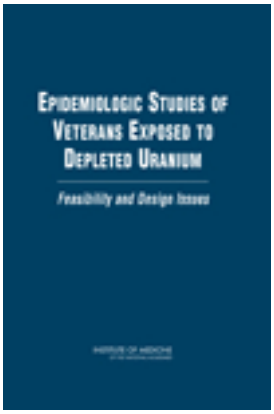

Epidemiologic Studies of Veterans Exposed to Depleted Uranium: Feasbility and Design Issues

Committee on Gulf War and Health: Updated Literature Review of Depleted Uranium, Institute of Medicine

ISBN: 0-309-12007-1, 58 pages, 6 x 9, (2008)

Epidemiologic Studies of Veterans Exposed to Depleted Uranium

Feasibility and Design Issues

Committee on Gulf War and Health:
Updated Literature Review of Depleted Uranium

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW 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 committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract V101 (049A3) P-0066, Modification 2 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: 978-0-309-12006-7
International Standard Book Number-10: 0-309-12006-3

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, NW, 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 Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2008. *Epidemiologic studies of veterans exposed to depleted uranium: Feasibility and design issues.* 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

COMMITTEE ON GULF WAR AND HEALTH: UPDATED LITERATURE REVIEW OF DEPLETED URANIUM

DAVID G. HOEL, PhD *(Chair),* Distinguished University Professor, Medical University of South Carolina, Charleston

MICHAEL ASCHNER, PhD, Gray E.B. Stahlman Professor of Neuroscience, Vanderbilt University, Nashville, TN

MELISSA D. BEGG, ScD, Professor of Clinical Biostatistics and Director of Academic Programs, Mailman School of Public Health of Columbia University, New York

VIVIEN W. CHEN, MPH, PhD, Professor and Director of Epidemiology Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans

HAROLD I. FELDMAN, MD, MSCE, Professor of Medicine and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia

PHILIP HARBER, MD, MPH, Professor and Chief, Division of Occupational and Environmental Medicine, David Geffen School of Medicine, University of California, Los Angeles

PATRICK J. HEAGERTY, PhD, Professor of Biostatistics, University of Washington School of Public Health and Community Medicine, Seattle

KIYOUNG LEE, MPH, ScD, Assistant Professor, University of Kentucky College of Public Health and Seoul National University School of Public Health, Republic of Korea

JONATHAN LINKS, PhD, Professor and Director, Center for Public Health Preparedness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Staff

ABIGAIL E. MITCHELL, PhD, Senior Program Officer

JENNIFER E. SAUNDERS, MPH, MPP, Senior Program Associate

RENEE WLODARCZYK, Research Assistant

JOSEPH GOODMAN, Senior Program Assistant

NORMAN GROSSBLATT, Senior Editor

ROSE MARIE MARTINEZ, ScD, Director, Board on Population Health and Public Health Practice

Reviewers

This report has been reviewed in draft form by persons 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 of 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 for their review of this report:

Patricia A. Buffler, School of Public Health, University of California, Berkeley
Bernard L. Cohen, Department of Physics and Astronomy, Professor Emeritus, University of Pittsburgh
Mitchell H. Gail, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health
Robert Herrick, Department of Environmental Health, Harvard School of Public Health
Margot Krauss, Independent Consultant, Kensington, Maryland
Michael J. Thun, Epidemiology and Surveillance Research, American Cancer Society

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 **David J. Tollerud,** School of Public Health and Information Sciences, University of Louisville, and **Johanna T. Dwyer,** Tufts University School of Medicine and Friedman School of Nutrition Science, Tufts-New England Medical Center. Appointed by the Institute of Medicine and the National Research Council, respectively, they were 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 authoring committee and the institution.

Contents

Tables and Figures

Summary

The 1991 Persian Gulf War, although considered a successful military operation, had a profound impact on the lives of troops who served overseas. Returning veterans reported numerous health problems that they associated with wartime exposures, including fatigue, sleep disturbance, and cognitive difficulties. Troops in the 1991 Gulf War and in other conflicts, including the Iraq War (Operation Iraqi Freedom), were exposed to a variety of hazardous agents, including depleted uranium (DU). DU is used to strengthen armor and to increase the penetration effectiveness of munitions. Troops were potentially exposed to DU during friendly-fire incidents, cleanup operations, and accidents (including fires).

Section 716 of the 2007 John Warner National Defense Authorization Act mandated that the Department of Defense (DOD), the Department of Veterans Affairs, and the Department of Health and Human Services "conduct a comprehensive study of the health effects of exposure to depleted uranium munitions on uranium-exposed soldiers and on children of uranium-exposed soldiers who were born after the exposure of the uranium-exposed soldiers to depleted uranium." In response to this charge to the agencies, DOD sought guidance from the Institute of Medicine (IOM) in evaluating the feasibility and design of an epidemiologic study that would assess health outcomes related to exposure to DU.

CHARGE TO THE COMMITTEE

In response to DOD's request, IOM entered into a contract to conduct the following study:

An IOM committee will examine and make recommendations regarding

the critical elements needed for an epidemiologic study of veterans who were exposed to DU while on active duty. Those might include veterans who

- were exposed to smoke from fires resulting from the burning of vehicles containing DU munitions or fires at depots at which DU munitions were stored,
- worked in environments containing DU dust or residue from DU munitions,
- were within a structure or vehicle when it was struck by DU munitions,
- climbed on or entered equipment or structures struck by DU munitions, or
- were medical personnel who provided initial treatment to members of the armed forces who were exposed to DU.

The committee also will identify elements needed to study veterans' children who were born after parental exposure to DU.

COMMITTEE'S APPROACH TO ITS TASK

To approach its task, the committee first considered the necessary elements of a comprehensive epidemiologic study to assess exposure to DU and related health outcomes (Chapter 2). The committee then evaluated DOD's available data and research efforts and identified limitations and data gaps in the databases (Chapter 3). Finally, it identified options for further study of potential health outcomes in DU-exposed military personnel and veterans (Chapter 4).

ELEMENTS OF AN EPIDEMIOLOGIC STUDY

The elements of an epidemiologic study essential for assessing the relationship between exposure to DU and health outcomes include identification of a relevant study population of adequate size; a comprehensive assessment of uranium exposure in the population, including the use of biomarkers; an evaluation of long-term health outcomes; adequate followup time; use of reasonable methods for controlling confounding and minimizing bias; and appropriate statistical analyses.

AVAILABLE DATASETS

The committee reviewed available datasets on health outcomes in DU-exposed military personnel and veterans and datasets on these populations that do not specifically assess DU exposure (they track health outcomes in general) but might be useful for future study. The datasets include the Depleted Uranium Medical Management Program, including the Depleted Uranium Follow-Up

Program at the Baltimore Veterans Affairs Medical Center (BVAMC); the Millennium Cohort study; and the DOD Birth and Infant Health Registry. In general, the studies are well designed; however, they lack either adequate sample size or accurate exposure information (for example, biomarkers of exposure and work-assignment locations) to assess fully whether DU exposure is associated with health outcomes.

CONCLUSIONS AND RECOMMENDATIONS

The committee examined four approaches to study health outcomes related to DU exposure in military and veteran populations. Two of the study designs use existing data, and two require collection of new data.

There are important limitations in each of the approaches, particularly the low statistical power and the lack of adequate and accurate exposure data. Given those limitations, it would be difficult to design a study to comprehensively assess the health outcomes of DU exposure in military and veteran populations with currently available data. Detecting a small increased risk for a given health outcome of DU exposure in those populations is not feasible in an epidemiologic study. Of the four approaches, the committee concludes that the one most likely to obtain useful information about DU-related health outcomes would be a prospective cohort study if future military operations involve exposure to DU.

To gain a sense of the expected sample sizes required for a high-quality epidemiologic study, the committee calculated sample-size estimates for a cancer outcome (lung cancer) and a renal-function outcome (serum creatinine concentration); these outcomes, lymphoma, respiratory disease, neurologic outcomes, and adverse reproductive and developmental outcomes were identified as having high priority for further study in the committee's report *Gulf War and Health: Updated Literature Review of Depleted Uranium*.[1] The committee determined that more than 1 million DU-exposed people would be required to detect a statistically significant difference in risk of lung cancer, a relatively common cancer. Fewer DU-exposed people would be needed to evaluate renal disease than lung cancer because renal disease is more prevalent than lung cancer (a range of potential study sizes, with the associated assumptions, is provided in Chapter 2 of this report). Beyond the size of future DU-exposed military populations, the success of any cohort study would depend on DOD's ability to collect accurate and complete individual-level exposure information on military personnel who enter a war theater in which DU munitions and armor are used.

[1]IOM (Institute of Medicine). 2008. *Gulf War and health: Updated literature review of depleted uranium.* Washington, DC: The National Academies Press.

The committee made several additional recommendations:

- DOD should investigate available in vivo assay techniques other than measuring urinary uranium to determine whether they offer advantages (for example, increased sensitivity) over urinalysis.
- DOD should consider assessing uranium concentrations in lung, kidney, and brain tissues from military personnel who were potentially exposed to DU and died while on active duty. Analysis of uranium in autopsy tissue might provide information on concordance between renal uranium concentrations and model-based estimates. It also would provide information on pulmonary retention of DU, which has implications for estimating lung cancer risk, and insight into the toxicokinetics of DU.
- DOD should continue to link and integrate available databases so that information can be assessed.
- DOD should determine the feasibility of collecting biomarker data from people in the Millennium Cohort Study who reported being exposed to DU and from military personnel who were at Camp Doha during the time of the fire in 1991. Any study participants who have positive bioassay results for DU exposure should receive health monitoring through the Depleted Uranium Follow-Up Program at the BVAMC throughout their lifespans.
- DOD should conduct further study of the potential reproductive and developmental toxicity of DU with animal models.

1

Introduction

The 1991 Persian Gulf War was largely considered a brief and successful military operation with few casualties, but veterans returning from the war theater reported health problems that they attributed to exposures during their service in the war. Commonly reported symptoms included fatigue, sleep disturbance, and cognitive difficulties.

The United States has since engaged in other conflicts in the Persian Gulf region, including the Iraq War (Operation Iraqi Freedom). The Iraq War began in March 2003 with the arrival of US and British troops in Iraq. Although major combat operations ended in May 2003, US and coalition troops continue to be deployed to Iraq to fight the insurgency and to assist in reconstruction efforts. About 1.5 million US troops have been deployed to Operation Iraqi Freedom and to Operation Enduring Freedom in Afghanistan (PCCWW, 2007).

Exposure to depleted uranium (DU) is of concern for active duty and veteran populations because it is used by the US military in the war theater. Exposure to DU can occur as a result of friendly-fire incidents, cleanup operations, and accidents. In recent conflicts, exposure to DU was a concern to veterans participating in a retrospective review of veterans' health and exposure concerns (Helmer et al., 2007).

Section 716 of the 2007 John Warner National Defense Authorization Act mandated that the Department of Defense (DOD), the Department of Veterans Affairs (VA), and the Department of Health and Human Services "conduct a comprehensive study of the health effects of exposure to depleted uranium munitions on uranium-exposed soldiers and on children of uranium-exposed soldiers who were born after the exposure of the uranium-exposed soldiers to depleted uranium." In response, DOD requested guidance from the Institute of Medicine

(IOM) in evaluating the feasibility and design of an epidemiologic study that would assess health outcomes related to exposure to DU.

