Free Executive Summary

Gulf War and Health: Updated Literature Review of Depleted Uranium

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

ISBN: 978-0-309-11919-1, 308 pages, 6 x 9, paperback (2008)

The 1991 Persian Gulf War was considered a brief and successful military operation with few injuries and deaths. A large number of returning veterans, however, soon began reporting health problems that they believed to be associated with their service in the gulf. Under a Congressional mandate, the Institute of Medicine (IOM) is reviewing a wide array of biologic, chemical, and physical agents to determine if exposure to these agents may be responsible for the veterans' health problems. In a 2000 report, Gulf War and Health, Volume 1: Depleted Uranium, Sarin, Pyridostigmine Bromide, and Vaccines, the IOM concluded that there was not enough evidence to draw conclusions as to whether long-term health problems are associated with exposure to depleted uranium, a component of some military munitions and armor. In response to veterans' ongoing concerns and recent publications in the literature, IOM updated its 2000 report. In this most recent report, Gulf War and Health: Updated Literature Review of Depleted Uranium, the committee concluded that there is still not enough evidence to determine whether exposure to depleted uranium is associated with long-term health problems. The report was sponsored by the U.S. Department of Veterans Affairs.

SUMMARY

The 1990-1991 Persian Gulf War was considered a military success, with few injuries or deaths. However, a number of veterans began experiencing symptoms—such as fatigue, cognitive difficulties, and sleep disturbances—after their return home. In response to growing concern about possible exposure to a biologic, chemical, or physical agent as the cause of the symptoms, Congress passed two laws in 1998: PL 105-277, the Persian Gulf War Veterans Act, and PL 105-368, the Veterans Programs Enhancement Act. Under the legislation, the Department of Veterans Affairs (VA) was directed to ask the Institute of Medicine (IOM) to evaluate the scientific literature regarding associations between illness and exposure to specific toxic agents, environmental or wartime hazards, or preventive medicines or vaccines related to Gulf War service.

In 1998, IOM began a program to examine health risks posed by specific agents and hazards to which Gulf War veterans might have been exposed during their deployment. Five reports have examined health outcomes related to depleted uranium, pyridostigmine bromide, sarin, and vaccines; insecticides and solvents; fuels, combustion products, and propellants; infectious diseases; and physiologic, psychologic, and psychosocial effects of deployment-related stress. A sixth IOM report examined the current health status of Gulf War–deployed veterans compared with their nondeployed counterparts. The present report updates the review of depleted uranium presented in the 2000 IOM report, *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines* (hereafter referred to as *Volume 1*).

The Gulf War marked the first time that depleted-uranium munitions and armor were extensively used by the US military. Depleted uranium is used by the US military for both offensive and defensive purposes. Heavy-armor tanks have a layer of depleted-uranium armor to increase protection. Offensively, depleted uranium is used in kinetic-energy cartridges and ammunition rounds. The Army used an estimated 9,500 depleted-uranium tank rounds during the Gulf War. Ammunition containing depleted uranium was used in Bosnia-Herzegovina in 1994-1995 and in Kosovo in 1999; about 10,800 depleted-uranium rounds were fired in Bosnia-Herzegovina, and about 30,000 in Kosovo. Depleted-uranium–containing weapons also have been used in Operation Iraqi Freedom (OIF), which began in 2003. Because depleted uranium continues to be used by the military, the charge to IOM has been expanded to include not only veterans of the Gulf War but veterans returning home from OIF.

Military personnel have been exposed to depleted uranium as a result of friendly-fire incidents, cleanup and salvage operations, and proximity to burning depleted-uranium–containing tanks and ammunition. During the Gulf War, an estimated 134-164 people experienced “level I” exposure (the highest of three exposure categories as classified by the US

Department of Defense) through wounds caused by depleted-uranium fragments, inhalation of airborne depleted-uranium particles, ingestion of depleted-uranium residues, or wound contamination by depleted-uranium residues. Hundreds or thousands more may have been exposed to lower exposure through inhalation of dust containing depleted-uranium particles and residue or ingestion from hand-to-mouth contact or contamination of clothing. Ten US military personnel who served in OIF had confirmed depleted uranium detected in their urine; all 10 had depleted-uranium embedded fragments or fragment injuries.

