Review of Toxicologic and Radiologic Risks to Military Personnel from Exposure to Depleted Uranium During and After Combat

Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat, Committee on Toxicology, National Research Council

ISBN: 0-309-11037-8, 172 pages, 6 x 9, (2008)

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Committee on Toxicology

Board on Environmental Studies and Toxicology

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THE NATIONAL ACADEMIES PRESS
Washington, D.C.
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This project was supported by Contract W81K04-06-D-0023 between the National Academy of Sciences and the U.S. Army. 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: 978-0-309-11036-5
International Standard Book Number-10: 0-309-11036-X

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The National Academies Press
500 Fifth Street, NW
Box 285
Washington, DC 20055

800-624-6242
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Preface

The U.S. armed forces used a new large-caliber (LC) anti-armor munition with a depleted-uranium (DU) penetrator in the 1991 Gulf War (Operation Desert Storm). The use of this high-density, self-sharpening munition helped to end that war quickly because of its effectiveness in reaching and perforating distant armored targets. In Operation Desert Storm, the U.S. armed forces used more than 300 tons of LC-DU munitions.

During the course of the 1991 Gulf War, misidentification of U.S. forces in distant vehicles led to a number of incidents in which U.S. armored vehicles were struck by the LC-DU munitions. About 115 U.S. soldiers in or on six Abrams tanks and 14 Bradley fighting vehicles were struck by LC-DU munitions. Some of the 104 crewmembers who survived were injured by DU shrapnel. Most of the large metal fragments in them were removed during treatment for their injuries, but many small fragments remain embedded in their muscle tissue, and the soldiers with embedded fragments continue to be medically monitored.

Because of exposure of many soldiers in Operation Desert Storm and the Balkan war and because of concern about the potential health effects on exposed soldiers and civilian contract workers in the battlefield area, the U.S. Department of Defense (DOD) requested that the National Research Council independently review the U.S. Army's "Capstone Report" *Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments*. The Capstone Report is a set of documents that detail the basis of the Army's assessment of the toxicologic and radiologic risks to military personnel from exposures to DU aerosols during and after combat. In response to DOD's request, the National Research Council convened the Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat, which prepared this report. The members of the committee were selected by the National Research Council for their expertise in pharmacokinetics, toxicology, inhalation toxicology, immunotoxicology, radiation health effects, epidemiology, physiologically based pharmacokinetic modeling, biostatistics, and risk assessment. The committee's report provides an independent evaluation of the exposure assessment and health-risk assessment provided in the Army's report. It focuses on exposures of and risks to soldiers exposed to DU during and after combat. It is intended to be useful to DOD in updating combat planning and training involv-

ing DU munitions and in developing policies concerning health-care management of military personnel exposed to or injured by DU munitions.

A draft of this report was reviewed by persons selected 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 thank the following for their review of this report: Gary Diamond, Syracuse Research Corporation; Judith Graham, American Chemistry Council; David Hoel, Medical University of South Carolina; Ralph Kodell, University of Arkansas for Medical Sciences; Loren Koller, Loren Koller & Associates, LLC; Richard Leggett, Oak Ridge National Laboratory; Roger McClellan, Consultant; Richard Schlesinger, Pace University; Michael Thun, American Cancer Society; Mark Utell, University of Rochester Medical Center; and Paul Ziemer, Purdue University.

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 the report was overseen by Floyd Bloom, Scripps Research Institute. Appointed by the National Research Council, he was responsible for ensuring that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the author committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following: David Alberth, Laurie Roszell, Glenn Leach, Steve Kistner, John Rowe, Mark Melanson, and Frances Szrom (all of the U.S. Army), who during public sessions provided technical materials on depleted uranium; and Aida Neel, the project associate. We are grateful to James J. Reisa, director of the Board on Environmental Studies and Toxicology, for his helpful comments. The committee particularly acknowledges Kulbir Bakshi, project director for the committee, and Susan Martel and Ellen Mantus for bringing the report to completion. Finally, I thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Meryl Karol, *Chair*
Committee on Toxicologic and Radiologic
Effects from Exposure to Depleted Uranium
During and After Combat

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Summary

Depleted uranium (DU) is a weakly radioactive, chemically toxic heavy metal derived from natural uranium and is used by the U.S. military for munitions and for armor on some tanks. DU is well suited as a munition because of its high density and "self-sharpening" nature, both of which help it to penetrate armor. Its high density also makes DU an effective shield. DU has been used by all branches of the U.S. military since the 1980s, and it has been used on the battlefield in the Persian Gulf War, the Balkans, and the Iraq War.

Concern about the adverse health effects on survivors of combat exposure to DU arose in response to "friendly-fire" incidents in which U.S. vehicles were accidentally struck with DU rounds. In the Gulf War, about 115 U.S. soldiers in or on six Abrams tanks and 14 Bradley fighting vehicles were caught in friendly-fire events that involved the use of large-caliber munitions containing DU penetrators. Some of the soldiers were injured by DU shrapnel. Most of the large metal embedded fragments in the surviving 104 soldiers were removed during treatment for their injuries. However, many small fragments remain embedded in their muscle tissue because their removal might lead to other health complications.

When used as an antitank armor-piercing munition, a DU penetrator can create an airborne spray of uranium with particles of various sizes that can be inhaled by the tank crew or escape into the environment. Soldiers may ingest DU oxide dust by hand-to-mouth contact or when inhaled dust is coughed up and swallowed. Exposure may also occur when DU oxide dust is absorbed through open wounds, burns, or other breaks in the skin. Some think that DU may be responsible for illnesses noted in veterans involved in the conflicts and civilians living near the battlefields. Because of the concern about health effects, the U.S. Army commissioned a report, *Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments*, referred to as the Capstone Report, that evaluates the health risks associated with exposure to DU aerosols and asked the National Research Council's Committee on Toxicology in collaboration with the

Nuclear and Radiation Studies Board to review it independently. As a result of the Army's request, the National Research Council convened the Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat, which prepared the present report.

The committee's task was to review the toxicologic, radiologic, epidemiologic, and toxicokinetic data on DU and to assess the Capstone Report on toxicologic and radiologic risks to soldiers posed by exposure to DU. It was to consider health-hazard and environmental reports prepared by such organizations as the World Health Organization, the UN Environment Programme (for the post-conflict Balkans), the International Atomic Energy Agency, the Agency for Toxic Substances and Disease Registry, and the UK Royal Society. The committee was also to identify relevant data deficiencies and offer recommendations for future research.

CAPSTONE REPORT

Exposure Assessment

The Capstone Report considered three kinds of scenarios of exposure to DU in combat and postcombat settings. Level I exposure involved soldiers who were in vehicles at the time of perforation with DU munitions or first responders who entered the struck vehicles shortly thereafter to rescue the injured. Five scenarios were considered for level I exposure: crew exiting a struck vehicle within 1 min, 5 min, 60 min, or 120 min or first responders entering a vehicle within 5 min to rescue injured crew members and exiting within 10 min. Level II exposure involved workers who were in or around vehicles containing DU fragments and particles at times after the event but were not in the vehicles at the time of impact and did not immediately enter vehicles after they were struck. Level III exposure was brief or incidental and was considered negligible.

The Army conducted an aerosol study to characterize the DU exposures that were likely to have occurred in combat situations. The study involved shooting DU munitions into stripped-down Abrams tanks and a Bradley fighting vehicle and collecting samples to estimate time-integrated concentrations of DU in the air in the vehicles. Intakes of DU were estimated, and biokinetic models were used to predict the chemical and radiologic doses to body tissues.

Overall, the committee found the methods and results of the Capstone exposure assessment to be appropriate and well done. To verify the exposure-assessment results, the committee made its own estimates on the basis of data developed largely outside the Capstone program. Using older datasets on the aerosol characteristics of the dusts and fumes produced when a DU penetrator strikes a hard target, the committee found that its estimated intakes in level I exposures were within a factor of 2 of the Capstone results. For levels II and III exposures, the committee calculated exposure rates resulting from surface contamination resuspended in the air and from incidental ingestion by using stan-

dard exposure-assessment values. The committee's rates were again similar to those in the Capstone Report. The committee concluded that the Capstone exposure results are reasonable and appropriate for use in the human health risk analysis of DU.

Health Risk Assessment

Noncancer Effects

In the Capstone Report, renal effects are used as the most sensitive end point for evaluating noncancer risks to soldiers. To evaluate that choice, the committee reviewed the literature on DU and uranium and their effects on various organ systems, such as the immune, cardiovascular, gastrointestinal, hematologic, reproductive, nervous, hepatic, and renal systems. On the basis of its review, the committee concurred with the Capstone Report that the kidneys are the most sensitive targets of uranium toxicity. Other toxic effects reported in the literature either were observed at uranium exposure concentrations unlikely to be encountered by military personnel in combat or postcombat scenarios or that required prolonged exposure. Furthermore, renal effects were consistently observed whenever other effects were observed.

The primary targets in the kidneys are the proximal tubules, but glomerular effects may also occur. Early evidence of the effects can be found by measuring markers of biochemical changes in the body. Biomarkers of tubular effects include increased urinary excretion of low-molecular-weight proteins, amino acids, and glucose. Biomarkers of glomerular effects include urinary excretion of high-molecular-weight proteins. Glucosuria (increased urinary concentration of glucose) is the most persistent biomarker of tubular effects observed after acute exposure of animals and humans. Biomarker measurements can be used in biokinetic models to estimate renal uranium concentration, which is considered the best estimate of exposure.

The Capstone Report developed a categorization scheme, termed the Renal-Effects Group, that correlates renal uranium concentrations, renal effects, and likely health outcomes (see Table S-1). The scheme is based on observations from human acute-exposure studies and estimates of renal uranium concentrations derived from biokinetic modeling. The committee encountered several difficulties in verifying the upper bound of the REG-0 value (2.2 μg/g) calculated by the Army. The difficulties included questions about the interpretation of some studies used to derive the REG values, uncertainties about the attribution of effects solely to uranium exposure, questions about the models that were used to estimate renal concentrations, and questions about the relevance of exposure scenarios in some studies to those encountered in military combat and postcombat settings.

The renal uranium concentrations found in some cases after acute exposure suggest that minimal, transient effects (such as proteinuria and albuminuria)

TABLE S-1 REG Predictions of Chemical Risk to Kidneys in the Army's Capstone Report

Renal-Effects Group	Renal Uranium Concentration (μg/g of renal tissue)	Acute Renal Effect	Predicted Outcome
0	≤2.2	No detectable effects	No detectable effects[a]
1	>2.2 to ≤6.4	Possible transient indicators of renal dysfunction	Not likely to become ill[b]
2	>6.4 to ≤18	Possible protracted indicators of renal dysfunction	May become ill[c]
3	>18	Possible severe clinical symptoms of renal dysfunction	Likely to become ill[d]

[a]The committee interprets *no detectable effects* to mean no low-level transient renal effects and no clinical symptoms.
[b]The committee interprets *not likely to become ill* to mean may exhibit low-level, transient renal effects.
[c]The committee interprets *may become ill* to mean may experience clinical symptoms of renal dysfunction and require medical attention.
[d]The committee interprets *likely to become ill* to mean likely to experience clinical symptoms of renal dysfunction and require medical attention.
Source: Guilmette, R.A., M.A. Parkhurst, G. Miller, E.F. Hahn, L.E. Roszell, E.G. Daxon, T.T. Little, J.J. Whicker, Y.S. Cheng, R.J. Traub, G.M. Lodde, F. Szrom, D.E. Bihl, K.L. Creek, and C.B. McKee. 2005. Human Health Risk Assessment of Capstone Depleted Uranium Aerosols. Attachment 3 of Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments. Columbus, Ohio: Battelle Press. Reprinted with permission; copyright 2005, Battelle Press.

may occur at concentrations as low as 1 μg/g. Similar effects have been reported at renal concentrations around 1 μg/g in workers with chronic occupational exposure to uranium and in Gulf War veterans with embedded DU fragments. The Royal Society has noted transient renal effects at renal concentrations of 1 μg/g and noted further that the trend in chronic exposure is toward greater renal effects with lower renal concentrations, possibly as low as 0.1 μg/g. Thus, the REG-0 kidney concentration for uranium may need to be redefined, and any revision of the upper-bound REG-0 value would also require that the REG-1 range be redefined. If the REG-0 value is lowered, some soldiers may have to be reclassified. The committee found REG 2 and 3 to be appropriately defined in the Capstone Report.

Cancer Effects

Evidence on the risk of cancer or other chronic diseases after exposure to DU in Gulf War soldiers is inadequate. Epidemiologic evidence indicates a very

low risk of cancer in people exposed to uranium. However, the possibility of a radiation-induced cancer caused by inhalation of insoluble DU particles cannot be ruled out, given that alpha particles are emitted by DU. The latent period associated with radiation-induced lung cancer is at least 10 y and might be much longer.

In animals, insoluble forms of uranium have been found to be weakly carcinogenic; lung cancer is the primary cancer that occurs after chronic inhalation exposure. Powdered or solid implants of uranium in the muscles of laboratory animals have shown evidence of carcinogenicity, and sarcomas have been observed in the vicinity of embedded uranium metal.

Chromosomal assessments of exposed human populations (such as uranium production workers, uranium miners, and Gulf War DU-exposed veterans) have given mixed results regarding the genotoxic effects of uranium and DU in humans. Uranium has been shown to cause mutations, cell transformation, and DNA strand breaks in both in vitro and in vivo studies. Proposed mechanisms of the genotoxicity of uranium include both chemical and radiologic effects.

The Capstone Report's cancer risk assessment for DU exposure is based on the radioactive properties of DU. The concern that DU may increase the risk of cancer is based on knowledge that radiation doses can be delivered to various organs from inhaled DU and that radiation is a known carcinogen. Because no cancer risk factors are specifically related to DU, estimation of the risk of developing cancer in the Capstone Report is based on the radiation risks posed by alpha-emitters.

For level I exposure, the Capstone Report calculated radiation dose estimates for the five exposure scenarios. To assess the Army's calculations, the committee performed its own calculations for selected scenarios (ventilated and unventilated Abrams tank and Bradley fighting vehicle with conventional armor) and found the Capstone estimates to be reasonable; the Capstone estimates agree to within a factor of about 2 (Table S-2). Those estimates are within U.S. radiation standards for occupational exposure (for example, the U.S. annual limit for routine occupational exposure is 5 rem). The doses accrue over 50 y instead of a single year and do not directly correspond to annual doses. Furthermore, the Capstone-estimated median exposure is below the U.S. Nuclear Regulatory Commission annual dose limit of 10 rem for occupational workers with planned exposure.

Radiologic cancer risks were calculated in the Capstone Report on the basis of the sum of individual organ risks rather than whole-body effective dose. Biokinetic models were used to calculate organ doses, which were then used with established organ-specific cancer risk factors for alpha-emitters to determine the individual organ risks. The committee found that approach to assessing cancer risks to be appropriate because it allows for the lack of uniformity in dose distribution among organs. Lifetime cancer mortality risks were calculated with a linear dose-response model (see Table S-3), which the Capstone Report acknowledges might overestimate risks at the low doses predicted for the exposure scenarios.

The decision to use *median* lifetime cancer-mortality risk estimates means that the inherent variability in the exposure estimates is not considered. At the 10th- and 90th-percentile estimates of exposure, the lifetime cancer-mortality estimates for some exposure scenarios could be lower by as much as a factor of 6 or higher by about a factor of 3, respectively. For the 90th-percentile exposure scenarios, the estimated lifetime cancer-mortality risks approach 0.6%; if a vehicle is struck twice with a DU penetrator, the lifetime cancer mortality would be expected to roughly double. That would result in median and 90th-percentile estimated lifetime cancer risks of 0.9% and less than 1.2%, respectively. However, at those levels of risk, it would not be possible to distinguish between increased cancer mortality from DU exposure and background lung-cancer rates.

The Capstone Report does not provide estimates of radiologic-cancer risks for levels II and III personnel. The committee finds that to be a deficiency in the

TABLE S-2 Committee and Capstone Estimates of Effective Lifetime Committed Radiation Dose Equivalents from DU in Air for Selected Level I Exposure Scenarios, rem (Sv)

	ABRAMS			
	Unventilated		Ventilated	
Scenario	Committee	*Capstone*	Committee	*Capstone*
A: Exit 1 min	0.94 (0.0094)	*2.0 (0.020)*	0.61 (0.0061)	*0.09 (0.0009)*
B: Exit 5 min	3.1 (0.031)	*3.7 (0.037)*	1.0 (0.010)	*0.44 (0.0044)*
C: Exit 60 min	6.5 (0.065)	*4.8 (0.048)*	1.0 (0.010)	*1.02 (0.0102)*
D: Exit 120 min	6.5 (0.065)	*5.0 (0.050)*	1.0 (0.010)	*1.20 (0.0120)*
E: First responder	2.3 (0.023)	*0.92 (0.0092)*	0.02 (0.0002)	*0.41 (0.0041)*
	BRADLEY			
	Unventilated		Ventilated	
Scenario	Committee	*Capstone*	Committee	
A: Exit 1 min	0.91 (0.0091)	*0.59 (0.0059)*	0.64 (0.0064)	
B: Exit 5 min	2.7 (0.027)	*1.7 (0.017)*	1.1 (0.011)	
C: Exit 60 min	4.2 (0.042)	*2.1 (0.021)*	1.2 (0.012)	
D: Exit 120 min	4.2 (0.042)	*2.4 (0.024)*	1.2 (0.012)	
E: First responder	1.3 (0.013)	*0.89 (0.0089*	0.04 (0.0004)	

TABLE S-3 Capstone Summary of Median (10th-, 90th-Percentile) Estimates of Increased Lifetime Risk of Fatal Lung Cancer (Expressed as %) from Inhalation Exposures of DU for Level I Personnel from Single Perforation of Vehicle

Exposure	Abrams Tank: Regular Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, Ventilation	Bradley Vehicle: Regular Armor, No Ventilation
Exit in 1 min	0.11 (0.07, 0.14)	0.12 (0.08, 0.24)	0.0049 (NA)	0.034 (0.009, 0.059)
Exit in 5 min	0.20 (0.17, 0.40)	0.32 (0.24, 0.52)	0.025 (NA)	0.099 (0.019, 0.180)
First responder	0.05 (0.03, 0.11)	0.10 (0.06, 0.16)	0.023 (NA)	0.052 (0.016, 0.077)
Exit in 60 min	0.27 (0.17, 0.44)	0.44 (0.32, 0.64)	0.057 (NA)	0.12 (0.06, 0.40)
Exit in 120 min	0.28 (0.16, 0.44)	0.45 (0.33, 0.65)	0.065 (NA)	0.14 (0.07, 0.41)

NA = not available.

Source: Parkhurst, M.A., E.G. Daxon, G.M. Lodde, F. Szrom, R.A. Guilmette, L.E. Roszell, G.A. Falo, and C.B. McKee. 2005. Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments (Capstone Summary Report). Columbus, Ohio: Battelle Press. Reprinted with permission; copyright 2005, Battelle Press.

report. On the basis of estimated exposure of levels II and III unprotected personnel working in or around a perforated vehicle 2 h or more after a single DU-munition perforation, the 50-y whole-body dose (inhalation + ingestion) is up to 0.079 rem/h of exposure, and the 50-y lung dose via inhalation is up to 0.56 rem/h of exposure. The estimated dose would be higher for extended exposure in a vehicle with multiple perforations.

The Capstone Report also does not include cancer risk estimates for soldiers who have embedded DU fragments. That was an intentional omission that perhaps is being addressed separately. However, its exclusion from the Capstone Report leads to an underestimation of risk due to increased, prolonged systemic exposure to DU in this cohort of soldiers and risk of developing sarcomas in the vicinity of the embedded fragments.

RECOMMENDATIONS

On the basis of its independent review of the Capstone Report and the toxicologic and epidemiologic literature concerning uranium, the committee offers the following recommendations. (Additional, more specific recommendations are listed at the ends of individual chapters.)

- The committee recommends that the Army review the accuracy of the acute-exposure data presented in the Capstone Report in support of its REG-0 and REG-1 values by verifying that uranium intakes were estimated appropri-

ately from the original data, by verifying that peak renal uranium concentrations were estimated appropriately with the same model, by re-evaluating its interpretation of some studies, and by re-evaluating the dataset by considering the relevance of route of exposure and chemical form to those in the military-exposure scenarios. Depending on the outcome of that review and later calculations, the upper bound of the REG-0 range might need to be revised and the lower bound of the REG-1 range modified accordingly. Because of the uncertainties associated with such estimates, the Army should avoid setting REG values that suggest a great deal of precision, particularly for renal concentrations below 3 μg/g.

- Cancer risk estimates should be calculated for levels II and III exposure to determine whether decontamination of vehicles perforated by DU munitions should be conducted to reduce the risk of fatal cancer from exposure of unprotected people.
- For level II personnel working in vehicles perforated by DU munitions, the number of hours should be limited, and protective equipment, particularly respirators, should be used to reduce potentially important cumulative DU exposure.
- If Gulf War level II personnel who had several hours of unprotected exposure to DU in perforated vehicles can be identified, they should receive health monitoring.

1

Introduction and Technical Background

Depleted uranium (DU) is a weakly radioactive, chemically toxic heavy metal derived from natural uranium. It is used commercially as an industrial catalyst, as a counterweight for airplane control surfaces, and for radiation shielding, particularly for particle accelerators and radioactive sources used in industrial radiography. The U.S. military uses DU for munitions and for armor on some tanks. DU is well suited as a munition because of its very high density and "self-sharpening" nature, both of which help it to penetrate armor. Its high density also makes it an effective shield. It has been used by all branches of the U.S. military since the 1980s, and it has been used on the battlefield in the Persian Gulf War, the Balkans, and the Iraq War.

When used as an antitank armor-piercing munition, a DU penetrator can create an airborne spray of uranium with particles of various sizes that can be inhaled by the tank crew or escape into the environment. Many think that DU may be responsible for some of the illnesses noted among veterans of the conflicts and civilians living near the battlefields. Because of the concern about health effects, the U.S. Army commissioned the report *Depleted Uranium Aerosols Doses and Risks: Summary of U.S. Assessments*—hereafter referred to as the Capstone Report—which evaluates the health risks associated with exposure to DU.

NATURAL URANIUM

Uranium is a silvery, dense, weakly radioactive metal. When finely divided, it is pyrophoric (it burns spontaneously) and forms various oxides. It is the heaviest commonly occurring natural element and is found in virtually all geologic materials and, as a consequence, in virtually all natural waters, plants, and animals, as shown in Table 1-1.

Natural uranium consists of three isotopes with atomic masses of about 234, 235, and 238. The three isotopes are chemically indistinguishable, behave

TABLE 1-1 Natural Uranium Concentrations

Location	Uranium Concentration	Reference
Seawater	3.2 ppb	Faure and Mensing 2005
Earth's crust	2.8 ppm	Eisenbud and Gesell 1997
Bulk earth	0.01 ppm	Faure and Mensing 2005
Human blood	0.074-0.94 ppm	Hamilton 1970

similarly in the body and the environment, and decay to stable lead isotopes through a series of radioactive decays. Table 1-2 lists the progeny, decay modes, half-lives, and other relevant characteristics of the two main isotopes, ^{235}U and ^{238}U. The half-life of ^{238}U is much longer than that of ^{234}Th, and relatively few atoms of ^{238}U will decay on a human timescale, so ^{238}U acts effectively as an inexhaustible source of ^{234}Th. Eventually, an equilibrium at which the rate of production of ^{234}Th will equal its decay rate will be reached (that is, secular equilibrium will be reached). That situation can be generalized to the entire decay chain, but reaching such an equilibrium takes a few million years.

DEPLETED URANIUM AND POSSIBLE CONTAMINANTS THAT AFFECT ITS CHEMICAL AND RADIOLOGIC TOXICITY

Of the two main uranium isotopes, only the less abundant ^{235}U is fissile, that is, capable of supporting a self-sustained chain reaction under particular circumstances. Natural uranium consists largely of ^{238}U, and it must be processed to increase the percentage of ^{235}U. The process is called uranium enrichment, and it has two end products: enriched uranium, in which the ^{235}U concentration has been increased; and depleted uranium, in which the ^{235}U concentration is lower than 0.72%.

Spent reactor fuel can be reprocessed and reintroduced into the uranium-enrichment process. Contaminants that remain in the uranium after chemical processing—such as fission products,[1] transuranic elements,[2] and other trace contaminants—can therefore enter the enrichment process. Minor amounts of fission products and transuranic elements were introduced into the uranium-enrichment system in the 1960s and 1970s when the United States reprocessed

[1]Uranium fission produces two atoms with unequal atomic mass known as fission products. Most fission products have relatively short half-lives, but a few have half-lives long enough for them to be present in measurable quantities for many years after the initial reaction.

[2]Uranium fission produces neutrons that can be absorbed by ^{238}U or other decay products; this absorption leads to the production of elements that have atomic numbers greater than that of uranium. Those elements are known as transuranic elements and share some chemical similarity to uranium.

TABLE 1-2 ^{235}U and ^{238}U Decay Series[a]

Nuclide	Half-life	Decay Mode	Energy (MeV)	Nuclide	Half-life	Decay Mode	Energy (MeV)
^{238}U	4.5×10^9 y	Alpha	4.198	^{235}U	7.0×10^8 y	Alpha	4.596
^{234}Th	24 d	Beta	0.199	^{231}Th	26 h	Beta	0.390
^{234m}Pa*	1.2 min	Beta	2.271	^{231}Pa	3.3×10^4 y	Alpha	5.059
^{234}U	2.5×10^5 y	Alpha	4.775	^{227}Ac*	22 y	Beta	0.045
^{230}Th	7.5×10^4 y	Alpha	4.688	^{227}Th	19 d	Alpha	6.038
^{226}Ra	1,600 y	Alpha	4.784	^{223}Ra	11 d	Alpha	5.871
^{222}Rn	3.8 d	Alpha	5.490	^{219}Rn	4.0 s	Alpha	6.819
^{218}Po*	3.1 min	Alpha	6.002	^{215}Po*	1.8 ms	Alpha	7.386
^{214}Pb	27 min	Beta	1.023	^{211}Pb	36 min	Beta	1.373
^{214}Bi*	20 min	Beta	3.272	^{211}Bi*	2.1 min	Alpha	6.623
^{214}Po	160 μs	Alpha	7.687	^{207}Tl	4.8 min	Beta	1.423
^{210}Pb*	22 y	Beta	0.064	^{207}Pb	Stable		
^{210}Bi*	5.0 d	Beta	1.163				
^{210}Po	140 d	Alpha	5.304				
^{206}Pb	Stable						

[a]Each decay series has multiple branches, each with its own probability. The pathways outlined in this table are the most common.

Note: Asterisks indicate branching points from most common pathways.

Source: Firestone and Shirley 1996. Reprinted with permission; copyright 1996, John Wiley and Sons.

spent reactor fuel. And the United States purchased highly enriched uranium from Russia after the dissolution of the Soviet Union for the purpose of "blending down" weapons-grade uranium. The Russian uranium may have contained fission and activation products as trace contaminants, and they may have been introduced into the uranium process stream. Those practices have inevitably led to the presence of very small amounts of the contaminants in both enriched uranium and DU. Many of the nuclides found in spent reactor fuel and possibly present as contaminants in DU are listed in Table 1-3.

Thus, DU does not consist of pure uranium. At least three processes can introduce contaminants: ingrowth of radioactive progeny nuclides due to series decay of ^{238}U (see Table 1-2), the presence of fission products from reprocessed reactor fuel (see Table 1-3), and the presence of transuranic elements from reprocessed reactor fuel (see Table 1-3). The presence of radionuclides from all those sources is noted in environmental-monitoring reports from uranium-enrichment facilities (see, for example, DOE 2004).

TABLE 1-3 Important Fission Products and Transuranic Elements Found in Spent Reactor Fuel

Nuclide	Half-life	Radiation Emitted	Energy (MeV)	Activity in Spent Light-Water Reactor Fuel, 180 Days after shutdown (GBq/tonne)
^{90}Sr	28.76 y	Beta	0.546 2.28[a]	3.03×10^6
^{91}Y	59 d	Beta	1.543	5.55×10^6
^{95}Zr	64 d	Beta Gamma	0.366, 0.399 0.724, 0.757	8.87×10^6
^{99}Tc	2.1×10^5 y	Beta	0.294	525
^{106}Ru	1.02 y	Beta	0.0394	1.28×10^7
^{129}I	1.6×10^7 y	Beta Gamma	0.152 0.30	1.19
^{131}I	8.04 d	Beta Gamma	0.606 0.364	7.04
^{134}Cs	2.06 y	Beta Gamma	0.658 0.605, 0.796	8.39×10^6
^{137}Cs	30.2 y	Gamma	0.662[b]	4.01×10^6
^{144}Ce	284 d	Beta	0.318, 0.185	2.89×10^7
^{239}Pu	24,000 y	Alpha	5.16	1.21×10^4
^{240}Pu	6570 y	Alpha	5.17	1.76×10^4
^{241}Pu	14.4 y	Beta	0.0208	3.90×10^6
^{241}Am	432 y	Alpha Gamma	5.49 0.595	6034

[a]From ^{90}Y progeny.
[b]From ^{137m}Ba progeny.
Source: Knief 1992. Reprinted with permission from the author; copyright 1992.

MILITARY USES OF DEPLETED URANIUM

Modern tanks are protected by heavy armor designed to safeguard their occupants against injury by most weapons. Modern antitank warfare requires the ability to penetrate that armor. The efficacy of armor-penetrating munitions depends primarily on two factors: the length of the penetrator and its density compared with that of the armor (Marshall 2005). The density of DU (18.95 g/cm^3) is about 1.6 times that of lead (11.7 g/cm^3) and is similar to that of tungsten (19.3 g/cm^3). However, unlike tungsten, DU is self-sharpening: as it penetrates armor, the outer layers peel away. Other materials tend to become dull and blunt because of "mushrooming" as they pass through armor, and this limits their penetrating ability. DU's other advantage as a weapon is that it is pyrophoric: the small particles created when a DU weapon penetrates a vehicle spontaneously ignite and can cause secondary explosions of onboard fuel and munitions (AEPI 1995). DU penetrators were used in combat by U.S. forces for the first

time in the 1990-1991 Gulf War and are now the most effective antitank weapon in the U.S. arsenal.

DU munitions are fired by a number of weapons platforms that saw service in Iraq, Kosovo, Saudi Arabia, and Kuwait. Airborne weapons platforms include the A-10 Warthog, the A-16 (a ground-attack version of the F-16 fighter aircraft), and the Marine Corps's AV8 Harrier. The aircraft fire 30-mm, 30-mm, and 25-mm penetrators, respectively, that contain about 280 g (about 0.6 lb) of DU each. Most DU used in the battlefield was fired by A-10 aircraft using the GAU-8 Gatling gun. Table 1-4 summarizes the use of DU penetrators in the Persian Gulf War, the Balkans, and the Iraq War.

The other primary weapons platforms that fired DU penetrators were the M1A1 Abrams tank and the UK Challenger tank, both of which fire a 120-mm, 4,700-g (about 10-lb) penetrator. In addition, some variants of the M1A1 use DU as armor in the forward part of the turret. The only weapon that is able to penetrate DU armor is a DU penetrator, which potentially exposes crews struck by friendly fire to even more DU.

COMBAT EXPOSURE TO DEPLETED URANIUM

When a DU penetrator strikes a tank, its kinetic energy is directed toward the part of the tank that is struck. The armor around the crew compartment is the portion of most interest for the purposes of this report. That armor comprises metal and ceramic set into a resin, possibly with other layers to add protection and durability. The inside of the turret may be lined with insulation, wiring, and piping that contains a variety of fluids; the turret is painted inside and outside. Thus, as the DU round is entering the crew compartment, it penetrates various materials, including polymers, paints, ceramics, and metals; and the spray of

TABLE 1-4 Amount of DU Used in Recent Wars

	Mass of DU Fired (kg)		
Weapons Platform	Persian Gulf War (Marshall 2005)	Balkans (DOD 2001)	Iraq War (USAF 2003)
M1 tank	1,930	0	0
M1A1 tank	37,293	0	0
U.K. Challenger tank	408	0	0
A-10 aircraft	236,319	11,480	75,282[a]
A-16 aircraft	302	0	0
AV8B aircraft	9,881	0	0
Total	286, 133	11,480	75,282

[a]USAF (2003) reports that a total of 311,597 30-mm rounds were fired by A-10 aircraft during Operation Iraqi Freedom. The Federation of American Scientists (FAS 2000) reports that in combat 80% of the 30-mm rounds fired by A-10 aircraft are DU armor-piercing rounds. Marshall (2005) reports that each 30-mm armor-piercing round contains 0.302 kg of DU.

particles that emerges in the compartment contains those materials. Many DU particles themselves ignite spontaneously (they are referred to as fireflies) and may burn or ignite other materials in the compartment; all of them emit fumes. The air in the crew compartment will therefore contain a complex mixture of fumes and particles from a number of sources, and the composition of the mixture will change according to the location struck by the penetrator and the materials incorporated in the plume that reaches the crew compartment. The substances may be toxic or carcinogenic, and their inhalation by the tank crew is inevitable. Their presence complicates the task of determining the effects that can be attributed to DU in this environment.

Concern about the health effects of combat exposure to DU in the Gulf War developed in response to incidents of so-called friendly fire. About 115 U.S. soldiers in six Abrams tanks that contained DU armor and 14 Bradley fighting vehicles were caught in friendly fire that involved the use of large-caliber munitions containing DU penetrators (OSAGWI 2000). Some of the soldiers in or on the Abrams tanks and Bradley fighting vehicles when they were hit were injured by DU fragments. Most of the large metal fragments in the surviving 104 soldiers were removed during treatment for their injuries, but many small fragments remain embedded in their muscle tissue (AEPI 1995; Hooper et al. 1999).

Soldiers involved in the friendly-fire events were also exposed to DU by inhalation, oral, and dermal pathways. Aerosols are created when DU particles ignite, and the aerosols—which vary in particle size, chemical composition, and solubility—fill a struck vehicle. Soldiers in or on the tanks and fighting vehicles and those who entered immediately after the vehicles were struck may have inhaled fine DU oxide particles or ingested DU oxide dust because of hand-to-mouth contact or by swallowing dust that was coughed up. Exposure may also have occurred by contamination of open wounds, burns, or breaks in the skin with DU oxide dust (AEPI 1995; OSAGWI 2000).

Several scenarios in addition to friendly fire led to exposure of soldiers to DU during the 1991 Gulf War. A number of fires involving Abrams tanks and an ammunition explosion and fire at Camp Doha, Kuwait, that burned, oxidized, and fragmented many DU rounds created potential exposure of soldiers operating in the vicinity and involved in cleanup operations. Other military personnel may have been exposed to DU by inhalation or ingestion of DU residues resuspended by their activities when they entered Iraqi vehicles damaged by DU munitions.

EXPOSURE SCENARIOS

In 1996, the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) in the Department of Defense (DOD) assumed responsibility for investigating specific DU exposure scenarios in which U.S. soldiers may have been involved. The scenarios were developed through interviews with Gulf War

combatants and eyewitnesses, reconstruction of military operations, and consultations with experts (OSAGWI 2000). An outcome of the investigation was the classification of DU-exposure scenarios based on the predicted risk of health effects as understood at the time. Three exposure levels were established to describe the military activities that gave rise to particular types of exposures; they are briefly described below (OSAGWI 2000).

- *Level 1*. Soldiers in, on, or near combat vehicles when vehicles were struck by DU munitions and soldiers who entered vehicles immediately after they were struck by DU munitions. These soldiers could have been struck by DU fragments, could have inhaled DU aerosols, and could have ingested DU residues, and DU particles could have landed on open wounds, burns, or other breaks in their skin.
- *Level II*. Soldiers and civilian employees who worked in or around vehicles that contained DU fragments and particles and soldiers who were involved in cleaning up DU residues from Camp Doha's North Compound after the July 1991 explosion and fires—they may have inhaled DU residues that were stirred up by their activities on or in the vehicles, ingested DU after transferring it from hand to mouth, or spread contamination on their clothing.
- *Level III*. Soldiers downwind of burning DU-contaminated equipment, personnel who entered DU-contaminated Iraqi equipment, and personnel who were present at Camp Doha during and after the motor-pool fire but did not take part in cleanup operations in the North Compound. These people could have inhaled airborne DU particles but are unlikely to have received enough to cause health effects.

OSAGWI exposure levels I, II, and III were used as the framework for the human health risk assessment in the Capstone Report. The report describes five scenarios (A-E) for level I exposures. Scenarios A-D estimate the DU mass intake by inhalation for level I soldiers who were in a tank at the time of impact by a DU round. The scenarios vary with the length of time that a soldier remained in the tank. Scenario E involves a level I soldier who entered a tank immediately (up to 5 min) after it was hit to perform a rescue operation, and remained in the vehicle for 10 min. The Capstone Report also included exposure estimates for level II and level III activities that involved Abrams tanks and Bradley fighting vehicles destroyed by DU munitions.

COMMITTEE TASK AND APPROACH

Because of exposure of many soldiers in Operation Desert Storm and the Balkan War and because of concern about potential future exposures of soldiers, civilian contractor workers, and civilian residents who reoccupy battlefield areas, the Army asked the National Research Council's Committee on Toxicology (COT), in collaboration with its Nuclear and Radiation Studies Board, to review

the Capstone Report. As a result of the Army's request, the National Research Council convened the Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat, which prepared the present report. (see Appendix A for biographic information on the committee members.)

The committee was asked specifically to review the toxicologic, radiologic, epidemiologic, and toxicokinetic data on DU and to assess the Capstone Report's estimates of toxic and radiologic risks to soldiers posed by exposure to DU. In preparing its report, the committee considered health-hazard and environmental reports prepared by such organizations as the World Health Organization, the UN Environment Programme (for the postconflict Balkans), the International Atomic Energy Commission, the Agency for Toxic Substances and Disease Registry, and the UK Royal Society. It identified relevant data deficiencies and offers recommendations for future research.