THE COMMITTEE'S TASK

In response to DOD's request, IOM entered into a contract to conduct the following study:

An IOM committee will examine and make recommendations regarding the critical elements needed for an epidemiologic study of veterans who were exposed to DU while on active duty. Those might include veterans who

- were exposed to smoke from fires resulting from the burning of vehicles containing DU munitions or fires at depots at which DU munitions were stored,
- worked in environments containing DU dust or residue from DU munitions,
- were within a structure or vehicle when it was struck by DU munitions,
- climbed on or entered equipment or structures struck by DU munitions, or
- were medical personnel who provided initial treatment to members of the armed forces who were exposed to DU.

The committee also will identify elements needed to study veterans' children who were born after parental exposure to DU.

THE COMMITTEE'S APPROACH TO ITS TASK

To approach its task, the committee first considered the necessary elements of a comprehensive epidemiologic study to assess exposure to DU and related health outcomes. The committee then evaluated DOD's available data and research efforts and identified limitations and data gaps in the databases. Finally, it identified options for further study of potential health outcomes in DU-exposed military personnel and veterans.

The committee views a well-designed epidemiologic study as a two-stage process. The first stage is a comprehensive assessment of exposure to DU that permits identification of the exposed and unexposed components of the study population. The second stage should incorporate the exposure information into a prospective study to assess intermediate health outcomes and ultimately the relationship of exposure to the health outcomes of interest (see Figure 1-1).

Regarding the first stage, the committee offers recommendations for addressing the major gaps in available exposure information and provides guidance for assessing exposure of active-duty personnel and veterans to DU. The exposure-investigation stage of the process is instrumental in identifying study

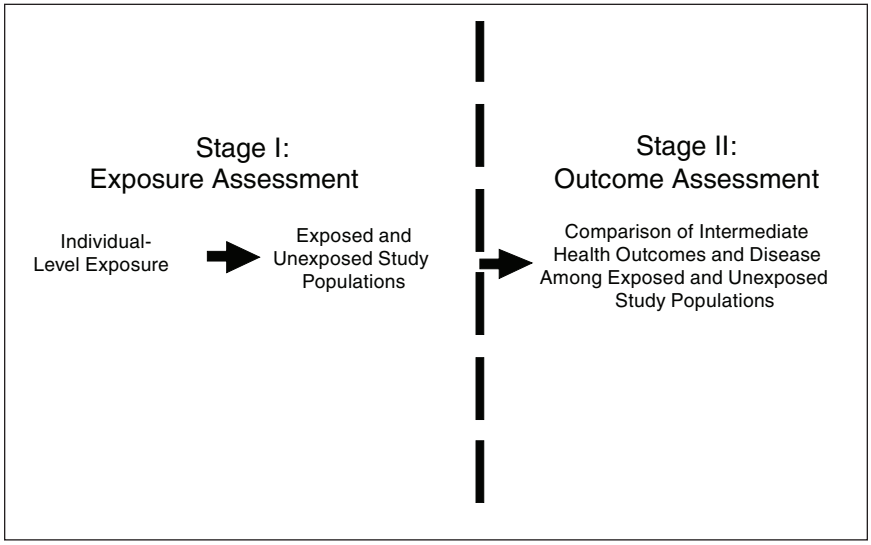

FIGURE 1-1 Stages of an epidemiologic study of DU exposure.

populations for an epidemiologic study that includes comparison groups. A well-conducted and comprehensive exposure assessment feeds into the second stage of an epidemiologic study, the outcome assessment, which is designed to understand exposure as it is related to a health effect or disease. During the second stage, the occurrence of the health outcome in the population of interest is assessed, and appropriate statistical analyses are conducted to determine whether there is a potential association between exposure to DU and development of the outcome. Accurate exposure information is critical in this evaluation.

ORGANIZATION OF THE REPORT

Chapter 2 of the report describes critical elements needed to conduct an epidemiologic study of DU. Chapter 3 provides a review of DOD's available databases and identifies gaps in and limitations of the databases. Chapter 4 lays out options for further study of potential health outcomes in DU-exposed military personnel and veterans and provides several additional recommendations.

REFERENCES

Helmer, D. A., M. Rossignol, M. Blatt, R. Agarwal, R. Teichman, and G. Lange. 2007. Health and exposure concerns of veterans deployed to Iraq and Afghanistan. *Journal of Occupational and Environmental Medicine* 49(5):475-480.

PCCWW (Report of the President's Commission on Care for America's Returning Wounded Warriors). 2007. *Report of the president's commission on care for America's returning wounded warriors report.* http://www.pccww.gov/ (accessed October 13, 2007).

2

Elements of an Epidemiologic Study

This chapter describes the elements of an epidemiologic study that are essential in assessing the relationship between exposure to depleted uranium (DU) and health outcomes. The elements include identification of a relevant study population of adequate size; appropriate assessment and accurate measurement of uranium exposure in the population, including the use of biomarkers when available; an evaluation of long-term health outcomes; adequate followup time; use of reasonable methods for controlling critical confounding factors and minimizing bias; and appropriate statistical analyses. Key issues related to sample size requirements for ensuring adequate statistical power in detecting small effects, the accuracy of exposure measurement, and the need to control critical confounders are addressed in detail. The chapter also briefly describes the various types of epidemiologic studies.

IDENTIFYING STUDY POPULATIONS

Identifying and ascertaining a relevant study population and a control or reference population are crucial steps in conducting a well-designed epidemiologic study. It is essential that the study population be representative of the population of interest and that it be large enough to ensure adequate statistical power. A representative sample that is large enough will be more likely to capture accurate information about a purported association. In fact, a primary method of reducing sampling error in an epidemiologic study is to enlarge the sample.

The population of interest is active-duty military and veterans, so it is critical that this population serve as the study population. By limiting the participants to military personnel or veterans, it will be possible to generalize the results to the

population of interest. Selection bias occurs when the study participants differ from nonparticipants in characteristics that might not be observed, that is, when the groups differ in measured or unmeasured baseline characteristics because of how participants were selected or assigned. Information on age would have to be captured, given the distribution of age among military personnel and the possibility that age is a confounding factor.

Sample Size

As discussed above, adequate sample size is critical in conducting a well-designed epidemiologic study. A previous Institute of Medicine (IOM) report discussed the importance of adequate sample size for studying the health of Gulf War veterans: "sufficient samples sizes for each cohort in the study are crucial to ensure adequate statistical power to find differences as well as to reliably identify the lack of differences between groups" (IOM, 1999).

Sample-size calculations are based on the expected magnitude of the difference between the exposed and unexposed groups, the relative sizes of the groups to be compared, and specified levels for type I error (the error of rejecting the null hypothesis when it is true) and type II error (the error of failing to reject the null hypothesis when the alternative hypothesis is true). Adequate followup time is also important, especially if the health outcome of interest has a long latent period (latency, followup, and other factors that should be taken into consideration in calculating sample size are discussed in more detail later in this chapter).

To gain a sense of the expected sample sizes required for a high-quality epidemiologic study, the committee generated sample-size estimates for a cancer outcome (lung cancer) and a renal-function outcome (serum creatinine concentration). Those outcomes were selected because they are among the ones identified as having high priority for further study by the committee in its report *Gulf War and Health: Updated Literature Review of Depleted Uranium* (IOM, 2008). Sample sizes for other high-priority health outcomes (lymphomas, respiratory disease, neurologic outcomes (including neurocognitive outcomes), and adverse reproductive and developmental outcomes) and for mortality should also be considered. Those outcomes may be defined either by the diagnosis of a specific disease entity (such as lymphoma) or by measurement of an important physiologic variable (such as serum creatinine or forced expiratory volume in 1 second as an indicator of renal function or lung function, respectively).

Lung Cancer

The committee estimated the minimum sample size required for detecting a statistically significant difference in risk of lung cancer between DU-exposed and unexposed subjects. Given that lung cancer is one of the more common can-

cers, the calculations can be viewed as a "best-case" scenario in that detecting outcomes that are less common would be even more difficult and require larger samples than those described below. For the committee's calculations, the type I error was set at the conventional value of 5%, and power at 80%. Without a large enough sample to ensure a reasonable probability of detecting an association of a specified magnitude when one exists, there is a risk of a false-negative result (that is, failure to detect an association in the sample when one truly exists in the population).

According to the American Cancer Society, the lifetime risk of a lung-cancer diagnosis is 7.91% (1 in 13) in men, and 6.18% (1 in 16) in women (ACS, 2008). Assuming that subjects can be followed long enough and closely enough to capture most lung cancers, the calculations are based on a lifetime risk of 7.91% in men. Estimates of excess lifetime risk of lung cancer from DU exposure have been reported and range from 0.06 to 0.3% (summarized in Chapter 5 of IOM, 2008). If those increases are applied to the baseline risk, the estimated likely value of the relative risk (RR) would be between 1.008 and 1.038. Because those values are only rough estimates of the relative increase in risk, the committee computed sample sizes for various RRs, including 1.005, 1.01, 1.025, and 1.05. Finally, given that exposure to DU is relatively rare, the committee calculated the sample size for a cohort study assuming that 4 times as many unexposed subjects as exposed subjects would be studied (a 4:1 ratio requires more subjects overall than using an equal number of unexposed and exposed subjects but requires fewer exposed subjects). That ratio of unexposed to exposed subjects was selected in recognition that sampling ratios greater than 4:1 yield only minimal increments in power and precision.

As shown in Table 2-1, the number of subjects required to detect a difference in lung-cancer risk in the hypothesized range (RR, 1.005-1.05) is prohibitive. Detecting smaller associations between DU and health effects would require studies with even greater numbers of exposed subjects to have sufficient statistical power.

The committee acknowledges the difficulty of detecting such a small relative risk in epidemiologic studies. In addition to the large sample size requirement

TABLE 2-1 Number of Subjects Required to Detect a Difference in Lung-Cancer Risk Due to DU Exposure

Relative Risk	No. Exposed	No. Unexposed	Total Sample
1.005	4,577,746	18,310,984	22,888,730
1.01[a]	*1,146,418*	*4,585,672*	*5,732,090*
1.025	184,376	737,504	921,880
1.05	46,488	185,952	232,440

[a]Anticipated value.

and the expected small effect of DU exposure on the health outcome of interest, adjustment for other potential confounding factors (that is, factors associated with both DU exposure and the health outcome of interest) is challenging. Furthermore, even if other factors are controlled for in the analysis, the question of whether any observed effects might be explained by residual confounding remains. Issues related to confounding are discussed in greater detail below.

Renal Function

The committee considered the minimal sample size required to detect a statistically significant difference in mean serum creatinine concentration, a biomarker for renal injury, between DU-exposed and -unexposed subjects. Again, the committee set the type I error at 5% and the power at 80%.

