ Yes
- ☐ No **(SKIP TO question 29)**
- ☐ Don't know **(SKIP TO question 29)**

28b. Now thinking about all pregnancies in which you were the biological father....

How many of the pregnancies ended in **live births**, even if the infant died shortly after birth? ☐

28c. How many of your children were born with birth defects or malformations? ☐

SMOKING

29. Have you ever smoked cigarettes regularly (at least one a day)?

- ☐ Yes
- ☐ No **(SKIP TO question 30)**

29b. Do you now smoke cigarettes regularly (at least one a day)?

- ☐ Yes **(SKIP to question 29d)**
- ☐ No

29c. At what age did you stop smoking cigarettes? ☐

29d. For how many years altogether (have you smoked/did you smoke) cigarettes regularly? ☐

29e. On average, about how many cigarettes a day (do/did) you smoke? ☐

ALCOHOL USE

30. Do you currently drink alcohol? _____ ☐ Yes ☐ No **(SKIP TO question 31)**

30b. How often do you drink alcohol?

- ☐ Daily
- ☐ 3-4 times/week
- ☐ 1-2 times/week
- ☐ 2-3 times/month
- ☐ <1 time/month
- ☐ Don't know

30c. Have you ever felt you should cut down on your drinking? ☐ Yes ☐ No

30d. Have people annoyed you by criticizing your drinking? ☐ Yes ☐ No

30e. Have you ever felt bad or guilty about your drinking? ☐ Yes ☐ No

30f. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hang-over (eye-opener)? ☐ Yes ☐ No

31. Did you ever drink alcohol? ☐ Yes ☐ No **(SKIP TO question 33)**

32. At what age did you stop drinking alcohol? ☐☐

MILITARY EXPERIENCE

33. In what month and year did you first enter the Armed Forces? M M / Y Y Y Y

34. In what month and year were you discharged or separated from the Armed Forces? M M / Y Y Y Y

35. While in the military did you ever handle, mix or spray

	Yes	No	Don't Know
a. Herbicides or defoliants	☐	☐	☐
b. Insecticides	☐	☐	☐
c. Hazardous chemicals.	☐	☐	☐

Please answer the following items only if you participated in Project SHAD.
If you did not participate in Project SHAD, then your questionnaire is complete.
Thank you for your time.

36. Did you receive a letter from the Department of Defense telling you that you were a participant in Project SHAD or Project 112?

☐ Yes, Project SHAD ☐ Yes, Project 112 ☐ No ☐ Don't know

37. Before the testing, did you think there would be any risk of serious **long term** effects to your **physical health**?

☐ Yes ☐ No (SKIP to question 38) ☐ Don't know (SKIP to question 38)

37b. Did you think the risk of serious long term **physical health** effects from the testing was high, moderate or low?

☐ High risk ☐ Moderate risk ☐ Low risk ☐ Don't know

38. Before the testing, did you think there would be any risk of serious **long term emotional or mental health** effects?

☐ Yes ☐ No (SKIP to question 39) ☐ Don't know (SKIP to question 39)

38b. Did you think the risk of serious long term **emotional or mental health** effects from the testing was high, moderate or low?

☐ High risk ☐ Moderate risk ☐ Low risk ☐ Don't know

---

39. How long (number of days) were you involved in Project SHAD, from the first test in which you participated to the final test? ☐ days

---

40. During the testing did you ever experience ...

a.	Problems in breathing	☐ Yes	☐ No
b.	Nausea or vomiting	☐ Yes	☐ No
c.	Loss of consciousness	☐ Yes	☐ No
d.	Seizures	☐ Yes	☐ No
e.	Physical pain	☐ Yes	☐ No
f.	Intense fear, hopelessness or horror	☐ Yes	☐ No
g.	Feeling emotionally numb, having no feelings	☐ Yes	☐ No
h.	Feeling in a daze not fully aware of what was going on around you	☐ Yes	☐ No
i.	Feeling detached from things around you	☐ Yes	☐ No
j.	Other, specify ☐	☐ Yes	☐ No

---

41. During the testing, did you ever think that you were in danger of being seriously physically harmed or of dying?

☐ Yes ☐ No ☐ Don't know

---

42. After the tests, did you ever experience...

a.	Headaches	☐ Yes	☐ No
b.	Nausea or vomiting	☐ Yes	☐ No
c.	Dizziness	☐ Yes	☐ No
d.	Fainting	☐ Yes	☐ No
e.	Loss of weight	☐ Yes	☐ No
f.	Difficulty in concentrating	☐ Yes	☐ No
g.	Memory loss or confusion	☐ Yes	☐ No
h.	Sleep disturbances	☐ Yes	☐ No
i.	Fatigue or loss of energy	☐ Yes	☐ No
j.	Seizures, numbness or tingling in both hands or feet	☐ Yes	☐ No
k.	Other, specify ☐	☐ Yes	☐ No