To prepare its report, the committee held several meetings and independently reviewed a large body of written material on health effects of DU. The available data included numerous research articles, literature reviews, and unpublished data submitted by various sources. Each paper or submission was evaluated on its own merits. The committee used a general weight-of-evidence approach to evaluate the literature, which included an evaluation of in vitro assays, animal research, and human studies and involved assessing whether multiple lines of evidence indicate a human health risk. The collective evidence was considered in perspective with exposures to DU that are likely in combat. Overall, the committee found the literature to be consistent with findings of other organizations, such as the Institute of Medicine and the Royal Society, that identified the primary health concerns associated with DU exposure to be toxic effects on the kidneys and cancer. The committee therefore focused its evaluation and report on those health end points.

The committee thoroughly evaluated exposures that were most likely encountered by U.S. military personnel during the Gulf War and verified the exposure estimates by performing its own independent calculation. It also reviewed and evaluated methods used for generating and measuring aerosols produced by the firing of DU projectiles into Abrams tanks and Bradley vehicles; the mathematical models used to calculate exposures to DU through inhalation, ingestion, and skin contact; and the methods used to assess noncancer and cancer risks to exposed military personnel.

REPORT ORGANIZATION

The remainder of this report is organized into seven chapters. Chapter 2 reviews the toxicokinetics of DU and the biokinetic models related to it. Chapters 3 and 4 discuss the toxic effects of uranium on the kidney and lung, respectively, and Chapter 5 the possible effects on other organ systems. Chapter 6 evaluates radiologic effects of DU. Chapter 7 evaluates studies on the carcino-

genicity and genotoxicity of uranium compounds, focusing on studies exploring the evidence for a chemical contribution to the carcinogenic potential of DU. Chapter 8 provides the committee's evaluation of the exposure assessment and health risk assessment presented in the Capstone Report. Appendix A provides biographic information on the committee, and Appendix B a detailed description of the epidemiologic studies mentioned in the report.

2

Toxicokinetics of Depleted Uranium

Natural uranium is a mixture of three isotopes—^{234}U, ^{235}U, and ^{238}U—that behave the same chemically. As discussed in Chapter 1, depleted uranium (DU) is a byproduct of uranium enrichment and has a decreased fraction of ^{235}U and ^{234}U. Uranium is found in the body in soluble form only as tetravalent and hexavalent complexes with carbonate ions and proteins (Berlin and Rudell 1986). The absorption, distribution, metabolism, and elimination of uranium compounds depend on their physical and chemical characteristics. Their toxic potency depends primarily on their solubility because solubility affects tissue dose, which is directly related to toxicity. Table 2-1 lists uranium compounds according to rough solubility (ATSDR 1999). Aerosol byproducts of DU munitions would primarily be the insoluble oxides uranium trioxide, triuranium octaoxide, and uranium dioxide (IOM 2000).

ABSORPTION

Table 2-2 provides information on absorption of uranium compounds on the basis of exposure route and solubility. Overall, absorption of uranium compounds is low except for soluble particles in the lung.

Absorption of inhaled uranium particles is determined by the aerodynamic diameter and solubility of the particles. Large particles (over 10 μm in activity median aerodynamic diameter [AMAD]) are exhaled or may deposit in the anterior nasal passages. Deposited particles that are not cleared by mechanical means, such as nose blowing, may be transported to the posterior nasal passages where they are swallowed. The small fraction of inhaled particles that deposits in the tracheobronchial compartments is cleared by the mucociliary escalator that transports them from there to the pharynx, from which they are swallowed and enter the gastrointestinal tract (IOM 2000), or by phagacytosis, which transfers the particles to the tracheobronchial lymph nodes. Smaller particles (less

TABLE 2-1 Solubility of Uranium Compounds

Uranium Compound	Chemical Formula
More water-soluble compounds	
Uranyl nitrate	$UO_2(NO_3)_2$
Uranyl nitrate hexahydrate	$UO_2(NO_3)_2 \bullet 6H_2O$
Uranium hexafluoride	UF_6
Uranyl fluoride	UO_2F_2
Uranium tetrachloride	UCl_4
Uranium pentachloride	UCl_5
Ammonium uranyl tricarbonate	$(NH_4)_4UO_2(CO_3)_3$
Less water-soluble compounds	
Sodium diuranate (yellow oxide of uranium)	$Na_2U_2O_7 \bullet 6H_2O$
Ammonium diuranate	$U_2(NH_4)_2O_7$
Uranyl acetate	$UO_2(CH_3CO_2)_2$
Insoluble compounds	
Uranium tetrafluoride	UF_4
Uranium trioxide	UO_3
Uranium dioxide	UO_2
Uranium peroxide	UO_4
Triuranium octaoxide	U_3O_8

Source: ATSDR 1999.

TABLE 2-2 Absorption by Exposure Route

Exposure Route	Absorption of Soluble Compounds	Absorption of Insoluble Compounds
Inhalation	5% or more	<1%
Ingestion	0.1-2%	0.01-0.2%
Skin contact	<1%	<1%

Source: Data from ATSDR 1999.

than 10 μm) are deposited predominantly deeper in the terminal bronchioles and alveoli. Soluble particles in the lungs and tracheobronchial lymph nodes are taken up into the systemic circulation within days (IOM 2000). Less-soluble particles are likely to remain in pulmonary tissue and associated lymph nodes for weeks. Relatively insoluble compounds are least likely to enter the systemic circulation and may remain in the lung and tracheobronchial lymph nodes for several years or decades.

Most inhaled uranium aerosol is cleared from the respiratory tract via the gastrointestinal tract, but a fraction is absorbed into the body fluids and distrib-

uted throughout the body. Solubility in body fluids is the most important factor in determining absorption. The International Commission on Radiological Protection (ICRP 1994a, 1995b) classifies inhaled aerosols broadly in terms of the rate of their absorption into the body as fast (F), moderate (M), or slow (S). Type F uranium compounds include uranium hexafluoride, uranyl fluoride, and uranyl nitrate; of the fraction not excreted via the gastrointestinal tract, 100% is absorbed with a half-life of 10 min. Type M uranium compounds include uranium trioxide, uranium tetrafluoride, uranium tetrachloride, and triuranium octaoxide, (the latter may behave like a type S compound under some circumstances, particularly if produced at high temperature); of the fraction not excreted via the gastrointestinal tract, 10% is absorbed with a half-life of 10 min, and the remaining 90% is absorbed with a half-life of 140 d. Type S uranium compounds include uranium dioxide (and, as indicated above, triuranium octaoxide under some circumstances) and have very low and slow absorption; most of the insoluble aerosol is excreted relatively quickly via the gastrointestinal tract, and of the remainder, 99.9% is absorbed from the respiratory tract with a half-life of 7,000 d (about 19 y). Of the particulate material cleared from the respiratory tract via the gastrointestinal tract, only 0.2% of type S compounds or 2% of type F and M compounds is absorbed (ICRP 1995b).

Uranium may enter the body through ingestion of food and water. As indicated above, gut absorption of uranium is poor, and only a small fraction of the uranium ingested is absorbed in the gut. Numerous observations in humans have shown that the uptake fraction of soluble uranium is about 1-2% and that of the insoluble oxide forms about one-tenth that (Wrenn et al. 1989a; Harduin et al. 1994; Medley et al. 1994; Leggett and Harrison 1995).

Dermal absorption of uranium compounds has not been characterized in humans, but animal studies indicate that they can penetrate the skin. The study results are difficult to compare because vehicles with differing physical characteristics were used. Orcutt (1949) found that large doses of uranyl nitrate, uranyl fluoride, uranium pentachloride, uranium trioxide, sodium diuranate, and ammonium diuranate were absorbed through the skin and caused poisoning and death in experimental animals. However, the insoluble oxides uranium dioxide, uranium tetroxide, and triuranium octaoxide did not cause toxicity. A later study confirmed the effect of water solubility on dermal toxicity; de Rey et al. (1983) found that uranyl nitrate and ammonium uranyl tricarbonate were more toxic (in terms of lethality and body-weight changes) than uranyl acetate and ammonium dianurate. In that study, de Rey et al. visualized the movement of uranyl nitrate through the skin with x-ray microanalysis and scanning electron microscopy. Electron-dense areas could be seen in the epidermis 15 min after application, and the electron-dense material could be seen in the capillary endothelial cells of the upper epidermis 24 h after one application; no traces were left in the skin 48 h after application. Topical application of uranyl nitrate to rats caused kidney and bone effects that were related to exposure area and time (Lopez et al. 2000); uranyl acetate and ammonium diuranate caused less toxicity, and uranium dioxide caused no toxicity. In vitro studies with uranyl nitrate have shown that

0.04% of the applied dose was absorbed by human skin after 2 h (Tymen et al. 2000), and the steady-state flux across hairless rat skin was 0.13 ng/cm^2 per hour (Petitot et al. 2004). Open wounds, burns, or other conditions in which the skin barrier is disrupted would enhance absorption through the skin.

The release of uranium from embedded fragments of DU has been studied in soldiers and laboratory animals. A 10-y followup of soldiers involved in "friendly-fire" incidents with DU munitions showed urinary uranium concentrations that suggested that DU was still being absorbed into the body from fragments (McDiarmid et al. 2004b). Several studies have investigated implantation of DU pellets in rats (Pellmar et al. 1999a,b; Arfsten et al. 2005, 2006). They all used DU and tantalum (control) pellets that were 1 mm in diameter and 2 mm long and weighed 38 mg. They changed the dose by surgically implanting different numbers of pellets (from four to 20) in the rats' gastrocnemius muscle. Twenty pellets (760 mg of DU) in a 250-g rat is the equivalent of about 0.22 kg (0.5 lb) of DU in a 70-kg (154-lb) person (Arfsten et al. 2006). Absorption studies in rats showed that DU release began within a day and that release continued throughout 18 months of observation (Pellmar et al. 1999a).

DISTRIBUTION

Once in the blood, hexavalent and tetravalent uranium compounds form complexes with carbonate ions and proteins (Berlin and Rudell 1986). About 47% of natural uranium forms a complex with bicarbonate in plasma, 32% binds to plasma proteins, and 20% binds to erythrocytes (Chevari and Likhner 1968, as cited in IOM 2000). After pulmonary intubation of rats, 50% of the ^{233}U was bound to transferrin, 25% to citrate, and 25% to bicarbonate (Cooper et al. 1982).

Absorbed uranium is found in all tissues but deposits preferentially in bone and kidney (ATSDR 1999). Initial distribution is affected by the route of entry, particle size, and solubility of the compound. After inhalation of uranium dioxide dust, the lungs and lymph nodes account for more than 90% of the body burden (Leach et al. 1970). Morris et al. (1990) exposed rats to a uranium dioxide aerosol with a median particle diameter of 2.7-3.2 μm. At 720 d, 82% of the body burden was in the lung and 10% in the lymph nodes. A normal adult's body burden of uranium is about 90 μg. It has been estimated that about 66% of that is in bone, 16% in the liver, 8% in the kidneys, and 10% in other tissues (ICRP 1975; ATSDR 1999). In bone, uranium replaces calcium in hydroxyapatite (IOM 2000) and has a half-life of 300 d (Harley et al. 1999). In the kidneys, uranium accumulates primarily in the proximal tubules, where it is reabsorbed (IOM 2000). After in vitro and in vivo dermal exposures to uranium as a nitrate solution, the majority of the uranium was localized to the epidermis after 2 h, and nearly all the applied uranium was associated with the skin (Tymen et al. 2000).

An 18-mo study of DU implantation in rats showed interesting tissue-distribution profiles (Pellmar et al. 1999a). Kidney and bone concentrations were highest 1 d after implantation and constituted the only significant changes. At 1 mo, bone and the kidneys still had the highest concentrations, but differences from controls were also seen in urine, muscles, the liver, the spleen, serum, and the brain. Kidney concentrations appeared to peak 6 mo into continuous exposure but remained increased. There were low concentrations of DU in the urine throughout the study, and they were relatively constant between 6 and 18 mo. Tibia and skull concentrations continued to increase over the course of the study. Brain concentrations were increased in the motor and frontal cortex, midbrain, cerebellum, and vermis at 18 mo. Other tissues that showed increases at 18 mo were lymph nodes, the testicles, the teeth, the heart, and the lungs.

Uranium can cross the placenta after parenteral administration (0.01-0.03% of an intravenous dose) in rats (Sikov and Mahlum 1968) and can cross the blood-brain barrier of rats (Pellmar et al. 1999a; Barber et al. 2005). Whole-body retention of hexavalent uranium after an intravenous injection in beagles was 17% at 7 d, 10% at 94 d, 7.6% at 1 y, and less than 5% at 2 y (Stevens et al. 1980).

METABOLISM

There is little information on the metabolism of uranium compounds (Berlin and Rudell 1986), but oxidation of tetravalent uranium to hexavalent uranium is likely to occur in the blood (ATSDR 1999).

ELIMINATION

In mammals, inhaled soluble uranium compounds are eliminated primarily by the kidneys and to a small extent in the feces. Inhaled insoluble uranium compounds are eliminated primarily in the feces. More than 90% of intravenously injected hexavalent uranium is excreted by the kidneys and less than 1% in the feces (Berlin and Rudell 1986). Renal clearance is rapid; human studies of comatose, terminally ill patients with brain tumors showed that two-thirds of an intravenous dose (0.07-0.28 mg/kg of body weight) left the bloodstream in 6 min and that 49-84% of the dose was excreted in the urine within 24 h (Luessenhop et al. 1958). In contrast, McDiarmid et al. (2004b) showed that uranium from DU fragments was still being cleared by the kidneys 10 y after friendly-fire incidents involving U.S. troops. In humans, there appears to be a two-phase pattern of excretion after occupational exposure to soluble and insoluble compounds (Berlin and Rudell 1986). In the case of soluble compounds, there is a fast phase in which about 70% of the dose is cleared in the first 24 h, followed by a slow phase with a half-life of months. In the case of insoluble compounds, the fast-phase half-life is 11-100 d, and the slow-phase half-life is 120-1,500 d.

Ingested uranium that is not absorbed is eliminated primarily (94-99%) in the feces (Hursh et al. 1969; Leggett and Harrison 1995; ATSDR 1999).

BIOKINETIC MODELS

Biokinetic models provide the means by which the dose of uranium, and the associated risk, can be assessed. Such models mathematically characterize the processes by which DU is taken up by various tissues, distributed in the body as a function of time, and cleared or excreted from various tissues and the body itself. Although human experience with uranium spans 2 centuries and uranium was once used therapeutically as a treatment for diabetes mellitus, the biokinetics of uranium are not well known. Over the years, a number of systemic models and refinements have been proposed (Bernard and Struxness 1957; ICRP 1977,1979; Lipsztein 1981; Durbin 1984; Wrenn et al. 1985a; ICRP 1988; Wrenn et al. 1989b; Fisher et al. 1991; Leggett 1992; Harduin et al. 1994; ICRP 1995a; Leggett and Harrison 1995; Leggett and Pellmar 2003). Generally, the models indicate that most DU absorbed into the systemic circulation by whatever route of entry is quickly excreted in urine. A small fraction of absorbed DU may be taken up by and incorporated into some tissues and irradiate them at the cellular level. Skeleton, liver, and kidneys are considered the primary sites of deposition of uranium. The dose delivered from the small fraction of uranium that is not quickly excreted determines the potential for radiologic effects.

Perhaps the most widely used and accepted biokinetic model for uranium—certainly for radiation-protection purposes—is the current comprehensive model put forth by ICRP (1995a,b), as shown in Figure 2-1. It is a recycling model; that is, uranium in the blood flows into organs and then back to the blood. Major compartments of the model are the skeleton, liver, kidneys, and a generic soft-tissue compartment. The generic soft-tissue compartment is modeled as all other organs and tissues and receives all the distribution from the blood not accounted for by other organs or excretion. Most of the uranium in soft tissue is retained only briefly, but a small amount (less than 1%) is retained essentially indefinitely. The skeleton is modeled as two compartments: one represents trabecular bone and one cortical bone. Additional subcompartments represent movement of uranium from the bone surfaces to bone volume and back. The skeleton receives about 15% of the uranium leaving the blood, but most of that is returned fairly rapidly (retention half-lives, 30 d or less); a very small amount of the uranium is retained in the skeleton for periods (years) consistent with normal turnover rates. The bone marrow is also included in the skeleton compartment to allow calculation of dose to red marrow. The liver is modeled as two compartments: one that receives uranium from the blood but returns most of it with a 7-d half-life and one that receives uranium from the other liver compartment and retains it with a half-life of about 10 y. About 1.5% of the uranium leaving the blood goes to the liver. The kidney is modeled as two

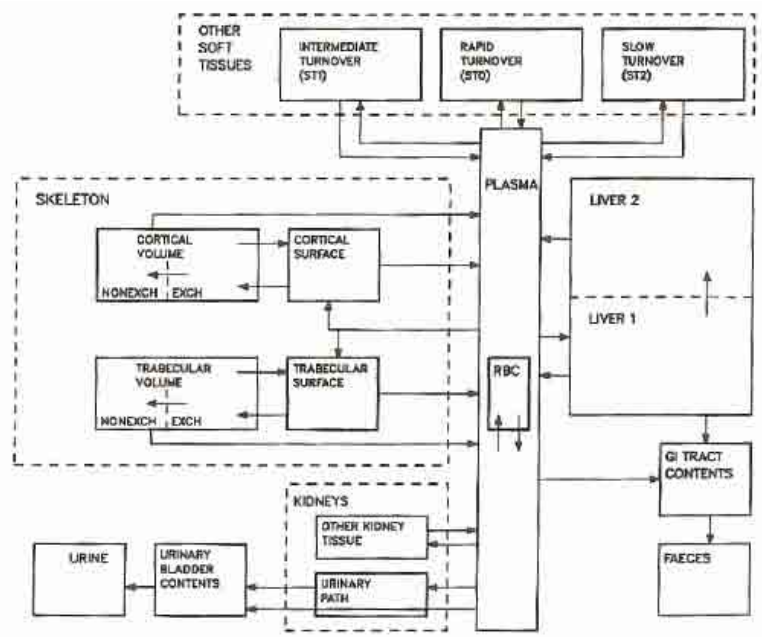

FIGURE 2-1 Biokinetic model for uranium. Source: ICRP 1995a. Reprinted with permission; copyright 1995, International Commission on Radiological Protection.

compartments: kidney tissue and a urinary path that flows only one way, to the bladder and excretion. The kidney tissue itself receives only about 0.05% of the uranium leaving the blood but retains it with a moderately long half-life of about 5 y.[1] Excretion is the largest pathway of removal of uranium from the blood. Of the uranium in the blood, 63% is modeled as being transported directly to the bladder; another 12%, which passes through the kidneys (renal tubules), is retained briefly (for days) and then passes on to the bladder. Systemic uranium is eliminated virtually entirely through urine.

Using this or other systemic models and the ICRP respiratory tract model for inhalation exposure, one can calculate the radiation dose to individual tissues and organs from a known intake of DU and thus gain an indication of the risk of stochastic effects (see Chapter 6).

[1]The cellular basis of renal retention of uranium is not well understood. Unlike retention of cadmium and lead, uranium retention has not been associated with an increase in a specific protein. Leggett (1989) suggested that concentration and insolubilization of uranium in lysosomes might be a protective mechanism. Alternatively, uranium may be retained by macrophages of interstitial cells, as has been shown to occur in alveoli (Tasat and de Rey 1987).

Recent studies have evaluated and applied the basic models. Chen et al. (2004) used the ICRP model to calculate a table of kidney burdens from inhalation and oral intakes of soluble and moderately soluble uranium. Leggett and Pellmar (2003) evaluated models for application to uranium migration from embedded DU fragments. The time-dependent rate of uptake into plasma from pellets was adjusted to match the urinary data in the DU-implanted rats from the Pellmar et al. (1999a) study. Leggett and Pellmar used data from Morris et al. (1990) on inhalation of insoluble uranium dioxide to mimic slow release from pellets. The data after the first 6 mo fit well, but the data for the first 6 mo did not, perhaps because of variable urinary excretion or some peculiarity of the biokinetics of uranium release from embedded DU metal. Leggett and Pellmar concluded that it is reasonable to apply ICRP's updated biokinetic model for uranium to assess chemical risk to soldiers who have embedded DU fragments.

SUMMARY

- Absorption of uranium compounds is low (less than 1%) by all exposure routes, except for soluble compounds, of which 5% or more is absorbed after inhalation.
- Initial distribution of uranium compounds depends on their solubility and the route of absorption. Uranium compounds complex with ions and proteins in the blood, are distributed to all tissues, and preferentially deposit in bone and kidneys. Uranium can cross the placenta and the blood-brain barrier.
- The metabolism of uranium is not well understood, but oxidation of tetravalent uranium to hexavalent uranium is likely to occur.
- After inhalation, elimination of soluble uranium is primarily by the kidneys, and insoluble uranium is eliminated primarily in the feces. In general, soluble compounds are cleared more rapidly than insoluble compounds.
- Release of DU from embedded particles is slow and occurs over many years.
- Well-established models are available to predict the toxicokinetics of uranium from inhalation exposures.

3

Toxic Effects of Uranium on the Kidneys

The U.S. Army's Capstone Report (Guilmette et al. 2005; Parkhurst et al. 2005) identifies the kidneys as the organs most sensitive to the chemical toxicity of uranium. This chapter reviews the kidney literature that is pertinent to a health risk assessment of exposure of soldiers to depleted uranium (DU) in combat situations (other health end points are considered in Chapters 4-7). It is not a comprehensive review of the uranium literature; many reviews are available (Voegtlin and Hodge 1949, 1953; Berlin and Rudell 1986; ATSDR 1999; IOM 2000; WHO 2001; The Royal Society 2001, 2002; Marshall 2005). Those reviews and the Capstone Report generally base exposure guidelines on relationships between estimates of the renal burden of uranium and renal injury and measurement of toxic end points reflected by changes in biomarkers in animal models and humans. This chapter therefore focuses on animal and epidemiologic studies in which kidney burdens of uranium are reported or sufficient information is provided to calculate the kidney burdens. The findings are used in Chapter 8 to consider whether the renal uranium-concentration thresholds chosen for the Capstone health risk assessments are consistent with the scientific literature.

BACKGROUND

Acute uranium exposure produces degeneration of renal tubular epithelium followed by regeneration. Biomarkers or biochemical indicators of effects of uranium exposure on various aspects of renal function are available, and those cited in animal and human studies are listed in Table 3-1. Tubular cell injury is associated with increased excretion of low-molecular-weight proteins and other substances that are normally reabsorbed by tubular cells. Enzymuria reflects release of enzymes from injured cells. Glucosuria due to renal tubular dysfunction occurs with normal blood glucose concentrations, in contrast with

TABLE 3-1 Selected Biomarkers or Biochemical Indicators of Renal Effects of Exposure to Uranium

Indicators of tubular toxicity	Increased excretion of low-molecular-weight proteins in urine: • β_2 microglobulin (β_2m) • retinol-binding protein (RBP) • other low-molecular-weight substances • amino acids and glucose Increased concentrations of enzymes in urine (enzymuria): • alkaline phosphatase (ALP) • aspartate aminopeptidase (ASP) • catalase • gamma-glutamyltransferease (GGT) • lactate dehydrogenase (LDH) • leucine aminopeptidase (LAP) • *N*-acetyl glucosaminidase (NAG)
Indicators of glomerular toxicity	Increased excretion of large-molecular-weight proteins in urine: • proteinuria • albuminuria • minialbuminuria
Indicators of renal failure	Increased serum concentrations of: • nonprotein nitrogen (NPN) • creatinine • urea

Sources: Nomiyama and Foulkes 1968; Nomiyama et al. 1974; Wedeen et al. 1998.

glucosuria in diabetes mellitus, which is due to blood glucose concentrations that are above the normal threshold for reabsorption. Uranium exposure may also produce glomerular injury that results in leakage of albumin and other high-molecular-weight proteins. Renal failure is characterized by inability to excrete metabolic wastes and is reflected by increases in nonprotein nitrogen (NPN), urea, or creatinine in blood or serum.

HUMAN STUDIES

Acute Exposure

Few reports have documented episodes of acute human exposure to uranium compounds. Table 3-2 is a compilation of data cited by the Royal Society (2002) and in the Capstone Report (Guilmette et al. 2005; Parkhurst et al. 2005) as modified here after committee review. The episodes varied in form of uranium and route of exposure. They include exposure to uranium hexafluoride,

TABLE 3-2 Renal Effects of Acute Exposure to Uranium in Humans

Route of Exposure	Chemical Form	Subjects	Intake (mg)	Peak Renal Uranium (μg/g)[a]	Renal Effects[b]	Outcome	Reference
Ingestion	Acetate	1 male	8,500	100	+++	Acute renal failure; glucosuria persisted beyond 32 wk of observation	Pavlakis et al. 1996
Skin (burn)	Nitrate	1 male	130	35	+++	Peak renal tubular dysfunction after 7 d; normal after 1 mo	Zhao and Zhao 1990
Inhalation	Tetra-fluoride	1 male	920	10[c]	++	Renal dysfunction, including increased NPN and proteinuria and aminoaciduria, 15 mo after exposure but gradual return to normal	Zhao and Zhao 1990
Injection	Nitrate	2 males	16	6	+	Increased NPN, urinary catalase, albumin	Luessenhop et al. 1958
		1 female	11	4	+		
			6	2	+		
Skin (burn)	Nitrate	1 male	10	3	++	Albuminuria persisting for 3 wk after exposure	Butterworth 1955
Injection	Nitrate	2 males	5	1.8	—	No abnormalities	Luessenhop et al. 1958
				1.4	—		
Inhalation	Hexa-fluoride	3 males	40-50[d]	4	+	Albumin and casts in urine after accident; no effects 38 y after exposure	Kathren and Moore 1986
				4	+		
				1.2	+		

Inhalation	Hexa-fluoride	1 adult male	24	2.5	+	Transient proteinuria and glucosuria	Fisher et al. 1990
		11 adult males	6-18	0.05-1.9	+	Transient proteinuria	
		19 adult males	6-18	0.05-1.9	—	No abnormalities	
Ingestion	Nitrate	1 adult male	470	1	+	Transient albuminuria; complete recovery within 24 h	Butterworth 1955
Inhalation	Hexa-fluoride	1 adult male	20	1	—	Apparently well 9 d after exposure	Boback 1975

[a]Modeled estimates.
[b]Severe clinical symptoms indicated by +++; biochemical indicators of renal dysfunction indicated by ++ (for protracted effects), + (for transient effects), and—(no detectable effects).
[c]Kidney concentration of uranium peaked 60 d after exposure at 10 µg/g, whereas urinary concentration of uranium and indicators of renal dysfunction peaked about 2 mo after exposure. Capstone Report indicted that these events occurred much later than predicted from ICRP models for uranium tetrafluoride and suggested that exposure of kidney was more chronic than acute.
[d]Potential exposure range was wide.
Sources: Adapted from Royal Society 2002 and Guilmette et al. 2005.

uranium tetrafluoride, uranyl nitrate, and uranyl acetate. Exposure was by ingestion, skin contact, inhalation, and injection. The cases presented in Table 3-2 are arranged in descending order of peak renal concentration. Peak renal concentrations are calculated estimates provided in the Royal Society report and the Capstone Report.

The highest renal concentration was the result of the deliberate ingestion of uranyl acetate, which resulted in acute renal failure that required dialysis (Pavlakis et al. 1996) and was followed by slow recovery. Glucosuria persisted beyond the 32-wk observation period.

Zhao and Zhao (1990) described a man originally reported in the Chinese literature (Wu and Fan 1982) who was burned over 70% of his body with hot (108°C) uranium oxide. Renal function worsened over the next 6 d, and the patient's condition became critical 7 d after the accident. Uranium exposure was due primarily to absorption from the skin. Renal tubular function recovered within a month. The peak renal concentration of uranium was estimated to be 35 μg/g 5 d after the accident.

Zhao and Zhao also described a patient who experienced an accidental inhalation exposure to uranium tetrafluoride powder for about 5 min. The lung deposition calculated in the Royal Society report was 915 mg. A week after exposure, the renal effects included proteinuria, increased NPN, and aminoaciduria. Concentrations of uranium increased over the first 2 mo after exposure and gradually declined to background concentrations about 3 y after exposure. The peak renal concentration of uranium was estimated to be 10 μg/g 60 d after exposure, and the urinary uranium and indicators of renal dysfunction peaked at about the same time. The Capstone Report indicated that those events occurred much later than predicted by the International Commission on Radiological Protection (ICRP) models for uranium tetrafluoride, so renal exposure might have been more chronic than acute. Nevertheless, renal-function test results gradually returned to normal.

In a study of radiation treatment for brain tumors, the tolerable intravenous dose of uranyl nitrate was investigated in five comatose or semicomatose patients (Luessenhop et al. 1958). The three patients with the highest estimated peak renal concentrations of uranium (2-6 μg/g) had renal dysfunction, including increased NPN, increased urea, proteinuria, and increased urinary catalase excretion (Royal Society 2002).

Butterworth (1955) reported a case of dermal exposure to hot uranyl nitrate. The Royal Society's calculated peak renal concentration of uranium was about 3 μg/g 10 d after the accident. Albuminuria persisted until the third week after exposure; this suggested glomerular injury, but there was no indication of tubular dysfunction.

Kathren and Moore (1986) evaluated the renal status of two of three people who were seriously injured by an accidental release of uranium hexafluoride. Uranium intake of the three was estimated to be about 40-50 mg, but peak renal concentrations were not estimated. Published and unpublished data indicate that all had albuminuria, which is evidence of renal injury. However, normal renal

function was found in two of the three examined 38 y after the accident. The authors noted an anomalous pattern of urinary excretion of uranium, which they attributed to pulmonary edema caused by hydrogen fluoride, a hydrolysis product of uranium hexafluoride. The pulmonary edema may have caused longer retention of uranium in the lungs. Thus, acute exposure to uranium hexafluoride might not be typical of or necessarily applicable to study of exposure other uranium compounds, including DU.

Fisher et al. (1990) reported data on a group of 31 workers exposed to uranium hexafluoride and hydrolysis products after the rupture of a large shipping container. The peak renal uranium concentrations calculated from the authors' own biokinetic model (not an ICRP model) ranged from 0.05 to 2.5 µg/g. The worker with the highest concentration also had high concentrations of protein (over 200 mg/dL) and glucose (1+ to 3+) in the urine in the first two samples submitted 4 d after the accident. Eleven other workers were reported to have positive tests for protein in at least one urine specimen during the first 20 d after the accident. None of the remaining 19 workers had abnormal tests of renal function. As in the Kathren and Moore (1986) study, the relevance of this study for predicting effects of DU is uncertain.

Butterworth (1955) also described an experiment in which a healthy volunteer ingested 1 g of uranyl nitrate to help to establish excretion. He experienced an illness that lasted about 24 h. Albuminuria was found in two urine samples taken 2-4 h after dosing but not in any other samples taken for 7 d thereafter. Peak renal uranium concentration was estimated by the Royal Society (2002) to be 1 µg/g 1 d after ingestion.

Boback (1975) described four subjects exposed to uranium-ore dust and six others exposed to uranium hexafluoride. Table 3-2 includes data on one person who had a uranium intake of 20 mg and peak renal uranium concentration estimated to be 1 µg/g, but biochemical indicators of renal dysfunction were negative in all subjects. Two subjects were evaluated 38 years later (see Kathren and Moore [1986] described above).

The cases listed in Table 3-2 show a relationship between renal effects and peak renal concentrations after acute exposure. There is uncertainty in the conclusions that can be drawn from those data, because the renal concentrations are modeled estimates and it is unclear whether the same models were used to derive them. The only episode of acute renal failure noted came after ingestion of a large quantity (8,500 mg) of uranyl acetate, but even in this extreme case, as in all others, there was eventual recovery. The question of whether uranium exposure can cause chronic or irreversible renal disease is still open and recognized in other reviews, including the Capstone Report.

In small numbers of subjects, transitory biomarkers of renal effects have been observed at renal uranium concentrations as low as 1 µg/g (Butterworth 1955; Kathren and Moore 1986; Fisher et al. 1990). Fisher et al. (1990) reported that 11 workers had transitory proteinuria but observed no other biomarkers associated with kidney damage. They noted that proteinuria is only one indicator of tubular dysfunction and that other positive indicators must be present to show

kidney damage. Proteinuria can be induced by many other causes, such as infection, exercise, dehydration, and stress (Carroll and Tempte 2000; Kashif et al. 2003), which were also experienced by the people in the acute-exposure studies. The lack of quantitative measurements of renal uranium in individual cases that demonstrate proteinuria creates uncertainty with regard to the association of uranium with this effect in these individuals.

Chronic Exposure

Studies of people chronically or continuously exposed to uranium for months or years should provide the most relevant information for predicting potential chronic renal effects of exposure to retained fragments of DU. However, the evidence to date is sparse. There are many epidemiologic studies of morbidity and mortality from chronic renal disease in workers who have inhaled uranium dust from mining, processing, and conversion of processed uranium into milled and fabricated metal products. Reviews by other organizations do not suggest any increase in morbidity or mortality from chronic exposure. For example, the Royal Society (2002) analyzed seven studies of deaths from chronic renal disease among uranium workers, but there was no specific evidence as to whether the disease was related to uranium exposure or to some other disease. The total of 85 deaths in the seven studies was 18% less than would have been expected from renal-disease mortality in the general population. Evaluation of epidemiologic studies of occupational exposure by the Agency for Toxic Substances and Disease Registry (ATSDR 1999) did not identify an increase in deaths from renal disease.

The following are brief reviews of reports of exposure and renal effects after three forms of chronic exposure: inhalation of yellowcake or ore by uranium process workers, ingestion of drinking water by the general population, and chronic exposure of Gulf War veterans due to systemic release of uranium from embedded fragments. Exposure information and renal effects are summarized in Table 3-3.

Occupational Studies

Thun et al. (1985) evaluated renal function in 39 uranium-mill workers and 36 local cement-plant workers of equivalent age, sex, and race. Mean urinary concentration of uranium measured in 1975 was 65.2 µg/L (median, 20 µg/L) and in 1981 was 7.2 µg/L (median, 6 µg/L). Biologic characteristics were measured in 1981 when the urinary uranium was below the action level for all workers. A relationship was found between the clearance of β_2m relative to that of creatinine and the length of time that a worker had potential exposure to soluble uranium. The increase in urinary β_2m was found to be due to both an increase in serum concentration and reduced renal tubular reabsorption. Renal

TABLE 3-3 Renal Effects of Chronic Exposure to Uranium in Humans

Reference	Exposure	Urinary Uranium Concentration	Renal Uranium Concentration	Renal Effects
Thun et al. 1985	Occupational: 36 workers, <10 y; 2 workers, >10 y; 1 worker, >20 y	Mean/median: 1975, 65.2/20 μg/L; 1981, 7.2/6 μg/L	Up to ~ 1 μg/g[a]	Mild increase in aminoaciduria; β_2m serum creatinine normal
Zamora et al. 1998	Drinking water: low-dose group, <1 μg/L; high-dose group, ≥1 μg/L; males, 2-410 μg/d; females, 2-570 μg/d	Range: 0.01-2.58 μg/L (from Zamora et al. 2002)	~ 0.1 μg/g[a]	Positive correlation of uranium intake with urine concentrations of glucose, ALP, β_2m, and increased LDH (7 males)
Kurttio et al. 2002	Drinking water: 325 persons; mean daily intake, 39 μg (7-224 μg)	Mean/Median: 0.424/0.078 μg/L	Not determined	Positive correlation of urinary uranium exposure with fractional excretion of calcium and phosphate; positive correlation of uranium in drinking water and daily intake with fractional calcium excretion; no association with glucose or β_2m; possible bone effect (see Kurttio et al. 2005)
Kurttio et al. 2006	Drinking water: 95 men and 98 women; median concentration, 25 μg/L; maximum, 1,500 μg/L	Not reported	Not determined	Battery of urinary enzyme and biochemical tests of renal cytotoxicity and function interpreted as evidence of no effect; however, glucosuria was noted

(Continued)

TABLE 3-3 Continued

Reference	Exposure	Urinary Uranium Concentration	Renal Uranium Concentration	Renal Effects
Squibb et al. 2005	Embedded metal fragments and inhalation of DU oxides; uranium released to blood, 0.025-0.7 mg for 6 y; 9.29-190 mg for 10 y	Mean of samples collected 1993-2001: 0.01-38.5 µg/g of creatinine	Highest to date: 0.95 µg/g	Increase in RBP in 2001 and in most recent assessment in 2003
McDiarmid et al. 2007	Embedded metal fragments, inhalation exposure to DU oxides	0.002-44.1 µg/g of creatinine	Not determined	No increase in RBP in 2005; battery of tests of glomerular and tubular function showed no evidence of effect

[a]Kidney concentrations from Capstone Report as calculated by Royal Society (2002) with ICRP model.

uranium concentration was calculated in the Capstone Report to be up to 1 μg/g. The study suggests that urinary β_2m and amino acids may be sensitive biomarkers of uranium renal toxicity.

Russell et al. (1996) reviewed the histopathology of kidneys from seven long-term uranium workers whose uranium intake ranged from a few to a few hundred milligrams. No differences were found between that group and a comparison group of six autopsied adults who had neither known kidney disease nor exposure to uranium. There were no distinguishing features in either group, only a continuum of changes from normal to slight abnormalities that might be expected in the general population.