According to data obtained from the National Health and Nutrition Examination Surveys (NHANES), the mean serum creatinine concentration in the United States is about 1.0 mg/dL, with a standard deviation of approximately 0.34 (Selvin et al., 2007). The smallest change that would be considered clinically meaningful in a person would be about 0.25 mg/dL; however, a mean difference this large between exposed and unexposed groups would not be expected. Rather, the committee assumed that it would need sufficient power to detect that a larger fraction of the DU-exposed subjects than of unexposed subjects—say, 10% more—experienced a clinically significant increase (around 0.25 mg/dL) over long-term followup (20 years). Thus, the overall difference in the change in mean serum creatinine concentration between exposed and unexposed subjects would amount to about 0.025 mg/dL over a 20-year followup period. The committee computed the minimal sample sizes required to detect that difference between DU-exposed and -unexposed groups and to detect several smaller and larger differences: differences of 0.005, 0.01, 0.025, 0.05, and 0.10 mg/dL, corresponding to 2%, 4%, 10%, 20%, and 40% more exposed than unexposed subjects having experienced an increase of 0.25 mg/dL in serum creatinine (see Table 2-2). The calculations assume that 4 times as many unexposed subjects as exposed subjects

TABLE 2-2 Number of Subjects Required to Detect a Difference in Serum Creatinine Concentration Due to DU Exposure

Mean Difference (mg/dL)	No. Exposed	No. Unexposed	Total Sample
0.005	45,367	181,468	226,835
0.01	11,342	45,368	56,710
0.025	1,815	7,260	9,075
0.05	454	1,816	2,270
0.10	114	456	570

would be recruited because it is anticipated that it will be much more difficult to identify and recruit sufficient numbers of DU-exposed subjects.

Note that for mean differences of 0.025-0.10 mg/dL, samples of around 9,000 or fewer subjects, and sometimes substantially fewer, would yield sufficient power. That might make it possible to conduct a high-quality study of the association between DU exposure and renal function, as measured by serum creatinine concentration, as long as accurate exposure assessment and outcome assessment are available. If such a study is undertaken, the committee advises the investigators to inflate the targeted sample sizes above to compensate for exposure-classification issues, attrition of subjects by dropout, other losses to followup, and deaths over the 20-year followup period. Finally, the committee cautions that differences of the indicated magnitudes have not been observed in 74 DU-exposed Gulf War veterans who have been followed clinically since 1993 (McDiarmid, 2007).

The committee also estimated the sample size required to detect an increased incidence of renal disease as defined by a serum creatinine concentration greater than 1.7 mg/dL. It considered a study in which military personnel are followed for a 20-year prospective followup after their discharge (and are assumed to be 30-39 years old at discharge). Information on the prevalence of renal disease (defined by increased serum creatinine) in age-, race-, and ethnicity-specific subgroups was based on NHANES data (Jones et al., 1998). To compute a disease incidence expected in subjects that are not exposed to DU, the committee made the following assumptions: the increase in prevalence when men 50-59 years old are compared with men 30-39 years old estimates the 20-year incidence, the racial and ethnic composition of the cohort would be similar to the reported composition of enlisted personnel (65% white non-Hispanic, 20% black non-Hispanic, 9% Hispanic, and 6% other) (DOD, 2004), and the prevalence in subjects of "other" racial and ethnic composition can be approximated on the basis of the overall US age-specific prevalence. Using those assumptions, race- and ethnicity-specific prevalence estimates could be combined to obtain an overall estimated disease prevalence (prevalence of increased serum creatinine concentration) of 0.81% in subjects 30-39 years old and an increase to a prevalence of 3.51% in subjects 50-59 years old, which yielded an estimated 20-year cumulative incidence of 2.71%.

The committee computed the sample sizes required to have 80% power to detect an increased risk of renal disease in DU-exposed veterans (see Table 2-3). The sample size required for various assumed RRs when RR characterizes the magnitude of the increase in incidence in exposed veterans compared with unexposed veterans was determined. For example, a RR of 1.50 assumes that the exposed veterans would have a cumulative incidence of disease that is 1.50 times as high as that in the unexposed veterans ($1.50 \times 2.71\% = 4.07\%$) over 20 years of followup. Table 2-3 presents the numbers of evaluated subjects that would be required. In practice, sample-size targets would need to be increased to factor in

TABLE 2-3 Number of Subjects Required to Detect an Increased Risk of Renal Disease Due to DU Exposure

Relative Risk	No. Exposed	No. Unexposed	Total Sample
1.10	37,117	148,466	185,583
1.25	6,356	25,423	31,779
1.50	1,760	7,038	8,798
2.00	523	2,092	2,615

exposure classification, anticipated attrition of subjects by dropout, other losses to followup, and death over the 20-year followup period. As in the above examples, the committee assumed a ratio of 4:1 unexposed to exposed subjects.

The calculations suggest that about 9,000 subjects would need to be enrolled to detect a RR of 1.50.

Comparison-Group Issues

Selecting an appropriate comparison group is another critical element in a study. In the present case, an ideal comparison group would include active-duty military personnel or veterans without the exposure of interest. Using an unexposed veteran or military population for the comparison group would help to reduce a type of selection bias called the healthy-warrior effect, which otherwise may underestimate the association between the exposure to DU and the outcome of interest. Military personnel are subject to this type of bias in that their expected mortality and morbidity are lower than those in the general population.

The previous IOM report (1999) notes that comparison groups should be sampled and surveyed in the same way (that is, at the same time and using the same methods) as the exposed group to maximize comparability of data obtained on all groups. The report also recommends collecting information on potential confounding factors in both the study and comparison groups, including education, sex, and other correlates of health status (for example, smoking status and alcohol intake) (IOM, 1999).

EXPOSURE ASSESSMENT

Accurate characterization of information on exposure is an essential component of an epidemiologic study. Rothman and Greenland (1998) note that the "quality of exposure measurement will determine the validity of an environmental epidemiology study. . . . The importance of exposure assessment in environmental epidemiology cannot be overstated."

Direct measurements of exposure at the individual level are always pref-

erable, but such data are not always available. Surrogate information may be obtained from a variety of other sources, including questionnaires designed to capture self-reported exposure information, data on specific job exposures (for example, information on job types and job-exposure matrices), and environmental monitoring.

Monitoring

Various methods are available for assessing individual exposure to agents of interest, including biomonitoring, personal monitoring, and environmental monitoring.

Biomonitoring

Biomonitoring is a method of assessing exposure to chemicals by measuring them or their metabolites in urine and blood. Biomarkers are alterations at the cellular, biochemical, or molecular level that can serve as an indicator of exposure to a chemical. They can indicate the absorbed dose or be used to provide an estimate of target-tissue dose. It is critical to understand the timeframe of exposure as reflected by biomarkers. For instance, a chemical with a short half-life might be detected in human tissue only a short time after exposure and be used to measure only recent exposure. In some cases, multiple measures of exposure can be used to develop an accurate assessment of historical exposures. Biomonitoring is useful for measuring the body burden of DU because it can remain in the body for long periods. Parrish and colleagues (2007) have demonstrated that urinary uranium concentration can reflect DU exposure up to 20 years after the fact.

The committee believes that collecting biomonitoring data (for example, urinary uranium concentration) is essential for assessing the burden of DU in military and veteran populations. Other approaches, such as questionnaires and review of military-activity records, are unlikely to yield as accurate an assessment of exposure because of recall bias and exposure misclassification. Study of biomarker data is a necessary first step in characterizing DU exposure for epidemiologic studies.

Clear interpretation and communication of biomonitoring data are critical. For example, it can be difficult to communicate to a person that the finding of a statistically significant difference in mean urinary uranium concentration does not necessarily imply important clinical toxicity. Statistical significance gives an indication of the probability that observed differences between groups are due to chance. In studies that have large samples, a result can be statistically significant even if little or no clinical importance is associated with it. And clinically significant findings may be missed when samples are too small to allow statistical significance.

Practical measures related to good communication of biomarker data, as dis-

cussed in a National Research Council report (NRC, 2006), include using consistent terminology and concepts, expanding biomonitoring for relevant populations, providing communication training, and documenting methods of reducing exposures. The report also includes recommendations regarding the interpretation of biomonitoring data and research on communicating results. In addition, the 2003 Department of Defense (DOD) Health Affairs Policy 03-012 states that DOD must use "effective health risk communication tools to ensure those exposed to DU understand the exposure assessment, urine DU bioassay results, if applicable, the VA referral, and have all their questions fully answered" (DOD, 2003).

Personal Monitoring

Occupational studies often use personal monitoring to measure the radiation exposure of each worker. Personal dosimetry film badges can indicate cumulative exposure to external radiation. The badges are worn on the clothing of the employees and continuously record exposure to x-rays, gamma rays, and beta particles. The advantages of using film badges include the ability to link a specific dose to a particular exposure incident and a specific dose to an individual worker. In addition to measuring radiation exposure, other types of personal monitoring devices can be used to assess chemical exposure.

Environmental Monitoring

Environmental monitoring to assess the concentration of agents in the environment is an important tool for assessing external exposure. Environmental monitoring can be used to measure ambient air, soil, sand, and water samples. It is important to distinguish between exposure measured in the external environment and internal dose measured in human tissue. Environmental monitoring can yield an ecologic measure that can be most valuable when exposure is widespread in some geographic areas or periods under study (Rothman and Greenland, 1998). It also can be used to determine individual exposures based on time-activity diaries and residential histories.

Using Work History to Assess Exposure

One approach to assessing exposure in occupational epidemiologic studies is to approximate individual exposure by modeling cumulative exposure on the basis of a worker's job history and the level of exposure in each worksite. Exposure to a particular agent is measured in various worksites. This information is used to model the cumulative lung dose per unit time in the worksite. Employment records are then used to determine the amount of time that each worker spent in each job and the worker's cumulative exposure in all worksites over the course of his or her employment.

The modeling approach in effect assigns to each worker the average exposure in each worksite. Compared with direct measurement, this approach loses information in that workers in a given site may vary in their exposure. Any approach that blurs the distinction between individual workers' exposure while maintaining the distinction between workers' health outcomes will reduce the variation in the sample. That biases a study toward failing to detect an association between exposure and health outcomes.

Another approach measures average environmental exposure in each worksite, as described in the preceding section, and combines worksites into a relatively small number of groups according to magnitude of exposure. In some cases, exposure is not measured; rather, the judgment of experts in classifying worksites by extent of exposure is used. However, instead of estimating cumulative exposure over all worksites, this method simply assigns a worker to the site that has the highest exposure of all the sites in which the employee worked for at least some minimal period (usually 1 month). The approach is a crude form of exposure modeling in that it reduces the variation among workers' exposure in two ways. First, it assumes that an employee spent his or her entire period of employment in one group of worksites, although the worker may have spent time in sites that varied considerably in exposure. Second, it combines sites that may vary widely in their magnitude of exposure. For those reasons, this approach is especially prone to false-negative results (failing to detect a dose–response relationship).