SUMMARY OF FINDINGS IN *VOLUME 1*

When *Volume 1* was published in 2000, few studies of health outcomes of exposure to depleted uranium had been conducted. Therefore, the committee studied the health outcomes of exposure to natural and processed uranium in workers at plants that processed uranium ore for use in weapons and nuclear reactors. After evaluating the literature, the committee concluded that there was inadequate or insufficient evidence to determine whether an association exists between uranium exposure and 14 health outcomes—lymphatic cancer, bone cancer, nervous system disease, reproductive or developmental dysfunction, nonmalignant respiratory disease, gastrointestinal disease, immune-mediated disease, effects on hematologic measures, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects, and musculoskeletal effects. It also concluded that there was limited or suggestive evidence of *no* association between uranium and clinically significant renal dysfunction and between uranium and lung cancer at cumulative internal doses lower than 200 mSv.

CHARGE TO THE COMMITTEE

Since *Volume 1* was published in 2000, a number of studies of health outcomes of exposure to natural and depleted uranium have been published. For that reason and because depleted uranium continues to be used by the military, VA asked IOM to update the 2000 report and to take into consideration information published since *Volume 1*. In response, IOM entered into a contract with VA to conduct the following study:

> An IOM committee will review, evaluate, and summarize the scientific literature regarding the association between exposure to depleted uranium and long-term human health outcomes. The study committee will incorporate literature published since the 2000 IOM report *Gulf War and Health, Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines* was written. The committee will make determinations on the strength of the evidence of associations between exposure to depleted uranium and human health outcomes.

THE COMMITTEE'S APPROACH TO ITS CHARGE

The committee began its evaluation by presuming neither the existence nor the absence of adverse health outcomes associated with exposure to depleted uranium. It sought to characterize and weigh the strengths and limitations of the available evidence. The committee

did not concern itself with policy issues, such as decisions regarding disability, potential costs of compensation, or any broad policy implications of its findings.

An extensive search of the scientific literature generated about 3,500 titles and abstracts. After examination of the titles and abstracts to identify articles that appeared to be relevant to the committee's task (that is, articles on health outcomes of exposure to uranium), about 1,000 articles—including epidemiologic, toxicologic, and exposure-assessment studies—remained in the committee's reference database. Additional information was obtained from invited experts and the public during a meeting held on June 28, 2007, in Washington, DC.

After securing the full text of the articles mentioned above, the committee had to determine which ones would be included in the review.

For an epidemiologic study to be included in the committee's review, it had to be published in a peer-reviewed journal or to have undergone an equally rigorous process. A study also needed to be judged as methodologically sound, on the basis of inclusion of details of its methods, use of appropriate control or reference groups, statistical adjustment to control for confounders and minimize selection bias, and appropriate assessment of uranium exposure in the study population. It needed to examine long-term health outcomes and had to have a followup time sufficient to detect a relevant clinical effect. Finally, it had to include a relevant study population, that is, uranium-exposed workers, military personnel deployed to the Gulf War, or people who lived near a uranium-processing facility (uranium exposure in such residents may be similar to low-level exposures of military personnel). Studies in uranium miners were not included in the committee's evaluation because several issues related to confounding substantially limited the usefulness of those studies.

The committee used the evidence in the scientific literature to draw conclusions about associations between exposure to depleted uranium and specific adverse health outcomes. Those conclusions are presented as categories of strength of association. The categories have been used in many previous IOM studies, and they have gained wide acceptance by Congress, government agencies, researchers, and veteran groups. The categories are summarized below.

- **Sufficient evidence of a causal relationship.** Evidence is sufficient to conclude that a causal relationship exists between the exposure to uranium and a specific health outcome in humans. The evidence fulfills the criteria for sufficient evidence of an association (below) and satisfies several of the criteria used to assess causality: strength of association, dose-response relationship, consistency of association, temporal relationship, specificity of association, and biological plausibility.
- **Sufficient evidence of an association.** Evidence is sufficient to conclude that there is an association. That is, a consistent association unlikely to be due to sampling variability has been observed between exposure to uranium and a specific health outcome in human studies that were free of severe bias and that controlled for confounding.
- **Limited/suggestive evidence of an association.** Evidence is suggestive of an association between exposure to uranium and a specific health outcome, but the body of evidence is limited by insufficient avoidance of bias, insufficient control for confounding, or large sampling variability.
- **Inadequate/insufficient evidence to determine whether an association exists.** Evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to uranium and a specific health outcome in humans.