Chronic kidney disease has been examined in other uranium-worker cohorts (see Table 3-4 and Appendix B for details of the individual studies). Overall results were compatible with no renal effect of uranium, although three studies (all with small numbers of renal-disease cases) showed suggestive excesses of chronic renal effects. That the number of chronic renal-disease cases in all nine studies was not excessive (68 observed vs 85 expected) suggests that the renal effects, if any, are small. However, the small number of cases and the sparseness of the information on exposure concentrations and solubility of workplace uranium compounds mean that there are substantial uncertainties in the risk assessment. Renal-cancer mortality or incidence has been evaluated in cohorts of uranium-processing workers, and the results have been uniformly negative (see Chapter 6).

Drinking-Water Studies

Zamora et al. (1998) compared the effects of uranium on renal function in two Candian communities, one of which had private wells supplied by groundwater whose uranium content was higher than the Canadian drinking-water guidelines. Subjects were divided into a low-exposure group (drinking water contained uranium at <1 μg/L) and a high-exposure group (2-781 μg/L). Time of residence of the low-exposure group was 1-33 years, and of the high-exposure group 3-59 years. The urinary glucose concentrations differed between the high- and low-exposure groups, and the glucose concentrations increased with uranium intake. Increases in glucose, alkaline phosphatase (ALP), and β_2m also correlated positively with increased uranium intake and are evidence of cell toxicity. There was also an increase in lactate dehydrogenase (LDH) excretion in seven subjects in the high-exposure group, but it was not directly related or coordinated with uranium intake. The authors suggest that the glucose, creatinine, and total-protein data indicate that the segment of the nephron most at risk of injury is the proximal tubule rather than the glomerulus. The Royal Society (2002) calculated the renal uranium concentration to be about 0.1 μg/g from ingestion of uranium at 80 μg/L of drinking water. That estimate is unexpectedly low. Urinary uranium was not reported in the study, but in a separate study on

TABLE 3-4 Standardized Mortality Ratios (95% Confidence Intervals) and [Observed Numbers of Deaths] from Renal Diseases in Uranium Workers

Study	Chronic Nephritis or Chronic Renal Failure	Reference
Colorado plateau uranium-mill workers (with no history of uranium mining)	1.35 (0.58-2.67) [8][a]	Waxweiler et al. 1983; Pinkerton et al. 2004
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, all workers	0.77 (0.53-1.08) [30]	Polednak and Frome 1981
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments	0.60 (0.29-1.09) [9]	Polednak and Frome 1981
Y12 (1947-1974): Oak Ridge uranium metal production and recycling	0.97 (0.31-2.27) [5]	Checkoway et al. 1988; Loomis and Wolf 1996
Mallinckrodt uranium-processing workers	1.88 (0.75-3.81) [6]	Dupree-Ellis et al. 2000
Portsmouth gaseous diffusion[b]	0.54 (0.11-1.56) [3]	Brown and Bloom 1987
Savannah River nuclear-fuel production	0.27 (0.04-0.89) [2]	Cragle et al. 1988
Springfields, UK: mortality[c]	0.61 (0.31-1.08) [10]	McGeoghegan and Binks 2000a
Capenhurst, UK: ^{235}U enrichment plant mortality[c]	1.82 (0.58-4.39) [4]	McGeoghegan and Binks 2000b
Total Observed/Expected Cases[d]	68/85	

[a]Waxweiler et al. (1983) indicate that three cases were associated with prostatic obstruction or prostatic cancer and probably represent secondary renal disease.
[b]Data not given for "Subcohort I," so include entire cohort.
[c]Data given only for those classified as radiation workers.
[d]Sums do not include row labeled "TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments," because those workers were already included in the TEC/Y12 row for all workers.

gastrointestinal absorption of uranium in the same communities, Zamora et al. (2002) reported urinary concentrations of 0.01-2.58 μg/L (converted from micrograms per day by 1.4 L/24 h).

Kurttio et al. (2002) measured uranium concentrations in drinking water and urine in 325 persons who had used drilled wells for drinking water. Urinary and serum concentrations of calcium, phosphate, glucose, albumin, creatinine, and β_2m were measured to evaluate possible renal effects. Uranium concentrations over 300 μg/L in drinking water were associated with increased calcium fractional excretion. Urinary calcium and phosphate excretion were greater in persons in the high-uranium-excretion group (over 300 μg/L) than in those with low uranium excretion (under 2 μg/L). Uranium exposure was not associated

with changes in indicators of renal glomerular function (creatinine clearance or urinary albumin) or with urinary β_2m, the biomarker of tubular dysfunction. Later, the authors provided evidence that uranium may affect calcium and phosphate metabolism in bone but not in the kidneys (Kurttio et al. 2005). In a more recent study of 95 men and 98 women with continuous uranium intake from drinking water, no evidence of renal cytoxicity or functional effects was reported even at relatively high exposures (median uranium concentration, 25 μg/L; maximum concentration, 1,500 μg/L) (Kurttio et al. 2006). However, cumulative uranium intake was associated with increased urinary glucose excretion, which may reflect an effect on the glucose transport site.

Gulf War Cohort Studies

Because early animal studies demonstrated the sensitivity of the kidneys to uranium exposure, special attention was paid to renal-function assessments in a cohort of 74 Gulf War veterans exposed to DU from embedded metal fragments. Results of the first examination, in 1993-1994, showed no evidence of a relationship between urinary uranium excretion and clinical measures of adverse renal function (serum creatinine, calcium, phosphate, and uric acid; and urinary creatinine and β_2m) (Hooper et al. 1999).

Urinary concentrations of uranium have been measured every 2 y since 1993. In a recent assessment, mean urinary uranium concentrations ranged from 0.01 to 38.5 μg/g of creatinine (Squibb et al. 2005). Renal concentrations were estimated from urinary excretion with the ICRP model (ICRP 1995a). In eight of the 16 soldiers, predicted renal urinary concentration peaked before the last measurements; that indicated that net accumulation of uranium in the kidney was no longer occurring. Uranium concentrations that were increasing and that were highest at the last measurement time suggest that net tissue accumulation was still occurring. Estimated renal uranium concentrations in those veterans 10 y after the war are as high as 0.95 μg/g (Squibb et al. 2005).

Other biomarkers of the early effects of uranium on proximal tubular cells were added in the 1997 health-surveillance examinations. In addition to an absence of changes in the standard clinical markers of renal function, there have been no observed statistically significant increases in urinary excretion of the proteins that serve as biomarkers of proximal tubular cell damage—*N*-acetyl glucoaminidase (NAG) and ALP—in the high-exposure group in any of the surveillance examinations. Increases have been observed in one of the low-molecular-weight proteins, retinol-binding protein (RBP), a marker of decreased proximal tubular protein reabsorption. Those increases were observed in both the 2001 and 2003 examinations although they were not significant in 2003, and they were not observed in 2005 (McDiarmid et al. 2004a, 2006, 2007). The lack of overt renal damage is consistent with recent modeling studies reported by Squibb et al. (2005), but the authors suggest that the small increases in RBP excretion observed in 2002 and 2003 may reflect the slow accumulation of ura-

nium in the veterans' kidneys in excess of the higher urinary excretion of uranium.

ANIMAL STUDIES

Acute Toxicity

Exposure concentrations that produce renal injury depend on the solubility of the uranium compound and the route of exposure. Study of the renal changes that follow injection of uranium compounds provides a model relating kidney burden to acute renal-cell injury and repair. Diamond et al. (1989) studied kidney effects after multiple intraperitoneal injections of uranyl fluoride in rats at two doses (cumulative dose, 0.66 or 1.32 mg/kg of body weight). Earlier studies by Morrow et al. (1982) showed that inhaled and parenterally administered uranyl fluoride results in nearly identical patterns of distribution and excretion of uranium. Injury and death of cells of the proximal renal tubule began about 3 d after injection and were followed by evidence of renal tubular dysfunction. Light microscopy revealed swelling and vacuolation of epithelial cells progressing to necrosis. Histologic changes were accompanied by glucosuria, increased excretion of amino acids, and transient enzymuria with increased excretion of aspartate aminotransferase (AST), LDH, NAG, ALP, catalase, and leucine aminopeptidase (LAP). The magnitude and duration of the increased excretion of LDH were greater than those of the increases in excretion of AST and NAG; this suggests that LDH may be the most sensitive enzymatic biomarker. The lowest observed-adverse-effect-level (LOAEL) was 0.7-1.4 μg/g and peaked when renal uranium concentrations were between 3.4 and 5.6 μg/g, followed by progressive reversal of both morphologic and functional effects, returning to normal about 3 wk after the last injection.

Subchronic Toxicity

Oral Exposure

Gilman et al. (1998a) administered uranyl nitrate in drinking water at 0.96, 4.8, 24, 120, or 600 mg/L to weanling male and female Sprague-Dawley rats for 28 and 91 d. There were no significant changes after 28 d (kidney dose, 0.92 μg/g), but both male and female rats exposed for 91 d had degenerative changes in tubular cells at the lowest concentration (kidney dose, 0.42 μg/g). Changes in tubular epithelial cells included apical nuclear replacement and vesiculation, cytoplasmic vacuolation, and tubular dilatation. At 600 mg/L, males showed only tubular changes (residual kidney concentration, 2.12 μg/g), whereas females showed irreversible glomerular sclerosis and interstitial fibrosis indicative of a chronic nonreparable nephropathy. Residual uranium concentration in the

kidneys of female rats was 1.67 µg/g. There was no apparent explanation of the difference in sensitivity between the kidneys of male and female rats.

In studies of New Zealand white rabbits, males were administered uranyl nitrate in drinking water at 0.96, 4.8, 24, 120, or 600 mg/L for 91 d (Gilman et al. 1998b). Females were similarly exposed for 91 d at 4.8, 24, or 600 mg/L. The 91-d LOAEL in males was 0.96 mg/L and in females it was 4.8 mg/L. However, the residual renal uranium concentration at the LOAEL was 0.04 µg/g in males and 0.019 µg/g in females; thus, male and female rabbits might have different pharmacokinetic characteristics. Rabbits appear to be more sensitive than rats (Gilman et al. 1998a) to ingestion of uranyl nitrate.

Reversibility of uranyl nitrate-induced renal injury was studied in male New Zealand white rabbits exposed at 24 or 600 mg/L in drinking water for 91 d followed by various recovery periods (Gilman et al. 1998c). Histologic changes in the renal tubular cells of rabbits that received 600 mg/L were not reversed after a 91-d recovery period. Urinary glucose, protein, and LAP were maximally increased during the first week of the recovery period and then gradually declined. The renal uranium concentration was 3.48 µg/g after 91 d of treatment, and uranium was completely excreted during the 91-d recovery period. Glucosuria persisted beyond the recovery period.

Dermal Exposure

Dermal application of soluble uranium compounds (uranyl nitrate hexahydrate, uranyl acetate hexahydrate, and ammonium uranyl tricarbonate) produced renal toxicity in rabbits, guinea pigs, rats, and mice (de Rey et al. 1983). Proteinuria continued for up to 10 d and was followed by recovery to control values. Rabbits had increased blood NPN at doses over 270 mg/kg. There was microscopic evidence of renal damage in the animals that died, but the kidneys were histologically normal in the ones that survived, and this suggested that renal tubular cells had regenerated.

Chronic Toxicity

Implanted Depleted-Uranium Pellets

The results of long-term effects of implanted DU pellets in animal models have particular relevance to understanding of the effects of embedded fragments in Gulf War veterans. Pellmar et al. (1999a) implanted DU in rat muscle. The greatest concentrations of uranium were found in the kidneys and bone from 1 d after pellet implantation until 18 mo after implantation. No nephrotoxcity occurred in rats after 12 mo despite renal uranium accumulation exceeding 5 µg/g and excretion in the urine at 1µg/mL. Urinary excretion of LDH, NAG, protein, and glucose; creatinine clearance; and fractional excretion were not altered after 6 or 12 mo of exposure.

Inhalation Exposure

Comparisons of renal burdens due to acute ingestion and acute inhalation show that inhaled uranium compounds generally result in higher burdens in the kidneys than ingestion of the same amount of uranium compounds (Chen et al. 2004). The renal effects of chronic or long-term inhalation of natural-uranium dust, as might occur in occupational exposure, have been studied in rats, dogs, and monkeys (Leach et al. 1970, 1973). No histologic changes were found in the kidneys immediately after inhalation of natural-uranium dust for up to 5 y and after followup periods of up to 1 y in rats and 75 mo in dogs and monkeys (see Table 3-5). Monkeys had the highest renal burdens. Renal burdens were greater in dogs than in rats. No evidence of uranium toxicity was found in the records of body weights, mortality, various hematologic measures, or histologic examinations of the kidneys. Beginning sometime during the first postexposure year and lasting until the fifth, some uranium-exposed monkeys consistently had higher blood NPN concentrations than controls; NPN concentrations were normal at the end of the postexposure followup. In the absence of abnormal renal histologic characteristics, the significance of that finding is unclear. Biomarkers of renal tubular function were not measured; renal effects were evaluated only through histologic examination.

Mechanisms of Uranium Renal Toxicity

The mechanisms whereby uranium produces injury to the cells of renal tubules and glomeruli are not fully understood. Various hypotheses are discussed by Leggett (1989) and Diamond and Zalups (2005). Autoradiography of rats administered [^{232}U] uranyl nitrate showed that uranium concentrates in the outer stripe of the outer medulla and along the medullary rays penetrating the inner cortex; this is consistent with the location of the pars recta of the proximal tubule. It has been suggested that uranium combines with bicarbonate, citrate, and plasma proteins in the blood. At low pH, the complexes split, and the resulting uranyl ion may combine with proteins and be deposited on the surfaces of tubular epithelium and cause renal-cell damage (Basset et al. 1948). Brady et al. (1989) have shown that exposure of rabbit renal cells to uranyl nitrate in vitro inhibited both sodium-dependent and sodium-independent adenosine triphosphate use. Uranyl nitrate absorbed in the cytoplasm of tubular epithelium may impair mitochondrial oxidative phosphorylation. The resulting impairment of energy metabolism may contribute to the tubular dysfunction and ultimately to cellular degeneration.

Leach et al. (1984) noted in animal studies that glucosuria was the most sensitive indicator of renal injury associated with exposure to uranium. Glucosuria is also the most persistent abnormality during recovery from DU toxicity in rabbits (Gilman et al. 1998c) and in humans (Pavlakis et al. 1996). Glucosuria

TABLE 3-5 Renal Effects of Chronic Inhalation of Uranium Dioxide[a] in Experimental Animals

Animal Species	Number and Sex	Duration	Renal Burden	Renal Effects
Wistar rats (Study 1)	80 females	Exposure for 1 y	0.8 µg/g	None
Wistar rats (Study 2)	120 females	Exposure for 1 y	1.1 µg/g	None
Beagles	72 females, 5 males	Exposure for 5 y	5.8 µ/g	None
Rhesus monkeys	20 females 5 males	Exposure for 5 y	13 µg/g	Increased NPN, significance or cause unknown; normal renal histology
Wistar rats (Study 1)	6	Followup for 1 y	1.2 µg/g	None
Wistar rats (Study 2)	6	Followup for 1 y	0.9 µg/g	None
Beagles	5	Follow up for 75 mo	2.1 µg/g	None
Rhesus monkeys	5	Followup for 75 mo	1.7 µg/g	None

[a]5 mg/m^3 for 6 h/d 5 d/wk.
Sources: Leach et al. 1970, 1973. Modified table reprinted with permission; copyright 1970, 1973, Lippincott Williams & Wilkins.

was noted in subjects exposed to uranium in drinking water in the absence of other indicators of renal toxicity (Kurttio et al. 2006). Recent studies indicate that uranium has a direct dose-dependent and pH-dependent inhibitory effect on the rat kidney's brush-border membrane vesicles (Goldman et al. 2006).

The pathogenesis of glomerular injury is not well understood, but Diamond and Zalups (2005) have suggested that uranium decreases outer renal cortical blood flow and glomerular perfusion and may induce acute renal failure. Leggett (1989) reviewed several possible mechanisms of uranium-induced glomerular injury, including evidence that uranium produces structural alterations that decrease the glomerular surface area available for filtration. In vitro studies of isolated glomeruli exposed to uranium bicarbonate suggest that a reduction in glomerular filtration rate may result from glomerular contraction and disorganization of the cytoskeleton (Mirto et al. 1999; L'Azou et al. 2002).

McDonald-Taylor et al. (1992) found thickening of the glomerular basement membrane in rabbits exposed to uranyl nitrate in drinking water (at 24 and 600 mg/L), as measured with electron microscopy. In addition, thickness increased during 45-d and 91-d recovery periods, and this suggested that the glomerular effect may become chronic or even progressive in contrast with the regeneration of injured tubular cells. Progression of ultrastructural glomerular

changes not discernible with light microscopy may reflect continued retention of even small concentrations of uranium during postexposure followup.

Renal Uranium Concentration and Renal Tubular Dysfunction

The renal uranium concentrations sometimes found after acute exposure suggest that minimal transient effects (such as proteinuria and albuminuria) may occur after exposure at concentrations as low as 1 μg/g (Kathren and Moore 1986; Fisher et al. 1990). Renal effects have also been reported at renal concentrations around 1 μg/g in workers with chronic occupational exposure to uranium (Thun et al. 1985) and in Gulf War veterans with embedded DU fragments (Squibb et al. 2005). The Royal Society (2002) report also noted that transient renal effects occurred in humans at renal concentrations of 1 μg/g and that the trend for chronic exposures is toward greater renal effects with lower renal concentrations—possibly as low as 0.1 μg/g. The duration of exposure may be an important factor. Groups with longer exposure appear to have the greatest effects. How those findings compare with the renal uranium concentration thresholds chosen for the Capstone health risk assessments is presented in Chapter 8.

SUMMARY

- The primary target of uranium in the kidney is the proximal tubule, but glomerular effects also may occur.
- Biomarkers of tubular effects include enzymuria and increased excretion of low-molecular-weight proteins, amino acids, and glucose.
- Biomarkers of glomerular effects include urinary excretion of high-molecular-weight proteins (albuminuria) and increased blood creatinine or NPN.
- Glucosuria is the most persistent tubular biomarker during recovery from acute uranium exposure in animals and humans.
- Transient biomarkers of renal effects (such as proteinuria and albuminuria) have been observed at peak renal uranium concentrations as low as 1 μg/g.

4

Toxic Effects of Uranium on the Lungs

Uranium is a heavy metal, so one needs to consider chemical effects when evaluating its toxicity (see Chapter 6 for a discussion of radiologic effects). Inhalation constitutes a major route of human exposure. Therefore, the respiratory system is evaluated here as a potential target organ for toxicity.

After aerosolization of DU munitions, uranium oxide aerosols may be inhaled and deposited in the respiratory tract. Particle deposition is determined by physical and chemical properties of the particles and anatomic and physiologic factors, such as ventilation rate and inhalation pathway (nose vs mouth). Specifically, it depends largely on particle size: in general, larger particles are deposited in the upper respiratory tract or extrathoracic region, which includes nasopharyngeal airways, and smaller particles are carried to the lower respiratory tract and deposited mainly in bronchioles and alveoli. Larger particles are trapped mostly in the nasopharyngeal region in nose-breathers, but mouth breathing can enhance their entry into and deposition in tracheobronchial and alveolar regions.

The clearance of uranium oxide from the lungs occurs by different mechanisms and depends on the deposition site. Uranium trioxide acts like a soluble uranyl salt rather than an insoluble oxide; an inhalation study of dogs (Morrow et al. 1972) determined that it is rapidly cleared from the lungs with a biologic half-life of 4.7 d. Uranium dioxide and triuranium octaoxide are less soluble. Because of their high density, particles of these compounds are deposited mostly in the tracheobronchial region, and their clearance occurs primarily by mucociliary transport, which leads to ingestion and transport through the gastrointestinal tract; only 1-5% of the particles reach the deeper region of the lungs (Harris 1961). Although the more soluble particles may be absorbed into blood, the less soluble particles deposited in alveoli and those transported to tracheobronchial lymph nodes may remain there for years (ATSDR 1999). The biologic half-life of uranium dioxide in the lungs after occupational exposure was estimated by Schieferdecker et al. (1985) to be 109 d.

HUMAN STUDIES

Epidemiologic studies of the respiratory effects of uranium have involved miners and workers in uranium-processing plants (see Table 4-1). Their results are difficult to interpret because of workers' coexposure to other respiratory toxicants, the grouping of multiple diseases, and inaccuracies in the coding of death certificates for nonmalignant respiratory diseases. Some of the human studies are described briefly below.

A study of workers at the Naval Products Division of the United Nuclear Corporation, a nuclear-fuels fabricating company, determined standardized mortality ratios (SMRs) and incidence ratios for employees (Hadjimichael et al. 1983). The SMR for all causes in industrial male workers was significantly lower than expected, but there was an excess of deaths due to obstructive pulmonary disease. Of the six people who died from obstructive pulmonary disease, five had emphysema, but smoking information on four of the five was not available. Because emphysema can be caused by smoking, the incomplete information on smoking prevented adequate interpretation of excess deaths.

In another study, 1,484 men employed in uranium mills in the Colorado Plateau were evaluated (Pinkerton et al. 2004). The study determined a significant increase in mortality from nonmalignant respiratory disease but identified several limitations, including low cohort size, little power to detect a moderately increased risk of some outcomes, inability to estimate individual exposures, and lack of smoking data. Furthermore, positive trends with employment duration were not observed.

Other studies of workers at uranium facilities did not find an association between nonmalignant pulmonary diseases and mortality. For example, Dupree-Ellis et al. (2000) compared mortality in 2,514 workers employed during 1942-1966 at a uranium-processing plant with overall U.S. mortality. They reported an SMR of 0.90 for all causes of death and 1.05 for all cancers. The SMR for respiratory diseases was 0.80. A retrospective cohort mortality study of workers at a facility for production of nuclear fuel (Cragle et al. 1988) found significantly fewer deaths in many categories of disease, including all respiratory diseases. Polednak and Frome (1981) described mortality in a cohort of 18,869 men employed at a uranium conversion and enrichment plant and reported that the causes of particular interest, including respiratory diseases, did not exhibit high SMRs.

Lung-cancer mortality has been estimated in a number of cohort studies that included nearly 110,000 uranium-processing workers (see Chapter 6 for discussion); nearly all the studies had null results. A nested case-control study based on the four largest U.S. cohorts did not find an exposure-response relationship. The few positive results, when combined with uncertainties due to lack of smoking data in the studies, mean, however, that the possibility of associations cannot be dismissed.

TABLE 4-1 Standardized Mortality Ratios (95% Confidence Intervals) [and Observed Number of Deaths] from Nonmalignant Respiratory Diseases in Uranium Workers

Study	Nonmalignant Respiratory Disease	Reference
Colorado Plateau uranium-mill workers (with no history of uranium mining)	1.43 (1.16-1.73) [100]	Waxweiler et al. 1983; Pinkerton et al. 2004
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, all workers	1.10 (0.98-1.22) [340]	Polednak and Frome 1981
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments	1.05 (0.87-1.26) [118]	Polednak and Frome 1981
Y12 (1947-1974): Oak Ridge uranium-metal production and recycling	0.88 (0.72-1.07) [106]	Checkoway et al. 1988; Loomis and Wolf 1996
Mallinckrodt uranium-processing workers	0.80 (0.62-1.01) [64]	Dupree-Ellis et al. 2000
Fernald fabrication of uranium products	0.66 (0.50-0.87) [53]	Ritz 1999
Portsmouth gaseous diffusion[a]	0.46 (0.24-0.79) [13]	Brown and Bloom 1987
Savannah River nuclear-fuel production	0.40 (0.27-0.57) [27]	Cragle et al. 1988
Linde uranium-processing facility (1943-1949)	1.02 (0.80-1.29) [71]	Dupree et al. 1987; Teta and Ott 1988
United Nuclear Corp. nuclear-fuel fabrication[b]	3.03 (1.11-6.59) [6]	Hadjimichael et al. 1983
Florida phosphate workers[b]	0.96 (0.82-1.11) [181]	Checkoway et al. 1996
Atomic Weapons Establishment, UK	0.74 (0.40-1.24) [14]	Beral et al. 1988
Springfields, UK, mortality[c]	0.79 (0.71-0.87) [379]	McGeoghegan and Binks 2000a
Capenhurst, UK ^{235}U enrichment plant mortality[c]	0.70 (0.53-0.92) [53]	McGeoghegan and Binks 2000b
Total Observed/Expected Cases[d]	1,407/1,590	

[a]Includes only "Subcohort I," which consists of those who at some time worked in one of the departments considered to have uranium exposure.
[b]SMRs were similar for white and nonwhite men, so results for combined groups are presented.
[c]Data given only for those classified as radiation workers.
[d]Sums do not include row labled "TEC/Y12 (1943-47): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments," because those workers were already included in TEC/Y12 row for all workers.

ANIMAL STUDIES

The respiratory effects in rats and mice of exposure to various uranium compounds include nasal irritation (Spiegl 1949) and nasal hemorrhage (Leach et al. 1984). No symptoms appeared after 30 d of exposure to uranium hexafluoride in any species at inhalation concentrations below 3 mg/m^3 (Spiegl 1949). In a 30-d inhalation study, Spiegl (1949) exposed dogs, rats, and rabbits to uranium hexafluoride at 20 mg/m^3 and found pathologic signs in the lungs typical of hydrogen fluoride poisoning in dying animals. The pulmonary effects included edema, hemorrhage, inflammation, and irritation. Spiegl noted that uranium hexafluoride hydrolysis liberates uranyl fluoride and hydrofluoric acid, which appear to be responsible for toxic effects in the lungs. Uranium hexafluoride toxicity presents a special situation in that the edema induced by hydrofluoric acid could increase the uptake of uranium by facilitating transport across the airway mucosa.

Dygert et al. (1949) exposed animals to uranium tetrafluoride at concentrations of 0.5-25 mg/m^3 for 30 d and reported rhinitis in cats and dogs only at the highest exposure. Uranium dioxide and triuranium octaoxide were not associated with pulmonary toxicity. Lung injury was not observed in rats, rabbits, guinea pigs, or dogs exposed to various uranium compounds at 0.05-10 mg/m^3 for 7-13 mo (Cross et al. 1981a,b). In another study, rats, dogs, and monkeys were exposed to uranium dioxide dust at 5 mg/m^3 for 5.4 h/d 5 d/wk for 1-5 y (Leach et al. 1970). A total of 446 animals (120 dogs, 31 monkeys, and 295 rats) were used for control and uranium dioxide exposures. No pathologic findings in the lungs were observed in rats and dogs, but monkeys developed patchy, hyaline pulmonary fibrosis, which was minimal after exposure for 3.6 y and progressed with longer exposure (up to 4.7 y). Mitchel et al. (1999) exposed Sprague-Dawley rats to uranium dust at 19 and 50 mg/m^3 for 4.2 h/d 5 d/wk for 65 wk and calculated the absorbed dose (in grays) to the lungs. Lung-tumor frequency was not directly proportional to dose, but a linear relationship was observed when lung-tumor frequency was calculated as a function of dose rate, measured as the retained lung burden at the end of inhalation exposure. The frequency of nonmalignant lung tumors did not show a linear correlation when examined as a function of lung burden but was biased toward low lung burden.

In addition to direct pulmonary toxicity, there is a potential for activation of an inflammatory response, release of inflammatory mediators, and lung injury. Secondary injury is discussed in Chapter 7.

SUMMARY

In animal studies, pulmonary toxicity was reported after exposure to uranium tetrafluoride and uranium hexafluoride, but uranium dioxide and triuranium octaoxide were not associated with acute lung injury. Pulmonary fibrosis was reported in monkeys exposed to uranium dioxide dust at 5 mg/m^3 for 5 y.

On the basis of the data reviewed here, the committee concludes that acute exposure to low concentrations of insoluble uranium compounds does not produce acute lung injury although chronic exposure to naturally occurring uranium dioxide dust is capable of producing pulmonary fibrosis.

5

Toxic Effects of Uranium on Other Organ Systems

Chapters 3 and 4 evaluated the effects of uranium on the kidneys and the lungs, respectively. This chapter examines effects on other organ systems.

CENTRAL NERVOUS SYSTEM EFFECTS

Human Studies

Animal studies have demonstrated uranium uptake by and possible functional effects on the brain, but human studies have not confirmed or substantiated a relationship between uranium exposure and neurologic disease (IOM 2000; Craft et al. 2004). McDiarmid et al. (2000) found a statistically significant relationship between increased concentration of depleted uranium (DU) and decreased performance on automated tests that assess performance accuracy in Gulf War veterans who have embedded fragments. The authors cautioned that the number of people with increased urinary uranium was small, and a few veterans who had complex histories may have contributed appreciably to the observed variance.

Neurocognitive function was assessed with a battery of tests consisting of traditional (paper and pencil) and automated measures. The traditional measures involved generating a neuropsychologic index from several tests: the California Verbal Learning Test; the Trail Making Test, Parts A and B; the Shipley Institute of Living Scale; and the Digit Span, Arithmetic, and Digit Symbol subtests of the Wechsler Adult Intelligence Test-Revised (Wechsler 1981). Three scores were developed from automated measures of neurocognitive function from the Automated Neuropsychological Assessment Metrics test library (Kane and Reeves 1997): A-IIac (accuracy), A-IIrt (speed), and A-IItp (computed score combining accuracy and speed). Psychiatric assessment included the Wide Range Achievement Test 3 (Jastak and Wilkinson 1993), the Symptom Check-

list-90 Revised (Derogatis 1983), the Beck Depression Inventory (Beck et al. 1996), the Beck Anxiety Inventory (Beck et al. 1988), and the Mississippi Scale for Posttraumatic Stress Disorder (Keane et al. 1988).

There were no statistically significant ($p < 0.05$) differences between the high and low uranium-exposure groups in any neurocognitive measure at any of the five surveillance visits, although a higher impairment score on the A-IIac was consistently observed in the high-exposure group during the 1997 visits. For that time, results on the automated tests demonstrated a statistically significant relationship between urinary uranium concentration and lowered performance efficiency. More robust regression analyses that controlled for confounding factors, such as emotional status and general intellectual level, were conducted on A-IIac impairment scores from the 2001 and 2003 visits and urinary uranium concentrations. The results revealed a marginal association between measured urinary uranium and the accuracy index; however, the authors commented that the relationship in both years was driven by two cases with persistent complications due to combat injuries and their high urinary uranium concentrations (Hooper et al. 1999; McDiarmid et al. 2000, 2001a, 2004b, 2006).

Animal Studies

Description of morphologic changes in the central nervous system caused by exposure to uranium is limited to early experiments at high exposures. However, more recent studies with lower exposures have identified functional electrophysiologic effects and perhaps neuropsychologic (behavioral) effects. Studies performed many years ago showed that exposure of dogs to near-lethal doses of uranyl nitrate produced changes in the epithelium of the choroid plexus (Purjesz et al. 1930). In a more recent study that used an in situ brain-perfusion technique, Lemercier et al. (2003) showed that uranium reached the brain parenchyma by blood circulation (microcirculation) and the vascular space.

In a 30-d inhalation study, dogs exhibited muscular weakness and gait instability on day 13 of exposure to uranyl fluoride gas at a uranium concentration of 1.8 mg/m^3 but showed no effects at lower concentrations (Dygert et al. 1949). In a study to determine the LD_{50}, groups of 10 male Sprague-Dawley rats and 10 male Swiss mice were given a single subcutaneous dose of uranyl acetate at 1.25, 2.5, 5, 10, 20, and 50 mg/kg. The LD_{50} in rats was 8.3 mg/kg, and that in mice was 20.4 mg/kg. Rats and mice that survived 6 d or longer showed central cholinergic neurologic signs (piloerection, tremors, hypothermia, papillary size decrease, and exophthalmos) that persisted until termination of the study at 14 d (Domingo et al. 1987). The relevance of those studies to potential human exposure has been questioned (IOM 2000).

More recently, Pellmar et al. (1999a) surgically implanted DU pellets in the gastrocnemius muscle of rats at three doses (low dose, four DU and 16 tantalum pellets; medium dose, 10 DU and 10 tantalum pellets; and high dose, 20 DU pellets). After 1 mo, the uranium concentrations in the brain were statistically

significantly higher in the high-dose rats than in controls; after 18 mo, there were dose-related increases in uranium concentrations in several areas of the brain in all three groups of DU-implant rats. The highest uranium concentrations were in the motor and frontal cortex, midbrain, and cerebellar vermis. The study demonstrated that uranium absorbed from embedded DU pellets may accumulate in the central nervous system.

In a followup study, Pellmar et al. (1999b) assessed the electrophysiologic changes in the hippocampus of rats that had implanted DU fragments. At 12 mo, the amplitude of synaptic potentials was significantly greater in tissues derived from the high-dose (20 fragments) DU-implant rats than in controls. In the same animals, uranium did not affect locomotor activity, discrimination learning, or a battery of general neurologic functional measures. The abnormal electrophysiologic measurements were not apparent 18 mo after exposure to 20 DU pellets. The authors suggest that by 18 mo the effects of aging and DU exposure converge, and the convergence obscures the effects of uranium. Thus, uranium from embedded DU pellets clearly can accumulate in the brain, but the significance of the effect on the function of the hippocampus is difficult to interpret.

Because of the inherent stress of combat and the potential for stress to alter blood-brain barrier permeability, Barber et al. (2005) investigated the impact of forced-swim stress on the temporal and regional distributions of brain uranium after a single peritoneal injection of uranyl acetate at a uranium concentration of 1 mg/kg in Sprague-Dawley rats. Uranium concentrations in serum, hippocampus, striatum, cerebellum, and frontal cortex were measured with inductively coupled plasma-mass spectrometry 6 h, 24 h, 7 d, and 30 d after exposure. Uranium entered the brain rapidly and was initially concentrated in the hippocampus and striatum but was distributed among various regions. Prior exposure to stress significantly reduced hippocampal and cerebellar uranium 24 h after exposure and tended to reduce uranium in all regions of the brain 7 d after exposure. That effect of stress is not peculiar to uranium: brain zinc concentrations also are reduced by stress (Izgut-Uysal et al. 2000). Although stress appears to reduce the brain burden of uranium, the combined effects of stress and uranium on brain function remain unclear. The stressed hippocampus has been shown to be hypersensitive to anticholinesterases (Meshorer et al. 2002).

Spontaneous locomotion activity increased and spatial working memory decreased after repeated inhalation exposure of rats to DU at 197 mg/m^3 30 min/d, 4 d/wk for 3 wk (Monleau et al. 2005). When rats ingested uranyl nitrate in drinking water (at a uranium concentration of 40 mg/L) for 1.5, 6, and 9 mo, acetylcholinesterase activity in the cerebellum was transiently impaired after 6 mo, and monoamine concentrations were low after 9 mo. Those effects might be caused by uranium accumulation in the brain or changes in oxidation balance, which could account for changes in neurobehavior (Bussy et al. 2006). In another study, decrease in food intake and shorter paradoxical sleep were observed 3 d after intraperitoneal injection of DU at 144 ± 16 µg/kg but not after a lower dose, 70 ± 8 µg/kg (Lestaevel et al. 2005). The studies indicate that exposure to uranyl nitrate and DU results in accumulation of uranium in the brain and possi-

ble neurochemical and neurobehavioral effects in rats. A study in the same laboratory found a correlation between uranium accumulation in the brain and an increase in paradoxical sleep and a reduction in spatial working memory capacities after exposure to 4% enriched uranium for 1.5 mo. The authors suggest that radiologic activity induces the effects of uranium (Houpert et al. 2005). Arfsten et al. (2007) surgically implanted DU pellets in young adult Sprague-Dawley rats and after 150 d did not find any evidence of effects on behavior and toxic end points.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Human Studies

A few studies (as reviewed by Craft et al. 2004) have indicated that uranium exerts effects on the reproductive system and consequently induces changes in the developing organism. Muller et al. (1967) reported that uranium exposure affects the sex ratio; the unusually high frequency of female births in uranium-mining workers indicates altered sperm function or reproductive-capacity dysfunction. Zaire et al. (1997) noted a significant reduction in testosterone concentrations and altered gonadal function in uranium miners; however, study limitations included inadequate characterization of exposure, a small sample, and the presence of other confounding factors.

McDiarmid et al. (2004b) conducted the most comprehensive followup study of a group of Gulf War veterans exposed to DU. Of a cohort of 74 veterans who were exposed to DU during friendly-fire incidents in February 1991, 39 were examined in Baltimore in April-July 2001. The items measured included serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid-stimulating hormone (TSH), free thyroxine, and testosterone concentrations. In addition, semen characteristics—including volume, sperm concentration, total sperm count, and functional measures of sperm motility—were determined. The study included veterans drawn from the cohort of DU-exposed veterans evaluated by McDiarmid et al. (2000, 2001b) in two previous investigations. The three studies demonstrate that some observations are contradictory even though they used subsets of the same population; this raises issues regarding the biologic relevance of the findings. For example, prolactin concentrations were significantly higher in the low-uranium group (n = 26; defined as less than 0.1 μg/g creatinine) in the 2004 study. However, in the 2000 study, the high-uranium group (n = 13; defined as over 0.1 μg/g creatinine) had higher prolactin concentrations; and in the 2001 study, there was no marked difference between the two groups. The relevance of the findings with respect to the use of prolactin as a biomarker of DU actions on the reproductive system is questionable in light of the variation in observations in the three studies. In all three studies, McDiarmid et al. found no marked changes in the concentrations of serum FSH, LH, testosterone, TSH, or free thyroxine. Another followup study (McDiarmid

et al. 2007) of 34 veterans found similar nonsignificant changes. Thus, the data suggest that DU exposure did not markedly affect neuroendocrine functions in humans.