Other Methods of Assessing Exposure

Other methods of collecting exposure information include face-to-face or telephone interviews, questionnaires distributed by mail or electronically, and combinations of these. Depending on the type of information needed for a study, a combination may be appropriate. When cost is a factor, a secure electronic questionnaire or survey is an appealing option. Face-to-face interviewing is generally considered a more reliable method of obtaining information because interviewers have the opportunity to observe study participants, ask followup questions, and clarify responses (IOM, 1999). Telephone interviewing and mail surveys are less expensive than face-to-face interviews, but may result in higher nonresponse rates. And mail surveys may encourage more honest responses.

Regardless of the method of data collection, response rate is always important to consider. There are a variety of reasons why participants may not respond; some cannot be located, others may be sick or not interested in participating, and so on. Obviously, the goal is to maximize the number of participants who respond. A previous Gulf War committee (IOM, 1999) recommended two options for improving response rates: encouraging veteran participation in organizing, designing, and implementing the study; and offering incentives for study participants.

Control of Bias and Confounding in Exposure Assessment

A study should use reasonable methods to control for confounders and minimize bias in both exposure and outcome assessments. Bias refers to systematic or nonrandom error. It causes an observed value to deviate from the true value and can weaken an association, exaggerate it, or reverse its direction. All studies are susceptible to bias, so a goal of study design is to minimize it or to adjust the observed value of an association by using special methods to correct for it. Bias related to self-reporting of exposure and bias related to exposure misclassification may compromise the results of an exposure assessment. Other common sources of information bias are the inability of study subjects to recall accurately the circumstances of their exposure (recall bias) and the likelihood that one group reports what it remembers more often than another group does (reporting bias).

Self-Reporting in Exposure Assessment

Self-reporting of exposure is a potential study limitation. A study participant's ability to recall details of exposure accurately over a long period can vary greatly and is likely to be severely limited. In addition, recall can be influenced by whether the participant has experienced adverse health outcomes. Self-reports of exposure can result in imprecise and even invalid assessments of both exposure and outcome.

Exposure Classification and Misclassification

Misclassification is defined as the "erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned" (Last, 1988). Exposure misclassification can occur when a study participant does not have detailed and accurate knowledge about a past exposure. In some cases, participants may not even be aware that they have been exposed. Misclassification may be differential or nondifferential. Differential misclassification occurs when the rate of misclassification differs between the study groups, and nondifferential misclassification occurs when the rate of misclassification does not differ between study groups (Gordis, 2000). Exposure misclassification can be reduced by obtaining information on exposure from more than one source, by validating exposure classification with an external dataset, or by measuring exposure objectively, such as with biomonitoring.

OUTCOME ASSESSMENT

Accurate and comprehensive exposure information is necessary to be able to complete the second step of an epidemiologic study: assessing the relationship of health outcomes to exposure. Discussed below are factors that should be incor-

porated into an assessment of health effects related to DU exposure, including a focus on ascertainment of outcomes, an adequate followup period, control of critical confounders, and appropriate statistical analysis.

Ascertainment of Outcomes

There are a variety of methods for ascertaining health outcomes, including reviewing death certificates, medical records, and data from clinical examinations; linkage to disease registries; and use of self-reported outcomes. Death certificates and medical records can be useful as sources of information on health outcomes. Diagnoses are usually provided by trained health-care providers, although recording errors or misdiagnoses may occur. Death certificates are comprehensive in coverage but do not capture nonfatal adverse health outcomes. Like self-reported exposure information, self-reported outcome information can include bias because subjects may not recall the information accurately. It is therefore important to verify self-reported information through physician diagnoses, death certificates, or disease registries.

Background Rate of Disease

To evaluate whether an increase in the number of cases of a particular disease is related to exposure to DU, it is necessary to have information about the background rate of the disease in the population not exposed to DU. The background rate of a disease can be used to determine whether there is an "excess" of cases or the rate is what would be expected in the population. A rate of disease in the study population that is in excess of the background rate may indicate an increased risk related to exposure to DU.

Adequate Followup Period

An adequate followup period is necessary to allow sufficient time after exposure for relevant health outcomes to occur. That is particularly true for outcomes that have long latent periods, as do most cancers and renal diseases. Biologic latency of cancer should be given consideration because there is a delay between exposure to a carcinogen and the onset of disease.

Control of Bias

As discussed above, a well-designed study should use appropriate methods to minimize bias. All studies are susceptible to bias, so the design of the outcome assessment should minimize bias or adjust the observed value of an association by using appropriate methods to correct for it. Information bias and bias related

to self-reporting of health outcomes may compromise the results of an outcome assessment.

Information bias can result from the method with which data are collected and ultimately can cause measurement errors and imprecision. Information bias can also result from misclassification of study subjects with respect to the outcome variable. It can lead to misinterpretation of study results when it affects one comparison group more than another.

Controlling for Confounders and Data Analysis

As mentioned above, an observation of association between DU exposure and any health outcome of interest could be confounded by other factors that are directly related to both the likelihood of exposure to DU and the outcome. For example, military personnel who serve in roles that pose an increased risk of DU exposure may be more likely to be smokers, and smoking has a well-known causal association with lung cancer. In principle, the influence of confounding factors on the assessment of the relationship between DU exposure and health outcomes can be overcome to some extent through study designs and data-analysis schemes that address such three-way relationships.

One approach to controlling for the influence of confounding factors is a study design that uses algorithms for matching study subjects according to the confounding factors, for example, ensuring that the DU-exposed and -unexposed study groups have nearly identical patterns of smoking. That technique can work well if there are only a few potential confounders of interest, but it becomes infeasible when there are many confounders. Alternatively, multivariable data-analysis techniques (such as stratified analysis and regression modeling) can effectively control for confounding by multiple factors simultaneously (for example, age, smoking, and sex). However, the effectiveness of such methods depends in part on the ability to ascertain exposures to potential confounding factors with accuracy and precision. Furthermore, the challenge of controlling for the confounding factors rises in settings where the association of interest (health outcomes of DU exposure) is small and the relationship between the confounder and either DU exposure or the health outcome is large.

Appropriate data analyses should incorporate methods for reducing bias and typically begin with careful examination of the distributions of the analytic variables, including exposures, health outcomes, and confounders. Statistical analyses should always be chosen to make the best use of all the available data, reduce potential sources of bias as much as possible, and closely reflect the aims and design of the study.

Before the implementation of analytic techniques, such as statistical modeling and stratification, to control for confounding factors, the potential for interactions between DU exposure and other factors should be considered. Interaction

effects are different from confounding effects. Their hallmark is a substantial difference in the magnitude of an association between DU exposure and a health outcome in subgroups, for example, a DU exposure-lung cancer relationship may differ between smokers and nonsmokers—owing to biologic synergy between the interacting factor (smoking) and DU with respect to their joint effect on an outcome (lung cancer). When interactions are detected, effects must be estimated and reported separately by subgroup (for example, in smokers and in nonsmokers) to assess the relationship between DU exposure and the health outcome validly. Such analyses would mandate an even larger total sample and expand the challenge of conducting such research, given the large number of subjects needed even in the absence of interactions.

ASSESSING THE STRENGTH OF THE EVIDENCE

A well-designed epidemiologic study that includes accurate exposure assessment and outcome assessment can be used to evaluate exposure to DU and reach conclusions about the potential for adverse health outcomes. Previous IOM reports, including *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines* (IOM, 2000), have noted the following general considerations for assessing the strength of evidence patterned after those introduced by Hill (1965): strength of association, dose–response relationship, consistency of association, temporal relationship, specificity of association, and biologic plausibility.

- *Strength of association* is typically expressed as the magnitude of the measure of effect (for example, a RR). The stronger the association, the less likely the relationship is due to confounding.
- A *dose-response relationship* is observed when study findings indicate a greater health effect or response after greater exposure. The steeper the dose–response relationship, the more confidence one can have that the association is real; however, the absence of such a relationship does not necessarily indicate that there is no possibility of an association.
- A *consistent association* is observed when the magnitude and direction are similar among several studies that include different populations, locations, and times. A larger number of studies that have the same results constitute a greater indication that there is a consistent association.
- A *temporal relationship*, evidence that exposure occurred before the outcome, is necessary to determine causality.
- *Specificity* is defined as the unique association between exposure to a specific agent and a specific health outcome; that is, the health outcome does not arise in the absence of exposure to the agent. Specificity of association is somewhat rare given the multifactorial etiology of many health outcomes and the broad spectrum of health outcomes that may occur after exposure.

• *Biologic plausibility* reflects knowledge of the biologic mechanism by which an agent can lead to a health outcome. That knowledge comes through a variety of studies (typically animal studies), including studies that assess mechanisms of action and studies in pharmacology, toxicology, microbiology, physiology, and other fields. Biologic plausibility is often difficult to establish, and it might not be known when an association is first documented.

EPIDEMIOLOGIC STUDY DESIGNS

Three major types of epidemiologic studies are cohort, case-control, and cross-sectional studies (study designs are discussed in more detail in IOM, 2000). A cohort, or longitudinal, study follows a defined group over time. It can test hypotheses about whether an exposure to a specific agent is related to the development of a health effect and can examine multiple health effects that may be associated with exposure to a given agent. A cohort study starts by classifying study participants according to whether they have been exposed to the agent under study, in this case DU. A cohort study compares health effects in people who have been exposed with those in people who have not been exposed. Such a comparison can be used to estimate a risk difference or a RR, two summary measures of association.

In a case-control study, case subjects (cases) are selected from among people in the population who have experienced a specific health effect, and controls are selected from among those in the population who have not experienced the health effect. Prior exposure of both cases and controls to specific agents is assessed. Such characteristics as age, sex, and socioeconomic status are recorded to permit control of their potential confounding influence in the analysis of the exposure–disease relationship of interest. The odds of exposure to an agent among the cases are then compared with the odds of exposure among controls to generate an odds ratio (OR), which is a summary measure that is typically interpreted as the RR of a health effect in those exposed to the agent compared with those not exposed.

In a cross-sectional study, exposure information and health-effects information are collected at the same time. The selection of people for the study—unlike selection for cohort and case-control studies—is independent of exposure to the agent and of health-effects characteristics. Cross-sectional studies seek to uncover associations between exposure to a specific agent and development of a health effect. In a cross-sectional study, effect size is measured as RR, prevalence ratio, or prevalence OR.

SUMMARY

This chapter has discussed the elements of an epidemiologic study that are essential in assessing the relationship between exposure to DU and health out-

comes. They include identification of a relevant study population of adequate size; appropriate assessment of uranium exposure in the population, including the use of biomarkers, when available; evaluation of health outcomes; adequate followup time; use of reasonable methods for controlling for confounders and minimizing bias; and appropriate statistical analysis. The committee estimated the minimal sample size required to detect statistically significant differences in risk of lung cancer and in renal malfunction between DU-exposed and -unexposed samples.

REFERENCES

ACS (American Cancer Society). 2008. *Cancer facts and figures.* Atlanta, GA: American Cancer Society.

DOD (Department of Defense). 2003. *HA policy 03-012: Policy for OIF DU medical management.* Washington, DC: Department of Defense.

———. 2004. *Population representation in the military services.* http://www.defenselink.mil/prhome/poprep2000/html/appendixb/b_25.htm (accessed October 13, 2007).

Gordis, L. 2000. *Epidemiology.* Vol. II. Philadelphia, PA: W.B. Saunders Company.