43. How likely do you think it is that those tests had any **serious long-term effects on your physical health?** Do you think it is .....
- ☐ Very likely
- ☐ Somewhat likely
- ☐ Somewhat unlikely
- ☐ Very unlikely
- ☐ Don't know

44. How likely do you think it is that those tests had any **serious long-term effects on your mental health and emotional well-being?** Do you think it is .....
- ☐ Very likely
- ☐ Somewhat likely
- ☐ Somewhat unlikely
- ☐ Very unlikely
- ☐ Don't know

45. How often do you think about the testing you went through in Project SHAD?
- ☐ Every day or nearly every day
- ☐ Several times a week
- ☐ Several times a month
- ☐ Several times a year
- ☐ Only when reminded of it
- ☐ Rarely or never
- ☐ Don't know

46. During the testing,

a. Did you ever use protective gear? _____ (if no, skip to question 46d) _____ ☐ Yes ☐ No

b. How often? _____ ☐ all the time ☐ most of the time ☐ rarely ☐ never

c. What type of protective gear? (specify) _____

d. Did you decontaminate your protective mask and clothing after tests? _____ ☐ all of the time ☐ most of the time ☐ rarely ☐ never

e. Did you provide any biological specimens during or after the test? (if no, skip to question 46g) ☐ Yes ☐ No

f. What kinds of specimens? (specify) _____

g. Were you evaluated medically after the tests? _____ ☐ Yes ☐ No

h. What percentage of time did you spend in berthing spaces? _____ work spaces? _____

i. Were experimental animals used on your ship? _____ (if no, skip to question 47a) _____ ☐ Yes ☐ No

If yes, did you come into contact with them after they were exposed? _____ ☐ Yes ☐ No

47. After the testing,

a. Did you decontaminate the ships? _____ (if no, skip to question 47c) _____ ☐ Yes ☐ No

b. What chemicals did you use? (specify) _____

c. Did you receive safety training in handling decontamination chemicals? _____ ☐ Yes ☐ No

d. Were the interior spaces of your ship decontaminated after tests? _____ ☐ Yes ☐ No

e. Do you remember outbreaks of 5 or more people in you unit becoming ill? _____ ☐ Yes ☐ No

f. Or seeking medical attention? _____ (if no, skip to question 48a) _____ ☐ Yes ☐ No

g. For what reason? (specify) _____

48a. Did you participate in the preparation of test chemical/biological agents for release via aircraft or ship? _____ ☐ Yes ☐ No

48 b. Which agents? (specify) _____

Your questionnaire is now complete. Thank you for your time.

Appendix C

Material Concerning Outreach Survey

April 2005

IDENTIFYING PROJECT SHAD PARTICIPANTS FOR THE IOM HEALTH STUDY

The Institute of Medicine (IOM), an independent, non-governmental organization, is under contract from the Department of Veterans Affairs (VA) to study the current health of participants in the 19 Project Shipboard Hazard and Defense (SHAD) tests and compare their health with that of a comparable group of non-participant veterans. SHAD was a series of tests conducted by the Department of Defense (DoD) in the 1960s to investigate the effectiveness of shipboard detection of and protection procedures against chemical and biological warfare agents, including sarin, VX and organisms that cause tularemia and Q fever. Live chemical and biological agents were used, as well as simulants such as zinc cadmium sulfide and bacillus globigii (BG)—which, at the time, were thought to be harmless. The IOM study is intended to shed light on whether participation in Project SHAD tests is statistically associated with current health problems.

The IOM study staff is asking any veteran who thinks he or she was involved in Project SHAD testing to contact them. You may fill out the form below and mail it to Project SHAD Study, Institute of Medicine (Keck 776), 500 Fifth Street, NW, Washington, DC 20001. Responses must be received by August 31, 2005.

The information you provide will be kept confidential and will be used only to validate your participation in Project SHAD and establish a current address at which you can be reached and offered an opportunity to be included in the study if your Project SHAD participation can be validated. You may specifically direct that the information NOT be shared with the Department of Defense as part of the validation process by checking "no" in item 10 on the form.

If you have already received a letter from the Department of Veterans Affairs concerning Project SHAD participation you do not need to fill out the form and will automatically be offered an opportunity to be included in the IOM study.