The semen characteristics of 35 DU-exposed Gulf War veterans were also examined by McDiarmid et al. (2004b, 2006). Eight veterans were excluded for such reasons as vasectomy and other medical conditions. No significant differences were observed between the low-exposure group (n = 16) and the high-exposure group (n = 11) in semen volume, sperm concentration, total sperm count, or percentage motile sperm. No significant effects were observed in uranium-exposed veterans in the following categories defined by the World Health Organization (WHO 1987): percentage progressive sperm, total progressive sperm, percentage rapid progressive sperm, and total rapid progressive sperm. Although the sample was small, the values obtained were all within the WHO normal guideline range. Similarly, McDiarmid et al. (2007) found no significant alterations in semen quality in a followup study of 24 veterans. Thus, DU concentrations did not appear to affect reproductive capacity in the men studied.

Information gathered through the continuing surveillance program of the male DU-exposed Gulf War veterans at the Baltimore Veterans Administration Medical Center contains no evidence of congenital anomalies or abnormal reproductive capacity. During the 8-y span from exposure in 1991 to the 1999 surveillance visit, 50 of the DU-exposed veterans fathered 35 children, all without birth defects (McDiarmid et al. 2001b).

Animal Studies

The reproductive system and fetal development are targets of uranium in animals (Domingo 2001). Paternain et al. (1989) administered uranyl acetate orally to mice at 5, 10, or 25 mg/kg per day. Male and female mice received uranyl acetate for 60 and 14 d, respectively, before mating. Females were exposed throughout mating, gestation, parturition, and lactation. At 25 mg/kg per day, uranyl acetate was lethal to some embryos and reduced growth rate in surviving offspring. The authors concluded that uranyl acetate did not markedly alter fertility, reproductive measures, or offspring survival at the lower doses.

Similarly, Domingo et al. (1989) found that oral administration of uranyl acetate at 0.05, 0.5, 5, or 50 mg/kg per day from day 13 of pregnancy until weaning on postnatal day (PND) 21 significantly decreased mean litter size in Swiss mice only at 50 mg/kg per day. In addition, viability was reduced, and the lactation index was diminished at the highest dose. However, no marked changes were observed in sex ratio, mean litter size, pup body weight, or pup length in the other groups. Domingo et al. (1989) estimated a safety factor of 1,000 between the no-observed-effect level (NOEL) in the rodent study and typical human exposure concentrations.

The influence of uranyl acetate on the male reproductive capacity of Swiss mice was examined by Llobet et al. (1991). Groups of mice were given uranyl

acetate in drinking water for 64 d at daily doses of 0, 10, 20, 40, or 80 mg/kg. To evaluate fertility, a male was mated with untreated females for 4 d. Uranium treatment was associated with a significant but non-dose-related decrease in pregnancy rate: groups of 16 mice had 13, four, five, four, and six pregnancies after treatment at 0, 10, 20, 40, and 80 mg/kg per day, respectively. However, there were no marked effects on the number of implantations, the number of resorptions, the number of dead fetuses, or the number of live fetuses. At 80 mg/kg, there was a significant decrease in body weight but no change in testicular weight. Testicular function and spermatogenesis were not affected by uranium. At 80 mg/kg, there was vacuolation of Leydig cells. Given uranium in drinking water at 100 μg/L, a 70-kg human consuming 2 L of water a day would receive a daily dose of 0.003 mg/kg, which is less than one-thousandth of the lowest dose at which apparent reproductive effects were observed in this study.

Subcutaneous administration of uranyl acetate at 1 and 2 mg/kg per day significantly decreased fetal body weight, increased the number of dead fetuses at birth, and increased the number of resorptions. Concerning teratogenic indexes, uranium was found to induce cleft palate, dorsal and facial hematomas, and skeletal malformations (Bosque et al. 1992, 1993). There were no apparent effects at 0.5 mg/kg per day.

It should be noted that the route of exposure is critical. In the studies described above, uranium was administered directly orally or subcutaneously, and some effects were noted at high doses. The studies described below differed with respect to exposure in that the route was muscle implantation of uranium and later transport to the target site.

Several studies were conducted to determine the effects of DU embedded in soft tissue and whether it might affect reproduction and development in rodents. The study was undertaken to simulate the human condition in which DU fragments from friendly fire would become embedded in a person. Arfsten et al. (2005) estimated human equivalent exposures from the pellets implanted in the rat. The surface area of four pellets, each 2 × 1 mm in diameter, is about 31 mm^2 and corresponds to 0.1% of the estimated body surface area of an adult rat (0.025 mm^2). Twelve 2 × 1-mm DU pellets are the equivalent of one 30-mm APFSDS–T DU solid projectile (about 425 mg of DU, 28 cm long). Twenty 2 × 1-mm, DU pellets in a 250-g rat is the equivalent of about 0.22 kg of DU in a 70-kg man.

As discussed above, Pellmar et al. (1999a) implanted four, 10, or 20 DU pellets into gastrocnemius muscle of rats for 18 mo. No uranium was present in the testes of the control or four-pellet group after 18 mo, but testicular uranium was found in the 10- and 20-pellet groups, indicating transport and translocation of uranium from the embedded site to testes. In female Sprague-Dawley rats, implantation of 32 DU pellets in the gastrocnemius muscle for 82 d resulted in uranium in the ovaries (Benson 1998). Furthermore, Benson and McBride (1997) implanted four, eight, or 12 DU pellets in female Sprague-Dawley rats and then bred them within days and euthanized them on gestational day 20. The

presence of uranium in placenta, whole fetus, fetal liver, and maternal kidney indicated placental transfer and fetal accumulation.

Arfsten et al. (2005) implanted 12 DU pellets (six pellets per gastrocnemius muscle) in male Sprague-Dawley rats and four, eight, or 12 DU pellets in females. Thirty days after surgery, the males and females were cross-mated, and parental females were monitored for weight gain on gestational days 5, 10, 15, and 20. On PND 4, the litters were culled to eight pups, and females nursed until PND 20. Pups were studied until PND 90. DU did not affect reproductive capacity, survival, or weight gain in parental males and females throughout the study period. There was no significant effect on birth weight, litter size, number of litters, percentage surviving pups on PND 4 and 20, or pup weight gain. In pups, there was no adverse effect on sperm motility or concentration and no significant difference in percentage motile sperm, curvilinear velocity, straight-line velocity, mean sperm path velocity, amplitude of lateral sperm-head displacement, or sperm-head beat-cross frequency up to PND 90. Surprisingly, uranium content was not detected in whole-body measurements of pups on PND 4 and 20. In a later study, Arfsten et al. (2006) implanted 20 uranium pellets (each 1 × 2 mm; equivalent to 0.22 kg of DU in a 70-kg man) into Sprague-Dawley rats, which were then assessed for male reproductive performance on postimplantation day 150. The concentration, motion, and velocity of sperm were not markedly affected. Furthermore, there was no evidence of adverse effects on mating or reproductive success 3-45 and 120-145 d after implantation.

The findings of Arfsten et al. (2005, 2006) clearly are at odds with those Benson and McBride (1997), who noted placental uranium transfer. Arfsten et al. (2005) attributed the differences to variations in methods of measuring uranium. That implanted DU pellets had no effects on breeding success, fetal developmental defects, and sperm quality in the Arfsten et al. studies (in contrast with the finding of uranium administered orally or subcutaneously) suggests that the presence of DU fragments at tissue sites other than the endocrine-reproductive system does not have a marked effect on reproductive capacity or neonatal development in rodents. The route of exposure appears to be a critical factor in the consequences on reproduction and development in rodents. It should be noted that the amount of uranium that produced an adverse reproductive effect in the Domingo et al. (1989) study was markedly higher than that used in the Arfsten et al. studies.

Mitchell et al. (2005) exposed embryos of the African clawed frog (*Xenopus laevis*), a sentinel species for environmental exposure, to DU at 5-78 mg/L in water for 96 h. That there were no marked effects on embryonic mortality, malformation, or growth indicates that DU did not induce teratogenic alterations. At high concentrations of DU (well above those in municipal drinking water), there was a delay in metamorphosis. With respect to humans, exposure from DU fragments is a more plausible scenario than exposure by ingestion; data indicate that uranium would not exert a significant effect on the reproductive system or fetal development.

HEMATOLOGIC EFFECTS

Human Studies

Uranium miners who worked less than 5-20 y showed small but significant decreases in hemoglobin and mean corpuscular hemoglobin and significant increases in red blood cell (RBC) and mean corpuscular volume (Vich and Kriklava 1970). All values were within the normal ranges according to the authors. The exposure concentrations were not reported. Studies of workers exposed to uranium have shown no excess mortality from leukemia, but there is uncertainty about lymphoma induction because a few studies have shown excess lymphoma mortality (see Chapter 6 and Appendix B).

Animal Studies

Zhao and Zhao (1990) reported no hematologic effects in a single animal exposed by inhalation to powdered uranium tetrafluoride for 5 min (concentration not reported). Hematologic effects have been observed in the rat, dog, and rabbit after subacute inhalation exposure (ATSDR 1999); however, ATSDR characterized the effects as minor because of statistical insignificance or inconsistency with other hematologic measures. Specifically, Dygert et al. (1949) exposed rats and rabbits to diuranate and ammonium diuranate, respectively, 6 h/dy for 30 d. The lowest observed-adverse-effect level (LOAEL) of uranium was 6.8 mg/m^3 for diuranate for decreased RBCs and hemoglobin in the rat. The LOAEL of uranium was 6.8 mg/m^3 for ammonium diuranate for increased neutrophils and decreased lymphocytes in the rabbit. Similarly, Roberts (1949) exposed rats, dogs, and rabbits to uranyl nitrate hexahydrate daily (time of day not specified) for 30 d. The LOAEL of uranium was 9.5 mg/m^3 for decreased RBCs and hemoglobin in the rat, 2.1 mg/m^3 for slightly decreased fibrinogen in the dog, and 0.13 mg/m^3 for increased plasma prothrombin and fibrinogen in the rabbit. Rothstein (1949) exposed rats to uranium trioxide 6 h/d for 28 d; this resulted in a LOAEL of uranium of 16 mg/m^3 for increased myeloblasts and lymphoid cells of the bone marrow.

Maynard and Hodge (1949) and Maynard et al. (1953) exposed rats orally to uranyl nitrate hexadydrate daily for 2 y. The LOAEL was 16.6 mg/kg per day for mild (defined as low-grade) anemia and increased number of leucocytes.

HEPATIC EFFECTS

Human Studies

Humans exposed once to uranyl acetate dihydrate demonstrated increased serum alanine amino transferase, aspartate amino transferase, and gamma glutamyl transpeptidase at 131 mg/kg per day (Pavlakis et al. 1996). Those en-

zymes can be associated with cellular necrosis of the liver. Studies of workers exposed to uranium have not shown any excess mortality from hepatic cirrhosis (see Table 5-1) or liver cancer (see Chapter 6).

Animal Studies

There are several studies of the hepatic effects of DU after chronic inhalation exposure of monkeys, rats, and dogs. Daily exposure of monkeys to uranium dioxide for 5 y resulted in a no-observed-adverse-effect level (NOAEL) of uranium of 5.1 mg/m^3 (Leach et al. 1970). Exposure of rats to uranium tetrachloride or uranium hexafluoride for 1 y resulted in a uranium NOAEL of 0.2 mg/m^3 for each compound (Stokinger et al. 1953). Exposure of dogs to uranium tetrachloride or uranyl nitrate hexahydrate for 1 y resulted in a uranium NOAEL of 0.2 or 2.0 mg/m^3, respectively, for increased bromosulfalein retention (Stokinger et al. 1953). The retention of bromosulfalein in plasma is an indication of impaired hepatic function. Under healthy conditions, it is rapidly removed from plasma by the liver. Focal necrosis of the liver was reported in rats exposed to uranium tetrafluoride at a uranium concentration of 0.4 mg/m^3 for 6 h/d for 30 d (Dygert et al. 1949).

IMMUNOLOGIC EFFECTS

The immune system differs from other organ systems in that it is not confined to a single site in the body. Rather, it comprises numerous lymphoid organs and diverse cell populations. Toxicity in the immune system can be evidenced by decreased immune function (immunosuppression as evidenced by tumor production or increased infection) or enhanced immune function (allergy or autoimmunity).

Inhaled uranium oxide particles deposited in the lung are transported by alveolar macrophages to the draining lymph nodes, where they may remain for several years. Retained alpha particles may cause some lymphocyte death as lymphocytes pass through the lymphoid tissues, but the decrease is unlikely to affect lymphoid function (Royal Society 2002). No report has been identified that indicates immune system dysfunction—either immunosuppression or immunoenhancement—in humans resulting from DU exposure. Furthermore, an Institute of Medicine report (IOM 2000) concluded that there is inadequate or insufficient evidence to determine an association between exposure to uranium and lymphocytic cancer or bone cancer. As discussed below, immunotoxic effects of DU have been studied in laboratory animals by using inhalation and oral exposure and implantation DU pellets. In vitro studies also have been performed.

TABLE 5-1 Standardized Mortality Ratios (95% Confidence Intervals) and [Observed Number of Deaths] for Hepatic Cirrhosis in Uranium Workers

Study	Hepatic Cirrhosis	Reference
Colorado Plateau uranium-mill workers (with no history of uranium mining)	0.52 (0.21-1.07) [7]	Waxweiler et al. 1983
Fernald fabrication of uranium products	0.92 (0.64-1.29) [34]	Ritz 1999
Savannah River nuclear-fuels production	0.51 (0.34-0.72) [28]	Cragle et al. 1988
Linde uranium-processing facility (1943-1949)	0.93 (0.66-1.28) [37]	Dupree et al. 1987; Teta and Ott 1988
Springfields, UK: mortality[a]	1.05 (0.69-1.53) [25]	McGeoghegan and Binks 2000a
Capenhurst, UK: ^{235}U-enrichment plant, mortality[a]	0.63 (0.16-1.72) [3]	McGeoghegan and Binks 2000b
Total Observed/Expected Cases	134/160	

[a]Data only on those classified as radiation workers.

Animal Studies

No lymph node tumors were found in rats exposed for 65 d to uranium ore at 19 mg/m^3 or 50 mg/m^3 (Mitchell et al. 1999). Studies in dogs suggest that cancers do not develop in the lymph nodes after inhalation of uranium dioxide (uranium at 5 mg/m^3; mass median diameter [MMD], 1 μm) for 5 y (Leach et al. 1973).

The short-term effect of DU on mucosal immunity of the digestive tract was studied in rats. The rationale for the study was that the digestive tract lumen is the first biologic system exposed to the chemical in ingestion. Rats received a single dose of uranyl nitrate dissolved in water (204 mg/kg in 1.5 mL; pH 3; Dublineau et al. 2006). That dose is known to be toxic to kidneys (equivalent to 1-3 μg/g of wet kidney). The intestine was assessed for cell proliferation, differentiation, and apoptosis 1 d later and then again 3 d later. Results indicated that DU was not toxic to the intestine although changes were noted in the production of chemokines and in the expression of cytokines. Production of monocyte chemoattractant protein-1 was decreased, and expression of interferon-gamma was increased. No changes were noted in the localization or density of neutrophils, Th1 lymphocytes, or cytotoxic T lymphocytes after DU administration. Long-term effects of DU were not studied.

As discussed above, Arfsten et al. (2005) studied the effects of DU pellets surgically implanted in adult rats on reproductive success and development in two consecutive generations. Immune function in the offspring was assessed.

Results indicated no effect on T-lymphocyte or B-lymphocyte function, NK-cell function, delayed hypersensitivity, or organ weights.

In Vitro Studies

In vitro effects of uranium compounds on macrophage viability and function have been reported. In one study, particulate uranium dioxide at increasing concentrations was added to rat alveolar macrophages that had been isolated after bronchoalveolar lavage (Tasat and deRey 1987). Cell viability and incorporation of uranium particles were assessed; the alveolar macrophages were able to phagocytose uranium particles despite toxicity in cell membranes and eventual cell death. The in vitro effect of soluble DU-uranyl chloride on the J774 mouse macrophage cell line was studied with flow cytometric analysis (Kalinich et al. 2002); treatment with 1-100 μM uranyl chloride resulted in apoptosis and decreased viability within 24 h.

The effect of DU on mouse macrophages and T lymphocytes was studied. Peritoneal macrophages and splenic CD4+ T cells were elicited in response to thioglycollate administration, and cells were assessed for viability, function, and cytokine gene expression after in vitro exposure of cells to increasing concentrations of uranyl nitrate (Wan et al. 2006). In both cell lines, cytotoxicity was dose-dependent. Apoptosis and necrosis of macrophages occurred within 24 h of exposure to 100 μM DU, but 50 μM was noncytotoxic. CD4+ T cells died when exposed to 500 μM DU, whereas 100 uM was noncytotoxic. DU altered gene-expression patterns in both cell types; genes related to signal transduction (for example, c-jun and NF-κ Bp65) were the most differentially expressed. Up-regulation of IL-10 and IL-5 was noted after in vitro exposure of cells to DU.

MUSCULOSKELETAL EFFECTS

Human Studies

There is a clinical report of deliberate ingestion of 15 g of uranyl acetate (Pavlakis et al. 1996). The dose was estimated to be the equivalent of 131 mg/kg for a 70-kg man (ATSDR 1999). The patient suffered from increasing rhabdomyolysis (characterized by increased serum creatine kinase). The condition was resolved at 6 mo after the ingestion. The etiology of the effect is unknown, but the presence of confounding factors in the suicide attempt makes interpretation difficult.

Uranium accumulates in bone, affects bone metabolism, and, when ingested in drinking water, increases urinary excretion of calcium and phosphate, important components of bone structure. To demonstrate those effects in humans, Kurttio et al. (2005) studied people who drank well water with high concentrations of natural uranium. On the basis of slightly increased concentrations of osteocalcin and serum type I collagen carboxy-terminal telopeptide in men,

but not women, the authors suggested that bone may be a target of uranium toxicity.

Medical followup of a cohort of Gulf War veterans who were exposed to DU during combat has been carried out since the early 1990s (McDiarmid et al. 2004b). Findings reveal a persistent increase in urinary uranium more than 10 y after exposure in veterans who had retained fragments; however, no evidence of musculoskeletal effects has been observed.

Animal Studies

Data from the available animal studies suggest that oral exposure to uranium does not cause detectable damage to the musculoskeletal system. Examination of muscle after exposure to uranyl nitrate in drinking water showed no effects in Sprague-Dawley rats after 28 d (uranium at up to 40 mg/kg per day; Gilman et al. 1998a) or 91 d (uranium at up to 53 mg/kg per day; Gilman et al. 1998a) or in New Zealand rabbits after 91 d (uranium at up to 43 mg/kg per day; Gilman et al. 1998c).

Two animal studies funded by the Department of Defense in response to concerns about the effects of DU fragments have been completed. The study of the distribution of uranium in rats with implanted DU pellets (Pellmar et al. 1999a) concluded that bone is one of the primary reservoirs of uranium redistribution from intramuscularly embedded fragments. In the other study, Hahn et al. (2002) evaluated the carcinogenic response to implanted tantalum metal, an injected colloidal suspension of radioactive thorium dioxide (Thorotrast), and implanted DU in the muscle tissue of rats. Squares (2.5 × 2.5 × 1.5 mm or 5.0 × 5.0 × 1.5 mm) or pellets (2.0 × 1.0 mm in diameter) of DU were surgically implanted in the thigh muscles of male Wistar rats. Tantalum was implanted as four squares (5.0 × 5.0 × 1.1 mm) per rat. Thorotrast was injected at two sites in the thigh muscles of each rat as a positive control. Control rats had only a surgical implantation procedure. Each treatment group included 50 rats. After lifetime observation, the incidence of soft-tissue sarcomas (malignant fibrous histiocytomas and fibrosarcomas) was increased significantly around the 5.0 × 5.0-mm squares of DU (in nine of 49). A slightly increased incidence occurred in rats with the 2.5 × 2.5-mm DU squares (in three of 50) and with 5.0 × 5.0-mm squares of tantalum (in two of 50). No tumors were seen in rats with DU pellets or in the controls.

Uranium dioxide powder (0.125 g/kg of body weight) was implanted subcutaneously in rats to evaluate the effects of an internal source of an insoluble form of uranium on bone. After 30 d, rats exposed to uranium weighed less than controls. Bone-formation activity in endochondral ossification and bone growth were lower in the experimental animals (Diaz Sylvester et al. 2002).

The toxic effect of uranium on bone modeling and remodeling in the periodontal cortical bone was studied in rats. Uranyl nitrate (2 or 0.8 mg/kg of body weight) was injected intraperitoneally, and the rats were killed 14, 30, and

60 d after injection (Ubios et al. 1991). There was a decrease in bone formation and an increase in bone resorption at 14 d.

The distribution and retention of intravenously injected ^{233}U (uranium VI) in the skeleton of the female rat have been investigated (Priest et al. 1982). About one-third of the injected uranium was deposited in the skeleton, where it was retained with an initial biologic half-life of about 40 d. The study also showed that uranium is initially deposited onto all types of bone surface but preferentially onto types that are accreting; uranium is deposited in the calcifying zones of skeletal cartilage; bone accretion results in the burial of surface deposits of uranium; bone resorption causes the removal of uranium from surfaces; uranium removed from bone surfaces enters the bloodstream, where most is either redeposited in bone or excreted via the kidneys; and the recycling of resorbed uranium in the skeleton tends to produce a uniform concentration of uranium contamination throughout mineralized bone.

Ubios et al. (1994) reports that 30 daily cutaneous applications of 2% or 4% insoluble triuranium octaoxide (vehicle and amount not specified) to Wistar rats resulted in impairment of bone formation. Tibiae and mandibles of the rats were affected.

Miller et al. (2003) examined the effects of DU on human osteoblasts in vitro. The exposure caused genomic instability manifested as delayed reproductive death and micronuclei formation.

CARDIOVASCULAR EFFECTS

Few studies are available to evaluate the effects of uranium exposure on the cardiovascular system. Studies of workers exposed to uranium have not shown any excess mortality due to cardiovascular or cerebrovascular disease (see Table 5-2).

No cardiac effects were observed in inhalation studies in several test species, including rats exposed to uranium (as uranium hexafluoride) at 0.2 mg/m^3 for 1 y (Stokinger et al. 1953) and rats, mice, guinea pigs, and rabbits exposed to uranium (as triuranium octaoxide) at 4.8 mg/m^3 for 26 d (Dygert et al. 1949).

Filippova et al. (1978) instilled ^{235}U-enriched soluble tetravalent and uranium hexahydrate salts into the tracheae of rats and found abnormalities of blood vessels and cardiac enlargement. Those findings are probably due to a radiation effect of uranium rather than a chemical effect. Gilman et al. (1998c) did not find any cardiovascular effect in rabbits exposed to uranyl nitrate in drinking water (at 0.96, 4.8, 24, 120, and 600 mg/L) for 91 d.

OCULAR EFFECTS

Chemical burns of the eyes have been reported in humans after accidental exposure to uranium hexafluoride (Kathren and Moore 1986). Conjunctivitis and

TABLE 5-2 Standardized Mortality Ratios with (95% Confidence Intervals) and [Observed Numbers of Deaths] for Circulatory, Heart, and Cerebrovascular Disease in Uranium Workers

Study	Circulatory Disease	Heart Disease	Cerebrovascular Disease	Reference
Colorado Plateau uranium-mill workers (with no history of uranium mining)	0.81 (0.71-0.92) [228][a]	0.84 (0.75-0.94) [293]	0.79 (0.56-1.08) [39][a]	Waxweiler et al. 1983; Pinkerton et al. 2004
TEC/Y12 (1943-1947): Oak Ridge uranium conversion/enrichment, all workers	0.85 (0.81-0.88) [2,571]	—	—	Polednak and Frome 1981
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments	0.83 (0.78-0.89) [908]	—	—	Polednak and Froome 1981
Y12 (1947-1974): Oak Ridge uranium-metal production and recycling	0.87 (0.81-0.93) [777][b]	—	—	Checkoway et al. 1988; Loomis and Wolf 1996
Mallinckrodt uranium-processing workers	0.89 (0.81-0.97) [474]	—	—	Dupree-Ellis et al. 2000
Fernald fabrication of uranium products	0.78 (0.71-0.86) [460]	0.80 (0.71-0.89) [339]	0.81 (0.59-1.07) [48]	Ritz 1999
Portsmouth gaseous diffusion[c]	0.70 (0.60-0.81) [107]	—	—	Brown and Bloom 1987
Savannah River nuclear-fuels production	0.81 (0.74-0.88) [519]	0.81 (0.73-0.88) [464]	0.71 (0.52-0.94) [45]	Cragle et al. 1988
Linde uranium-processing facility (1943-1949)	0.94 (0.86-1.02) [534]	—	0.71 (0.54-0.92) [56]	Dupree et al. 1987; Teta and Ott 1988
United Nuclear Corp. nuclear-fuels fabrication[d]	0.82 (0.64-1.04) [63]	0.82 (0.65-1.02) [74]	0.68 (0.27-1.41) [7]	Hadjimichael et al. 1983

(Continued)

TABLE 5-2 Continued

Study	Circulatory Disease	Heart Disease	Cerebrovascular Disease	Reference
Florida phosphate workers[d]	—	0.88 (0.83-0.93) [1,232]	0.96 (0.85-1.08) [288]	Checkoway et al. 1996
Atomic Weapons Establishment, UK	0.91 (0.72-1.14) [72]	—	—	Beral et al. 1988
Springfields, UK: mortality[e]	0.90 (0.86-0.94) [1763]	0.91 (0.86-0.96) [1191]	0.95 (0.85-1.06) [327]	McGeoghegan and Binks 2000a
Capenhurst, UK: ^{235}U enrichment plant, mortality[e]	0.86 (0.76-0.96) [289]	0.92 (0.80-1.06) [213]	0.66 (0.47-0.90) [37]	McGeoghegan and Binks 2000b
Total Observed/Expected Cases[f]	7,857/8,853	3,806/4,376	847/912	

[a]From Waxweiler et al. 1983.
[b]Ischemic heart disease.
[c]Includes only "Subcohort I," which consists of those who at some time worked in one of the departments considered to have uranium exposure.
[d]SMRs were similar for white and nonwhite men, so results for the combined groups are presented.
[e]Data only on those classified as radiation workers.
[f]Sums do not include row labeled "TEC/Y12 (1943-47): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments," because those workers were already included in the TEC/Y12 row for all workers.

eye irritation have also been reported in animals after exposure to uranium hexafluoride (Spiegel 1949) and uranium tetrachloride (Dygert et al. 1949). Uranium hexafluoride rapidly dissociates into hydrofluoric acid and uranyl fluoride on contact with moisture in the air (ATSDR 1999). Similarly, uranium tetrachloride forms hydrochloric acid. Therefore, ocular effects were probably due to direct contact of caustic vapors or aerosols, rather than uranium, with the eye. No studies of ocular effects in humans or animals after exposure to other uranium compounds by other routes (oral, dermal, and implantation) were located.

GASTROINTESTINAL EFFECTS

No gastrointestinal effects were observed in various animals exposed orally to uranyl nitrate at 664 mg/kg per day for up to 2 y (Maynard and Hodge 1949) or in rats exposed to uranyl nitrate hexahydrate in drinking water at 40 mg/kg per day for 28 d, or in rabbits exposed to uranyl nitrate hexahydrate in drinking water at up to 600 mg/L for 91 d (Gilman et al. 1998a,b,c). Gastrointestinal tracts did not show abnormalities in dogs that ingested uranium dioxide or triuranium octaoxide. Mild hemorrhage was observed in animals that received the highest dosage of uranium tetrafluoride (20 mg/kg per day) (Maynard and Hodge 1949).

DERMAL EFFECTS

Uranium compounds have been found to be slightly irritating to the skin of laboratory animals, but there is no evidence of skin sensitization or skin cancer. Three of the more water-soluble uranium compounds (uranyl nitrate, uranium tetrachloride, and uranium pentachloride) caused mild to moderate transient irritation when applied to the skin of rabbits (Orcutt 1949). In rats, 30 daily topical applications of triuranium octaoxide caused epidermal atrophy and increased the permeability of the skin (Ubios et al. 1997). Local skin toxicity seems to be mainly limited to irritation, which may be caused by direct cutaneous contact with some of the compounds. ATSDR (1999) concluded that there are no studies relating skin cancers to uranium compounds. As discussed in Chapter 2, uranium can be absorbed through the skin, and resulting toxicity depends on the solubility of the uranium compounds and the vehicle used.

SUMMARY

- Neurobehavioral studies in Gulf War veterans are inconclusive.
- Studies in experimental animals have shown that uranium crosses the blood-brain barrier and accumulates in the brain. Accumulation after large exposure is associated with abnormal electrophysiologic effects, changes in monoamine metabolism, and neurobehavioral changes.

- Forced-swim stress reduces uranium and zinc in the hippocampus and cerebellum.
- Continuing surveillance (14 y) of DU-exposed 1991 Gulf War veterans has yielded no evidence of reproductive-system dysfunction in males, abnormalities in sperm, or alterations in neuroendocrine function after DU exposures that occurred in friendly-fire incidents. Nor is there evidence of excess spontaneous abortions, fetal mortality, congenital anomalies, developmental delays, or abnormal infant neurobehavioral difficulties to date in the offspring of those veterans.
- The findings from animal studies are inconsistent with respect to uranium placental transfer and the presence of metal in the fetus. However, it should be noted that uranium concentrations to which dams were exposed were high (equivalent to about 200 g in a 70-kg person) in studies that reported placental uranium transfer.
- Although studies cited here indicated hematologic and possibly heptatic effects of DU, the exposure durations or concentrations do not appear to be appropriate for extrapolation to human exposure conditions.
- No effects of DU on the human immune system have been identified. Rats given high doses of DU by gavage did not demonstrate intestinal musosal immunotoxicity.
- The effects of uranium compounds on the musculoskeletal system in laboratory animals are changes in bone formation and remodeling after oral, intraperitoneal, intravenous, and implantation exposure. It is not known whether DU has those effects, but there is not much potential for the large doses used in the studies to enter the body by inhalation or dermal exposure. Large fragments of DU embedded in muscle tissue caused soft-tissue sarcomas in experimental studies with rats and may have deleterious effects (sarcomas) in soldiers if large DU fragments are left in place over a lifetime.
- There are no reports of chemical toxicity in the cardiovascular system from uranium exposure.
- Absorption of uranium across the gastrointestinal mucosal lining is solubility-dependent, and most uranium compounds are not readily absorbed. In animal studies, no toxicity was observed after ingestion of uranyl nitrate, uranyl nitrate hexahydrate, uranium dioxide, or triuranium octaoxide. Mild hemorrhage occurred in animals exposed to a high dose.
- Studies in several animal species have shown that lethality and toxicity can result from cutaneous exposure to uranium compounds solublizied in a variety of vehicles. Soluble uranium compounds cause transient irritation of the skin, and repeated applications may cause changes in epidermal integrity.

RECOMMENDATIONS

- Monitoring of Gulf War veterans for neurologic and neurobehavioral effects should be continued.

- Experimental studies should be conducted to determine the nature of and the LOAEL for neurologic and neurobehavioral effects of exposure to DU.
- On the basis of available reproductive-toxicity and developmental-toxicity data, samples of blood, urine, or semen of DU-exposed military personnel should be collected for the measurement of uranium content and signs of abnormal reproductive function in men and women. In addition, the reporting of spontaneous abortions and congenital anomalies should be continued.
- The committee does not recommend additional studies of the hematologic or hepatotoxic effects of DU.

6

Radiologic Effects of Depleted Uranium

Depleted uranium (DU) is naturally radioactive, so there is a potential for radiation-induced effects in addition to the chemical toxicity discussed in the preceding chapters. On a weight basis, U.S. Department of Defense DU is 99.8% ^{238}U and 0.2% ^{235}U, with trace amounts of ^{234}U and ^{236}U. Because of the long half-lives of the various uranium isotopes (see Table 6-1), DU has a low specific activity and hence is only weakly radioactive, with various uranium isotopes undergoing alpha decay and emitting x and gamma radiation. The weighted specific activity of DU is 14.9 kBq/g, or about 60% of the specific activity (25.4 kBq/g) of natural uranium, which contains 0.71 wt % ^{235}U. The process by which DU is created from natural uranium not only reduces the high-specific-activity ^{235}U but reduces even more the higher-specific-activity ^{234}U. Much of the radioactivity in both natural and DU is attributable to trace amounts of the ^{234}U isotope, which accounts for 49% of the activity in natural uranium and about 10% in DU.

For a given deposition of uranium in tissues, the dose will be determined largely by and approximately proportional to the specific activity; 1 μg of ^{234}U would deliver about 20,000 times the dose of 1 μg of ^{238}U. However, in considering the dose from uranium deposited in tissues, the mass fraction also needs to be taken into account. Multiplying the mass fraction by the specific activity provides the relative activity or number of disintegrations for each uranium isotope, which can then be converted to the activity fraction, as shown in Table 6-1. For DU, the ^{238}U isotope accounts for 88.8% of the activity and for more than 80% of the dose. Virtually all the rest of the dose from DU deposition in tissues will be from the ^{234}U isotope; the contributions of the other two uranium isotopes are negligible.

BIOLOGIC EFFECTS OF IONIZING RADIATION

The hazard posed by ionizing radiation is derived from the energy it transfers to tissue that it traverses, which may cause ionization and other molecular

effects, including chromosomal breaks and additional effects in DNA that may result in genetic damage. All isotopes of uranium undergo decay by the emission of alpha particles from the nucleus with photons of x and gamma radiation. Most of the energy released by the radioactive decay of a uranium nucleus is in the form of kinetic energy imparted to the alpha particle, typically about 4.2 MeV. Despite the large amount of energy, alpha particles have a limited range in soft tissue—about 30 μm—and so are unable to penetrate the superficial dead layer of skin. Thus, alpha particles pose a hazard only if taken into the body. Photons, however, are able to penetrate the body, depositing relatively small amounts of energy as they traverse tissues, and may pose a hazard both internally and externally. Beta particles, which are emitted by some uranium decay products, have a variable range in tissue that depends on their kinetic energy, which is typically a fraction of that of an alpha particle. The most energetic beta particles have a range of only about 1 cm in soft tissue.

Biologic effects of radiation are typically classified as deterministic or stochastic. A deterministic effect is one for which there is a clearly defined threshold and that increases in severity as the dose increases above the threshold. An example of radiation-induced deterministic effect (in this case, nonionizing-radiation-induced) is ordinary sunburn, which requires a minimal dose and increases in severity as the dose increases. A stochastic effect has a probability of occurrence that increases in proportion to the dose, but its severity is unrelated to the dose. An example of stochastic effects is the increased probability of skin cancer caused by exposure to sunlight. Stochastic risks posed by exposure to ionizing radiation include radiogenic cancers and genetic mutations. Deterministic effects are usually associated with high doses and typically occur relatively soon after exposure; thus, they are said to have a short latent period (time between exposure and manifestation of the effect). Stochastic effects, such as carcinogenesis, may not manifest themselves for many years and thus have a long latent period.

Although compelling evidence to the contrary exists for some cancers, stochastic risks are generally assumed to follow a linear-no-threshold (LNT) dose-response curve, at least for the purposes of determining potential health effects and establishing radiation-protection standards. Thus, doubling the dose is assumed to double the incremental risk, tripling the dose triples the incremental risk, and so on. However, even if the risk coefficients (see discussion below) are accurately and precisely known and the LNT hypothesis is an accurate characterization of the dose-response relationship, the risk is most likely overstated because an exposed person could die from other causes before the radiogenic cancer would be manifested, particularly if the cancer has a long latent period. Furthermore, the simplistic LNT model of response does not consider possible other low-dose effects now under study, such as bystander effects and adaptive responses, that may or may not be significant.

The primary radiologic concern related to chronic low-level exposure to DU, as might result from intake of DU and deposition in tissues or from external exposure due to living in a contaminated environment, is the development of a

fatal radiation-induced cancer. This is, as noted above, a stochastic effect, and its likelihood is characterized in terms of risk coefficients. A risk coefficient is a simplified mathematical statement of the probability that a specific type of malignancy will develop as a result of a specific dose.[1] Although in their simplest form risk coefficients imply that the risk of developing a specific cancer is directly proportional to the dose received—that is, they imply a linear dose-response curve—the determination of risk is much more complex and is a function of other factors, including the specific type of cancer, dose rate, latent period, and age.

Dose-response curves derived from epidemiologic studies typically serve as the cornerstone and primary basis of the development of risk coefficients. Data on stochastic effects in survivors of the atomic bombings in Japan, who received high radiation doses, are most widely used for that purpose. Epidemiologic studies of exposed worker populations are also extensively used. Because stochastic radiation effects in study populations are rare and often difficult to detect, they are typically observed at doses much higher than zero. In such studies, stochastic effects are not observed or cannot be determined at low doses, so there is a wide gap between a zero dose and the lowest dose at which they are observed. The theoretical low-dose response is therefore obtained by extrapolation, that is, extending the dose-response curve in a linear fashion down to zero—zero dose and zero effect. The risk coefficient is derived from the slope of this straight-line extrapolation.

RADIATION DOSE

As it decays, DU and its associated decay products emit alpha particles, beta particles, and photons of ionizing electromagnetic radiation (IER), that is, x rays and gamma rays.[2] Unlike ultraviolet radiation, used in the sunburn example above, IER has the ability to displace electrons in atoms or to remove electrons, thereby producing ionization or charged particles as it traverses matter, giving up in the process some of or all its energy. The amount of energy deposited in a given mass of tissue is the dose, which determines the extent and severity of

[1]Genericaly, the term *risk coefficient* defines the probability of an adverse event per unit of exposure (for example, the probability of a fatal automobile collision per 100,000 miles driven). As applied in radiation exposure, it usually refers to the probability of a fatal cancer or other stochastic effect per unit of exposure or dose (for example, a 0.04 risk of a fatal cancer per sievert).