Hill, A. B. 1965. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 58:295-300.

IOM (Institute of Medicine). 1999. *Gulf War veterans: Measuring health.* Washington, DC: National Academy Press.

———. 2000. *Gulf War and health, volume 1: Depleted uranium, sarin, pyridostigmine bromide, vaccines.* Washington, DC: National Academy Press.

———. 2008. *Gulf War and health: Updated literature review of depleted uranium.* Washington, DC: The National Academies Press.

Jones, C. A., G. M. McQuillan, J. W. Kusek, M. S. Eberhardt, W. H. Herman, J. Coresh, M. Salive, C. P. Jones, and L. Y. Agodoa. 1998. Serum creatinine levels in the U.S. population: Third national health and nutrition examination survey. *American Journal of Kidney Disease* 32(6):992-999.

Last, J. M. 1988. *A dictionary of epidemiology.* 2nd ed. New York: Oxford University Press.

McDiarmid, M. 2007 (unpublished). *Depleted uranium (DU) follow-up program update. Presentation to the IOM committee on Gulf War and health: Depleted uranium.* University of Maryland.

NRC (National Research Council). 2006. *Human biomonitoring for environmental chemicals.* Washington, DC: The National Academies Press.

Parrish, R. R., M. Horstwood, J. G. Arnason, S. Chenery, T. Brewer, N. S. Lloyd, and D. O. Carpenter. 2007. Depleted uranium contamination by inhalation exposure and its detection after approximately 20 years: Implications for human health assessment. *Science of the Total Environment* 390(1):58-68.

Rothman, K. J., and S. Greenland. 1998. *Modern epidemiology.* 2nd ed. Philadelphia, PA: Lippincott-Raven.

Selvin, E., J. Manzi, L. A. Stevens, F. Van Lente, D. A. Lacher, A. S. Levey, and J. Coresh. 2007. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004. *American Journal of Kidney Disease* 50(6):918-926.

3

Available Datasets

The information described in this chapter represents the committee's understanding about available sources of data on health outcomes in military personnel and veterans exposed to depleted uranium (DU) that might be useful for future study of this population. The chapter discusses the committee's evaluation of the available datasets and their limitations.

DEPLETED-URANIUM EXPOSURE IN THE MILITARY POPULATION

DU munitions and armor were extensively used by the US military during the 1991 Gulf War, and military personnel were first exposed to DU as a result of friendly-fire incidents, cleanup and salvage operations, and proximity to burning DU-containing tanks and ammunition (DOD, 2000). In an effort to characterize exposures to DU, the Department of Defense (DOD) Office of the Special Assistant for Gulf War Illnesses developed three levels of exposure scenarios (DOD, 2000):

- *Level I exposure.* This highest exposure level occurred when soldiers were in or near combat vehicles when they were struck by DU rounds or entered vehicles soon after the impact. It is estimated that 134-164 people may have experienced level I exposure. The Depleted Uranium Follow-Up Program at the Baltimore Veterans' Affairs Medical Center has provided clinical surveillance of Gulf War veterans who were exposed to DU through friendly-fire incidents.
- *Level II exposure.* This intermediate level of exposure occurred when soldiers and civilian employees worked on DU-contaminated vehicles or were

involved in cleanup efforts after a 1991 fire at Camp Doha in Kuwait. More than 700 people may have experienced level II exposure (Kilpatrick, 2008).

- *Level III exposure.* This lowest level of exposure occurred when troops were downwind of burning DU ammunition, DU-contaminated vehicles, or the Camp Doha fire, or when they entered DU-contaminated Iraqi tanks. DOD estimates that thousands of people may have experienced level III exposure (Kilpatrick, 2008).

DU-containing weapons systems have been used in the military operations that began in Iraq in 2003 (Operation Iraqi Freedom, OIF), and there is potential for exposure of military personnel to DU in that war theater as well.

AVAILABLE DATASETS

Discussed below are select available datasets that are being used to track exposure of and health outcomes in military and veteran populations. Some were developed to study long-term health outcomes in general (for example, that of the Millennium Cohort Study), and others were designed to assess DU exposure and health outcomes specifically (for example, that of the Depleted Uranium Follow-Up Program). In most cases, some component was designated to record environmental exposure. The limitations of the datasets are discussed below. Information about each dataset is summarized in Table 3-1.

Department of Defense Depleted Uranium Medical Management Program

DOD's Depleted Uranium Medical Management Program is a component of the overall health-surveillance program for military personnel returning from deployment. The program includes identifying DU-exposed OIF military personnel both by identifying events involving DU munitions or other DU-containing materials that may have resulted in internal exposure and through the postdeployment health-assessment process and patients' self-reporting of DU exposure to medical personnel. A testing program for collecting urine to monitor for DU exposure is in place, and the Depleted Uranium Follow-Up Program provides continuing health monitoring of military personnel exposed to DU during the 1991 Gulf War and OIF.

Several DOD policies provide guidance on identifying DU-exposed military personnel, quantifying and documenting exposures, analyzing embedded fragments, referring military personnel and veterans to the Depleted Uranium Follow-Up Program, and reporting and archiving bioassay results (DOD, 2003, 2004a,b, 2008c).

TABLE 3-1 Information in Available Datasets

Critical Elements	Datasets			
	Depleted Uranium Follow-Up Program	PDHA (Form 2796) and Reassessment (Form 2900), DU Questionnaire (Form 2872)	Millennium Cohort Study	Birth and Infant Health Registry
Study design	Case series, clinical surveillance	Survey (continuing activity)	Prospective cohort	Registry
Study population	<100 male Gulf War veterans +3 male OIF personnel (as of February 2008)	PDHA/reassessment: >900,000 OIF personnel, of whom 27,000 reported potential DU exposure Followup DU questionnaire: about 1,200 OIF personnel (about another 1,200 received urinalysis but did not fill out DU questionnaire)	>100,000 military personnel (active duty, reserve) Panel 1: 77,047 people (9,251 Gulf War veterans) Panel 2: 31,110 people Panel 3: about 40,000 people (panel being recruited as of February 2008) Study population will be followed for up to 21 years	>750,000 infants born in 1998-2004 to military families (those with DOD health-care benefits)
Exposure assessment for DU				
Biomonitoring conducted?	Yes, urinalysis Also measure seminal and blood uranium	Yes, urinalysis for 2,447 OIF personnel	No	No

continued

TABLE 3-1 Continued

	Datasets			
Critical Elements	Depleted Uranium Follow-Up Program	PDHA (Form 2796) and Reassessment (Form 2900), DU Questionnaire (Form 2872)	Millennium Cohort Study	Birth and Infant Health Registry
Work records (assignment and location) evaluated?	Yes, veterans and military personnel with level I exposure included in study	Yes, primary-care manager may review work records to determine DU exposure (level I, II, or III)	No	Parental demographic, military exposure data available from DEERS, DMDC
Self-report data collected?	Yes	Yes, PDHA and reassessment, DU questionnaire	Yes, participants fill out surveys in 3-year intervals to assess physical, mental-health status Participants asked whether they had been exposed to DU during previous 3 years	No
Health-outcome assessment				
Mortality recorded?	Yes	No, but could be in future	Yes, recorded for study duration; could be linked to National Death Index periodically	NA

Morbidity recorded?	Yes, following are assessed: hematologic measures, renal markers, semen measures, reproductive endocrine measures, neurocognitive effects, chromosomal measures Clinical surveillance and monitoring	Yes, PDHA and reassessment ask about general health In addition to form, there is face-to-face assessment with trained health-care provider, clinical validation of disease	Yes, self-reported Data could be validated by additional data collection	NA
Adverse outcome in offspring recorded?	Yes	No	No	Yes (for first year of life among live births)
Controlling of confounders and bias?	Adjusted for age, race, education, intelligence, smoking, marital status, military rank, exposure to genetic toxicants, depression, use of prescription psychotropic and antidepressant drugs, recent x-ray exposure	NA	Controlled for sex, age, education, marital status, race or ethnicity, short- and long-term service, deployment status, pay grade, active-duty status, service branch, occupation	NA
Adequate followup period?	Population followed since 1993 Study continues	NA	Population has been followed since 2001 Study continues	Data collected since 1998 Study continues
Analytic approach and data analysis	Case series with longitudinal followup	Retrospective analysis	Longitudinal analysis	Descriptive

continued

TABLE 3-1 Continued

	Datasets			
Critical Elements	Depleted Uranium Follow-Up Program	PDHA (Form 2796) and Reassessment (Form 2900), DU Questionnaire (Form 2872)	Millennium Cohort Study	Birth and Infant Health Registry
Limitations	Small population Level I exposure only Lacks sufficient statistical power	Self-reported exposure Small sample, low statistical power	Small sample of those potentially exposed Lacks sufficient statistical power Recall bias related to self-reporting of previous exposure Potential for misclassification of exposure Self-selected population Use of standard instruments as surrogate for clinical diagnosis	Limited to live births; no information on early pregnancy losses, stillbirths, abortions Registry does not follow infants past first year of age, may not capture important defects or diseases that occur after that Severity of effects not captured in ICD-9-CM codes Not designed to assess birth defects associated with exposure to DU; no information on parental exposure to DU Limited to active-duty military in military-health system. Small number of subjects; lacks statistical power to detect effect
Corroboration of biomonitoring data with work record or self-reported data?	Yes	Yes	Could be done if biomonitoring data were collected	Could be done through linkage with other DOD databases

NOTE: DEERS = Defense Enrollment Eligibility Reporting System, DMDC = Defense Manpower Data Center, DOD = Department of Defense, DU = depleted uranium, ICD-9-CM = International Classification of Diseases, 9th edition, NA = not available, OIF = Operation Iraqi Freedom, PDHA = postdeployment health assessment.

Depleted Uranium Follow-Up Program

The Depleted Uranium Follow-Up Program, established in 1993, has provided clinical surveillance of veterans of the 1991 Gulf War who were exposed to DU through friendly-fire incidents (level I exposure). During the course of the Gulf War conflict, soldiers in or on vehicles and tanks "were mistakenly fired on and struck by munitions containing DU" (McDiarmid et al., 2000) and are thought to have inhaled or ingested DU particles, experienced wound contamination by DU, or received multiple tiny fragments of DU scattered throughout muscle and soft tissue. The medical-surveillance program was designed to assess health effects in veterans exposed to DU and to evaluate techniques for measuring uranium (McDiarmid, 2007).

Study Population. Since the inception of the program, researchers have prospectively evaluated about 70 of the estimated 100 Gulf War veteran survivors of friendly-fire incidents (McDiarmid et al., 2006).

In 1998, DOD and the Department of Veterans Affairs (VA) began offering DU medical screening to any other Gulf War veterans concerned about DU exposure. The screening included 30 questions about exposure and a 24-hour urine collection (Kilpatrick, 2008). From 1998 to 2002, about 400 veterans were enrolled in the voluntary program. Their median urinary uranium concentration was 0.01 μg/g of creatinine. Three of the veterans had higher than normal uranium concentrations. Researchers noted that only one of the 30 exposure questions (which was related to embedded metal fragments) was predictive of increased uranium concentration (Kilpatrick, 2008). The three veterans with increased uranium concentrations were enrolled in the Depleted Uranium Follow-Up Program.