- **Limited/suggestive evidence of no association.** Evidence is consistent in not showing an association between exposure to uranium of any magnitude and a specific health outcome. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies.

CONCLUSIONS

The committee drew on information from the many studies published since 2000 and from *Volume 1* and reached its conclusions by interpreting the new evidence in the context of the entire body of literature. Most of the evidence on health effects of exposure to uranium came from studies of workers in uranium-processing mills and other facilities, and the committee relied heavily on those studies in developing its conclusions. Also taken into consideration in the evaluation were studies of Gulf War veterans exposed to depleted uranium and of residential exposure to uranium. All those studies were valuable in drawing conclusions, but they also had limitations. For example, the number of exposed people in many of the studies was relatively small, and this decreased the statistical power to detect a small excess risk of disease. The period of followup in several studies might have been too short to detect some diseases that are typically characterized by long latency; this limitation is of particular concern with respect to studies of cancer outcomes. And assessment of exposure to uranium was inadequate in many of the studies reviewed by the committee.

On the basis of the available literature, the committee concluded that there is *inadequate/insufficient evidence to determine whether an association exists* between exposure to uranium and all the health outcomes examined: lung cancer, leukemia, lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma), bone cancer, renal cancer, bladder cancer, brain and other nervous system cancers, stomach cancer, prostatic cancer, testicular cancer, nonmalignant renal disease, nonmalignant respiratory disease, neurologic effects, reproductive and developmental effects, and several other health outcomes (cardiovascular effects, genotoxicity, hematologic effects, immunologic effects, and skeletal effects). The committee's conclusions on lung cancer and nonmalignant renal disease differ from those in *Volume 1* (see "Summary of Findings in *Volume 1*" above). With respect to lung cancer, the committee decided not to place quantitative limits on the dose, primarily because of the wide variety of exposure-assessment methods used in the studies reviewed and the uncertainty in measurement of uranium exposure. With respect to nonmalignant renal disease, the committee decided that it could not rule out the occurrence of a renal effect "after exposure of any magnitude", as required to meet the definition of *limited/suggestive evidence of no association*.

In summary, the committee assigned the category *inadequate/insufficient evidence to determine whether an association exists* to each health outcome described above for one or more of the following reasons:

- Well-conducted studies showed equivocal results.
- The magnitude or frequency of a health outcome may be so low that it cannot be reliably detected given the sizes of the study populations.
- The available studies had limitations (such as inadequate exposure assessment or followup that was too short) that made it impossible to reach clear conclusions about health outcomes.

Gulf War and Health: Updated Literature Review of Depleted Uranium

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 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 0-309-XXXXX-X (Book)
International Standard Book Number 0-309- XXXXX -X (PDF)
Library of Congress Control Number: 00 XXXXXX

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. *Gulf War and Health: Updated Literature Review of Depleted Uranium.* 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, SC

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

H. TIM BORGES, PhD, Research Staff Member, Oak Ridge National Laboratory, Oak Ridge, TN *(resigned February 2008)*

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

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

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, WA

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
PETER JAMES, Senior Program Associate (through May 2007)
A. WEZI MUNTHALI, MPH, Senior Program Associate (through November 2007)
DEEPALI M. PATEL, Senior Program Associate (through November 2007)
JENNIFER E. SAUNDERS, MPP, MPH, Senior Program Associate (from November 2007)
RENEE WLODARCZYK, Research Assistant
JOSEPH GOODMAN, Senior Program Assistant
DANIELLE K. STOLL, Intern
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:

Odile David, University of Illinois College of Medicine
Fletcher Hahn, Lovelace Respiratory Research Institute, Scientist Emeritus
Robert Herrick, Department of Environmental Health, Harvard School of Public Health
Howard Hu, University of Michigan Schools of Public Health and Medicine
Ronald L. Kathren, Washington State University, Professor Emeritus
William N. Rom, Division of Pulmonary and Critical Care Medicine, New York University School of Medicine
Michael J. Thun, Epidemiology and Surveillance Research, American Cancer Society
Bailus Walker, Jr., Howard University Medical Center
Walter Willett, Department of Nutrition, Harvard School of Public Health
Judith T. Zelikoff, Department of Environmental Medicine, New York University School of Medicine

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,** Institute of Public Health Research, 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 author committee and the institution.

CONTENTS

Tables and Boxes

(Note that the tables for Chapters 3, 7, and 8 are at the ends of the chapters)