[2]X rays and gamma rays are forms of electromagnetic radiation that differ only in their mode of production. Gamma rays are electromagnetic radiation emitted from the nucleus of an excited atom; x rays are produced by excitation of the electron field surrounding the nucleus. Typically, x rays are of lower photon energy than gamma rays, but this is not necessarily the case, and the reader is cautioned about the scientific impropriety and inaccuracy of characterizing low-energy IER as x rays and higher-energy IER as gamma rays.

biologic effects. Over the years, a complex and extensive system of dose quantities has evolved; although all dose quantities are based on energy absorption, one may be numerically different from another even though quantified in the same units. The set of radiologic quantities and units in current use internationally is based on the Systéme International d'Unités (commonly known as the SI), developed by the International Bureau of Weights and Measures (BIPM 1998). The evolution of the SI and its relation to an earlier and now obsolete system of quantities and units that is still in use in the United States are noted briefly below (for more detail, see Kathren 2001).

The basic physical quantity of ionizing radiation is *absorbed dose*, the amount of energy deposited or absorbed by a material as a result of irradiation per unit of mass. It has the SI unit of joules of energy deposited per kilogram of absorbing medium and has been given the special name in the SI of *gray* (Gy); 1 Gy = 1 J/kg). The older system, still widely used in the United States and prevalent in the older literature, quantifies absorbed dose with the *rad*, defined as the deposition of 100 ergs/g of absorbing material. The gray and the rad characterize the same physical quantity (absorbed dose), and there is a simple correspondence: 100 ergs = 0.01 J, and 1 kg = 1,000 g; hence, 1 Gy = 100 rad.

The dose from any ionizing radiation can be expressed as absorbed dose, but this is not a satisfactory method for relating dose to biologic effect or, in the case of stochastic effects, risk, because some kinds of radiation are more effective than other kinds in producing adverse biologic effects, and some tissues are more radiosensitive than others. Thus, two different kinds of radiation may result in the same absorbed or physical dose and have very different effects. To account for such differences, other dose quantities have been devised on the basis of radiation weighting factors (ICRP 1991). Multiplying the absorbed dose by the appropriate radiation weighting factor yields a single dose quantity that normalizes the risk posed by various kinds of radiation and tissues; this quantity is known as *dose equivalent* (DE) and is expressed in the SI in sieverts (Sv). A dose of 1 Sv carries the same stochastic risk irrespective of the type of radiation or the tissues being irradiated. For photons and beta radiation, the radiation weighting factor is unity, and the absorbed dose and DE will be numerically equal. For alpha particles, the weighing factor is 20, and the DE will be numerically 20 times greater than the absorbed dose.

DE is sometimes known as biologic dose to differentiate from absorbed dose or physical dose. In the old system still widely used in the United States, DE was expressed in terms of rem. If the same weighting factors are used to calculate DE in both the old system and the SI, there is a direct correspondence: 1 Sv = 100 rem.

DE is a useful quantity for normalizing or expressing the risks posed by exposure to different kinds of radiation. However, it does not account for the various sizes, radiosensitivities, and likelihoods of cancer induction in specific tissues and organs. To account for those differences, a tissue-weighting factor representing the proportion of stochastic risk posed by irradiation of a specific tissue is applied to the DE for each tissue and organ, and the results are summed.

The final result is a single value in sieverts equivalent to a total body irradiation that would result in the same overall risk as the sum of the exposures of the various tissues and organs, and this quantity is termed the *effective dose* (E).

Although E is a defined dose quantity (ICRP 1977, 1991), it is basically a statement of risk. It is conceptually important in that it enables an exposure of one organ or a few organs, as might occur from an internal deposition, to be equated with a dose to the whole body by using the risk of fatal cancer induction as the basis. The underlying logic is relatively straightforward and can be understood by noting that uniform irradiation of the whole body will produce a risk of a fatal cancer in each tissue, and the sum of the stochastic risks to all the tissues is equal to the total stochastic risk. If only a portion of the body is irradiated—that is, one or two specific organs, as might be the case with a radionuclide incorporated into their tissues—the total radiogenic stochastic risk comes from those irradiated tissues. The radiation-induced carcinogenic risk to the unirradiated portions of the body is zero. Thus, the total stochastic risk to all the tissues posed by irradiation of only a portion of the body would be expected to be less than if all the tissues were irradiated at the same level. Through the use of tissue-weighting factors, the DE delivered to the irradiated tissues is adjusted to account for the fact that only a portion of the body was irradiated.

There are some important caveats with respect to the use of DE and E quantities. DE should never be specified as a pure number of sieverts; it needs to be qualified by noting what organs or tissues were irradiated. E does not need such a qualification, because it is inherent in its definition that it refers to the whole body. And although both DE and E are expressed in sieverts, only in the case of a uniform whole-body irradiation will the numerical values of the two quantities be equal. If only a portion of the body was irradiated, the DE to that portion of the body will be numerically greater than E, and the converse will be true for the unirradiated portions of the body. The statement of the magnitude of E does not tell how it was obtained; there is no specification of the doses to the individual tissues and organs from which it was derived.

Assessment of the tissue dose from DU that is taken into the body is a complex process that requires knowledge of the physical and chemical properties of the material and its biokinetics. Once uranium is incorporated into the body, it delivers a dose to the surrounding tissues primarily in alpha radiation. The energy of the typical alpha particle emitted by the uranium isotopes that constitute DU is about 4.2 MeV, which is perhaps 10 times or more greater than the average energy of a typical beta particle or photon emitted by the decay of uranium and its products. Alpha particles with that energy can travel about 30 μm through tissues—about the diameter of a single cell. Therefore, all the alpha-particle energy is deposited in a very small volume of tissue, and, inasmuch as dose is simply energy absorbed or deposited per unit of mass, the dose absorbed by this small volume will be much greater than the absorbed dose resulting from a single photon or beta-particle interaction. However, the general practice is to average the dose over the entire tissue or organ. With a weighting factor of 20, the DE from an alpha particle averaged over the entire tissue or organ into which

the uranium is incorporated will typically be more than 100 times greater than the DE from a single photon or beta particle. Thus, the primary radiologic concern related to uranium incorporated into tissues is alpha irradiation.

EXTERNAL EXPOSURE TO DEPLETED URANIUM: DIRECT RADIATION

The uranium isotopes that constitute pure DU all undergo decay by emission of alpha particles accompanied by x and gamma radiation. In addition, there is considerable ingrowth of the uranium decay-series progeny after 50 y. The DU decay series will not reach equilibrium for over a million years.

As discussed above, the alpha particles emitted by the uranium isotopes that constitute DU have low penetrating power and cannot penetrate the inert or nonliving outer layer of skin that covers most of the body. Hence, the alpha radiation from DU and its decay products is not of concern from the standpoint of external exposure. More important are the beta radiation emitted by the uranium decay products and the associated x and gamma radiation from the decay of the uranium isotopes and their decay products, and it is possible to achieve an external exposure from these kinds of radiation. The magnitude of such an exposure would be determined primarily by three factors: the quantity of DU, the distance and interposition of shielding materials between the body and the DU, and the duration of exposure.

The maximal exposure would occur from direct contact of the skin with a chunk or slab of metallic DU or with simple compounds of DU. The dose rate at the surface of the metallic DU or DU compound (that is, the surface dose rate) is the maximal external dose rate. A sufficiently large slab of metallic DU provides what is termed an infinite-thickness slab under specified conditions, and increasing the thickness or size does not increase the dose rate. Fetter and von Hippel (1999) performed a comprehensive theoretical evaluation of the hazards posed by DU munitions and calculated the maximal dose rate to the skin from direct contact to be 2.5 mSv/h (250 mrem/h), mostly from beta radiation. Their calculated value is close to measured values that have been reported for various compounds and compositions of uranium over the years (Kinsman 1954; BRH 1970; Healy 1970; Kathren 1975). For a slab of natural uranium, the measured beta dose rate in air at the surface through a 7-mg/cm^2 polystyrene filter, used to mimic the cornified (dead) layer of skin, is 2.33 mSv/h (233 mrem/h).[3] Photons are reported to contribute another 10% to the surface dose rate, bringing the total to 2.55 mGy/h (255 mrad/h; Kathren 1975). The measured value of about 0.23 mSv/h (23 mrem/h) for x and gamma radiation is about 10 times greater than the

[3]The measured values were originally reported in units of absorbed dose, which were converted to DE by multiplying by a radiation weighting factor of unity for beta and photon radiation to avoid confusion caused by the use of different radiation quantities and units and to provide a common basis for comparison.

theoretically determined 0.025 mSv/h (2.5 mrem/h) reported by Fetter and von Hippel (1999), but the difference could be accounted for by bremsstrahlung from the interactions of beta particles with the air or within the slab itself, which were included in the measured values but not fully in the calculations by Fetter and von Hippel. In either case, the external dose rates associated with uranium are relatively low and would require continuous direct contact of weeks to months to reach the threshold for deterministic effects (erythema) on the skin.

The external dose rate from a large mass of DU decreases as a function of distance from the material, largely because of attenuation of the beta particles and to a lesser extent of x and gamma radiation by interactions with air. The dose rate near the surface of an infinite slab of uranium is remarkably constant for the first few millimeters but drops off steeply as the distance from the source increases: 10 cm from the source, the total air dose rate from beta, x, and gamma radiation combined is only 0.12 mGy/h, or 0.04 times the dose at the surface (Kathren 1975). Measurements have shown that the relative contribution of x and gamma radiation to the total dose also increases because of the large attenuation of beta radiation by the air. At or near the surface of a natural uranium slab, x and gamma radiation contributes about 10% of the dose; 10 cm from the surface, that fraction increases to about 20%; and 1 m from the source, the dose is almost exclusively from x and gamma radiation and about a few tenths of 1 mGy/h—somewhat greater than observed by Fetter and von Hippel but still small enough to preclude, for all practical purposes, deterministic effects.

Although deterministic effects of external exposure to DU are extremely unlikely, external irradiation of the skin by DU and its decay products would pose a risk of stochastic effects. A contact time with the skin of 400 h, corresponding to a dose of about 1 Gy, has been calculated to increase the risk of skin cancer by about 40% (UNSCEAR 2000). If one assumes a linear-no-threshold response for skin cancer, that dose equates to an increased risk of 0.1%/h of exposure. Similarly, tissues lying below the skin would suffer an increased stochastic risk, but it would be smaller than the already low stochastic risk to the skin.

Widespread contamination of the ground with DU would produce measurable external ionizing-radiation fields, but, as indicated above, the dose rates would be smaller than that from direct contact and thus insufficient to produce deterministic effects. However, assuming once again a linear-no-threshold response for cancer induction, exposure to such radiation fields would produce an additional stochastic risk, albeit small, of radiogenic cancer. Fetter and von Hippel (1999) estimated the effective dose rate for a person standing on ground uniformly contaminated with DU at 1 g/m^2, which they considered an upper limit for a battlefield area, to be 0.01 mSv/y or about 0.1 times the dose rate from uranium naturally present in the soil and less than 2% of the typical dose rate associated with terrestrial and cosmic radiation. Even continuous exposure at that level for a period of several years would result in a negligible increase in the stochastic risk of radiogenic cancer or in the genetic effect relative to the natural incidence. A full decade of continuous exposure would provide a theoretical

increase in the risk of a stochastic effect—that is, radiogenic cancer or genetic effect—of less than 1% on the basis of the risk coefficients put forth by the International Commission on Radiological Protection (ICRP 1991); exposure for 70 y would increase the theoretical increase in risk to about 3.5%.

INTERNAL EXPOSURE TO DEPLETED URANIUM

Uranium may enter the body by inhalation, ingestion, or dermal exposure. Its uptake, distribution, and elimination from the tissues depend on the physicochemical characteristics of the uranium, the route of entry, and the biokinetics of uranium in the body. As discussed in Chapter 2, mathematical models have been developed to describe the biokinetic processes of DU. Irrespective of the biokinetic model used, it is clear that chemical toxicity is so overwhelming relative to radiotoxicity that radiation-induced deterministic effects from intake of uranium are extremely unlikely or impossible (ICRP 1988). However, stochastic effects—such as an increased likelihood of cancer for which no threshold is postulated—are possible. The organs at risk are those with the greatest concentration of DU, and dose and associated risk of stochastic effects can be calculated for each tissue and organ.

Ingestion of DU does not pose substantial risk, and indeed the chemical effects would far outweigh the radiologic effect. Using the ICRP schema, one can calculate the effective-dose coefficients for DU. For ingested soluble DU, the effective dose coefficient is about 4.5×10^{-8} Sv/Bq. That corresponds to an effective dose of about 0.67 mSv for an intake of 1 g of DU, which would produce a total stochastic risk, including both carcinogenesis and genetic risk, of about 3.3×10^{-5}. In other words, the total risk of a stochastic effect from ingestion of 1 g of DU is about 33 in a million. If linearity of the response is assumed, a person would have to ingest about 300 g—more than a half-pound—of soluble DU to be subjected to a 1% risk of a stochastic effect. Ingestion of such a large quantity of soluble DU is virtually certain to produce chemotoxic effects on the kidneys. If insoluble DU is ingested, the fraction absorbed is one-tenth that of the fraction of soluble DU absorbed, and the stochastic risk per unit intake is concomitantly lower.

A much larger stochastic risk is posed by inhaled DU than by ingested DU. The stochastic risk posed by inhaled DU, which is almost exclusively a risk of lung carcinogenesis, is greater when insoluble DU is involved, in contrast with the risk posed by ingested DU. That is particularly true because insoluble particles, once deposited in the lungs, may reside there and irradiate lung tissue for years. For example, for an inhaled insoluble (class S[4]) DU aerosol with 1-μm active median aerodynamic diameter (AMAD), the effective dose coefficient, calculated according to ICRP (1994b), is 7.5×10^{-6} Sv/Bq. Thus, the risk posed

[4]As discussed in Chapter 2, ICRP broadly classifies inhaled aerosols in terms of their absorption rate in the body as fast (F), moderate (M), and slow (S).

by inhalation of 1 mg of DU is about 5.6 x 10^{-6}, or about 5 in a million. For class M and class F aerosols, the risk to the lungs is lower because of the more rapid clearance, although the risk to other tissues of the body is somewhat higher because of increased absorption. Effective dose coefficients calculated according to ICRP (1994b) for class M and class F aerosols of DU with the same AMAD are 2.7×10^{-6} and 5.0×10^{-7} Sv/Bq, respectively, which are stochastic risks smaller than associated with class S material.

More detailed radiation dose and risk factors can be obtained from ICRP (1996), which considers such factors as age at the time of intake, and from the Environmental Protection Agency (EPA 1999). The summary of radiation dose and risk factors presented in Tables 6-2 and 6-3 was developed from the data in those documents; the values are normalized to both 1-Bq and 1-mg intakes for inhaled and ingested DU and for morbidity and mortality. The data presented below are by no means complete but merely representative of the risk factors associated with common routes of exposure and based on currently available data from the scientific literature.

TABLE 6-2 Radiation Dose (Sv) and Risk per Becquerel (Bq) Intake of Depleted Uranium

Summary of Radiation Dose and Risk Factors

Route of Intake	Organ				
	Kidney	Lung	Bone	Liver	Effective
Radiation dose (Sv) per Bq DU intake					
Inhalation					
Class M	1.29×10^{-6}	2.27×10^{-5}	3.58×10^{-5}	4.81×10^{-7}	2.92×10^{-6}
Class S	1.72×10^{-7}	6.79×10^{-5}	4.61×10^{-7}	6.29×10^{-8}	8.18×10^{-6}
Ingestion	2.57×10^{-7}	2.48×10^{-8}	7.19×10^{-7}	9.69×10^{-8}	4.50×10^{-8}
Injection	1.29×10^{-5}	1.24×10^{-6}	3.59×10^{-5}	4.84×10^{-6}	2.25×10^{-6}
Radiation-morbidity risk per Bq DU intake					
Inhalation					
Class M	9.45×10^{-10}	1.47×10^{-7}	3.55×10^{-10}	5.51×10^{-10}	1.51×10^{-7}
Class S	1.04×10^{-10}	4.08×10^{-7}	3.93×10^{-11}	5.96×10^{-11}	4.08×10^{-7}
Ingestion	2.04×10^{-10}	1.11×10^{-10}	9.92×10^{-11}	1.2×10^{-10}	1.75×10^{-9}
Radiation-mortality risk per Bq DU intake					
Inhalation					
Class M	6.14×10^{-10}	1.4×10^{-7}	2.49×10^{-10}	5.24×10^{-10}	1.42×10^{-7}
Class S	6.81×10^{-11}	3.88×10^{-7}	2.75×10^{-11}	5.67×10^{-11}	3.88×10^{-7}
Ingestion	1.23×10^{-10}	7.18×10^{-11}	4.85×10^{-11}	2.06×10^{-11}	6.11×10^{-10}

TABLE 6-3 Radiation Dose (Sv) and Risk per Milligram Intake of Depleted Uranium

Summary of Radiation Dose (Sv) and Risk Factors					
Route of Intake	Organ Kidney	Lung	Bone	Liver	Effective
Radiation dose (Sv) per milligram DU intake					
Inhalation					
Class M	1.80×10^{-5}	3.17×10^{-4}	5.00×10^{-4}	6.72×10^{-6}	4.09×10^{-5}
Class S	2.41×10^{-6}	9.48×10^{-4}	6.44×10^{-6}	8.78×10^{-7}	1.14×10^{-4}
Ingestion	3.60×10^{-6}	3.47×10^{-7}	1.00×10^{-5}	1.35×10^{-6}	6.29×10^{-7}
Injection	1.80×10^{-4}	1.73×10^{-5}	5.02×10^{-4}	6.77×10^{-5}	3.15×10^{-5}
Radiation-morbidity risk per milligram DU intake					
Inhalation					
Class M	1.32×10^{-8}	2.06×10^{-6}	4.96×10^{-9}	7.70×10^{-9}	2.12×10^{-6}
Class S	1.46×10^{-9}	5.70×10^{-6}	5.50×10^{-10}	8.33×10^{-10}	5.70×10^{-6}
Ingestion	2.84×10^{-9}	1.56×10^{-9}	1.39×10^{-9}	1.68×10^{-9}	2.45×10^{-8}
Radiation-mortality risk per milligram DU intake					
Inhalation					
Class M	8.58×10^{-9}	1.96×10^{-6}	3.48×10^{-9}	7.31×10^{-9}	1.99×10^{-6}
Class S	9.51×10^{-10}	5.42×10^{-6}	3.84×10^{-10}	7.92×10^{-10}	5.42×10^{-6}
Ingestion	1.71×10^{-9}	1.00×10^{-9}	6.77×10^{-10}	2.88×10^{-10}	8.53×10^{-9}

There is some suggestion that the biokinetic models put forth by ICRP and others may not completely characterize absorption and distribution in the tissues and thus may lead to inaccurate assessments of risk. Recent analysis of the tissues of a former uranium worker who died at the age of 83 years from an acute cerebellar infarct expectedly showed that the greatest depositions of uranium were in the respiratory tract and the skeleton (Russell and Kathren 2004). The quantity of uranium in the kidneys was unexpectedly small, and the spleen and urinary bladder contained 4.27 and 1.76 times the quantity in the liver, respectively. More important than total organ content is concentration (grams of uranium per gram of tissue) because dose is directly proportional to concentration in the tissue. Other than the respiratory tract, the highest concentrations were in the bladder and the spleen, and this raises the question of whether the models adequately address stochastic risk. In this case, the concentration in the spleen was more than 40 times that in the liver; therefore, the dose to the spleen might have been 40 times that to the liver. Similarly, the concentration in the bladder was nearly 10 times greater than that in the liver. A high concentration was also found in the thyroid.

What weight should be given to the tissue distributions in the above case is problematic because high uranium concentrations were not found in the spleen and bladder in postmortem analysis of the tissues of two other people with no history of exposure to uranium although a high uranium concentration was found in the thyroid of one (Kathren 1997). The high spleen concentrations are consistent with the observations of Hedaya et al. (1997), who noted high concentrations of uranium in the spleens of rats after intraperitoneal injection of uranium. Because high concentrations of uranium in the spleen have not been reported in other animal studies, the observations of Hedaya et al. may simply be an anomaly or may reflect a very short residence time in the spleen. Given that the function of the spleen is macrophagic removal of abnormal erythrocytes and that blood has been found to contain relatively high concentrations of uranium, the evidence may suggest a mechanism of brief retention in the spleen (Russell and Kathren 2004).

Of perhaps greater importance are the observations of low uranium concentrations in the kidneys in the above cases and others (Wrenn et al. 1985b; Fisenne and Welford 1986), which suggest that the risk of radiation-induced stochastic effects on the kidney may be lower than indicated by the various biokinetic models. In any case, for a given concentration in the kidneys, the risk of chemotoxic effects of DU far outweighs the risk of radiologic effects.

Despite the above indications of potential shortcomings, the biokinetic models and dose-calculation methods are adequate to provide a good indication of the radiologic risks posed by DU. Even if the biokinetic models need to be revised along the lines indicated above, such revision would result in only a small change in calculated risks.

EPIDEMIOLOGIC STUDIES

Since the late 1970s, the Committee on the Biological Effects of Ionizing Radiations of the National Research Council has carried out exhaustive reviews of the scientific literature pertaining to the effects of low-level radiation on human populations (NRC 1980, 1988, 1990, 1999, 2006). Reviews of DU have also been performed by the Royal Society (2002) and the Institute of Medicine (IOM 2000). Epidemiologic studies of natural uranium and cancer must consider total risk of both chemical and radiologic carcinogenicity of uranium because it is impossible to separate them in such studies (see discussion of chemical carcinogenicity in Chapter 7). The large body of radioepidemiologic literature (discussed below) includes studies of Gulf War veterans, uranium miners, other occupationally exposed groups, and the general population. Uranium miners have long been known to have a higher risk of lung-cancer mortality than the general population, associated primarily with the inhalation of radon progeny and other factors, such as smoking, that potentiate the effects of the exposure (NRC 1999). More relevant are the numerous epidemiologic studies of populations occupationally exposed to radiation, especially studies of uranium workers,

studies of military personnel and civilians exposed to DU from munitions used in Kosovo and Iraq, and the recent large study of 13,960 British uranium workers (McGeoghegan and Binks 2000a). Although the studies provide some support for the risk coefficients, the epidemiologic studies of human populations have revealed no definitive evidence linking uranium exposure to human deaths (ATSDR 1999).

Studies of Gulf War Veterans

Information on possible radiologic health effects of DU in humans has come from extensive followup studies over a 12-y period of military personnel exposed to DU, notably by Hooper et al. (1999), McDiarmid et al. (2000, 2001a,b, 2004a,b), and Squibb et al. (2005). Those studies and others (Mitchel et al. 1999; Leggett and Pellmar 2003; Mitchel and Sunder 2004) generally confirm the applicability of the current biokinetic models and should point to additional refinements, particularly with respect to the biokinetics of embedded DU fragments in combat wounds. The studies have demonstrated none of the classic chemotoxic effects associated with uranium exposure or deterministic effects of irradiation.

No cases of leukemia, bone cancer, or lung cancer have occurred in the 10 y of followup of 15 U.S. Gulf War veterans with high uranium excretion and documented DU fragment wounds (McDiarmid 2001; McDiarmid et al. 2004b). However, little meaning can be attached to that result because of the small number of exposed veterans and the short followup.

An 11-y followup has been conducted of UK Gulf War veterans by Macfarlane et al. (2003). Among the 2,092 veterans who reported being exposed to DU, seven incident cancers were found compared with 139 in 26,426 Gulf War veterans who reported no DU exposure. The rate ratio (rate of disease in an exposed group divided by the rate in an unexposed group) was 0.63 (95% confidence interval, 0.3-1.36). Details of the types of cancer in the seven cases were not reported, but it was stated that there were no excesses of specific cancer types. The exposure to DU was by self-report only and was not verified.

Studies of Uranium Workers

Studies of uranium workers are summarized in Table 6-4 (detailed descriptions are provided in Appendix B). The evidence on specific cancers is discussed below.

Lung Cancer

The evidence on uranium exposure and lung cancer is mixed. The two largest U.S. studies of uranium-processing workers had increased standardized

TABLE 6-4 Standardized Mortality Ratios with (95% Confidence Intervals) and [Observed Number of Deaths] for Selected Cancers in Uranium Workers

Study (Reference)	Total Cancers	Lung Cancer	Renal Cancer	Hepatic Cancer[a]	Brain and CNS Cancer	Testicular Cancer	Bone Cancer	Leukemia and Aleukemia	Lymphoma[b]
Colorado Plateau uranium-mill workers (with no history of uranium mining) (Waxweiler et al. 1983; Pinkerton et al. 2004)	0.90 (0.78-1.04) [184]	1.13 (0.89-1.41) [78]	0.81 (0.22-2.06) [4]	0.79 (0.22-2.03) [4][c]	—	—	—	0.66 (0.21-1.53) [5]	2.29 (1.06-4.34) [8]
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, all workers (Polednak and Frome 1981)	0.85 (0.80-0.91) [886]	1.09 (0.98-1.22) [324]	0.75 (0.47-1.14) [20]	0.57 (0.32-0.93 [14]	0.95 (0.66-1.32) [32]	0.55 (0.17-1.33) [4]	0.90 (0.36-1.87) [6]	0.92 (0.66-1.24) [40]	0.62 (0.42-0.90) [26]
TEC/Y12 (1943-1947): Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments (Polednak and Frome 1981)	0.85 (0.76-0.95) [335]	0.99 (0.82-1.19) [116]	—	—	—	—	0.78 (0.13-2.58) [2]	0.65 (0.34-1.13) [11]	—
Y12 (1947-1974): Oak Ridge uranium-metal production and recycling (Checkoway et al. 1988; Loomis and Wolf 1996)[d]	1.02 (0.93-1.12) [459]	1.20 (1.04-1.38) [194]	1.39 (0.80-2.26) [16]	0.92 (0.39-1.81) [8][c]	1.28 (0.76-2.02) [18]	0 (0-1.63) [0/2.26]	0 (0-2.53) [0/1.2][e]	0.60 (0.29-1.10) [10]	0.60 (0.26-1.19) [7]
Mallinckrodt uranium-processing workers (Dupree-Ellis et al. 2000)	1.05 (0.93-1.17) [283]	1.02 (0.83-1.24) [98]	1.17 (0.54-2.18) [8]	0.42 (0.07-1.30) [2][c]	1.57 (0.84-2.64) [12]	0.93 (0.05-4.08) [1]	—	1.11 (0.57-1.89) [11]	0.52 (0.13-1.42) [3]

Fernald: fabrication of uranium products (Ritz 1999)	1.09 (0.98-1.22) [332]	1.01 (0.83-1.21) [112]	0.63 (0.20-1.46) [5]	1.62 (0.70-3.20) [8][c]	1.24 (0.64-2.17) [12]	0.67 (0.01-3.74) [1]	0 (0-3.7) [0/0.99][e]	1.16 (0.62-1.98) [13]	1.81 (1.03-2.96) [14]
Linde uranium-processing facility (1943-1949) (Dupree et al. 1987; Teta and Ott 1988)	1.06 (0.83-1.32) [74]	0.97 (0.60-1.48) [21]	—	0 (0-1.84) [0/2.0]	0.43 (0.12-1.09) [4]	—	0 (0-2.63) [0/1.4]	1.00 (0.50-1.79) [11]	0.89 (0.32-1.93) [6][f]
Portsmouth gaseous diffusion (Brown and Bloom 1987)[g]	0.87 (0.71-1.05) [107]	0.93 (0.67-1.25) [43]	—	—	—	—	1.25 (0.03-7.0) [1][h]	1.18 (0.43-2.55) [6]	1.72 (0.91-2.99) [11]
Savannah River nuclear-fuel production (Cragle et al. 1988)	0.74 (0.65-0.85) [216]	0.83 (0.66-1.02) [83]	0.38 (0.10-1.02) [3]	0.85 (0.27-2.05) [4]	0.55 (0.24-1.08) [7]	—	—	1.46 (0.89-2.26) [18]	0.53 (0.17-1.29) [4][i]
United Nuclear Corp. nuclear-fuel fabrication (Hadjimichael et al. 1983)[j]	0.87 (0.68-1.10) [71]	1.06 (0.63-1.69) [18]	1.10 (0.22-3.20) [3]	—	2.70 (0.99-5.88) [6]	—	0.95 (0.01-5.30) [1]	1.78 (0.30-5.88) [2]	2.13 (0.24-7.71) [2][i]
Florida phosphate workers (Checkoway et al. 1996)[k]	0.94 (0.88-1.00) [1061]	1.18 (1.07-1.29) [459]	0.83 (0.54-1.24) [22]	0.56 (0.29-0.97) [11]	0.85 (0.57-1.23) [27]	—	—	0.99 (0.72-1.33) [40]	0.61 (0.35-0.98) [15]
Atomic Weapons Establishment, UK (Beral et al. 1988)	0.88 (0.63-1.20) [37]	0.65 (0.34-1.13) [11]	4.30 (0.89-12.6) [3]	—	0.85 (0.02-4.74) [1]	—	—	0 (—) [0]	1.44 (0.04-8.02) [1]
Capenhurst, UK, ^{235}U-enrichment plant, mortality (McGeoghegan and Binks 2000b)[l]	0.88 (0.75-1.02) [178]	0.89 (0.70-1.13) [67]	0.49 (0.08-1.62) [2]	0.60 (0.10-1.98) [2][c]	1.39 (0.61-2.75) [7]	0 (0-5.55) [0/0.54]	0 (0-6.51) [0/0.46]	0.69 (0.22-1.68) [4]	1.23 (0.54-2.42) [7]

(Continued)

TABLE 6-4 Continued

Study (Reference)	Total Cancers	Lung Cancer	Renal Cancer	Hepatic Cancer[a]	Brain and CNS Cancer	Testicular Cancer	Bone Cancer	Leukemia and Aleukemia	Lymphoma[b]
Capenhurst, UK: ^{235}U- enrichment plant, incidence (McGeoghegan and Binks 2000b)[l]	0.82 (0.70-0.95) [181]	0.84 (0.63-1.11) [49]	0.45 (0.08-1.48) [2]	0.45 (0.08-1.50) [2][c]	1.03 (0.33-2.48) [4]	0.96 (0.16-3.18) [2]	0 (0-7.68) [0/0.39]	0.74 (0.24-1.78) [4]	0.59 (0.19-1.43) [4]
Springfields, UK: mortality (McGeoghegan and Binks 2000a)[l]	0.86 (0.81-0.91) [971]	0.85 (0.77-0.95) [360]	0.60 (0.33-1.00) [13]	1.18 (0.76-1.75) [22][c]	0.67 (0.41-1.03) [18]	0.61 (0.10-2.01) [2]	0.67 (0.11-2.22) [2]	1.00 (0.69-1.39) [32]	0.77 (0.51-1.13) [24]
Springfields, UK: cancer incidence (McGeoghegan and Binks 2000a)[l]	0.81 (0.76-0.86) [923]	0.75 (0.65-0.85) [225]	0.63 (0.36-1.03) [14]	0.53 (0.29-0.90) [12][c]	0.64 (0.35-1.09) [12]	0.92 (0.43-1.75) [8]	0 (0-1.56) [0/1.92]	0.79 (0.51-1.18) [22]	0.92 (0.63-1.30) [30]
Total Observed/Expected Cases[m]	4,859/5,339	1,868/1,824	99/121	75/96	144/154	8/16	11/17	192/197	128/154

[a]Some studies reported only "liver, biliary tract, and gall bladder" combined.
[b]Unless otherwise noted, lymphoma was defined as *International Classification of Diseases-8* (*ICD-8)* codes of 200 ("Lymphosarcoma and reticulosarcoma" and 201 ("Hodgkin's disease") or their equivalent in other *ICD* versions.
[c]Includes both liver and gall bladder.
[d]White men only. There were few nonwhite workers, and there was underascertainment of mortality in women.
[e]When there were no observed cases, both the observed and the expected values are given.
[f]Includes all lymphohematopoietic cancers (*ICD-8* 200-209).
[g]Includes only "Subcohort I," which consists of those who at some time worked in one of the departments considered to have uranium exposure.
[h]Data not given for "Subcohort I," so entire cohort included.
[i]Includes only lymphosarcoma and reticulosarcoma (*ICD-8* 200).
[j]Cancer-incidence data on "industrial" male employees, which excluded office workers.
[k]Standardized mortality ratios similar for white and nonwhite men, so results for combined groups are presented.
[l]Mortality or cancer incidence in radiation workers only. For incidence data, standardized incidence ratios are given.
[m]Sums do not include row labled TEC/Y12 (1943-47): "Oak Ridge uranium conversion and enrichment, alpha and beta chemistry departments," because those workers were already included in the TEC/Y12 row for all workers.

mortality ratios (SMRs) that were statistically significant (Loomis and Wolf 1996) or nearly so (Polednak and Frome 1981), as did a study of phosphate workers (Checkoway et al. 1996). But other studies did not show lung cancer-excesses, and a study that included the four largest U.S. cohorts of uranium workers (Dupree et al. 1995) did not show an exposure-response trend with respect to internal uranium exposure. One possibility is that high smoking rates in the workers, which was confirmed by the few data available, may have led to increased overall rates of lung cancer. Nevertheless, it cannot be ruled out that inhaled uranium particles may lead to an increased incidence of lung cancer, especially given that alpha particles are emitted by uranium.

Lymphoma

Lymphoma is a biologically plausible outcome of inhalation exposure to uranium, given that uranium deposited in the lungs tends to migrate to the thoracic lymph nodes (Singh et al. 1987). An early study of Colorado Plateau uranium millers suggested an increase in nonleukemic lymphopoietic cancers (four observed and 1.02 expected; Archer et al. 1973). Additional followup of the cohort confirmed the finding with a significantly increased risk (Pinkerton et al. 2004). A statistically significant SMR of 1.81 was found in Fernald workers, and a suggestively increased rate in the Portsmouth gaseous-diffusion workers (Brown and Bloom 1987). In contrast, the two largest studies (Polednak and Frome 1981; McGeoghegan and Binks 2000a) and several others found no indication of an increased risk, so uncertainty remains. Another source of uncertainty regarding lymphoma is that lymphoma's *International Classification of Diseases* coding has changed appreciably, so death-certificate codes are somewhat inconsistent, and there were variations among studies in the reporting of lymphomas.

Leukemia and Bone Cancer

Uranium tends to deposit in the bone, so bone cancer and leukemia are diseases of interest. The collective uranium-worker studies had too few bone cancers for a useful assessment. None of the individual studies showed a statistically significant increase in the rate of leukemia, and the pooled observed number of leukemias was less than expected on the basis of general population rates. If the "true" SMR for leukemia were about 1.5, the TEC/Y12 study or the phosphate-workers study would probably have been able to detect it. Most other studies would have adequate statistical power to detect only much higher risks.

Renal Cancer

The kidneys are suspected target organs because of the nephrotoxicity of uranium. However, the degree of nephrotoxicity depends on the route of expo-

sure, the solubility of the uranium compound, and the concentration of exposure. The proportion of exposure to various uranium compounds was not documented in most of the studies, so only rough assessments can be made. It is noteworthy that the TEC/Y12 chemistry workers were exposed to uranium tetrachloride and a number at Y12 workers to uranium hexafluoride, and both compounds are relatively soluble. There were nonsignificant suggestions of excess renal cancer in Y12 workers (but not TEC/Y12 workers) and UK Atomic Weapons Establishment workers and a suggestion of a deficit among the UK Springfields workers. Overall, about 18% fewer renal cancers were observed than would be expected on the basis of general population rates. There were nonsignificant suggestions of excess chronic nephritis in Mallinckrodt and Colorado Plateau uranium workers but a 15% deficit in chronic nephritis across all the studies. An increased mortality rate (SMR, 2.6) from chronic renal failure among U.S. uranium miners has been reported, but details were not given (Thun et al. 1982).

Testicular Cancer

One study reported an early excess of testicular cancer in Gulf War veterans (Gray et al. 1996), but followup failed to support the finding (Knoke et al. 1998); neither study had data with reference on DU. None of the uranium-worker studies showed an excess of testicular cancer, but a number of them did not report on testicular cancer.

Other Cancers

Only the Fernald study showed a nominal (nonsignificant) increase in hepatic cancer; the others had uniformly negative results. Several studies showed suggestive increases in brain and central nervous system (CNS) cancer, but only one small study (United Nuclear Corporation) approached statistical significance. Overall, the numbers of observed and expected brain and CNS cancers were almost identical.

Strengths and Weaknesses

Perhaps the greatest weakness of the uranium-worker studies is the lack of information on individual (or work-location-based) uranium exposure concentrations, so exposure-response analyses could not be performed in most studies. Similarly lacking were uranium urinary bioassay data, which would have yielded an estimate of exposure concentrations (once solubility of the uranium compounds was taken into account).

The data on lung cancer are difficult to interpret because most studies had little or no data on smoking. Even a nested case-control study of four uranium facilities that made a concerted effort to gather smoking information from medical records obtained it on fewer than half the study subjects (Dupree et al. 1995).

Most of the studies had to rely on death-certificate information with its questionable accuracy as to cause of death. Some pertinent types of disease, such as thyroid cancer, cannot be studied adequately with mortality data, because their case-fatality rates are low.

Nearly all the studies relied on comparisons with external general populations to evaluate the mortality experience of study workers (that is, SMRs). It is well known that SMRs tend to be less than unity in working groups because such groups do not include people who are too ill to work. Similarly, those who work for longer periods and hence have the potential to accrue more exposure are also those who tend to maintain good health over a sustained period. Hence, SMRs tend to be biased downward and so to be are less likely to demonstrate excesses, and SMR statistics tend to be on the conservative side. SMRs in an entire worker cohort may also fail to detect excesses that are largely confined to the subgroup of workers who received high exposures because such excesses are "diluted" out by the typically much greater number of workers who had smaller exposures.

However, given the weaknesses, the studies cited above included nearly 110,000 workers with potential uranium exposure, many of whom had substantial and prolonged exposures and long followups. That little excess risk of cancer or renal disease was seen suggests that uranium compounds are not highly carcinogenic or nephrotoxic in humans. The final row of Table 6-4 shows the overall observed and expected numbers of various cancers. Only for lung cancer and leukemia are the numbers of deaths about as large as the expected numbers, and in no case is there an important excess.