More recently, OIF military personnel and veterans with confirmed DU exposure have been enrolled in the Depleted Uranium Follow-Up Program (see discussion of the postdeployment health-assessment program below) (McDiarmid, 2007).

Assessment of Exposure and Outcomes. The surveillance protocol consists of a detailed questionnaire documenting medical history, socioeconomic background, and occupational exposure; clinical testing, including hematologic and blood clinical-chemistry measures, urinalysis, seminal and blood uranium, renal markers, semen analysis, and reproductive endocrine measures; neurocognitive testing; and chromosomal analysis (McDiarmid et al., 2001).

Thirty-three veterans were initially examined in 1993-1994. Nearly half were confirmed as having uranium fragments embedded in a number of locations throughout their soft tissue. They also had much higher mean urinary uranium concentrations than those without retained fragments (4.47 vs 0.03 μg/g of creatinine); no other abnormalities were detected (McDiarmid et al., 2000).

The cohort has been examined every 2 years to assess functioning of the major target organ systems (primarily the kidneys, the central nervous system, and the reproductive system).

Continuous evaluation of the cohort since 1993 has yielded a number of studies to assess outcomes related to exposure. There have been no clinically significant findings of health outcomes related to exposure to DU, and researchers found no major birth defects in the 70 children born to the veterans in the cohort (McDiarmid et al., 2007; Kilpatrick, 2008).

Limitations. The Depleted Uranium Follow-Up Program is a well-designed surveillance program that has adequately captured information on a set of veterans of the Gulf War and OIF with level I exposure. However, the program does not constitute a comprehensive epidemiologic study of veterans exposed to DU in that the study population is small (so statistical power is low) and includes only those who were determined to have level I exposure.

Postdeployment Health Assessment

DOD administers a postdeployment health assessment (PDHA) to all service members returning from OIF. The PDHA includes a face-to-face assessment with a trained health-care provider and a detailed questionnaire. The purpose of the PDHA is to "review each service member's current health, mental health, or psychosocial issues commonly associated with deployments, special medications taken during the deployment, possible deployment-related occupational/environmental exposures, and to discuss deployment-related health concerns" (DOD, 2008a). The questionnaire includes a variety of questions related to health outcomes and exposure to environmental contaminants during deployment. The standard PDHA questionnaire includes date of birth, sex, service branch, marital status, location of operation, total deployments in preceding 5 years, rating of overall health, number of times a health-care provider was consulted, injury during deployment, deployment-related conditions, family conflicts, alcohol consumption, and mental-health concerns (DOD, 2008a).

Regarding exposure to DU, question 16 on the form asks: "Are you worried about your health because you were exposed to: Depleted uranium?" with a possible response of either "yes" or "no." Question 18 asks: "Did you enter or closely inspect any destroyed military vehicles?" If the veteran marks "yes" to question 16 (related to DU exposure) or question 18 and the health-care provider deems that there may be "potential exposure to depleted uranium," the veteran will be referred to the primary-care manager for completion of the DU questionnaire (Form 2872; see below) and a possible 24-hour urinalysis.

DOD also identifies people with potential exposure by using Form 2900 (January 2008) "Post-Deployment Health Re-Assessment." That form includes

a question about possible exposure to DU. Question 10 asks: "Do you have any persistent major concerns regarding the health effects of something you believe you may have been exposed to or encountered while deployed?" One possible response is "depleted uranium" (DOD, 2008b).

Form 2872, "Depleted Uranium (DU) Questionnaire," asks nearly 50 questions, including specific questions about location of service and whether the person may have been exposed at Camp Doha at the time of the fire in 1991, was involved in cleanup operations or entered a tank or Bradley fighting vehicle to perform rescue, was hit by friendly fire, was exposed to smoke, or had other concerns about exposure. On the basis of the exposure information provided on the DU questionnaire, the health-care provider assigns the person to one of the three exposure levels (I, II, or III). The results of a urine bioassay can also be recorded on the form. For those with potential level I or II exposure, bioassays are required. Although a bioassay is not required for someone with level III exposure, health-care providers may provide testing if requested by the person or if there are medical concerns about exposure. Bioassays must be performed as soon as possible, preferably within 180 days after exposure, but should be conducted even if more than 180 days have elapsed since exposure. Twenty-four-hour urine samples are collected to determine uranium concentration. If the person reports potential exposure while in theater and a 24-hour sample is not possible, a spot urine sample is collected. In addition, a 24-hour sample must be collected 7-10 days after exposure if the initial 24-hour sample was collected 24-48 hours after exposure.

If a urine sample is high in uranium (total uranium concentration at least 50 ng/g of creatinine) or isotopic analysis indicates the presence of DU at 10% or more of total uranium and/or the person has embedded fragments or fragment-type injuries, he or she is referred to the Depleted Uranium Follow-Up Program (see above). If the results of the urinary-uranium test and the isotopic analysis are high and there is no evidence of embedded fragments in the radiologic skeletal survey, the person may also be referred to the program.

As of September 30, 2007, 2,447 OIF military personnel had been tested (Casscells, 2008). The tests were performed within days to a few months after their return from theater. Of the 2,447 tested, 10 had confirmed detection of DU in their urine (see Table 3-2). The 10 were found to have retained metal fragments or had recently had fragments removed. Three of the 10 were enrolled in the Depleted Uranium Follow-Up Program (Kilpatrick, 2008).

Limitations. There are a number of limitations in the data available through this program. Exposures are largely self-reported, although there is opportunity to follow up with urine samples. The sample is small and does not permit adequate statistical power to detect most health outcomes.

TABLE 3-2 Summary of DU Bioassay Results (2003-2007)

Exposure Level	Army	Navy and Marines	Air Force	Total	Depleted Uranium Detected in Urine
I	244	71	2	317	8
II	464	98	10	572	0
III	244	85	8	337	0
Uncategorized	1,208	13	0	1,221	2
TOTAL	2,160	267	20	2,447	10

SOURCE: Adapted from Casscells, 2008.

Millennium Cohort Study

Launched in 2001, the Millennium Cohort Study is the largest prospective health study in military history. The study was established in response to a DOD recommendation for a long-term study of deployment-related exposure and an Institute of Medicine report (IOM, 1999) recommendation for a longitudinal population-based study of the health of service members (Ryan et al., 2007). The objective of the study is to "evaluate the impact of military service, including deployments and other occupational exposures, on long-term health" (DOD Center for Deployment Health Research, 2007). Chronic health outcomes—such as hypertension, heart disease, diabetes, and other multisymptom illnesses—are a major focus of the study.

Study Population

The study began its phased enrollment process in 2001 with the hope of enrolling a representative sample of over 100,000 US military personnel, including active-duty and reserve members. Participants would be followed for up to 21 years and researchers planned to resurvey participants in 3-year intervals until at least 2022. Three panels have been or are being recruited. Panel 1, recruited in 2001, has 77,047 members; 9,251 (12%) had been deployed in the 1991 Gulf War (B. Smith, personal communication, February 14, 2008). Panel 1 includes randomly selected service members; the researchers also oversampled female reservists for this panel. Panel 2, recruited in 2004, has 31,110 members, again randomly sampled but with an effort to oversample women. Panel 3, which is being recruited, will have about 40,000 members, and women will be oversampled. Enrollment into Panel 3 is being conducted through mailed surveys and electronically (Smith, 2008).

Assessment of Exposure and Outcomes

The survey instruments for the first phased enrollment included over 450 questions to collect such information as symptoms, psychosocial status, physical

and functional status, occupation, military exposure, demographic information, and use of alcohol and drugs. The study uses standardized instruments to collect data, including the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (used to assess psychologic disorders), Medical Outcomes Study short form-46 for veterans (used to assess functioning, pain, general health, and mental disorders), the CAGE questionnaire to assess alcohol problems, the Posttraumatic Stress Disorder Checklist-Civilian Version, and a VA Gulf War survey of specific wartime exposure, including exposure to DU (Ryan et al., 2007). As mentioned above, subjects will be surveyed triennially, and results will be linked to other large databases, including deployment data, data from VA, and pharmacologic data. Researchers are also planning to link survey results to data from DOD Serum Repository data, civilian inpatient and outpatient care data, and the DOD Birth and Infant Health Registry. Environmental exposure will be assessed by using the US Army Center for Health Promotion and Preventive Medicine's air, soil, and water sampling data (Smith, 2008).

Burden of Depleted Uranium in Study Population

Regarding exposure to DU, participants in the study were asked whether they had been exposed to DU during the preceding 3 years. Participants had the option to indicate "yes," "no," or "don't know." In Panel 1 of the cohort, 2,823 people[1] marked "yes" for having been exposed to DU in the preceding 3 years. Of the 9,251 Gulf War veterans (12%) enrolled in Panel 1, 558 (6%) reported "yes" to DU exposure during the previous 3 years, 961 (10.4%) reported "don't know," 7,584 (82%) reported "no," and 148 (1.6%) did not answer the question.

Limitations

The Millennium Cohort study population is not ideal for evaluating health effects related to DU exposure, because it was not designed to assess specifically this relatively rare exposure. Although the intent is to enroll 100,000 study participants, the number reporting DU exposure is quite low and may be reduced if biomonitoring data indicate that even fewer have confirmed exposure. The study also lacks sufficient statistical power to assess exposure to DU and related health outcomes.

In addition, administering a self-reported survey that asks participants to recall exposure to DU without specific followup questions about conditions where exposure may have occurred is problematic. Exposure to DU in the Gulf War theater will not be captured in veterans who respond "yes" on being asked about being exposed to DU, because the question focuses on exposures during

[1]This number is not limited to Gulf War veterans and includes all those in Panel 1 who responded "yes" when asked whether they had been exposed to DU in the preceding 3 years.

the 3 years before 2001 (the questionnaire was administered in 2001). The time since potential Gulf War exposure is substantial and may introduce recall bias and misclassification of exposure in this population.

The investigators also acknowledge a number of study limitations, including the following: the study includes a self-selected population (the respondents) that may not be representative of all military personnel or those who are deployed, there is a potential for recall bias due to self-reporting of exposure, service members who are already ill may decline to participate, and the use of surveys as a surrogate for clinical diagnosis of illness may be inaccurate (Smith, 2008).

Department of Defense Birth and Infant Health Registry

The assistant secretary of defense for health affairs established the Birth and Infant Health Registry in 1998 in response to a Senate Committee on Veterans' Affairs recommendation to establish a birth-defects registry for military service members. The registry collects data on birth and health outcomes in infants born into military families.

Study Population

The registry focuses specifically on families enrolled in the DOD health-care program, and the children are followed up to the age of 1 year. The infants were born in all 50 states and Washington, DC, and abroad. As of 2001, 39% of the DOD births were to Army personnel, 25% to Air Force personnel, 24% to Navy personnel, 11% to Marine Corps personnel, and 3% to Coast Guard or other service personnel; at that time, fewer than 19% of the births were to active-duty mothers (Ryan et al., 2001).