Although the Project SHAD tests were originally classified, DoD has declassified information about the tests and made it publicly available. The IOM study staff has received a list of Project SHAD participants from DoD and is attempting to find any additional unidentified Project SHAD participants. Units known to have incomplete participant rosters include the crews of Army tugs, the Project SHAD Technical Staff, and several unidentified Air Force and Marine aviation units. Further details on the study may be found on the study's website (http://www.iom.edu/project.asp?id=4909), and you may call the IOM study staff on their toll-free number, 1-800-556-9896. Further details regarding Project SHAD may be found on DoD's DeploymentLINK website at: http://www.deploymentlink.osd.mil/current_issues/shad/shad_intro.shtml, or the Department of Veterans Affairs website: http://www1.va.gov/shad/.

Questionnaire for Project SHAD participants

Section I: Identifying data

1. Name: _____
2. Military branch: _____
3. Military service number: _____
4. Military rank/rating (at separation from service): _____
5. Current address: _____
   (street, apartment number)
   _____ _____ _____
   (city) (state) (zipcode)
6. Telephone number (with area code): _____
7. Social Security Number (**optional**): _____

Section II. Project SHAD data

8. Please list your Project SHAD participations:
   Note: If you need to consult the list of ships and military units for Project SHAD tests, consult the study's website or write to us requesting a copy of this list.

Ship or military unit	Test name	Test dates
a.		
b.		
c.		

9. Do you have written documentation of your Project SHAD participation? yes ☐ no ☐
   If yes, please send us a copy (not the originals) of your documentation with this form (Project SHAD Study, Institute of Medicine (Keck 776), 500 Fifth Street, NW, Washington, DC 20001).
10. May we share your information with the Department of Defense for validation purposes?
    If yes, check this box: ☐
11. Check this box ☐ if you would like us to send you more information about this study as posted on our website.

SAMPLE LETTER

26 April 2005

Mr. James E. Sursely
Disabled American Veterans
3725 Alexandria Pike
Cold Springs, KY 41076

Dear Veteran Service Organization Representative:

I am writing this letter to inform you of our ongoing study of the health of participants in Project SHAD (shipboard hazard and defense) and to enlist your aid in identifying Project SHAD participants. The Institute of Medicine (IOM), an independent, non-governmental organization, is under contract from the Department of Veterans Affairs (VA) to study the current health of participants in the 19 Project Shipboard Hazard and Defense (SHAD) tests and compare their health with that of a comparable group of non-participant veterans. SHAD was a series of tests conducted by the Department of Defense (DoD) in the 1960s to investigate the effectiveness of shipboard detection of and protection procedures against chemical and biological warfare agents, including sarin, VX and organisms that cause tularemia and Q fever. Live chemical and biological agents were used, as well as simulants such as zinc cadmium sulfide and bacillus globigii (BG)—which, at the time, were thought to be harmless. The IOM study is intended to shed light on whether participation in Project SHAD tests is statistically associated with current health problems.

Enclosed is a letter explaining in more detail the study as well as a form for potential Project SHAD participants to fill out and mail to us. Please note that there is no charge for participating in the study. You may distribute the enclosed letter to your members as you think appropriate.

If you have any questions about the study or our outreach letter, please contact me by email (wpage@nas.edu or toll-free telephone number 1-800-556-9896). Thank you for your attention to this matter.

Sincerely,

William F. Page, Ph.D.
Study Director

VETERAN SERVICE ORGANIZATION REPRESENTATIVES

Mr. William A. Boettcher
AMVETS
4647 Forbes Boulevard
Lanham, MD 20706-4380

Mr. James E. Sursely
Disabled American Veterans
3725 Alexandria Pike
Cold Springs, KY 41076

Mr. George R. Kaye
Fleet Reserve Association
125 N. West Street
Alexandria, VA 20024-2410

Ms. Helen F. Hicks
Marine Corps League
8626 Lee Highway
Suite 201
Fairfax, VA 22031

Mr. John Dorrity
National Association of County Veterans Service Officers, Inc.
2200 Wilson Blvd.
Suite 102-530
Arlington, VA 22301-3324

BG (Ret) Leslie E. Beavers
National Association of State Directors of Veterans Affairs
Kentucky Department of Veterans Affairs
1111 Louisville Road
Frankfort, KY 40601

Mr. H. Gene Overstreet
Non Commissioned Officers Association
10635 IH 35 North
San Antonio, TX 78233

Mr. Randy L. Pleva, Sr.
Paralyzed Veterans of America
801 18th Street, NW
Washington, DC 20006

Military Officers Association of America
201 N. Washington Street
Alexandria, VA 22314