Community Studies

Uranium-mill tailings have been used since 1951 as construction fill material in some counties in Colorado. Mason et al. (1972) investigated whether the counties that used uranium-mill tailings extensively had higher cancer rates. They evaluated lung cancer, leukemia, and all other cancers combined and found no correlation in either males or females in the rates of these cancers with mill-tailings use.

Boice et al. (2003a) evaluated cancer mortality in counties adjoining the Apollo and Parks uranium-plutonium-processing facilities in western Pennsylvania in comparison with six control counties. They found no excess total cancers, childhood leukemia, or cancers of the lungs, kidneys, bone, or liver. Those results agreed with the findings on cancer incidence in those counties (Boice et al. 2003b).

A study of cancer mortality during 52 y was conducted in Karnes County, Texas, which for 40 y had over 40 uranium mines and three uranium mills (Boice et al. 2003c). Cancer mortality in that county—including deaths in a number of uranium workers and those exposed to uranium dust, mill tailings, and so forth—was compared with that in four other counties in the region that

were matched on sociodemographic characteristics. There were no differences in cancer mortality between the uranium-industry county (1,223 cancers) and the other counties, nor were there differences between periods before and after uranium operations began. Relative risks comparing Karnes County with the other counties for cancer sites of interest include total cancers (RR, 1.00), lung (RR, 1.08), kidney and renal pelvis (RR, 0.58), liver (RR, 0.81), brain and CNS (RR, 0.92), non-Hodgkin lymphoma (RR, 1.00), Hodgkin disease (RR, 1.79; 95% confidence interval, 0.9-3.6), and leukemia (RR, 1.15).

Lopez-Abente et al. (1999, 2001) conducted a study of cancer mortality in Spanish towns that were within 30 km of a uranium-processing plant. On the basis of the closer-in region of 0-15 km from any of the four sites, the SMRs were 0.89 for all cancers, 0.98 for leukemia, 0.55 for non-Hodgkin lymphoma, 1.00 for Hodgkin disease, 0.92 for lung cancer, 0.74 for brain cancer, and 0.93 for renal cancer. When trend tests were examined according to distance from a processing plant, there were no statistically significant trends if only exposed areas were included, but there was a significant trend for renal cancer if control areas (more than 50 km from a site) were included. That appears to have occurred because the SMR for the control areas was very low. The exposed areas more than 20 km from a uranium-processing facility had higher SMRs than those closer in, so it is unlikely that that was a uranium effect.

RADIOACTIVE CONTAMINANTS IN DEPLETED URANIUM

Because of the nature of its production, DU may contain trace amounts of fission products and transuranic elements, which have biokinetic and dosimetry characteristics different from those of DU and may be taken up by different organs and irradiate these organs preferentially. However, if they are present at all, the quantities of those contaminants are so small that the dose and risk associated with them are trivial and for practical purposes can be ignored.

SUMMARY

In summary, the following can be concluded with respect to the radiologic effects of DU:

- DU is only weakly radioactive and does not pose a reasonable risk of acute deterministic effects.
- For intakes of soluble DU, the chemical toxicity is of much greater concern than the potential radiologic effects.
- The external radiation hazard posed by DU is small, and long-term direct contact with bare skin is required to produce important effects.
- Inhalation of insoluble DU, if great enough, may provide a small but significant risk of lung cancer and possibly lymphoma due to irradiation of pulmonary-associated lymph nodes.

- Epidemiologic studies have yielded inadequate evidence of a risk of cancer or other chronic diseases after exposure of Gulf War soldiers to DU.
- The epidemiologic data on workers exposed to uranium compounds are substantial (nearly 110,000 exposed, or potentially exposed, workers followed for long periods). Those data have weaknesses—such as little exposure-response information, inability to adjust for smoking habits, and no evidence on exposure of children or other presumptively susceptible populations—but the preponderance of the evidence indicates that there is not an appreciable risk of cancer in humans exposed to uranium.

RECOMMENDATIONS

Additional followup studies of exposed populations have the potential to improve knowledge of the health effects of DU. To permit an adequate assessment of the risks of cancer, renal toxicity, and other possible health effects faced by DU-exposed soldiers, a careful followup of the exposed groups should be continued, including the cohort of DU-exposed soldiers now being followed by the Department of Veterans Affairs. Furthermore, continued followup of the largest groups of workers and those who had the greatest highest exposure is recommended.

If sufficiently detailed records are still available, it would be valuable to reconstruct individual exposures in a few of the largest studies with the greatest range of exposures. That would permit the evaluation of exposure-response analyses that would help to solve the problems in evaluating health end points caused by the "healthy-worker effect." More information is needed on other exposures sustained in the uranium-cohort workplaces, such as exposures to solvents, other metals, and asbestos.

A program of examination of subgroups of workers with high, medium, and low exposure to uranium, with appropriate matching on other risk factors, should be implemented for selected health-related end points and biomarkers, including renal function, genotoxicity, and bone enzymes and activity.

7

Uranium Carcinogenicity and Genotoxicity

Reviews of uranium compounds (ATSDR 1999; IOM 2000; Royal Society 2002) have found that their carcinogenicity in animals depends on exposure conditions and the chemical nature, particularly the solubility, of the uranium compound. Some inhalation-exposure studies of insoluble uranium oxides that remain in the lungs and pulmonary lymph nodes have shown that lung cancers develop after extended periods; other studies have shown damage to lung tissue but no evidence of neoplasia. Powdered or solid implants of metallic uranium placed in muscle tissue have also shown evidence of uranium carcinogenicity. Exposure studies of soluble uranium compounds that clear the lungs quickly, however, have not shown evidence of tumor development in the lungs or other tissues of animals.

The carcinogenic potential of uranium compounds has historically been attributed to its radioactivity (see Chapter 6 for discussion of radiologic effects), inasmuch as studies of natural uranium with and without coexposure to radon have suggested that carcinogenicity associated with uranium exposure is due to DNA damage resulting from radiation alone. However, more recent genotoxicity findings suggest that the chemical properties of uranium might enhance its carcinogenic potential. Nonradioactive metals, such as nickel and chromium, are well-established carcinogens in their insoluble or partially soluble forms. Whether uranium is a chemical carcinogen is critical in that potential carcinogenic effects of DU exposure determined in the Capstone Report are based solely on estimates of radiologic doses. This chapter explores the evidence of a chemical contribution to the carcinogenic potential of DU.

ANIMAL CARCINOGENICITY STUDIES

Natural Uranium

An early study of the carcinogenicity of uranium reported that sarcomas developed in rats in which powdered metallic uranium was injected in the femo-

ral or pleural cavity (Hueper et al. 1952). Eleven of 33 rats with injection of uranium in the right femur developed sarcomas that surrounded or were in the immediate vicinity of uranium deposits. Six of the sarcomas produced metastases in the inguinal, abdominal, or mediastinal lymph nodes or the lungs. Sarcomas also developed at the site of intrapleural injections in two of 33 rats. The authors concluded that the results clearly established the carcinogenic nature of uranium; however, a definitive conclusion could not be reached regarding the role of the chemical vs radiologic properties of uranium in the cause of the sarcomas. The latent period and the histologic structure of the sarcomas that formed in response to the uranium injections were noted to be similar to those of sarcomas induced by injection of metallic nickel powder, and this suggested a similar chemical-based mechanism of action. Both nickel and uranium injections produced local necrotizing, hyalinizing, and fibrosing reactions, which were often associated with a local proliferation of periosteal and endosteal cancellous bone. However, the authors noted that the intensity of exposure to alpha radiation in tissue immediately adjacent to uranium deposits was much higher than the radiation intensity that occurs from uranium stored in bone after systemic exposure to soluble uranium. In addition, the latent period for the uranium-induced sarcomas in these experiments was similar to reported latent periods for sarcomas produced in rats by the radioactive elements radium and thorium. Thus, the basis of the powdered metallic uranium's carcinogenic effects remained uncertain. Since the 1950s, when this study was conducted, research has suggested that local sarcomas forming around many types of embedded metals may be due to chronic local inflammation (IARC 1999); this mode of action should be considered in determining cancer risks associated with DU exposure.

Leach et al. (1970, 1973) conducted 5-y inhalation studies in monkeys, dogs, and rats with natural uranium dioxide dust about 1 μm in mass median diameter. Animals were exposed to uranium at 5 mg/m^3 6 h/d 5 d/wk for up to 5 y. Evidence of neoplastic changes (pulmonary glandular neoplasms and atypical epithelial proliferation) was observed 2-6 y after exposure ceased and only in dogs. That finding was important because tumor incidence was 50-100 times higher than in controls. Evidence of pulmonary neoplasia was observed in six of 13 dogs followed for up to 6.5 y after exposure to uranium dioxide. In contrast, no pulmonary tumors or areas of atypical epithelial proliferation were observed in six monkeys followed for up to 7.5-y after exposure (Leach et al. 1973). One monkey had lymphoma that involved some tracheobronchial lymph nodes. The difference in cancer incidence between the dogs and the monkeys, the authors noted, might have been due to the different proportions of the life spans over which the dogs and monkeys were tested and observed. Leach et al. also noted that glandular neoplasms occur infrequently in humans, so quantitative extrapolation of the results of this study to humans would be difficult. The authors were concerned, however, that neoplasms developed in the dogs at radiation doses that were about 20-25% lower than those produced by ^{239}Pu, leading them to propose that natural uranium might exert both chemical and radiologic effects.

The carcinogenicity of uranium after chronic inhalation exposure to uranium-ore dust was also studied by Cross et al. (1981a) in Syrian golden hamsters exposed to carnotite uranium dust with an activity-median-aerodynamic diameter of 1.5-2.1 μm. At a uranium-ore concentration of 19 mg/m^3, there was no evidence of neoplasia in alveolar regions of the lung in 99 animals and only one area of bronchiolar epithelial hyperplasia with squamous metaplasia after 16-27 mo of exposure. No areas of bronchial or alveolar metaplasia were observed in control animals. The primary lung lesions observed in animals exposed to uranium dust were inflammatory responses (macrophage accumulation) and proliferative responses (alveolar-cell hyperplasia and adenomatous alteration of alveolar epithelium). Small (statistically nonsignificant) differences in tumor incidences in other tissues were noted in the uranium-dust-exposed animals (one pheochromocytoma, one melanoma, and one adrenal-cell carcinoma) and none in the control animals.

Cross et al. (1981a) also exposed hamsters to radon and radon daughters alone or in combination with uranium dust. The animals exposed to only radon and radon daughters showed higher occurrence of both bronchiolar and alveolar epithelial squamous metaplasia than controls (nine in 96 animals vs none in 82 animals, respectively). Combined exposures to uranium ore and high doses of radon and radon daughters increased the occurrence of lung epithelial squamous metaplasia (13 alveolar carcinomas and seven bronchiolar carcinomas in 101 animals). The statistical significance of that increase was not reported. In animals exposed to both uranium dust and radon and radon daughters, there were two osteosarcomas and none in the control animals, four reticulum-cell sarcomas and three in the controls, and one adrenal-cell sarcoma and zero in the controls. Those results suggest that radon in uranium ore is an important factor in the carcinogenicity associated with exposure to natural uranium ore. Cross et al. concluded that the hamster may not be an appropriate animal model for studying the pulmonary carcinogenic potential of uranium ore, in that evidence from other laboratories indicated that the Syrian golden hamster is highly refractory to carcinoma induction by inhaled alpha-emitting radionuclides.

Mitchel et al. (1999) used a nose-only inhalation system to expose rats to natural uranium ore at two concentrations. Exposure to uranium-ore dust at 19 mg/m^3 or 50 mg/m^3 (containing 44% uranium and no significant radon content) took place for 4.2 h/d 5 d/wk for 65 wk. The animals were observed for their remaining lifetime. The frequency of primary malignant and nonmalignant lung tumors was higher in both exposure groups than in controls. Primary malignant tumors were observed in one of 63 control rats, 22 of 126 rats in the 19-mg/m^3 group, and 20 of 61 rats in the 50-mg/m^3 group. Similarly, primary nonmalignant tumors were found in one, 17, and eight rats of the three groups, respectively. There was no difference in tumor latency between the two dose groups. Calculations indicated that malignant lung-tumor frequency was more directly related to the radiation dose rate (determined from uranium concentrations in pulmonary tissues at the end of the exposure period) than to absorbed dose to the lung. Nonmalignant lung tumors correlated significantly with lower lung bur-

dens. It should be noted that the strength of evidence that inhalation of uranium dust is associated with lung cancer is weakened by the fact that the uranium-exposed rats in this study lived longer than the nonexposed animals.

Taken together, those studies indicate that long-term inhalation exposure to natural uranium-ore dust can cause malignant changes in lung tissue. Results from the Mitchel et al. study suggest that inhalation of uranium ore (without substantial radon and radon-daughter content) can be carcinogenic to lung tissue after an extended period in animals. Leach et al. (1973) used a different strain of rats and did not observe lung tumors after chronic exposure to uranium dust but did observe lung tumors in dogs exposed in a similar manner. The collective findings suggest that both the chemical and radiologic properties of natural uranium may play a role in its carcinogenicity.

Depleted Uranium

Recent studies have been designed specifically to assess the carcinogenicity of DU under exposure conditions experienced by Gulf War soldiers who had embedded DU metal fragments. Hahn et al. (2002) conducted a carcinogenicity study of DU metal fragments embedded in the thigh muscles of rats. They used three sizes of DU containing 0.75% titanium: 1.0 × 2.0-mm pellets and 2.5 × 2.5 × 1.5-mm and 5.0 × 5.0 × 1.5-mm fragments). Tantalum metal fragments were used as negative controls, and a colloidal suspension of radioactive thorium dioxide injected into the thigh muscle was used as a positive control. The study was designed with 50 rats per group and was extended for the lifetime of the animals. More soft-tissue sarcomas were found in the immediate vicinity of the DU metal implants than the tantalum controls; the incidence was greater near the larger implants. No significant increases in the number of benign or malignant tumors were found in any other tissues.

Hahn et al. concluded that DU fragments embedded in muscle tissue are carcinogenic if they are large enough; however, the mechanism involved is unclear. The number of tumors that developed around the DU implants was not proportional to the surface area of the implants; this suggests the absence of a foreign-body response, which is critical because rats are sensitive to foreign-body carcinogenesis (Oppenheimer et al. 1956; O'Gara and Brown 1967; Autian et al. 1975; Brand et al. 1976; Greaves et al. 1985; McGregor et al. 2000). A foreign-body mechanism of tumor formation was considered unlikely because the DU implants did not remain smooth—an important criterion for foreign-body carcinogenesis. Tantalum pellets remained smooth, whereas DU fragments became corroded and roughened. In addition, DU implants were associated with more inflammation and fibrosis than the tantalum fragments.

Although it was not possible from the Hahn et al. study to determine whether the mechanism of carcinogenicity of the DU fragments involved only radiation effects, the authors suggested that the observed correlation between the number of tumors and the initial surface alpha radioactivity of the implanted

materials indicated that radioactivity may have played a role. The chronic tissue damage indicated by the inflammation and fibrosis associated with the DU implants also may have played a role and could be a response to cytotoxic effects of uranium related to its radiation or chemical toxicity.

A second study examining the development of sarcomas near embedded DU pellets in rats also found thick fibrous capsules, black granular material, and mild to moderate inflammation but no evidence of proliferation or preneoplastic changes at the implantation sites (Arfsten et al. 2007). The absence of neoplastic changes may well have been due to the short period that elapsed between implantation of the pellets and the end of the study (150 d).

GENOTOXICITY OF URANIUM

A number of in vivo and in vitro studies have demonstrated that uranium is a genotoxic metal and provided support for a mixed chemical-radiologic mechanism of uranium carcinogenicity.

In Vitro Studies

Using Chinese hamster ovary (CHO) cells, Lin et al. (1993) demonstrated that uranyl nitrate is genotoxic and cytotoxic. Uranium exposure decreased cell viability with a 50% inhibitory concentration (IC_{50}) of 0.049 mM. Over a concentration range of 0.01-0.3 mM, uranyl nitrate depressed cell-cycle kinetics and increased micronuclei, sister-chromatid exchange (SCE), and chromosomal aberrations.

More recently, in vitro studies of the carcinogenicity of DU showed that human osteoblasts exposed to DU-uranyl chloride were transformed to a tumorigenic phenotype characterized by anchorage-independent growth and tumor formation in nude mice (Miller et al. 1998a). Transformation frequency increased by a factor of 9.6 ($\pm$ 2.8) in DU-exposed cells compared with 7.1 ($\pm$ 2.1) in cells exposed to nickel sulfate, a well-established metal carcinogen. DU-transformed cells also expressed high levels of the *k-ras* oncogene, reduced production of the Rb tumor-suppressor protein, and had increased frequencies of SCE per cell. In a followup study, Miller et al. (2003) reported genetic instability in the human osteoblast line after DU exposure manifested as delayed lethality and micronuclei formation. Wise et al. (2007) showed that human bronchial fibroblasts exposed for up to 72 h to soluble uranium (as uranyl acetate) at concentrations that decreased cell viability did not increase DNA damage above background levels but that exposure to insoluble uranium (as uranium trioxide) caused chromosomal aberrations in 15% of metaphase cells.

Knobel et al. (2006) used a variety of assays to study the genotoxicity of uranyl nitrilotriacetate in nontransformed human colon cells and in a human colon adenoma cell line. Uranium caused DNA strand breaks measured by using the comet assay at concentrations that did not arrest cell growth or decrease cell

viability. Evaluation of damage induced in the gene TP53, known to be altered during carcinogenesis, showed a concentration-dependent migration of TP53 into the comet tail. Fluorescence-in-situ-hybridization (FISH) analysis for chromosomal aberrations showed a concentration-dependent increase in aberrant metaphases; uranium caused proportionally more deletions and fewer translocations than the positive control ethylmethanesulfonate.

To address the question of whether genotoxicity of uranium occurs through chemical rather than radiologic mechanisms, Miller et al. (2002a) conducted in vitro experiments with uranyl nitrates of different isotopic compositions and specific activities. The frequency of dicentric chromosomes in human osteoblasts increased in a radiation-dose-dependent manner that suggested that alpha radioactivity was responsible for at least this specific type of chromosomal aberration.

The mechanism of uranium's genotoxicity was studied by Yazzie et al. (2003) with a cell-free system. Their work demonstrated that uranyl acetate caused DNA strand breaks in the presence of ascorbate. Addition of catalase inhibited strand breaking, and this indicated that hydrogen peroxide is involved in the DNA damage; however, there was a lack of protection by hydroxyl-radical scavengers. Miller et al. (2002b) and Periyakaruppan et al. (2007) reported results indicating the involvement of oxygen radicals in uranium-induced DNA damage. Hamilton et al. (1997) had shown that uranyl ion in the presence of hydrogen peroxide catalyzes hydroxyl-radical–mediated oxidation.

Direct evidence of a chemical-based mechanism of uranium genotoxicity was recently reported by Stearns et al. (2005), who studied CHO cells. Uranium-DNA adducts were formed under exposure conditions that increased hypoxanthine phosphoribosyl transferase (HPRT) mutations and DNA strand breaks. The authors concluded that molecular analysis of the HPRT mutations induced by uranyl acetate exposure showed mutation spectra consistent, at least in part, with a chemical-induced effect. Uranyl acetate exposure induced more major genomic rearrangements (multiexon insertions and deletions) than occurred spontaneously. Similarities between hydrogen peroxide and uranyl acetate mutation spectra, however, suggested that oxidative DNA damage also played a role in the uranyl acetate mutagenesis (Coryell and Stearns 2006).

Hartsock et al. (2007) reported evidence of a chemical mechanism by which uranium might alter DNA transcription and repair. In in vitro assays, uranyl acetate, but not sodium arsenite, inhibited the DNA-binding activity of both zinc-finger (Aart and Sp1) and non-zinc-finger (AP1 and NFκB) DNA-binding proteins.

Animal Studies

Evidence that DU is mutagenic, as measured by the Ames *Salmonella* reversion assay (strain TA98 and AmesII™ mixed strains TA7001 to 7006), was reported by Miller et al. (1998b) in a study of rats with embedded DU pellets.

The gastrocnemius muscles of Sprague-Dawley rats had implants of various combinations of 20 DU and tantalum pellets. The high dose consisted of 20 implanted DU pellets; the medium dose, 10 DU and 10 tantalum pellets; and the low dose, four DU and 16 tantalum pellets. Controls received 20 tantalum pellets. Urine and serum samples were collected 6, 12, or 18 mo after implantation. Urine was passed through a chromatograph column of Amberlite XAD-4 resin, and the effluent was collected and passed through a column of Amberlite XAD-8 resin. The serum was separated by centrifugation, vacuum-dialyzed, and then tested. Both the urine samples and the serum samples were tested in the Ames assay with strain TA98 and strains TA7001-7006. The latter is made up of six individual strains in equal numbers all measuring base pair substitution. The XAD-4 urine fraction produced statistically significant increases at all periods and at all doses in the TA98 strain. For strains TA7001-7006, results were variable for the 6-mo period, but the 12- and 18-mo results were statistically significant for all doses. The XAD-8 fraction produced less mutagenicity, with no significant increases at 6 mo, and only the medium and high doses produced significant increases at 12 and 18 mo in TA98. In strains TA7001-7006, statistically significant increases were seen at all doses and all periods. Serum did not produce significant increases in TA98 or TA7001-7006. If the standard of "a doubling of the control rate" is used to indicate a positive response, the study established that exposure to urine from rats with implants of DU increases the mutation frequency of *S. typhimurium*, causing frame-shift and base-pair substitution mutations.

Monleau et al. (2006) recently reported evidence of DNA damage in bronchoalveolar lavage (BAL) cells from rats exposed by inhalation to an insoluble form of DU. Animals were exposed to uranium dioxide in an acute and repeated regimen or to uranium peroxide in an acute regimen only. The animals were killed at various times after exposure (see Table 7-1), and DNA damage was assessed in BAL cells and in the kidneys. The comet assay was used to determine single- and double-strand breaks in DNA. It was conducted under alkaline and neutral pH conditions. Alkaline conditions allow detection of single- and double-strand breaks, whereas neutral conditions allow detection only of double-strand breaks. The olive tail moment was used to quantify DNA damage; this index measures the amount of DNA damage and the distance of migration of the genetic material in the tail.

In BAL cells, the highest single exposure to uranium dioxide, 375 mg/m^3 for 3 h, caused a significant increase in DNA breaks at days 1 and 8 after exposure, whereas exposures at 375 mg/m^3 for 2 h and 190 mg/m^3 for 30 min were without effect (alkaline condition). Repeated exposures to uranium dioxide (190 mg/m^3 for 30 min 4 d/wk for 3 wk) resulted in significant DNA breaks under alkaline conditions on all days after exposure. Acute exposure to uranium peroxide did not cause any significant increases. Under neutral pH conditions, cells with the highest acute exposure (375 mg/m^3 for 3 h) and repeated exposure to uranium dioxide showed increases in double-strand DNA breaks. The authors

TABLE 7-1 Experimental Protocol for Inhalation Study

Inhalation Type	Duration	Aerosol Concentration	Euthanasia after Exposure
Acute UO_2	30 min	190 mg/m^3 ± 41 mg/m^3	4 h and 1, 3, 8 d
Acute UO_2	2 h	375 mg/m^3 ± 70 mg/m^3	1, 3, 8 d
Acute UO_2	3 h	375 mg/m^3 ± 70 mg/m^3	1, 3, 8, 14 d
Repeated UO_2	30 min 4 d/wk for 3 wk	190 mg/m^3 ± 41 mg/m^3	1, 3, 8, 14 d
Acute UO_4	30 min	116 mg/m^3 ± 60 mg/m^3	4 h and 1, 3, 8 d
Air	30 min 4 d/wk for 3 wk	—	1, 3, 8, 14 d

Note: UO_2, uranium dioxide; UO_4, uranium peroxide.
Source: Monleau et al. 2006. Reprinted with permission; copyright 2006, Oxford University Press.

concluded that uranium dioxide induces both single- and double-strand breaks in BAL cells. In renal cells, only the repeated-exposure group demonstrated a significant increase in DNA damage under alkaline conditions; the damage occurred 3 and 8 d after exposure.

The authors also investigated the expression of genes associated with inflammation, given that the inflammatory process may play a role in the generation of reactive oxygen species and thereby cause genotoxicity. They discovered that gene expression was increased for interleukin-8 and tumor-necrosis factor alpha. They also showed increases in aqueous and lipid hydroperoxides in the lungs. The genotoxicity thus seen was attributed to a secondary result of activation of reactive oxygen species. Therefore, the genotoxicity observed should have a threshold.

Human Studies

A number of researchers have conducted cytogenetic assessments in uranium-exposed populations. Martin et al. (1991) reported increases in SCE and chromosomal aberrations in lymphocytes of uranium-production workers exposed to a mix of soluble and insoluble uranium compounds and possibly enriched uranium. Studies of two populations of uranium miners, however, had mixed results. Lloyd et al. (2001) reported no increased incidence in chromosomal aberrations in the white blood cells of Namibian uranium miners, whereas Popp et al. (2000) observed a significantly increased incidence of micronuclei in the lung macrophages of former German miners.

Cytogenetic assessments of DU-exposed Gulf War veterans conducted biennially since 1999 have had mixed, generally negative, results with respect to an effect of uranium exposure on SCE and chromosomal-aberration frequencies

(McDiarmid et al. 2001b, 2004b, 2006, 2007). Mutations of the HPRT gene in peripheral blood lymphocytes, however, have been consistently about twice as high in veterans with higher uranium exposure than with lower uranium exposure as measured by urinary uranium. The correlation between HPRT mutations and urinary uranium, however, has not always been statistically significant. That may be due in part to the relatively small number of soldiers involved in each of the assessments, which ranged from 32 to 39. Chromosomal abnormalities measured with FISH analysis in 2005 provided additional evidence of a weak genotoxic effect of DU in this Gulf War cohort (McDiarmid et al. 2007). Interpretation of the results is difficult because the studies were not designed to determine whether the incidence of abnormalities was larger than expected in "normal" people; the studies were designed only to determine a difference between low- and high-exposure groups and thus an association with urinary uranium. Consequently, there were no control cultures for comparison.

SUMMARY

Experimental evidence indicates that insoluble forms of uranium are weakly carcinogenic in animals. Lung cancer is the primary cancer that occurs after inhalation exposure to insoluble uranium compounds. However, it should be noted that many of the animal studies involved exposures to exceptionally high concentrations of uranium particles, so particle load could have been a factor in the responses. Sarcomas have also been observed in the vicinity of injected or embedded uranium metal. Although in vitro studies suggest that uranium can have genotoxic effects because of both its chemical and radiologic nature, cytogenetic assessments in exposed human populations (uranium-production workers, uranium miners, and Gulf War DU-exposed veterans) are few and have had mixed results, most likely owing to differences in the solubility and size of the uranium compounds involved. Overall, the carcinogenicity and genotoxicity results are consistent with the relatively low lung-cancer risks predicted by the Capstone study for soldiers who inhaled DU in the Gulf War friendly-fire incidents.

RECOMMENDATIONS

- Assessment of the risk of cancer and organ dysfunction posed by military exposure to DU is limited by lack of knowledge of the mechanisms by which uranium causes cancer and by the absence of experimental animal data from studies with exposure scenarios similar to those during the Gulf War. Additional animal studies should be performed that use DU oxide particles that are similar in size and solubility to those created by the penetration of DU armor by DU munitions; that involve a single, short (up to 1-h) inhalation exposure to DU particles at concentrations similar to those predicted in the Capstone Report (up to 10,000 mg/m^3); and that extend observations over the entire lifetime of the

animals. Measured outcomes from such studies should include gross and histologic pathology of the lungs, pulmonary lymph nodes, and kidneys for evidence of fibrosis, proliferative lesions, and tumors and include tumor-frequency data based on dose and tissue uranium concentrations. Biomarkers of cytogenetic effects (such as SCEs, micronuclei, HPRT mutations, and chromosomal abnormalities) in lymphocytes should be measured immediately after exposure and periodically thereafter. Spermatogonial cells also should be examined for chromosomal aberrations in the testes. The latter would provide information on the possible heritable nature of the aberrations.

- Dust collected from inside tanks should be analyzed for other metals and chemicals that could potentially enhance the carcinogenicity of DU through such mechanisms as inhibition of DNA repair. On the basis of such analyses, it may be necessary to factor in the effects of coexposures to other carcinogens in cancer risk assessments.
- The committee recommends research into whether there is a chemical mechanism of uranium carcinogenesis.

8

Evaluation of the Army's Capstone Report

In this chapter, the committee evaluates the U.S. Army's Capstone Report (Guilmette et al. 2005; Parkhurst et al. 2005, 2004a,b). First, the committee evaluates the Army's estimates of exposure to depleted uranium (DU) in various scenarios. It then reviews potential health risks to exposed personnel in the context of the exposure estimates and the toxicologic and health information presented in the preceding chapters.

EXPOSURE ASSESSMENT

The Capstone Report estimated the exposure of military personnel to DU from "friendly-fire" incidents in the first Gulf War. The assessment used the results of the Capstone DU-aerosols study (Parkhurst et al. 2004a) and a series of exposure scenarios based on interviews with veterans of Operation Desert Storm, after-action reports, and discussions with other military experts (OSAGWI 1998, 2000; USACHPPM 2000). Three exposure groups were defined as follows:

- *Level I* includes military personnel in, on, or near combat vehicles at the time of impact and perforation by DU munitions and personnel who entered vehicles immediately after they were struck (and perforated) by DU munitions. Those personnel could have been exposed to DU from fragments resulting from impact, inhalation of DU aerosols, ingestion of DU residues, or any combination thereof.
- *Level II* includes military personnel and a small number of U.S. Department of Defense (DOD) civilian employees whose jobs required them to work in and around vehicles containing DU fragments and particles. They were not in vehicles at the time of impact and did not immediately enter a vehicle after it was struck. They performed a variety of tasks, such as battle-damage assessment, repairs, explosive-ordnance disposal, and intelligence-gathering.

They typically entered vehicles well after the initial suspended aerosol had dissipated or settled on interior surfaces. They may have inhaled DU residues that were resuspended by their activities, ingested DU through hand-to-mouth transfer, or spread contamination on their clothing.

- *Level III* is an "all others" group whose exposures were brief or incidental.

The Capstone program performed a series of experiments to provide information on the amounts and characteristics of aerosols generated in or near vehicles hit by DU munitions. The experiments (Parkhurst et al. 2004a,b) involved 12 firings of large-caliber (LC) DU cartridges into Abrams tanks and a Bradley fighting vehicle. Specifically, the scenarios involved firing into three types of stripped-down vehicles (with no operating ventilation systems): an Abrams tank with conventional armor, a Bradley fighting vehicle with conventional armor, and an Abrams tank with DU armor. In addition, one shot was fired into an operational Abrams tank with DU armor that had an operating ventilation system. Aerosols were sampled in the vehicles by using filter cassettes, eight-stage cascade impactors, a five-stage cyclone separator, and a moving filter sampler. Sampling outside the vehicles was accomplished with high-volume air samplers or cascade impactors, and wipe samples were collected to evaluate potential DU ingestion.

Aerosol samples were collected in the target vehicles as a function of elapsed time after the shot, and the samples were analyzed for uranium content, particle size distribution, and other chemical and physical characteristics. The resulting dataset formed the basis of estimates of the amount and characteristics of aerosols that might be inhaled by soldiers in vehicles struck by DU munitions. The total quantity of DU aerosol generated by impact with armor cannot be measured directly, because of losses of absorption into or spallation of the DU onto the target. Using aerosol data, the Capstone study estimated that a maximum of 7% of the LC-DU penetrator was aerosolized inside the heavily armored Abrams tank and a maximum of 1% in the lighter-armored Bradley vehicle.

DU intakes, chemical concentrations, and radiation doses to selected organs were calculated for each phase (vehicle type), shot, and sampling position for each scenario. The intakes were based on scenarios of human exposure (described below) that included exposure duration and breathing rates. The time histories of uranium concentration in key organs (including maximal concentrations in kidneys) and the resulting radiation doses were estimated with human biokinetic models developed by the International Commission on Radiological Protection (ICRP). Specifically, three models were integrated in the computer programming to mathematically describe the toxicokinetics of uranium: the human respiratory tract model, the gastrointestinal tract model, and the uranium systemic biokinetic model. The respiratory and gastrointestinal tract models are described below, and the uranium systemic biokinetic model is described in Chapter 2.

The human respiratory tract model (ICRP 1994a, 1997) divides the respiratory tract into five distinct anatomic compartments: the anterior portion of the nose (anterior nasal passage); the back of the nose and mouth and the throat (posterior nasal and oral passages, pharynx, and larynx); the trachea, the split of the air pathway into the two lobes of the lung, and the first seven later divisions of the two pathways into the lung (trachea, main bronchi, and generations 2-8 bronchi); the next seven divisions (bronchioles and terminal bronchioles); and (5) the final divisions of the airway and the alveolar sacs where gas exchange with blood occurs (alveolar-interstitial region). Separate lymphatic tissues are included in the model. Physiologic data include breathing rate and the amount of air space in the lung that is typically used during breathing. The deposition portion of the model describes deposition of particles as a fraction of the intake in each of the five regions of the respiratory tract in terms of particle size, from 0.6 nm to 100 μm. Each region is modeled as a filter, and all five regions act as a series of filters for both the inhalation and exhalation phases of breathing. Deposition is not considered to depend on the element, radionuclide, or chemical form. Particulate material is removed from the respiratory tract by particle transport (mechanical clearance) and by absorption into blood, which act independently and competitively on the material in each deposition region. In the anterior nose, only mechanical clearance applies, and material is removed quickly out of the body through the front of the nose. In the other regions of the respiratory tract, particle transport includes clearance to the gastrointestinal tract and the lymphatic system. Concurrent with the mechanical clearance of particles is dissolution of the particles and absorption into blood. This mechanism depends on the physical and chemical forms of the deposited material, and the rates of dissolution are modeled to occur at the same rates in all respiratory tract regions. Dissolution is modeled by assuming that a fraction of the deposited material dissolves relatively rapidly and the rest more slowly. The Capstone Report used dissolution rates obtained from in vitro dissolution experiments to define specific dissolution rate constants and associated fractions for the mixtures of uranium forms encountered in the aerosols measured in the vehicle interior.

The gastrointestinal tract model (ICRP 1979) consists of four compartments that represent the stomach, small intestine, upper large intestine, and lower large intestine. Material enters the stomach and clears to the small intestine, from which a fraction is absorbed by blood and the remainder clears to the upper large intestine. The material in the upper large intestine clears to the lower large intestine, and material in the lower large intestine is excreted in feces. There is no feedback between the compartments. The absorbed fraction depends on the solubility of the material in gastrointestinal tract fluids and is generally related to the absorption type used in the respiratory tract model.

The biokinetic models used in the Capstone Report reflect scientific consensus based on years of studies of animals and on human data where possible. Capstone scientists programmed special applications of the models for the human respiratory tract, the gastrointestinal tract, and uranium systemic biokinetics. Best estimates of intakes, radiologic doses, and peak chemical concentra-

tions were calculated. Uncertainty analyses were also performed. The committee found that the models used in the Capstone analyses provide adequate information to support the risk analysis.

Two principal types of uncertainty are associated with the calculation of organ doses and committed effective doses (lifetime radiation doses) from inhaled DU aerosols: uncertainty due to variability in the measurement data and uncertainty in the biokinetic and dosimetric models used to calculate doses as central estimators for the population. The uranium concentration values were derived from beta-radioactivity counting of cascade-impactor collection substrates. Uncertainty calculations in the Capstone Report considered counting statistics, uncertainty in regression-model parameter values, and uncertainty in the ingrowth correction applied to account for the state of disequilibrium of the beta-emitting progeny. The measurement uncertainties were evaluated in terms of the likelihood function by using Bayesian statistics. Posterior distributions were calculated, and then all the distributions for a particular vehicle type were summed. The summed distribution represents the probability distribution of dose when all the shots and positions making up the dataset for a particular phase are considered equally likely; in other words, it is the probability distribution when the type of vehicle and the intake scenario are known but the geometry of the shot or subject placement is not known. Uncertainty analyses showed that the resulting distributions could not be described by any standard distribution, so the results were reported as medians with 10th and 90th percentiles. The committee found that the uncertainty analyses were appropriately performed and well done.

Level I Exposures

The primary focus of modeling level I exposures was to provide estimates of DU inhalation exposure to personnel in an Abrams tank or a Bradley fighting vehicle. Modeling of the level I inhalation exposures in a vehicle is a matter of determining the aerosol source characteristics in the vehicle (DU concentration, particle size, and solubility), the timing, the duration of exposure, and the breathing rates associated with the physical activities being performed. Those factors influence the magnitude of the intake and the consequent doses. Five level I exposure scenarios were modeled in the Capstone Human Health Risk Assessment (Guilmette et al. 2005): four for crew members present in the vehicle at the time of perforation and one for first responders who entered the vehicle after perforation.

Four exposure times were selected: 1 min, 5 min, 1 h, and 2 h. The first two exposure times assumed that the crew members would be able to leave the vehicle readily. The second two assumed continued exposure in a still-functioning vehicle. Longer stay times would increase exposure, but the DU aerosol concentrations after 2 h are orders of magnitude smaller and therefore add little to the intake. The assumptions used in creating the four scenarios for personnel in a vehicle during vehicle perforation are presented in Table 8-1.