Assessment of Exposure and Outcomes

The registry draws on a number of large datasets. Births and diagnoses are captured from inpatient and outpatient data by using the following databases: the Standard Inpatient Data Record, the Standard Ambulatory Data Record, and the Health Care Service Record. Demographic data and exposure data on military families are captured by using the Defense Enrollment Eligibility Reporting System and the Defense Manpower Data Center. The registry uses the *International Statistical Classification of Diseases, Ninth Revision* codes in 45 major-malformation categories. On the basis of guidelines established by the National Birth Defects Prevention Network, data are validated to assess overrecording and underrecording of birth defects (Conlin, 2008).

The prevalence of birth defects in 1998-2004 was 3-4%. The most commonly diagnosed defects were atrial septal defect, ventricular septal defect, patent ductus arteriosus, and hypospadias and epispadias. Prevalence was higher with

multiple gestation, male sex, and increasing maternal age (Conlin, 2008). Overall, researchers have found that the prevalence of birth defects in military families is similar to that in the civilian population.

The registry is complementary to civilian public-health efforts to collect data on birth defects and in the future may be linked with data on environmental and occupational exposure.

Burden of Depleted Uranium in Study Population

The burden of DU in the study population has not been studied, but information may be assessed in the future by linking with other databases.

Limitations

The investigators acknowledge that the surveillance efforts are limited to live births and do not capture information on early-pregnancy losses, stillbirths, or abortions. In addition, the ICD-9-CM codes are not useful in capturing the severity of effects. Defects or diseases which may be present at birth but not diagnosed until after the age of 1 year are not captured in the registry (Conlin, 2008). Those limitations are common to many birth defects monitoring programs.

The registry is not designed to assess birth defects associated with exposure to DU. It is limited to active-duty military in the military health system. It is not designed to assess parental exposure to DU. The number of subjects in the registry lacks statistical power to detect an effect related to exposure to uranium. Loss of followup would occur if a parent left military service during the first year.

Other Department of Defense Databases

DOD maintains numerous health-related databases that can be linked to provide information about health status and potential exposure (Cox, 2007). Select databases are discussed below.

The Military Health System (MHS) includes a data repository, personnel tracking, health-care encounter information, and environmental databases. The MHS Data Repository includes comprehensive datasets from a variety of sources (including information about medical treatment, pharmacy information, and demographic data) that can be exported for analysis. Other MHS databases include the Defense Occupational and Environmental Health Readiness System, the DU testing archive (contains results of all urine testing for DU), the Master Death File, the DOD Mortality Registry, and the Medical Evaluation Board database. Many of the databases track deployment-related information, such as in-theater health-care data and environmental-hazard identification and exposure data. Regarding available environmental- and occupational-exposure data, DOD notes that most of the data are not available in real time but must be entered manually

and that sampling capabilities depend on the reporting site. It is possible to link personnel, medical, serologic, and deployment data. The DOD Medical Mortality Registry, administered by the Armed Forces Medical Examiner System, provides real-time notification of fatalities during active duty (Cox, 2007).

SUMMARY

This chapter summarizes several programs and datasets that are available to study the health of military and veteran populations. Some are designed specifically to assess DU exposure and health outcomes; others are tracking health outcomes in general but might be useful in further study of DU-exposed military and veteran populations. Examples of limitations of the datasets are inadequate sample size and statistical power, inadequate exposure assessment, and substantial potential for recall bias and exposure misclassification.

REFERENCES

Casscells, S. W. 2008. *Operation Iraqi freedom depleted uranium bioassay results—eighth semiannual report and request for data submission for ninth semiannual report.* Falls Church, VA: TRICARE Management Activity.

Conlin, A. M. 2008 (unpublished). *The Department of Defense (DOD) birth and infant health registry.* Presentation to the IOM committee on Gulf War and health: Depleted uranium. San Diego, CA: Department of Defense Center for Deployment Health Research, Naval Health Research Center. Available: National Academies' Public Access Records Office (publicac@nas.edu).

Cox, K. L. 2007 (unpublished). *Department of Defense health data sets.* Presentation to the IOM committee on Gulf War and health: Depleted uranium. Washington, DC: Department of Defense Center for Deployment Health Research, Naval Health Research Center. Available: National Academies' Public Access Records Office (publicac@nas.edu).

DOD (Department of Defense). 2000. *Environmental exposure report: Depleted uranium in the Gulf (II).* Washington, DC: Department of Defense.

———. 2003. *HA policy 03-012: Policy for OIF DU medical management.* Washington, DC: Department of Defense.

———. 2004a. *HA policy 04-004, Department of Defense deployment biomonitoring policy and approved bioassays for depleted uranium and lead.* Washington, DC: Department of Defense.

———. 2004b (unpublished). *Memorandum: Operation Iraqi freedom depleted uranium medical management.* Washington, DC: Department of Defense. Available: National Academies' Public Access Records Office (publicac@nas.edu).

———. 2008a. *Enhanced post-deployment health assessment (PDHA) process (DD form 2796).* Washington, DC: Department of Defense.

———. 2008b. *Post-deployment health reassessment: DD form 2900.* Washington, DC: Department of Defense.

———. 2008c. *Supplemental information and clinical guidance for DOD depleted uranium (DU) medical management program.* Washington, DC: Department of Defense.

DOD Center for Deployment Health Research. 2007 (unpublished). *The millennium cohort study: Fact sheet.* Washington, DC: Department of Defense. Available: National Academies' Public Access Records Office (publicac@nas.edu).

IOM (Institute of Medicine). 1999. *Gulf War veterans: Measuring health.* Washington, DC: National Academy Press.

Kilpatrick, M. E. 2008 (unpublished). *Potential exposures to depleted uranium during the 1991 Gulf War.* Presentation to the IOM committee on Gulf War and health: Depleted uranium. Washington, DC: Department of Defense. Available: National Academies' Public Access Records Office (publicac@nas.edu).

McDiarmid, M. 2007 (unpublished). *Depleted uranium (DU) follow-up program update.* Presentation to the IOM committee on Gulf War and health: Depleted uranium. Baltimore: University of Maryland. Available: National Academies' Public Access Records Office (publicac@nas.edu).

McDiarmid, M. A., J. P. Keogh, F. J. Hooper, K. McPhaul, K. Squibb, R. Kane, R. DiPino, M. Kabat, B. Kaup, L. Anderson, D. Hoover, L. Brown, M. Hamilton, D. Jacobson-Kram, B. Burrows, and M. Walsh. 2000. Health effects of depleted uranium on exposed Gulf War veterans. *Environmental Research* 82(2):168-180.

McDiarmid, M. A., K. Squibb, S. Engelhardt, M. Oliver, P. Gucer, P. D. Wilson, R. Kane, M. Kabat, B. Kaup, L. Anderson, D. Hoover, L. Brown, and D. Jacobson-Kram. 2001. Surveillance of depleted uranium exposed Gulf War veterans: Health effects observed in an enlarged "friendly fire" cohort. *Journal of Occupational and Environmental Medicine* 43(12):991-1000.

McDiarmid, M. A., S. M. Engelhardt, M. Oliver, P. Gucer, P. D. Wilson, R. Kane, M. Kabat, B. Kaup, L. Anderson, D. Hoover, L. Brown, R. J. Albertini, R. Gudi, D. Jacobson-Kram, C. D. Thorne, and K. S. Squibb. 2006. Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. *International Archives of Occupational and Environmental Health* 79(1):11-21.

McDiarmid, M. A., S. M. Engelhardt, M. Oliver, P. Gucer, P. D. Wilson, R. Kane, A. Cernich, B. Kaup, L. Anderson, D. Hoover, L. Brown, R. Albertini, R. Gudi, D. Jacobson-Kram, and K. S. Squibb. 2007. Health surveillance of Gulf War I veterans exposed to depleted uranium: Updating the cohort. *Health Physics* 93(1):60-73.

Ryan, M. A., M. A. Pershyn-Kisor, W. K. Honner, T. C. Smith, R. J. Reed, and G. C. Gray. 2001. The Department of Defense birth defects registry: Overview of a new surveillance system. *Teratology* 64(Suppl 1):S26-S29.

Ryan, M. A., T. C. Smith, B. Smith, P. Amoroso, E. J. Boyko, G. C. Gray, G. D. Gackstetter, J. R. Riddle, T. S. Wells, G. Gumbs, T. E. Corbeil, and T. I. Hooper. 2007. Millennium cohort: Enrollment begins a 21-year contribution to understanding the impact of military service. *Journal of Clinical Epidemiology* 60(2):181-191.

Smith, B. 2008 (unpublished). *The millennium cohort study.* Presentation to the IOM committee on Gulf War and health: Depleted uranium. San Diego, CA: DOD Center for Deployment Health Research, Naval Health Research Center. Available: National Academies' Public Access Records Office (publicac@nas.edu).

4

Conclusions and Recommendations

In Chapter 2, the committee detailed the critical elements necessary to conduct a well-designed epidemiologic study to identify health outcomes in military and veteran populations related to exposure to depleted uranium (DU). In Chapter 3, the committee reviewed available datasets on health outcomes in DU-exposed military personnel and veterans and datasets that do not specifically assess DU exposure but might be useful for future study. This chapter draws on the information presented in Chapters 2 and 3 to identify options for further study of potential health outcomes in DU-exposed military personnel and veterans.

For several reasons, studies of military and veteran populations (the Depleted Uranium Medical Management Program, including the Depleted Uranium Follow-Up Program at the Baltimore Veterans Affairs Medical Center; the Millennium Cohort Study; and the Department of Defense Birth and Infant Health Registry) have not been able to determine comprehensively whether exposure to DU is associated with health outcomes (see Chapter 3). Although those studies are well designed, they lack either adequate sample size or accurate exposure information (for example, biomarkers of exposure and work-assignment locations) to assess fully whether DU exposure is associated with health outcomes. For example, the Depleted Uranium Follow-Up Program includes extensive assessment of DU dose and health outcomes, but it is limited by the small study population (fewer than 100 veterans) and therefore lacks statistical power to detect many long-term health outcomes of interest. The Millennium Cohort Study has a large study population (more than 100,000 military personnel and veterans will eventually be enrolled) but is limited because assessment of exposure to DU is based on self-reported data and there is no followup through more detailed questionnaires or biomonitoring.

The remainder of this chapter contains the committee's conclusions and recommendations. The next section describes four approaches to assessment of health outcomes in DU-exposed military personnel and veterans and the committee's conclusion regarding the approach most likely to obtain useful information about DU-related health outcomes in this population. The chapter concludes with recommendations aimed at improving future epidemiologic studies and identifying current active-duty military personnel and veterans with potential DU exposure.

PROPOSED APPROACHES TO THE STUDY OF HEALTH OUTCOMES OF EXPOSURE TO DEPLETED URANIUM

As summarized in Table 4-1, the committee examined four general approaches to study health outcomes related to DU exposure in military and veteran populations. Two of the study designs use existing data, and two require new data collection.