TABLE 8-1 Capstone Summary of Level I Exposure Scenario Conditions

Scenario	Time of Exposure	Exposure Duration	Breathing Rate
Crew Inside Vehicle			
A	From impact to exit 1 min after shot	1 min	3 m^3/h
B	From impact to exit 5 min after shot	5 min	3 m^3/h
C	From impact to exit up to 1 h after shot	1 h	3 m^3/h for first 15 min, 1.5 m^3/h thereafter
D	From impact to exit up to 2 h after shot	2 h	3 m^3/h for first 15 min, 1.5 m^3/h thereafter
First Responder			
E	Entry 5 min after shot, exit 10 min later	10 min	3 m^3/h

Source: Parkhurst et al. 2005. Reprinted with permission; copyright 2005, Battelle Press.

The key input for each of the scenarios is a description of the amount and characteristics of DU in the air, including total mass, particle size distribution, and solubility. For the present review, the committee performed an independent assessment of those characteristics.

Before the Capstone experiments, a number of experiments were performed with DU munitions to determine the aerosol characteristics of the dusts and fumes produced when a DU penetrator strikes a hard target (e.g., Glissmeyer and Mishima 1979; Jette et al. 1990; Parkhurst et al. 1995; Gilchrist et al. 1999). The committee used the earlier datasets to make its own estimates of exposure.

Finely divided uranium metal is reactive (pyrophoric), oxidizing to triuranium octaoxide in air. The chemical form of the pure uranium oxide is uranium trioxide when formed at 1 atm oxygen pressure and below 500ºC; triuranium octaoxide is the stable phase when formed above 500ºC. In low-oxygen environments, or as an intermediate, uranium dioxide is formed (Parkhurst et al. 1995). In outdoor tests, Glissmeyer and Mishima (1979) found that 105-mm penetrators striking metal targets produced uranium oxides as 75% triuranium octaoxide and 25% uranium dioxide in particles that had an aerodynamic equivalent diameter (AED) of about 2.5-3 μm and of which about 50% were in the respirable size range. Particles created with 105-mm rounds as measured by Gilchrist et al. (1999) had an AED of 2.3-5.8 μm. Jette et al. (1990) found that aerosols from 120-mm rounds had particles of which 91-96% were less than 1 μm in AED and from 105-mm rounds particles of which 61-89% were less than 10 μm in AED. Through statistical sampling of walls, floors, equipment, ducting, and filters, Sutter et al. (1985) were able to recover up to 97% of the uranium from projectiles fired in an indoor testing range as nonaerosol particles (for example, pieces) and particulate oxides.

From those data and evaluation of the Capstone information, the committee developed a simplified description of the particulate material in the air immediately after a DU munition penetrates a target vehicle. It is assumed that about 50% of the dust generated by an impact is larger than respirable size. The remaining 50% is evenly distributed between "large" respirable particles (mean, 5 μm) and "small" respirable particles (mean, 1 μm). The material is assumed to be in a moderately soluble form (corresponding to ICRP solubility classification M [for moderate]; see Chapter 2).

The initial concentration of dust and fumes generated in the vehicle depends on the event. Approximations made after outdoor tests indicated peak concentrations greater than 10^6 μg/m^3 (Glissmeyer and Mishima 1979); these tests are not directly applicable to concentrations inside vehicles. In the Capstone firing tests (Parkhurst et al. 2004a), the peak concentrations in the Abrams tank was around 10^7 μg/m^3, which was used in the committee's analysis as the starting point.

The Capstone studies evaluated air concentrations as functions of time after impact in two vehicle types: with and without functional ventilation systems. That provided a complex set of curves that the Capstone staff used to analyze potential impacts. A simplified theoretical approach was taken for the committee's independent assessment. The reduction in particle concentration in the air will be a function of both the ventilation and the settling of the particles and can be described mathematically as

$$\frac{dC}{dt} = -VC - sC,$$

where C is the DU concentration in air as a function of time, V is the ventilation rate in air exchanges per hour, and s is the deposition rate constant. The deposition rate constant will be a function of the particle size; larger particles deposit more rapidly than smaller ones. The deposition rate may be approximated by using a particle-deposition velocity v_d as

$$s = \frac{v_d}{h},$$

where h is the distance from the floor to the ceiling, approximated as 2 m. The three particle-size classes described above were assigned the following approximate values, which are commonly used in environmental assessments (Sehmel 1984):

Particle-Size Category	Deposition Velocity (m/s)
Very large (>10 μm)	0.1
Large (~5 μm)	0.01
Small (~1 μm)	0.001

The ventilation rates for Abrams tanks and Bradley fighting vehicles are described in Parkhurst et al. (2004a). Even an "unventilated" vehicle will have some leakage, which results in loss of particles from the vehicle. The assumed rates of ventilation and leakage are as follows:

Vehicle	Unventilated (h^{-1})	Ventilated (h^{-1})
Abrams	4	47.2
Bradley	8	40

The removal of particles by ventilation and deposition will be countered to some extent by resuspension of deposited material in the air by the activities of the personnel in the vehicle. A lower limit of concentration is assumed to be 10 $\mu g/m^3$ for unventilated vehicles and 1 $\mu g/m^3$ for ventilated vehicles (see discussion below on resuspension).

With those assumptions, the time history of the air concentration in the vehicle after penetration by a DU munition can be estimated. The results are presented in Table 8-2 for the two vehicles and ventilation states. The results, shown graphically in Figure 8-1, compare favorably with both the early experiments (Gilchrist et al. 1999) and the Capstone measurements (Parkhurst et al. 2004a).

The curves were used to estimate the time-integrated air concentrations of DU particles in each size category (very large and nonrespirable, large respirable, small respirable) for the five exposure scenarios for the two types of vehicles. Those are presented in Table 8-3. The values are somewhat larger than those estimated on the basis of outdoor shot tests by Gilchrist et al. (1999), as would be expected.

The time-integrated air concentrations may be used with the breathing rates defined for the five Capstone level I exposure scenarios to estimate intakes. Those are shown in Table 8-4. The intakes estimated for the unventilated Abrams tank are very close to the Capstone estimates. The intakes for the ventilated Abrams tank are 2-10 times larger than the corresponding Capstone estimate. For the unventilated Bradley fighting vehicle, the independent estimates are about 3 times larger than the Capstone estimates. (However, the initial quantity of DU measured in the Capstone Report for Bradley vehicles was only about one-third the initial value assumed in these independent re-estimations.) A Bradley vehicle with an operational ventilation system was not available for the Capstone study. Intakes were also independently estimated by the Royal Society (2001); the upper-bound estimates were about 3 times higher than any of these. However, the approximations to the time-integrated air concentrations were grounded on less information.

To estimate radiation-dose equivalents, the dose-conversion factors for DU presented in Chapter 6 (Table 6-2) were used to calculate the effective doses. The committee's estimated doses are generally within a factor of about 2 of the more sophisticated Capstone estimates, of which the results for vehicles

with conventional armor are compared in Table 8-5. The only exception is the dose to the first responder, for which the committee's estimates are somewhat lower than the Capstone values. Overall, there is excellent agreement between the estimates, and the committee's independent assessment supports the validity of the Capstone results.

TABLE 8-2 Committee-Predicted Concentrations of DU in Air in Vehicles after Impact (mg/m^3)

	Abrams		Bradley	
Time (min)	Unventilated	Ventilated	Unventilated	Ventilated
0	10,010	10,001	10,010	10,001
1	4,245	2,062	3,972	2,325
5	1,952	54	1,401	98
10	1,025	2	531	4
15	607	1	229	1
30	148	1	29	1
45	42	1	12	1
60	18	1	10	1
120	10	1	10	1

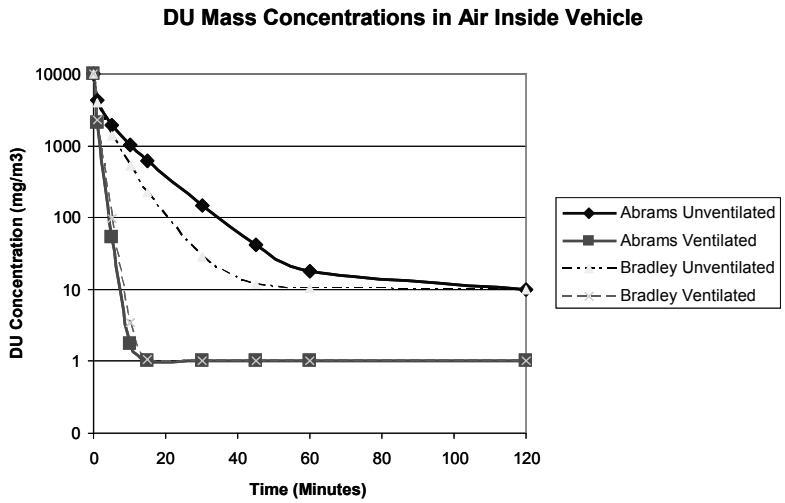

FIGURE 8-1 Committee-predicted mass concentrations of DU in air in vehicles after impact.

TABLE 8-3 Committee's Estimated Time-Integrated Concentrations of DU in Air for Various Conditions after Impact (mg-h/m^3)

	Start Time	Stop Time	Abrams		Bradley	
			Unventilated	Ventilated	Unventilated	Ventilated
Large Respirable Particles						
A: Exit 1 min	0	1	39.6	25.9	38.5	27.2
B: Exit 5 min	0	5	99.1	38.6	88.9	43.2
C: Exit 60 min	0	60	115.7	38.8	98.9	43.5
D: Exit 120 min	0	120	115.7	38.8	98.9	43.5
E: First responder	5	15	18.7	0.3	11.9	0.5
Small Respirable Particles						
A: Exit 1 min	0	1	45.0	29.0	43.8	30.5
Small Respirable Particles						
B: Exit 5 min	0	5	171.5	50.7	148.6	58.5
C: Exit 60 min	0	60	437.6	51.6	262.4	60.4
D: Exit 120 min	0	120	438.9	51.6	262.4	60.4
E: First responder	5	15	173.8	1.7	99.6	2.7

TABLE 8-4 DU Intakes Independently Estimated by Committee for Five Capstone Level I Exposure Scenarios

	Abrams		Bradley	
Scenario	Unventilated	Ventilated	Unventilated	Ventilated
Total Intake (mg)				
A: Exit 1 min	254	165	247	173
B: Exit 5 min	812	268	713	305
C: Exit 60 min	1 660	271	1,084	312
D: Exit 120 min	1 664	271	1,084	312
E: First responder	577	6	335	10
Delivered Dose (mg/kg)				
A: Exit 1 min	3.6	2.4	3.5	2.5
B: Exit 5 min	11.6	3.8	10.2	4.4
C: Exit 60 min	23.7	3.9	15.5	4.5
D: Exit 120 min	23.8	3.9	15.5	4.5
E: First responder	8.2	0.1	4.8	0.1

TABLE 8-5 Committee's Estimates of Effective Lifetime Committed Radiation Dose Equivalents from DU in Air for Level I Exposure Scenarios [rem (Sv)] and Selected Capstone Results for Comparison

	ABRAMS			
	Unventilated		Ventilated	
Scenario	Committee	*Capstone*	Committee	*Capstone*
A: Exit 1 min	0.94 (0.0094)	*2.0 (0.020)*	0.61 (0.0061)	*0.09 (0.0009)*
B: Exit 5 min	3.1 (0.031)	*3.7 (0.037)*	1.0 (0.010)	*0.44 (0.0044)*
C: Exit 60 min	6.5 (0.065)	*4.8 (0.048)*	1.0 (0.010)	*1.02 (0.0102)*
D: Exit 120 min	6.5 (0.065)	*5.0 (0.050)*	1.0 (0.010)	*1.20 (0.0120)*
E: First responder	2.3 (0.023)	*0.92 (0.0092)*	0.02 (0.0002)	*0.41 (0.0041)*

	BRADLEY		
	Unventilated		Ventilated
Scenario	Committee	*Capstone*	Committee
A: Exit 1 min	0.91 (0.0091)	*0.59 (0.0059)*	0.64 (0.0064)
B: Exit 5 min	2.7 (0.027)	*1.7 (0.017)*	1.1 (0.011)
C: Exit 60 min	4.2 (0.042)	*2.1 (0.021)*	1.2 (0.012)
D: Exit 120 min	4.2 (0.042)	*2.4 (0.024)*	1.2 (0.012)
E: First responder	1.3 (0.013)	*0.89 (0.0089*	0.04 (0.0004)

Assessment of Level II and Level III Exposures

Exposures to DU via inhalation were estimated from breathing-zone monitors of Capstone personnel (which measured both internal vehicle exposures and external exposures) and from area monitors that measure only exposures in vehicles. Exposure estimates in the Capstone Report are for unprotected personnel not using such equipment as respirators or gloves. The Capstone Report provides estimates of DU exposures via inhalation and hand-to-mouth ingestion for levels II and III unprotected personnel. Exposures are highest for levels II and III personnel involved in activities in perforated vehicles. Hence, durations of exposure in perforated vehicles particularly need to be monitored for these personnel.

The primary exposure pathways are the same for level II and level III personnel; however, the time spent by personnel in the vehicles is different. The physical activities performed in and around the vehicles may also be different for level II and level III personnel. Level II personnel spend more time in vehi-

cles because their jobs require them to work in and around damaged vehicles to repair them, gather intelligence, assess battle damage, or dispose of explosive ordnance. Level III personnel enter damaged vehicles because of curiosity rather than mission requirements. Therefore, because the exposures are not better defined, Capstone and this independent evaluation looked at the rates of exposure.

Evaluation of Resuspension

The Capstone measurements included samplers running in the vehicles for 2-3 h after initiation of the test. As described in Szrom et al. (2004), during these periods personnel were actively taking pictures and retrieving samples in the vehicles. Resuspension arrays (PI-6-L and PI-7-L) were running during this period. With the methods described in Szrom et al., it was determined for this analysis that resuspended concentrations of DU in air ranged from about 4 to 25 mg/m^3 during periods of personnel activity in the vehicles. The resuspended material had a distribution of particle sizes somewhat different from that of the original material: there was a much lower concentration of the very large (non-respirable) particles. Reanalysis of the data indicated that about an hour after impact, the resuspended particles were primarily in the respirable range. On the basis of the results of resuspension array PI-7-L, it is estimated that perhaps 16% of the resuspended DU was in the roughly 5-μm fraction and about 83% in the 1-μm fraction. Therefore, it is assumed that the concentration of resuspended respirable particles averaged about 10 mg/m^3: 1.6 mg/m^3 at 5 μm and 8.4 mg/m^3 at 1 μm. This value was also used as a minimum for the level I inhalation exposures described above.

For military personnel involved with postbattlefield conditions, a breathing rate associated with moderate levels of activity is assumed to be 1.2 m^3/h. As a result, DU would be inhaled at about 12 mg/h. That corresponds with a radiation effective dose of about 0.052 rem/h of exposure, which corresponds with values estimated by Capstone (Szrom et al. 2004) of about 14.5 mg/h and 0.078 rem/h. The agreement between the Capstone and committee estimates is reasonable.

It should be noted that both these and the Capstone estimates are based on entry into a contaminated vehicle that has not been cleaned. Neither assumes any sort of respiratory protection. Although the dose rates are not extreme, they indicate that training in ALARA (as low as reasonably achievable) techniques and some degree of respiratory protection would be appropriate for personnel working in the vehicles.

Evaluation of Incidental Ingestion

For comparability with the above inhalation estimates, it is assumed that the initial dust loading in the vehicles is about 10,000 $\mu g/m^3$. The vehicle interior dimensions are about 3 m × 2 m × 2 m (Royal Society 2001), for a volume

of 24 m^3 and a simple surface area of about 32 m^2. It may be assumed that equipment, personal effects, and so forth result in a surface area at least twice that (64 m^3). If the initial contamination deposits relatively uniformly, the ultimate surface contamination with DU dust particles would be about (24 $m^3 \times 10$ g/m^3)/(64 m^2), or 3.75 g/m^2.

Personnel in the vehicles would contact the dust, get some on their hands, and, without mitigating training or protective gear (such as respirators), probably ingest small amounts. In routine environmental assessments, it is common to assume that adults typically ingest about 10 mg of soil daily (EPA 1991). Alternative approaches have estimated that workers in remediation or construction activities ingest materials that are the equivalent of 10^{-4} m^2/h, or up to about 10^{-3} m^2/d (Kennedy and Strenge 1992). For an 8-h workday and the DU value of 3.74 mg/m^2 estimated above, that would be up to about 3-4 mg/d of DU. For work on the very dusty surfaces initially present in the confined space of a tank or Bradley vehicle, an inadvertent ingestion rate of 10 mg/d would be reasonable; this corresponds with an ingestion effective-dose accumulation rate of about 8×10^{-5} rem/h.

The Capstone program (Szrom et al. 2004) performed an estimate of ingestion based on measurements made on cotton gloves worn into the contaminated vehicles and supplemented with a stochastic analysis of various transfer factors. They estimated that there was a 90% probability that the amount ingested would be 0.3-30 mg/h for level II and 0.26-3.8 mg/h for level III exposures (effective-dose accumulation rates of 2×10^{-5} to 2×10^{-3} and 2×10^{-5} to 3×10^{-4} rem/h, respectively). Those values are reasonably compatible with the independent estimate given here. The Capstone results are deemed to be reasonable.

HEALTH RISK ASSESSMENT

As noted in Chapters 3-7, DU poses both chemical and radiologic risks. The chemical risks associated with DU are similar to those associated with naturally occurring uranium, but the radiologic risks differ from those posed by natural uranium because of removal of the radioactive isotopes ^{234}U and ^{235}U during the enrichment process. Chemical toxicity may occur when DU is internalized in the body by ingestion, inhalation, or fragment implantation. Radiologic toxicity may occur from internal or external exposure.

The committee's analysis of the human health risk assessment presented in the Capstone Report (Guilmette et al. 2005; Parkhurst et al. 2004a) follows. It is presented in two sections: noncancer effects and carcinogenic effects.

Noncancer Effects

Primary Target Organ

The Capstone Report assumes that the primary target for chemical effects

of DU is the kidneys. To verify that assumption, the committee evaluated the literature regarding the chemical toxicity of uranium in humans and animals (see preceding chapters).

In acute-exposure studies, no adverse immunologic effects were noted in uranium miners or rats (Kalinich et al. 1998; Conrad and Mehlhorn 2000; Arfsten et al. 2005). Hematologic effects—including decreased red-cell counts, decreased hemoglobin, mild anemia, and increased white-cell counts—were observed in rats, dogs, and rabbits (Dygert et al. 1949; Maynard and Hodge 1949; Roberts 1949; Maynard et al. 1953). It should be noted, however, that the effects were observed only after repeated exposures (30 d to 2 y) and are not considered applicable to the short-term exposures likely for level I personnel. Epidermal atrophy and increased skin permeability were noted in rats repeatedly exposed to triuranyl oxide (Ubios et al. 1997), and dermal burns were noted in a human exposed to uranyl nitrate (Butterworth 1955). Pulmonary edema and fibrosis, nasal hemorrhage, and rhinitis were noted after acute and subchronic inhalation exposures to uranium hexafluoride and uranium tetrafluoride in monkeys, rats, mice, rabbits, dogs, and cats (Dygert et al. 1949; Spiegl 1949; Leach et al. 1970, 1984); however, these effects were probably due to the hydrogen fluoride hydrolysis product and not to uranium (kidney effects were also observed in these studies and are discussed later). Variations in nuclear size, nuclear pyknosis, and extensive cytoplasmic vacuolation were noted in male rabbits in a 91-d repeated-exposure study (Gilman et al. 1998c); these effects of longer exposure are not likely to be relevant to exposure experienced by military personnel who do not have embedded DU metal fragments.

Kidney effects, including urinary biomarkers and histopathologic conditions, have been noted in numerous animal reports (Leach et al. 1970; Leach et al. 1973) and human reports (Butterworth 1955; Luessenhop et al. 1958; Boback 1975; Kathren and Moore 1986; Fisher et al. 1990; Zhao and Zhao 1990; Pavlakis et al. 1996). Furthermore, many studies that report effects on targets other than the kidneys also report effects on the kidneys. On the basis of those studies and the more detailed assessments provided in Chapters 3-7, the committee agrees with the Capstone Report that the kidneys are the primary target organs for uranium's chemical effects.

Severity of Renal Effects

The Capstone Report (Guilmette et al. 2005) identifies median peak renal uranium concentrations predicted for each exposure scenario in each vehicle configuration tested for level I personnel and for inhalation and hand-to-mouth ingestion for levels II and III personnel. The report then compares those renal burdens with the de facto occupational standard (3 μg/g) and with a category scheme termed the renal-effects groups (REGs). In the REG system, the renal uranium concentration is correlated with acute renal effects and a predicted outcome (see Table 8-6).

TABLE 8-6 REG Predictions of Chemical Risk to Kidneys in the Army's Capstone Report

Renal Effects Group	Renal Uranium Concentration (μg/g of renal tissue)	Acute Renal Effect	Predicted outcome
0	≤2.2	No detectable effects	No detectable effects[a]
1	>2.2 to ≤6.4	Possible transient indicators of renal dysfunction	Not likely to become ill[b]
2	>6.4 to ≤18	Possible protracted indicators of renal dysfunction	May become ill[c]
3	>18	Possible severe clinical symptoms of renal dysfunction	Likely to become ill[d]

[a]The committee interprets "no detectable effects" to mean no low-level transient renal effects and no clinical symptoms.
[b]The committee interprets "not likely to become ill" to mean may exhibit low-level transient renal effects.
[c]The committee interprets "may become ill" to mean may experience clinical symptoms of renal dysfunction and require medical attention.
[d]The committee interprets "likely to become ill" to mean likely to experience clinical symptoms of renal dysfunction and require medical attention.
Source: Guilmette et al. 2005. Reprinted with permission; copyright 2005, Battelle Press.

The REG predictions in the Capstone Report were based on the acute-exposure studies presented in Table 8-7. The data from those studies were used to determine the range of renal concentrations for each REG. The committee encountered several difficulties in verifying the upper bound of the REG-0 value (2.2 μg/g or less) calculated by the Army:

TABLE 8-7 Human Renal Effects of Acute Exposure to Uranium Cited in the Capstone Report

Intake Route	Chemical Form	Subjects	Uranium Intake (mg)	Peak Renal Uranium (μg/g)[a]	Effect[b]	Reference
Ingestion	Acetate	1	8,500	100	+++	Pavlakis et al. 1996
Dermal (burn)	Nitrate	1	130	35	+++	Zhao and Zhao 1990
Inhalation	Tetrafluoride	1	920	10	++	Zhao and Zhao 1990
Injection	Nitrate	1	16	6	+	Luessenhop et al. 1958
		1	11	4	+	

(Continued)

TABLE 8-7 Continued

Intake Route	Chemical Form	Subjects	Uranium Intake (mg)	Peak Renal Uranium (μg/g)[a]	Effect[b]	Reference
Dermal (burn)	Nitrate	1	10	3	++	Butterworth 1955
Inhalation	Hexafluoride	1	24	2.5	+	Fisher et al. 1990
Injection	Nitrate	1	5.9	2	+	Luessenhop et al. 1958
		1	5.5	2	—	
		1	4.3	1.5	—	
Inhalation	Hexafluoride	1	40-50	4	+	Kathren and Moore 1986
		1	40-50	4	+	
		1	40-50	1.2	+	
Inhalation	Hexafluoride	1	18	1.9	—	Fisher et al. 1990
		1	18	1.9	—	
		1	17	1.8	—	
		1	15	1.5	—	
		1	12	1.2	—	
		1	11	1.1	—	
		1	11	1.1	—	
Ingestion	Nitrate	1	470	1	+	Butterworth 1955
Inhalation	Hexafluoride	1	20	1	—	Boback 1975
Inhalation	Hexafluoride	1	8.7	0.90	—	Fisher et al. 1990
		1	8.4	0.87	—	
		1	7.4	0.76	—	
		1	6.0	0.62	—	
		1	6.0	0.62	—	

[a]Modeled estimates.
[b]Clinical symptoms of renal dysfunction: +++ = severe; ++ = protracted biochemical indicators of renal dysfunction; + = transient biochemical indicators of renal dysfunction; — = no detectable effects.
Source: Guilmette et al. 2005. Reprinted with permission; copyright 2005, Battelle Press.

- *Interpretation of the study by Fisher et al. (1990).* This study reported that 11 of 31 people had transient proteinuria but that no long-term renal effects were found. The Army's REG-0 definition appears to require that transient increases in urinary protein be classified as "+" rather than as "−," however, this is not how the Fisher et al. study was categorized in Table 8-7. Also, the Capstone Report provides detailed information on individual intakes and outcomes for 13 people. Because individual data were not provided in the original paper and no other reference or information was provided, it is unclear how the exposure estimates were made and the effects on these people interpreted.

- *Uncertainties in the data presented*. Most of the subjects in the acute-exposure studies were exposed because of accidents and were injured or became ill from the exposures. Because their physical condition (for example, stress, dehydration, and burns) could have caused or contributed to such effects as transient proteinuria, it is difficult to ascribe such effects solely to uranium exposure. There is also considerable uncertainty in the estimated renal concentrations in the studies in that they are modeled estimates, and it was not clear whether the same model was used to estimate all concentrations. The committee notes that relatively few data are available for establishing the REGs, and the exposure routes and chemical forms involved in the studies may not provide the best models for the exposure scenarios encountered in the military (see the following paragraph).
- *Relevance of uranium hexafluoride exposure to DU risk*. Uranium hexafluoride hydrolyzes to uranyl fluoride and hydrogen fluoride, which causes tissue damage. In the Kathren and Moore (1986) study, the anomalous pattern of urinary excretion of uranium was attributed to pulmonary edema induced by hydrogen fluoride. Similarly, some of the transient effects observed in the Fisher et al. (1990) study might have been the result of tissue damage by hydrogen fluoride. As noted above, it is unclear that studies involving exposure to uranium hexafluoride provide a good model for the exposure scenarios addressed in the Capstone Report.

As noted in Chapter 3, the renal uranium concentrations found in some cases after acute exposures suggest that minimal transient effects (such as proteinuria and albuminuria) may occur at concentrations as low as 1 μg/g (Kathren and Moore 1986; Fisher et al. 1990). Similar effects have been reported at renal concentrations around 1 μg/g in workers with chronic occupational exposure to uranium (Thun et al. 1985) and in Gulf War veterans with embedded DU fragments (Squibb et al. 2005). The Royal Society (2002) report also noted transient renal effects at renal concentrations of 1 μg/g and further noted that the trend after chronic exposure is toward greater renal effects with lower renal concentrations, possibly as low as 0.1 μg/g. Table 8-8 presents the predicted peak renal uranium concentrations for level I personnel in context with published human data, and Table 8-9 presents predicted renal uranium concentrations for level II and level III personnel from the Capstone Report. Data in Tables 8-8 and 8-9 are organized by uranium intake and peak renal uranium concentration. Values are presented in micrograms per gram per hour for levels II and III because of the longer-term exposure.

On the basis of the data presented, the REG-0 value may have to be redefined after the issues and uncertainties with the dataset are resolved. Any revision of the upper-bound REG-0 value would also require that the REG-1 range be redefined. If the REG 0 is lowered, the predictions for four scenarios might be affected: crew exiting in 1 min from the Bradley fighting vehicle with con-

TABLE 8-8 Renal Effects of Acute and Chronic Exposure of Humans to Uranium from Published Data: Comparison with Level I Estimates in Capstone Report

Route of Exposure	Chemical Form	Subjects	Uranium Intake (mg)	Peak Renal Uranium (μg/g)	Renal Effects[a]	Outcome	Reference
Ingestion	Acetate	Man	8,500	100	+++	Acute renal failure, glucosuria	Pavlakis et al. 1996
Dermal (burn)	Nitrate	Man	130	35	+++	Renal tubular dysfunction	Zhao and Zhao 1990
Inhalation	Tetra-fluoride	Man	920	10	++	Renal dysfunction, NPN, proteinuria, aminoaciduria	Zhao and Zhao 1990
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 1 h			760	8.2	REG 2	May become ill[b]	Guilmette et al. 2005
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 2 h			780	8.0	REG 2	May become ill[b]	Guilmette et al. 2005
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 5 min			590	6.4	REG 2	May become ill[b]	Guilmette et al. 2005
Injection	Nitrate	Man	16	6	+	Increased NPN, urine catalase, albumin	Luessenhop et al. 1958
		Man	11	4	+		
		Woman	6	2	+		
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 2 h			380	4.0	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; crew exits in 2 h			1000	3.7	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; crew exits in 1 h			970	3.5	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 1 h			330	3.5	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; crew exits in 1 min			280	3.0	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Occupational Guideline				3.0			

Dermal (burn)	Nitrate	Man	10	3	++	Albuminuria	Butterworth 1955
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 5 min			220	2.9	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; crew exits in 5 min			710	2.6	REG 1	Not likely to become ill[c]	Guilmette et al. 2005
Inhalation	Hexafluoride	Man	24	2.5	+	Transient proteinuria and glucosuria	Fisher et al. 1990
Injection	Nitrate	Two men	5	1.8 1.4	— —	No abnormalities	Luessenhop et al. 1958
Inhalation	Hexafluoride	Three men	40-50	4 4 1.2	+ + +	Albumin and casts in urine	Kathren and Moore 1986
Inhalation	Hexafluoride	11 men	6-18	0.05-1.9	+	Transient proteinuria	Fisher et al. 1990
Inhalation	Hexafluoride	19 men	6-18	0.05-1.9	—	No abnormalities	Fisher et al. 1990
Level I: Abrams tank; DU armor, no ventilation; first responders			160	1.5	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Bradley vehicle; conventional armor, no ventilation; first responders			99	1.4	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; crew exits in 1 min			250	1.1	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Bradley vehicle; conventional armor, no ventilation; crew exits in 1 min			83	1.0	REG 0	No detectable effects[d]	Guilmette et al. 2005
Ingestion	Nitrate	Man	470	1	+	Transient albuminuria	Butterworth 1955
Inhalation	Hexa-fluoride	Man	20	1	—	No abnormalities	Boback 1975
Occupational (<10 to >20 y)	Yellowcake	39 workers	ND	1	++	Mild increase in aminoaciduria, $ß_2$m	Thun et al. 1985

(Continued)

TABLE 8-8 Continued

Route of Exposure	Chemical Form	Subjects	Uranium Intake (mg)	Peak Renal Uranium (μg/g)	Renal Effects[a]	Outcome	Reference
Embedded, inhalation (6-10 y)	Metal and oxides	16 soldiers	ND	1	++	Increased retinol binding protein excretion	Squibb et al. 2005
Level I: Abrams tank; DU armor, no ventilation; first responders			200	0.67	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, ventilation operating; crew exits in 2 h			110	0.56	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, ventilation operating; crew exits in 1 h			91	0.46	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, ventilation operating; crew exits in 5 min			43	0.23	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, no ventilation; first responders			27	0.14	REG 0	No detectable effects[d]	Guilmette et al. 2005
Level I: Abrams tank; DU armor, ventilation operating; crew exits in 1 min			10	0.05	REG 0	No detectable effects[d]	Guilmette et al. 2005

[a]Biochemical indicators of renal dysfunction: +++ = severe with clinical symptoms; ++ = protracted; + = transient; — =, no detectable effects.
[b]Committee interprets "may become ill" to mean may experience clinical symptoms of renal dysfunction and require medical attention.
[c]Committee interprets "not likely to become ill" to mean may exhibit low-level transient renal effects.
[d]Predicted outcome from Guilmette et al. 2005. Committee interprets "no detectable effects" to mean no low-level transient renal effects and no clinical symptoms.

TABLE 8-9 Capstone Predicted Renal Uranium Concentrations in Level II and Level III Personnel

Exposure	DU Intake (mg/h)	Peak Renal Uranium (μg/g-h)	Renal Effects	Predicted Outcome
Levels II and III: inhalation, breathing zone (mean)	0.447	2.8E-03	REG 0	No detectable effects[a]
Levels II and III: inhalation, area monitor (mean)	14.5	1.43E-01	REG 0	No detectable effects[a]
Level II: ingestion, hand to mouth (mean)	10.6	7.67E-02	REG 0	No detectable effects[a]
Level III: ingestion, hand to mouth (mean)	1.78	1.30E-02	REG 0	No detectable effects[a]

[a]Committee interprets "no detectable effects" to mean no low-level transient renal effects and no clinical symptoms.
Source: Adapted from Szrom et al. 2004.

ventional armor and no ventilation, level I crew exiting in 1 min from the Abrams tank with DU armor and no ventilation, level I first responders in the Bradley fighting vehicle with conventional armor and no ventilation, and level I first responders in the Abrams tank with conventional armor and no ventilation. With a lower REG-0 range, people in those exposure categories may exhibit transient renal effects, including excretion of albumin and low-molecular-weight proteins; time of recovery from these effects depends on excretion of the uranium. The committee agrees that for all other level I personnel exposures and for all level II and level III exposures modeled, detectable renal effects are not likely to occur.

The committee found REG 2 and REG 3 to be appropriately defined in the Capstone Report as over 6.4 to 8 μg/g and over 18 μg/g, respectively.

Cancer

Comparison of Radiation-Dose Estimates

The Capstone Report's cancer risk assessment for DU exposure is based on the radioactive properties of DU. In the absence of cancer risk factors specifically related to DU, the estimate of the risk of developing cancer in the Capstone Report is based on the radiation risks posed by alpha-emitters. The concern that DU may increase the risk of cancer is based on knowledge that radiation doses can be delivered to various organs by inhaled DU and that radiation is a known carcinogen.

The radiation dose estimates in the Capstone Report (presented earlier in Table 8-5) are within U.S. radiation standards for occupational exposure. The

U.S. annual limit for routine occupational exposure is 5 rem (10 CFR 20). The committed effective doses listed in Table 8-5 accrue over 50 y instead of a single year and do not directly correspond to annual doses. The true annual dose is much less than the 50-y committed effective dose. Thus, this is a conservative comparison. Furthermore, the Capstone-estimated median exposures are below the U.S. Nuclear Regulatory Commission annual dose limit of 10 rem for occupational workers with a planned special exposure (10 CFR 20), for example, protecting critical property during an emergency.

Estimates of radiation exposure in the Capstone Report compare well with previously reported exposure estimates. For a crew exiting in 1 min from a perforated vehicle without ventilation, the Capstone Report estimates median 50-y lung exposure as 5.2-17.5 rem; the Royal Society (2001, 2002) obtained a central estimate of 17.8 rem, and the U.S. Army Center for Health Promotion and Preventive Medicine (2000) estimate ranged from 1.5 to 13.2 rem.

Lifetime Cancer-Mortality Risk Estimate

Increased mortality based on organ-specific cancer risk coefficients of alpha-emitting radionuclides was used in the Capstone Report to estimate the risk of fatal cancer in selected organs. Biokinetic-model calculations of organ doses multiplied by organ-specific cancer risk factors estimate that the cancer risk posed by internally deposited DU is primarily to the lungs, which are relatively sensitive organs.

One of the strengths of the Capstone Report is that the calculated risks of cancer mortality were based on the sum of individual organ risks rather than on the whole-body effective dose. That provides a more refined assessment in that use of organ risk factors allows for the nonuniformity of dose distribution among organs. The approach could be used because of the availability of risk factors for lung-cancer mortality and mortality from cancer of other major organs as a function of alpha-emitter dose (ICRP 1991). The risk-factor coefficients for various organs are listed in Table 8-10. Summed organ risks resulted in total cancer-mortality risks that were about 35% higher than the estimated risks based on whole-body effective doses.

Lifetime cancer mortality risks were calculated with the conservative linear (no-threshold) dose-response model. That is, the estimated cancer mortality risk for an organ is proportional to the organ dose. The model might overestimate risks at the low doses predicted in the Capstone Report. The following is an example of the risk-assessment calculations included in the Capstone Report. For crew members who left an Abrams tank with DU armor and no ventilation 5 min after perforation, the median 50-y radiation dose to the lungs is estimated to be 44 rem. The cancer risk-factor coefficient for the lungs is 0.68×10^{-4} per rem. Using the linear model, the committee estimated the median lifetime risk of fatal lung cancer to be 3.0×10^{-3}, or three in 1,000 [$(0.68 \times 10^{-4}$ per rem) $\times$ 44 rem]. Similarly, the fatal lifetime risks for the other organs

TABLE 8-10 Risk-Factor Coefficients for Fatal Cancers in Worker Population

Organ or Tissue	Probability of Fatal Cancer per rem
Bladder	0.24×10^{-4}
Bone marrow	0.40×10^{-4}
Bone surface	0.04×10^{-4}
Breast	0.16×10^{-4}
Colon	0.68×10^{-4}
Extrathoracic tissues	0.10×10^{-4}
Kidney	$0.11 \times 10\text{-}^{4}$
Liver	0.12×10^{-4}
Lung	0.68×10^{-4}
Esophagus	0.24×10^{-4}
Ovary	0.08×10^{-4}
Skin	0.02×10^{-4}
Stomach	0.88×10^{-4}
Thyroid	0.06×10^{-4}
Remainder	0.19×10^{-4}
Whole body	4.00×10^{-4}

Source: Guilmette et al. 2005. Reprinted with permission; copyright 2005, Battelle Press.

were calculated by multiplying their cancer risk factors by their estimated 50-y alpha-radiation doses and summed with the lung-cancer risk to find the estimated median total fatal-cancer risk of 3.2×10^{-3}. The total estimated fatal-cancer risk is due primarily to the alpha-radiation exposure from DU retained in the lungs.

As noted earlier in this chapter, the committee found the Capstone Report's radiation-dose estimates to be reasonable predictions. The committee's estimates of level I exposures for the unventilated Abrams tank and Bradley fighting vehicle with conventional armor and the Capstone Report's estimates agree to within a factor of about 2 (see Table 8-5). The cancer risk estimate is proportional to exposure, so estimates of cancer risks also would agree to within a factor of about 2 for the level I exposure scenarios.