The first approach is a case-control study that uses existing data. The study population would be drawn from Department of Defense (DOD) and Department of Veterans Affairs (VA) health records and registries. Cases would be selected on the basis of a health outcome identified as having high priority for further study by the committee in its report *Gulf War and Health: Updated Literature Review of Depleted Uranium* (IOM, 2008). That report contains an extensive review of the scientific literature on long-term health outcomes of exposure to natural uranium and DU in several populations, including uranium-processing workers, people whose drinking water contains high concentrations of uranium, and Gulf War veterans. Although the committee's overall conclusion is that the data are inadequate and insufficient to determine whether an association between exposure to uranium and a number of long-term health outcomes exists, it judged that several health outcomes should be given high priority for further study: lung cancer, lymphoma, renal disease, respiratory disease, neurologic outcomes (including neurocognitive outcomes), and adverse reproductive and developmental outcomes. Prior DU-exposure history would be assessed through a variety of means, including urinalysis, existing questionnaires, and interviews. Several limitations are associated with this approach, including a potentially small number of cases because of the low rate of disease occurrence and the low prevalence of exposure to DU. In addition, the followup time may be too short to capture some health outcomes because of their latency.

The second approach, similarly, uses a case-control study design but adds collection of new data by including future cases of disease and appropriate controls. Thus, the study population would be expanded by prospectively adding new cases with health outcomes of interest and controls from military personnel in war theaters where DU is or will be in use. Information about exposure to DU before the development of diseases and outcome data would be collected

TABLE 4-1 Proposed Epidemiologic Study Designs to Assess Health Outcomes of Exposure to DU

Study Type	Existing Data	New Data
Retrospective Analysis	*Case-Control*	*Case-Control*
Study population	Drawn from existing DOD and VA databases (such as military health records and registries) to identify people with relevant diseases (see below) and appropriate controls without those diseases who served in a war theater where there was opportunity for exposure to DU Cases: Representative set of all persons in study population identified as having one of the following[a] • Lung cancer • Lymphoma • Renal disease • Respiratory disease • Neurologic outcomes • Adverse reproductive and developmental outcomes Controls: Representative set of persons in study population who are free of those conditions	Same as under "Existing Data" except that study population would be expanded by prospectively adding people as they enter military service in war theaters where DU exposure could occur
Exposure assessment	Exposure history before becoming diseased (case) or before analogous time for controls, including information from existing questionnaires, interviews, work assignments and tasks, urinalysis	Exposure history before becoming diseased (case) or before analogous timepoint for controls, including information from existing or prospectively administered questionnaires, interviews, urinalysis; prospective collection of exposure information could be tailored and intensified beyond what is possible from historical questionnaire, interview data
Outcome assessment (used to determine disease [case], control status)	Use existing databases, such as military health records and registries, to identify people with relevant diseases	Existing health conditions would be ascertained from historical records, prospective onset of conditions ascertained from similar sources; prospective ascertainment of health conditions could be intensified beyond what is possible with existing health records

continued

TABLE 4-1 Continued

Study Type	Existing Data	New Data
Limitations	Small number of identifiable cases of disease because of low rate of disease occurrence Low prevalence of exposure to DU Followup time may not be adequate to capture some health outcomes because of latency	Although small number of identifiable cases of disease, according to existing data, can be expanded, prospective collection of data defers timing of study
Longitudinal Analysis	*Nonconcurrent or Historical Cohort*	*Prospective Cohort*
Study population	Veterans exposed or reportedly exposed to DU (such as those at Camp Doha at time of 1991 fire) Veterans with no history of exposure to DU	Same as for existing data plus addition of military populations assembled prospectively
Exposure assessment (used to determine exposure status)	Exposure history, including information from questionnaires, interviews, urinalysis	Better and more accurate measures (or indicators) of exposure information, including opportunities for corroboration by biologic data, such as individual urinalysis or more details on work assignment (location and length of time in proximity to theater)
Outcome assessment	Documentation of occurrence of relevant adverse health outcomes via linkages with death certificates or disease registries	In addition to assessment of outcome with existing data, study population would be monitored for relevant adverse health outcomes via clinical surveillance or linkages with death certificates or disease registries
Limitations	Identifying study population likely to be challenging given time elapsed since 1991 Gulf War Characterizing exposure may be problematic Low disease rates	Small study population unless new persons (beyond current military rosters) are recruited Few health outcomes, low disease rates Time and cost to conduct study may be considerable

NOTE: DOD = US Department of Defense, DU = depleted uranium, VA = US Department of Veterans Affairs.

[a]Health end points listed were identified as having high priority for further study by committee in its report *Gulf War and Health: Updated Literature Review of Depleted Uranium* (IOM, 2008).

prospectively. Because this approach requires prospective ascertainment of exposure and outcome data, the study would be deferred until troops are sent into relevant war theaters.

The third approach is a cohort study that uses existing data. The study population would consist of veterans with exposure or reported exposure to DU (for example, soldiers at Camp Doha during the 1991 fire) and a comparable group of military personnel unexposed to DU. Exposure would be assessed through questionnaires, interviews, and urinalysis. Adverse health outcomes would be documented by linkage with registries or death certificates. This type of study has several limitations. First, given the time that has elapsed since the Gulf War, it would be problematic to identify the potentially exposed population and characterize their specific individual exposures. And selection of an appropriate unexposed comparison group that would be matched to the DU-exposed group on all known prognostic factors related to the health outcomes of interest would be challenging.

The final approach is a cohort study that would expand the study population of the historical cohort study (as in the study description above) with military personnel either exposed or unexposed to DU added prospectively. This study design provides opportunities to gather extensive exposure information, including biomonitoring data and detailed work records for people enrolled prospectively. In addition to determination of health outcomes by using disease registries and death certificates, the study population would be monitored clinically. Limitations of such a study include low rates of health outcomes of interest and a small study population of DU-exposed military personnel. And the length of time and the cost to conduct a prospective cohort study could be considerable.

The committee recognizes that information from the 1991 Gulf War and from Operation Iraqi Freedom concerning the extent of exposure and identification of exposed people is suboptimal and that this limits the ability to conduct epidemiologic studies of health outcomes of DU exposure. Given the limitations of the studies described above, particularly the low statistical power and the lack of adequate exposure data, the committee concludes that it would be difficult to design a study to assess health outcomes of DU exposure in military and veteran populations comprehensively.

Detecting a small increased risk for a given health outcome of DU exposure in military and veteran populations is not feasible in an epidemiologic study. For example, as detailed in Chapter 2, a minimal sample of more than 1 million DU-exposed people (for a relative risk of 1.01) would be required to detect a statistically significant difference in risk of lung cancer, a common cancer, between DU-exposed and DU-unexposed populations. Fewer DU-exposed people would be needed to evaluate renal disease than lung cancer because renal disease is more prevalent than lung cancer in the population. A range of potential study sizes is provided in Chapter 2 of this report with the associated assumptions. As discussed there, the committee advises that if a study is undertaken, the sample-

size requirements be viewed as guidelines that are likely to be underestimates given the challenges of exposure classification, anticipated attrition of subjects from study dropout, other losses to followup, and death over the 20-year followup period. Before DOD considers undertaking an epidemiologic study, it should re-examine the sample-size estimates for lung cancer and renal disease and calculate sample-size requirements for lymphoma, respiratory disease, neurologic outcomes, and adverse reproductive and developmental outcomes to determine whether there is a reasonable possibility of detecting an effect.

The committee believes that of the four approaches outlined above, the approach most likely to obtain useful information about DU-related health outcomes would be a prospective cohort study if future military operations involve exposure to DU. The committee's power analysis (that is, of minimal sample-size estimates) demonstrates that the feasibility of an epidemiologic study will depend primarily on the ability to define sufficient numbers of people exposed to DU.

Beyond the size of future DU-exposed military populations, the success of any cohort study would depend on DOD's ability to collect accurate and complete individual-exposure information on military personnel who enter war theaters in which DU munitions and armor are used. DOD should design and implement a data-collection system to assess potential exposure, obtain biologic and environmental samples, and define the cohort for long-term followup of health outcomes.

RECOMMENDATIONS FOR IMPROVING FUTURE EPIDEMIOLOGIC STUDIES

- DOD should use the most sensitive assays when collecting biomarker data and should investigate available in vivo assay techniques other than measuring urinary uranium to determine whether they offer advantages (for example, increased sensitivity) over urinalysis.
- DOD should consider assessing uranium concentrations in lung, kidney, and brain tissues from military personnel who were potentially exposed to DU and died while on active duty. It is the committee's understanding that DOD maintains a repository of autopsy material from all military personnel who die while on active duty (M. Kilpatrick, personal communication, March 22, 2007, and February 11, 2008). Analysis of uranium in autopsy tissue might provide information on concordance between renal uranium concentrations and model-based estimates, such as those presented in a Royal Society report on the health hazards associated with DU munitions (Royal Society, 2001). It also would provide information on pulmonary retention of DU, which has implications for estimating lung cancer risk, and insight into the toxicokinetics of DU.
- DOD should continue to link and integrate available databases so that information can be assessed. With additional data-linkage capabilities, DOD and

VA will be better able to use available data to assess DU exposure and related health outcomes.

ADDITIONAL RECOMMENDATIONS

The committee commends DOD's Depleted Uranium Medical Management Program and recommends that DOD expand its efforts to identify all active-duty military personnel and veterans with potential DU exposure to determine their DU body burdens. Specifically, the committee recommends that

- DOD determine the feasibility of collecting biomarker data through the Millennium Cohort Study from the 2,823 members of Panel 1 (or potentially from members of all three panels if such information is available) who reported being exposed to DU in the preceding 3 years. That information could be used to conduct an exposure study to assess the accuracy of surrogate exposure measurements (material on questionnaires). Any study participants who test positive for DU exposure should receive health monitoring through the Depleted Uranium Follow-Up Program throughout their lifetime. Comprehensive clinical assessments of exposed people provide extensive data on health outcomes potentially related to DU exposure and might have value in stimulating further study.
- DOD determine the feasibility of identifying military personnel who were at Camp Doha during the time of the fire in 1991 and of collecting biomarker data on them. This work could provide exposure information on level II exposure and level III exposure during the Gulf War. Any veteran who tests positive for DU exposure should receive health monitoring (see above).

The committee's final recommendation is related to studying adverse reproductive and developmental outcomes.

- The committee recommends further study of the potential reproductive and developmental toxicity of DU with animal models (a review of reproductive and developmental toxicity studies of DU is included in *Gulf War and Health: Updated Literature Review of Depleted Uranium* [IOM, 2008]). Specific studies may address reproductive measures (for example, the number of motile sperm, which is highly predictive of intrauterine-insemination success and, thus, correlated with fertilization rate). Important observations on the effects of DU on developing animals might be derived from in vivo animal studies. For example, they could provide information on growth, reproductive capacity, cancer, neurobehavioral function, and transplacental exposure. Animal studies focusing on the health effects of DU on the progeny's health might be useful for corroborating findings reported in epidemiologic studies, and outcomes may be correlated with DU exposure (as measured by urinary DU excretion).

REFERENCES

IOM (Institute of Medicine). 2008. *Gulf War and health: Updated literature review of depleted uranium.* Washington, DC: The National Academies Press.

Royal Society. 2001. *The health hazards of depleted uranium munitions: Part I.* London, UK: The Royal Society Working Group on the Health Hazards of Depleted Uranium Munitions.