For unprotected level II personnel working in and around vehicles with a single perforation by a DU munition, the committee estimates a DU inhalation rate of up to about 12 mg/h compared with the Capstone Report's estimate of up to 14.5 mg/h; both considered ingestion of DU to be negligible. Because the estimated cancer risk is proportional to exposure, level II cancer risk estimates would be similar on the basis of the committee's estimate or the Capstone Report's estimates.

Limitations and Interpretation of Level I Risk Estimates

Exposures and cancer mortality risks were estimated for level I personnel. For the most likely exposure scenarios, median lifetime cancer mortality risk estimates presented in the Capstone Report ranged from 2.3×10^{-5} to 3.2×10^{-3} (one in 43,500 to one in 312; see Table 8-11). For the upper-bound exposure scenarios of 1 and 2 h, estimated median lifetime cancer mortality risks ranged scenarios of 1 and 2 h, estimated median lifetime cancer mortality risks ranged from 5.7×10^{-4} (one in 1,750) to 4.5×10^{-3} (one in 222) for the crew members confined in an Abrams tank with DU armor and no ventilation for 2 h after perforation.

A limitation of the median estimates in the Capstone Report is that they do not consider the inherent variability in the exposure estimates. At the 10th and 90th percentile estimates of exposure, lifetime cancer mortality estimates for some exposure scenarios are lower by as much as a factor of about 6 and higher by as much as a factor of about 3, respectively. For the 90th percentile of the exposure scenarios evaluated, the estimated lifetime cancer mortality risks approach 6×10^{-3} (0.6%). If a vehicle is penetrated twice, the lifetime cancer mortality would be expected roughly to double. That would result in median and 90th percentile estimated lifetime cancer risks of 9×10^{-3} (0.9%) and less than 12×10^{-3} (1.2%), respectively.

Given those levels of risk, it would be difficult to distinguish increased cancer mortality rates in exposed Gulf War personnel from background lung-cancer rates because 7.35% of U.S. males smoke and the overall lifetime risk of fatal cancers in males is 23.6% (Ries et al. 2003). In the small group of about 100 level I personnel, most of whom had lower exposure to DU, it is not likely that whatever fatal tumors develop could be attributed to DU exposure. Consistently with that conclusion, the Health Physics Society (HPS 1995) has issued a position statement that recommends against calculating risk estimates for exposure of less than about 10 rem (lifetime), because the risks would be either too small to be observed or possibly zero. It should be remembered, however, that multiple perforations can occur on the battlefield. As noted in the Capstone Report, cancer risks would roughly double if a vehicle suffered two perforations. for soldiers in tanks penetrated by two DU munitions, estimated radiation exposure in the Abrams tank without ventilation ranges from 1.8 to 17.4 rem. Hence, for the worst-case level I exposure scenario of 2 h in a twice-perforated Abrams tank with DU armor and no ventilation, the estimated median increased risk of fatal lung cancer would be 0.9% (one in 111), which is not an insignificant cancer risk.

The cancer risk estimates in the Capstone Report are also limited by their lack of consideration of additional risks to personnel who sustained DU fragment wounds and thus have higher exposure to DU over their lifetime than those calculated in the Capstone Report. Risks from embedded fragments were explicitly excluded from the Capstone Report. Thus, the cancer risks to people with embedded DU fragments are probably underestimated.

TABLE 8-11 Capstone Summary of Median (10th-, 90th-Percentile) Estimates of Increased Lifetime Risk of Fatal Lung Cancer (Expressed as %) from Inhalation Exposures of DU for Level I Personnel from Single Perforation of Vehicle

Exposure	Abrams Tank: Regular Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, Ventilation	Bradley Vehicle: Regular Armor, No Ventilation
Exit in 1 min	0.11 (0.07, 0.14)	0.12 (0.08, 0.24)	0.0049 (NA)	0.034 (0.009, 0.059)
Exit in 5 min	0.20 (0.17, 0.40)	0.32 (0.24, 0.52)	0.025 (NA)	0.099 (0.019, 0.180)
First responder	0.05 (0.03, 0.11)	0.10 (0.06, 0.16)	0.023 (NA)	0.052 (0.016, 0.077)
Exit in 60 min	0.27 (0.17, 0.44)	0.44 (0.32, 0.64)	0.057 (NA)	0.12 (0.06, 0.40)
Exit in 120 min	0.28 (0.16, 0.44)	0.45 (0.33, 0.65)	0.065 (NA)	0.14 (0.07, 0.41)

NA = not available.
Source: Parkhurst et al. 2005. Reprinted with permission; copyright 2005, Battelle Press.

Level II and Level III Risk Estimates

The Capstone Report is limited in not providing estimates of fatal cancer risks for potential exposure scenarios for level II or level III personnel. Such risks are difficult to predict because they depend on the duration and level of exposure. Because levels II and III exposures are not in the battlefield setting, some mitigating factors need to be considered, such as the use of personal protective equipment and decontamination of the vehicles. On the basis of exposure estimates in the Capstone Report (see Table 8-12), the potential for cumulative exposure suggests that fatal-cancer risks might be substantial in unprotected level II personnel working for several hours in perforated vehicles. The committee recommends that the number of hours that level II personnel work in perforated vehicles be limited or that protective equipment, particularly respirators, be used. The committee also recommends that if level II Gulf War personnel who had several hours of unprotected exposure in perforated vehicles can be identified, they should be included in the Department of Veterans Affairs health-surveillance program for DU-exposed soldiers.

Exposure of level III unprotected personnel in vehicles with a single DU-munition perforation is expected to be the same as that of level II personnel. Hence, exposure estimates for unprotected level III personnel in perforated vehicles are the same as the upper estimates reported for level II personnel, and similar risk estimates would apply.

For other exposure scenarios, estimates of level III exposure were presented in the Capstone Report. Upper estimates of level III exposure are listed

TABLE 8-12 Various Methods of Estimating Level II Mean Exposures of DU per Hour of Work by Unprotected Personnel Around and in Vehicles with Single Perforation by DU Munition

Dose Metric	Lower Estimate	Upper Estimate
Cumulative 50-y lung dose via inhalation	0.012 rem/h	0.56 rem/h
Intake via inhalation (ingestion risk negligible)	0.45 mg/h	14.5 mg/h
Cumulative 50-y whole-body dose (inhalation + ingestion)	2.7×10^{-3} rem/h	7.9×10^{-2} rem/h

Source: Adapted from Parkhurst et al. 2005.

here in Table 8-13. The estimates are very low, so it is reasonable not to calculate fatal cancer risks for these exposure scenarios.

Uncertainty of Estimates of Cancer Risk

The risk of fatal cancer is estimated by multiplying exposure to DU (expressed as rem) by the risk coefficient (expressed as risk per rem). That assumes a linear nonthreshold relationship of risk to exposure, which may overestimate risk at low doses by an unknown amount. Conversely, the risk coefficient is based only on the radiologic (alpha-emitter) effects of DU and does not include any potential risk due to chemical carcinogenesis of DU, so it might underestimate risk by an unknown amount. The uncertainty of risk estimates depends primarily on the uncertainty of exposure estimates and the uncertainty associated with the risk coefficient.

Potential cancer mortality from exposure to DU appears to be due almost entirely to lung cancer. Capstone lung-cancer risk estimates used a risk coefficient of 0.68×10^{-4} per rem (ICRP 1991), which is consistent with the data presented in Chapter 6 (Tables 6-2 and 6-3). The NRC (1988) estimated a lung-cancer risk coefficient of 0.35×10^{-4} per rem, which is about half the ICRP value. Koshurnikova et al. (1998) estimated a lung-cancer risk coefficient of 1.2×10^{-4} per rem, which is roughly twice the ICRP value.

Uncertainty of Chemical Carcinogenicity of Uranium

The cancer risk estimates in the Capstone Report were calculated on the basis of radiation doses associated with DU exposure and did not take into account chemical genotoxic effects of DU. That is consistent with historical approaches and recent reports, such as that of the Royal Society (2001), but it does not consider carcinogenic risks that could be posed by the chemical properties of uranium. Recent research has indicated that the mechanism of uranium's carcinogenicity might involve chemical reactions of the uranium ion with DNA (see Chapter 7) and DNA damage due to uranium's radioactive properties (re-

TABLE 8-13 Capstone Upper Estimates of Dose per Hour of Exposure via Inhalation by Unprotected Level III Personnel

Exposure Scenario	Intake (mg/h)	50-y Dose (rem/h)
Downwind of burning uploaded Abrams tank	2.8×10^{-3}	4.0×10^{-5}
Entry of burned uploaded Abrams tank	2.5×10^{-2}	4.0×10^{-4}
Downwind of vehicle perforated by DU munition	4.4×10^{-2}	7.0×10^{-5}

Source: Adapted from Parkhurst et al. 2005.

viewed in Chapter 6) and suggests that cancer risk from exposure to DU might be higher than estimated in the Capstone Report.

The extent to which the chemical carcinogenicity of DU affects cancer risk estimates is not clear and should be studied in greater detail. The committee recommends that studies be conducted to determine the relative contribution of chemical and radiologic mechanisms of uranium carcinogenesis. If the chemical contribution is found to be substantial, studies should be undertaken to calculate cancer risks resulting from DU's combined chemical and radiologic effects.

SUMMARY

The committee independently evaluated the Capstone exposure assessment. It used data developed largely outside the Capstone program to estimate the time-integrated concentrations of DU in the air in Abrams tanks and Bradley vehicles struck by DU munitions. The results compare favorably with the Capstone measurements. The estimated time-integrated air concentrations were used to estimate inhalation intakes for the five level I exposure scenarios defined in the Capstone Report. The committee's intake estimates are within a factor of about 2 of the Capstone results. Using those intake estimates, the committee also independently assessed the Capstone dose and risk estimates; its estimates are within a factor of about 2 of the Capstone estimates. The committee's results for level II and level III exposure resulting from surface contamination resuspended in the air and from incidental ingestion are similar to the Capstone results.

The committee concurs with the Capstone Report that the kidneys are the critical organs for acute chemical effects of uranium. Toxicity is due primarily to damage to renal tubular cells that leads to nephritis. Human occupational and accidental exposure to uranium consistently results in renal effects, and renal effects are also consistently noted in animal studies that report effects on targets other than the kidneys.

The committee had difficulty in verifying the REG-0 classification range for renal effects presented in the Capstone Report; it had questions about the interpretation of some studies and the relevance of the exposure in the studies to that encountered in military settings. Human exposure data suggest that transient proteinuria and albuminuria have occurred in humans with renal uranium concentrations as low as 1 μg/g. Thus, the REG-0 value may have to be redefined;

any revision to the upper-bound REG-0 value would also require that the REG-1 range be redefined. REG 2 and 3 should remain as defined in the Capstone Report.

Although epidemiologic studies of uranium workers indicate that the risk of cancer from exposure to uranium is low, the possibility of radiation-induced cancer from inhalation of insoluble DU particles cannot be ruled out, especially given that DU emits alpha particles. However, the latent period associated with radiation-induced lung cancer is at least 10 y and might be much longer.

The committee's estimates of level I, II, and III exposure are similar to those in the Capstone Report. The radiologic-cancer risk estimates are proportional to exposure, so cancer risk estimates based on radiation doses would be similar on the basis of Capstone Report exposure estimates or committee exposure estimates. On the basis of the exposures provided in the Capstone Report, the committee agrees with the radiologic-cancer risk estimates calculated in the Capstone study for the level I inhalation-exposure scenarios.

The Capstone Report does not provide estimates of radiologic-cancer risks for levels II and III personnel. The committee believes that that constitutes a deficiency in the report. On the basis of estimated exposure of levels II and III unprotected personnel working in and around vehicles 2 h or more after a single DU munition perforation, the 50-y whole-body dose (inhalation plus ingestion) is up to 0.079 rem/h of exposure, and the 50-y lung dose via inhalation is up to 0.56 rem/h of exposure. The estimated exposure would be higher and not insignificant for extended exposure in vehicles with multiple perforations.

The Capstone Report does not include cancer risk estimates for soldiers who have embedded DU fragments. That intentional omission is perhaps being addressed separately. Its exclusion from the Capstone Report leads to an underestimation of risk due to increased, prolonged systemic exposure to DU in this cohort of soldiers and of the risk of developing sarcomas in the vicinity of the embedded fragments.

RECOMMENDATIONS

- The committee recommends that the Army review the accuracy of the data presented in the Capstone Report on acute human exposures by verifying that uranium intakes were estimated appropriately from the original data, verifying that peak renal uranium concentrations were estimated appropriately with the same model, re-evaluating its interpretation of the Fisher et al. (1990) study, and re-evaluating the dataset by considering the relevance of route of exposure and chemical form to the military exposure scenarios. Depending on the outcome of that review and later calculations, the upper bound of the REG-0 range might need to be revised and the lower bound of the REG-1 range modified. Because of the uncertainties associated with any estimate, the Army should avoid setting REG values that suggest a great deal of precision, particularly in renal concentrations below 3 μg/g.

- Cancer risk estimates should be calculated for levels II and III exposure to determine whether vehicles perforated by DU munitions should be decontaminated to reduce the fatal-cancer risk from later exposure of unprotected people.
- For level II personnel working in vehicles perforated by DU munitions, the number of hours should be limited, or protective equipment, particularly respirators, should be used to reduce otherwise potentially important cumulative exposure to DU.
- If Gulf War level II personnel who had several hours of unprotected exposure to DU in perforated vehicles can be identified, they should receive additional health monitoring.

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Appendix A

Biographic Information on the Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat

Meryl Karol is professor emerita at the University of Pittsburgh. She received her PhD from Columbia University. Her expertise is in general toxicology, inhalation toxicology, and immunotoxicology. She is a past president of the Society of Toxicology and a former secretary-general of the International Union of Toxicologists. She previously served as chair of the National Research Council Subcommittee on Arthropod Repellants and was a member of the Committee on Pesticides and Children. She was an associate editor of *Toxicological Sciences*, and was on the editorial boards of numerous other toxicology journals. Dr. Karol currently serves on the science advisory board of the U.S. Environmental Protection Agency. She has served on the board of directors of the Academy of Toxicological Sciences and on advisory panels of the National Institute of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Office of Technology Assessment. She has also served on numerous international committees.

Cheryl Bast is a toxicologist in the Toxicology and Hazard Assessment Group at Oak Ridge National Laboratory. She earned a PhD in biomedical science (with emphasis on genetics and genetic toxicology and radiation biology) from the University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences in 1989. Dr. Bast's research interests include risk-assessment methodology, quantitative risk assessment, and chemical-hazard evaluation. She has performed health risk assessments and written numerous reports for federal agencies, including data-evaluation reports on pesticide registration, acute-exposure guideline level (AEGL) documents for the National Advisory Committee on AEGLs, and various other technical documents used to support hazard evaluations and risk assessments. Dr. Bast was certified by the American Board of Toxicology in 1993.

Deepak K. Bhalla is professor of toxicology in the Department of Occupational and Environmental Health Sciences at Wayne State University. He received his PhD from Howard University. His research is focused in air pollution, pulmonary toxicology, and immunotoxicology. He is chair of Wayne State University's Research Committee and has served on several National Institute of Environmental Health Sciences (NIEHS) and Environmental Protection Agency panels. He is on the editorial boards of the *Journal of Toxicology and Environmental Health* and *Inhalation Toxicology*. He has served on study sections of the National Institutes of Health and NIEHS and was a member of the American Society for Cell Biology's Congressional Liaison Committee.

David Gaylor is an adjunct professor of statistics at the University of Arkansas for Medical Sciences. He received his PhD from North Carolina State University in statistics. He is the recipient of the Shewell Award and the Frank Wilcoxon Prize from the American Society for Quality Control and of the Distinguished Achievement Medal from the Statistics and Environment Section of the American Statistical Association. He is a fellow of the American Statistical Society and the Society for Risk Analysis. He was a member of the National Research Council Committee on Toxicology and served on several of its subcommittees.

Robert A. Goyer is a clinical pathologist and an internationally recognized expert in health effects of toxic and nutritionally essential metals. He is professor emeritus at the University of Western Ontario. His research interests are experimental pathology, toxicology of heavy metals and metal interactions, and nephrotoxicity. He received his MD from St. Louis University. Dr. Goyer has published extensively on the toxicity of cadmium, lead, and arsenic and on risks associated with essential elements. He was chair of the National Research Council Subcommittee on Arsenic in Drinking Water and Committee on the Toxicological Effects of Methylmercury.

Sidney Green is professor of pharmacology at Howard University, where he received his PhD in pharmacology. Previously, he was director of the Department of Toxicology at Covance Laboratories and director of the Division of Toxicological Research at the U.S. Food and Drug Administration in the Center for Food Safety and Applied Nutrition. He was also director of the Toxic Effects Branch in the Office of Toxic Substances at the Environmental Protection Agency. Dr. Green has expertise in genetic toxicology and systemic toxicology. He is a former member of the National Research Council Committee on Toxicology and Subcommittee on Smokes and Obscurants. He is a past president of the American College of Toxicology.

Kathryn A. Higley is an associate professor in the Department of Nuclear Engineering at Oregon State University in Corvallis. She earned her MS and PhD in radiologic health sciences from Colorado State University. Her fields of interest include environmental transport and fate of radionuclides, radiochemistry,

radiation dose assessment, and environmental regulations. Her research has included the use of nuclear-track detectors for determination of plutonium and uranium particle size in soils, analysis of the micromorphologic distribution and association of these contaminants with soil structural features, kinetics of radionuclide movement in environmental systems, development of novel methods for estimating radiation dose to nonhuman biota, relationship of morphologic characteristics of radiologically contaminated surfaces on radiation-detector efficiency, and effects of scanning speeds of radiologic survey systems on detector efficiency. Dr. Higley has published several book chapters on the modeling of radioactive contaminants in environmental systems.

Sam Kacew is a professor in the Department of Pharmacology at the University of Ottawa. He received his PhD in pharmacology from the Ottawa University. His research focuses on the pharmacology of environmental contaminants. Dr. Kacew is a fellow of the Academy of Toxicological Sciences and recipient of the Velyien E. Henderson Award from the Society of Toxicology of Canada and the Achievement Award from the Society of Toxicology. He is on the grants committee of the National Institutes of Health and has served on several national and international panels. Dr. Kacew was a member of the Committee on Toxicology Subcommittee on Jet Propulsion Fuel 8 and chair of the Subcommittee on Iodofluoromethane. He is editor-in-chief of the *Journal of Toxicology and Environmental Health* and an associate editor of *Toxicology and Applied Pharmacology*.

P. Andrew Karam is a research assistant professor at the Rochester Institute of Technology. He received his PhD in environmental sciences from Ohio State University. Dr. Karam is a nationally and internationally respected board-certified radiation-safety professional with particular expertise in issues related to radiologic terrorism, the safe use of radioactive materials, and practical aspects of managing radioactive-materials programs. His extensive experience includes military radiation safety, radiation-safety program management, and occasional work as a consultant to the International Atomic Energy Agency. His current research interests include matters related to radiologic and nuclear terrorism, radiation-instrument development, and alpha-voltaic micropower-supply development.

Ronald L. Kathren is professor emeritus of pharmaceutical sciences at Washington State University and president of the Kathren Group, Inc., a safety and health-physics consulting firm formed in 1999. While at the university, he was director of the U.S. Transuranium and Uranium Registries and managed and performed research related to the biokinetics, dosimetry, and radiobiology of plutonium, americium, and the other actinides in humans. His other special interests include environmental radioactivity, education and training, and the historical aspects of the radiologic sciences. He received his MSc from the University of Pittsburgh. His scientific honors include the Elda E. Anderson Award for

outstanding contributions to the science and art of health physics, the Health Physics Distinguished Scientific Achievement Award, the Arthur F. Humm, Jr., Award of the National Registry of Radiation Protection Technologists, the Herbert M. Parker Award, and election to Delta Omega and the Society of Sigma Xi. In 1995, he was named Radiation Centennial Hartman Medalist and Orator. He is a diplomate of the American Board of Health Physics and the American Academy of Environmental Engineers, and he is a licensed professional engineer in California.

James McDougal is professor and director of toxicology research at Wright State University. He received his PhD from the University of Arizona. His research interests are in the mechanisms of skin penetration and irritation of toxicants and in developing biologically based mathematical models that can be used to estimate risks to humans from dermal exposures to chemicals. Dr. McDougal was formerly the director of research for the Toxicology Division of the Air Force Armstrong Laboratory. He has served on a number of national scientific advisory panels, including the National Research Council Subcommittee on Flame-Retardant Chemicals. He is a fellow of the Academy of Toxicological Sciences.

Bruce A. Napier is a staff scientist at the Environmental Health Sciences Group at Pacific Northwest National Laboratory. He received his MS in nuclear engineering at Kansas State University and is pursuing a doctorate in radiologic health physics at Oregon State University. He has over 27 years of experience in environmental health physics and has studied radionuclide transport, fate, and impact on humans and the environment. He is the author of the internationally accepted radiation-dosimetry computer package GENII. He was the chief scientist of the Hanford Environmental Dose Reconstruction Project, which evaluated the fate of radionuclides released into the air and Columbia River from the U.S. Department of Energy's Hanford site. He is a principal investigator in U.S.-Russia Joint Coordinating Committee on Radiation Effects Research projects on dose reconstruction for the public around the Russian Mayak (Chelyabinsk-65) nuclear-materials production site in Siberia. He has contributed to NATO evaluations of oceanic contamination.

Roy E. Shore is vice chairman and chief of research at the Radiation Effects Research Foundation. He received his PhD from Syracuse University and his DrPH from Columbia University. His research interests include radiation, environmental, and molecular epidemiology. He has served on the standing committees on radiation biology and risk assessment of the International Commission on Radiological Protection and the National Council on Radiation Protection and Measurements. He has served on several scientific advisory groups for the National Cancer Institute, the Department of Energy, and the Environmental Protection Agency and on the editorial boards of the *Journal of the National*

Cancer Institute, *Radiation Research*, and *Cancer Epidemiology, Biomarkers and Prevention*.

Katherine S. Squibb is a professor in the Department of Epidemiology and Preventive Medicine at the University of Maryland in Baltimore and head of the University of Maryland System-Wide Graduate Program in Toxicology. She received her PhD in biochemistry from Rutgers University. In addition to a basic-research interest in subcellular mechanisms of metal-ion toxicity and carcinogenicity, Dr. Squibb's research involves the study of health effects of ambient-air particles and the renal toxicity of heavy metals with a focus on depleted uranium through her work with the Baltimore VA Depleted Uranium Follow-Up Program. Since 1994, Dr. Squibb has also worked in risk assessment and public health, providing technical support to citizen groups involved in the evaluation of health effects and remediation of hazardous-waste sites in their communities.

Appendix B

Risk of Selected Cancers and Nonmalignant Diseases in Uranium Workers

COLORADO PLATEAU URANIUM MILLERS

At the Colorado Plateau uranium mills, uranium was extracted from ores to produce "yellowcake," a semirefined mixture of diuranates, basic uranyl sulfate, and hydrated uranium oxides that consists of 80-96% uranium (Pinkerton et al. 2004). The processes involved ore handling and preparation, extraction, concentration and purification, and precipitation, drying, and packaging. The uranium ore dusts in the preparation areas consisted principally of insoluble uranium oxides, although a small fraction was soluble uranium compounds. The mills dried the yellowcake at relatively high temperatures (370-538°C) in a process in which it was principally triuranium octaoxide with low solubility. Workers at the mills were also exposed to silica and vanadium in the dusts, and most of the mills recovered vanadium as part of the processing.

Pinkerton et al. (2004) conducted a mortality followup through 1988 of a cohort of 1,485 men who worked at seven uranium mills during 1940-1971 on the Colorado Plateau. Most of the cohort had previously been studied by Waxweiler et al. (1983) and Archer et al. (1973). The men were employed for 1-36 y (median, 3.6 y) in milling operations. Those who had worked in uranium mining were excluded because radon-exposure effects would probably predominate in that group. In addition to obtaining mortality data, the researchers linked the workers to the end-stage renal-disease data maintained by the Health Care Financing Administration (HCFA), which documents people who received renal dialysis or renal transplants.

Pinkerton et al. (2004) observed no statistically significant excess of cancer mortality overall or related to any specific site of interest. The lung-cancer risk was not statistically significant (relative risk [RR], 1.13), and there was a significant negative trend with duration of uranium-milling employment. The negative trend may be due to the "healthy-worker survivor effect" or to differences in smoking habits between short- and long-term employees. It may also be due to the fact that before 1955, when uranium-mill dust concentrations were higher, the workers tended to be short-term employees, whereas those employed after 1955 were exposed to lower concentrations of uranium dust and tended to

have longer employment. Lymphopoietic malignancies are of interest because human data indicate that inhaled insoluble uranium compounds accumulate in the tracheobronchial lymph nodes (Singh et al. 1987). The trend by duration of employment was in the positive direction for lymphopoietic cancers other than leukemia but was not significant.

Within the category of nonmalignant respiratory disease, there were excesses of emphysema (standardized mortality ratio [SMR], 1.96; 95% confidence interval [CI], 1.21-2.99; n = 21) and pneumoconioses and other respiratory diseases (SMR, 1.68; 95% CI, 1.26-2.21; n = 52). However, all nonmalignant respiratory diseases and emphysema were inversely associated with duration of milling work.

There was a suggestion of an excess of deaths from chronic renal failure in the Colorado uranium-miller cohort for the period 1940-1998, when only the primary cause of death was examined (SMR, 1.35; 95% CI, 0.6-2.7; 8 observed, 5.9 expected). In support of a possible increase in risk was the trend with duration of uranium-milling employment (SMRs, 1.27, 1.33, and 1.53 for 1-2, 3-9, and over 10 y of employment, respectively). However, when multiple causes of death as given on a death certificate were examined, there was no excess (SMR, 1.05); and when the incidence of treated end-stage renal disease was evaluated with HCFA's program data, there again was no excess (standardized incidence rate [SIR], 0.71; 95% CI, 0.26-1.65). A possible explanation for not finding significant effects is that renal exposures may have been low because the workers were exposed mainly to uranium compounds of low solubility.

TENNESSEE EASTMAN CORPORATION, OAK RIDGE, TENNESSEE

From June 1943 to May 1947, the Tennessee Eastman Corporation (TEC) plant was engaged in the enrichment of uranium with the electromagnetic separation process. Polednak and Frome (1981) determined the mortality experience through 1974 of a cohort of 18,869 white men who worked at the TEC Y12 plant. A substantial number of the employees (8,345) worked in the chemical departments (code named alpha and beta to refer to stages in the electromagnetic separation process), where exposures were high. In the alpha departments, uranium trioxide was converted to enriched uranium tetrachloride. Those departments, which had the highest uranium concentrations, operated until September 1945. Thereafter, uranium hexafluoride from the Oak Ridge K-25 (gaseous-diffusion) facility was fed to the beta stage of the process. Before late 1945, uranium trioxide was received from Mallinckrodt Chemical Works and converted to uranium tetrachloride, but thereafter exposure to the insoluble oxides was partly replaced by exposure to the more soluble uranium hexafluoride and uranyl fluoride. Uranium hexafluoride was converted to the oxides uranium tetraoxide and uranium trioxide and then to "green salt" in the beta departments. Other toxic exposure in the workplace included exposure to phosgene gas, mercury, carbon tetrachloride, and trichloroethylene.

The average uranium concentrations in the air in 1945 by department and activity are shown in Table B-1. Many readings were considerably higher, including occasional concentrations greater than 10,000-20,000 $\mu g/m^3$. There were no statistically significant increases in risk of total cancer, lung cancer, bone cancer, renal cancer, lymphoma, or leukemia, nor was there an excess of chronic renal disease or other diseases.

Cookfair et al. (1983) later conducted a case-control study at the facility to examine the possible association of uranium exposure and lung cancer in more detail. They had smoking information on about half the 330 cases and their controls. They reported no association overall but did find a nominal increase in risk in those who were over age 45 y old at exposure and received a lung dose of at least 200 mGy.

URANIUM-MATERIALS FABRICATION PLANT, OAK RIDGE, TENNESSEE

In 1947, the TEC uranium-enrichment operations ceased, and the Y12 facility shifted its function to fabrication and assembly of nuclear-weapons materials and the recovery and recycling of nuclear products or materials on behalf of the U.S. government. The production processes involved the conversion of uranium hexafluoride to uranium tetrafluoride and its reduction to uranium metal (Loomis and Wolf 1996). Exposure was primarily through inhalation of uranium-bearing dusts. Other workplace toxicants included solvents, machine oils, mercury, lead, and beryllium.

The Y12 worker cohort consisted of 10,597 men and women employed during 1947-1974; mortality was ascertained through 1990 (Checkoway et al. 1988; Loomis and Wolf 1996). The primary statistics were based on 6,591 white men because the nonwhite contingent was relatively small; there was substantial underascertainment of mortality in the women beause of difficulties in linking records. In the white men, the only cancer that had a statistically significant excess was lung cancer (RR, 1.20; 95% CI, 1.04-1.38; n = 194 deaths). However, there was no consistent pattern in lung-cancer risk by number of years since beginning Y12 employment or by duration of employment (SMRs for less than 5, 5-9, 10-19, 20-29, and 30+ y of employment were 1.23, 1.87, 1.87, 1.11, and 0.73, respectively). A recent reanalysis of the lung-cancer data that used external-dose measurements and estimated internal doses to the lungs, primarily from uranium dust, did not reveal a consistent relationship for the internal exposures, although the group with the highest external and internal exposures had the highest risk (RR, 2.2; 95% CI, 0.7-6.7; n = 7 lung cancers) (Richardson and Wing 2006).

In the 452 nonwhite (99% black) men, there were no statistically significant excesses of cancer or other mortality, although there was a suggestion of an excess of digestive-system cancers (SMR, 1.6; n = 7). Of the other common causes of death, no excess was seen for lung cancer (SMR, 0.60) or cardiovascu-

TABLE B-1 Average Air Concentrations of Uranium

Department and Activity	Average Concentration of Uranium Compounds (as Uranium) in Air ($\mu g/m^3$)
Alpha chemistry	
Sublimation (purification of UCl_4)	300
Bottle filling with UCl_4	250
Recovery of uranium, conversion to UO_3	500
Alpha process, Calutron, first stage	25
Beta chemistry	
UCl_4 production and bottle filling; recovery	50
Beta process (Calutron; second stage)	25

Source: Polednak and Frome 1981. Reprinted with permission; copyright 1981, Lippincott Williams & Wilkins.

lar disease (SMR, 0.55). In the 1,073 female employees, there was a nominal, nonsignificant excess of breast cancer (SMR, 1.21), a nominal deficit of lung cancer (SMR, 0.78), and a statistically significant deficit of circulatory diseases (SMR, 0.40; 95% CI, 0.2-0.8).

There was no excess mortality from either renal cancer or chronic renal disease in the Y12 cohort. Loomis and Wolf (1996) noted, however, that soluble uranium is more nephrotoxic than insoluble uranium and that the Y12 exposure was primarily to insoluble forms, although some people were working with uranium hexafluoride.

MALLINCKRODT CHEMICAL WORKS, ST. LOUIS, MISSOURI

The mortality experience of 2,514 white men employed during 1942-1966 at the Mallinckrodt uranium-processing facility in St. Louis, Missouri, has been assessed through 1993 (Dupree-Ellis et al. 2000). Mallinckrodt processed "pitchblende" uranium ore from the Belgian Congo, which contained up to 70% uranium and high concentrations of radium, so external radiation exposure (mean, 47.8 mSv) was more of an issue with this cohort than with other uranium-processing cohorts. Processing methods were crude by modern standards. Daily average uranium-dust concentrations in poorly ventilated processing areas were as high as 5,000-10,000 $\mu g/m^3$. Silica and sulfuric acid were other hazardous substances in the workplace.

White men were studied because other race-sex groups were too small. They had worked for a mean of 5.2 y and had a median followup of 36 y. There were no apparent excesses of total cancer, lung cancer, lymphoma, or leukemia. There was a slight suggestion of an excess of renal cancer (SMR, 1.17), and the researchers reported a significant trend in renal-cancer risk with external-radiation dose (excess RR, 10.5/Sv; 90% CI, 0.6-57.4). There was also a sugges-

tive excess of chronic nephritis. They reported nominal excesses of 30% or more for cancers of the esophagus, rectum, and brain and for multiple myeloma, although these excesses were not statistically significant.

FERNALD FEED-MATERIALS PRODUCTION CENTER, OHIO

Mortality was ascertained through 1990 in a cohort of 4,014 workers employed at the Fernald (Ohio) uranium-processing facility during 1951-1989 (85% were hired before 1960; Ritz 1999). Fernald workers processed uranium-ore concentrate and low-grade enriched uranium into fabricated uranium metal products. Most uranium exposure was to relatively insoluble compounds. Urine samples were routinely obtained to monitor uranium exposure. Radiation doses from both external and internal radiation sources were obtained; 33% of the cohort was estimated to have cumulative internal lung doses exceeding 50 mSv; only 9% of the cohort was estimated to have external doses exceedeing that level. Many workers also had exposure to solvents, especially trichloroethylene, and cutting oils; there was also exposure to tributyl phosphate, ammonium hydroxide, and hydrogen fluoride. Smoking information was available on 17% of the workers.

The workers were followed for an average of 31 y since hiring. There was no excess of total cancers or of lung, renal, brain, or testicular cancers. There was a suggestive but nonsignificant excess of hepatic cancer (SMR, 1.62) and a statistically significant excess of lymphomas (SMR, 1.81; 95% CI, 1.0-3.0). There was no excess of circulatory disease, nonmalignant respiratory disease, or hepatic cirrhosis. Chronic renal disease was not examined.

LUNG-CANCER CASE-CONTROL STUDY

Dupree et al. (1995) conducted a case-control study of lung-cancer risk in workers with uranium-dust exposure at four processing facilities (TEC/Y12, Y12, Mallinckrodt, and Fernald). The primary advantages of their study over the studies of lung cancer at the separate facilities (above) are the larger number of cases from the pooling across facilities, that they were able to perform a more detailed exposure assessment of the 787 lung-cancer cases and their 1:1 matched controls than was possible in the large cohorts, and that they were able to extract data to control, at least roughly, for socioeconomic status (pay codes) and smoking (ever vs never). Smoking information was available on only 48% of cases and 39% of controls. The smoking frequency among controls was high (75%) and was higher in the people with lung cancer (91%), as expected. No association was found between lung cancer and the lung dose resulting from internal exposures to uranium dust. Compared with a baseline group of those with internal lung exposures of less than 0.5 mGy, the odds ratios for those with estimated doses of 0.5, 2.5, 5, 25, 50, and 250+ mGy were 1.0, 0.6, 0.9, 0.8, 0.6, and 2.1 (95% CI, 0.2-21), respectively.

PORTSMOUTH URANIUM-ENRICHMENT FACILITY

This plant used a gaseous-diffusion process to enrich uranium up to 98% ^{235}U. Plant operations began in 1954. The 5,773 white men employed through 1982 were chosen for study by the National Institute for Occupational Safety and Health (Brown and Bloom 1987). The median length of employment at the plant was about 5 y. Potential exposure at the plant included exposure to uranyl fluoride and uranium hexafluoride. Because the uranium compounds were very soluble, urinary measurements of uranium were used. The exposures were relatively low: 94% of reported urinary measurements were below the limits of detection, 5.1% were 10-50 μg/L, and 0.6% were 50-200 μg/L. Exposures at the plant included exposure to hydrogen fluoride and technetium-99.

The study found no excess mortality from total cancers or lung cancer. There was no gradient of lung-cancer risk with amount of exposure. There was also no greater cancer mortality in those with longer employment. Although there was a nominal, nonsignificant increase in gastric and lymphohematopoietic malignancies, a subcohort selected for the greatest potential uranium exposure had reduced risks of these malignancies. Likewise, there was no excess mortality from chronic renal disease (SMR, 0.54), nonmalignant neurologic disease (SMR, 0.40; 95% CI, 0.21-0.68), or chronic respiratory disease (SMR, 0.46).

SAVANNAH RIVER NUCLEAR-FUELS PRODUCTION FACILITY

Operations at this plant included uranium and thorium processing; nuclear-fuel fabrication; nuclear-reactor operation, overhauling, modification, maintenance, and refueling; and nuclear-fuel reprocessing. There was a potential for varied internal exposure, including exposure to tritium, uranium, fission products, iodine, activation products, and several transuranics. A detailed analysis of the cause of death of 9,400 past employees showed deficits of all cancers, lung cancers, digestive cancers, brain cancers, and several types of nonmalignant disease. There was a nominal deficit of renal cancer and a significant deficit of chronic nephritis (2/7.42; SMR, 0.27; 95% CI, 0.03-0.97). The low mortality ratios were most likely due in part to a healthy-worker effect. The one suggestive finding was an excess of leukemia in hourly workers first employed before 1956. However, among the 14 people with leukemia in this group, only six had an indication of any kind of internal exposure, so it seems doubtful that uranium played a role in the excess. No information was provided on subgroups with exposure to uranium or other specific agents, so this study provides little information on the health effects of uranium exposure.

LINDE AIR PRODUCTS

From 1943 to 1949, the Linde Air Products Ceramics Plant near Buffalo, New York, was a uranium-processing facility. It mainly converted Belgian

Congo pitchblende and domestic uranium ores to uranium tetrafluoride; the relatively insoluble uranium oxide, uranium trioxide, and uranium dioxide were intermediate products. There was also exposure to cutting oils, welding fumes, organic solvents, and asbestos. The vital status of the 995 white men employed during 1943-1949 was determined through 1979 (Dupree et al. 1987). The results showed no excess of total cancers, lung cancers, or lymphopoietic malignancies. Teta and Ott (1988) extended the followup for an additional 2 y. They reported excesses of soft-tissue sarcomas and lung cancers, although the lung-cancer excess was not associated with length of employment. Hepatic cirrhosis was also found to be increased, perhaps because of the use of carbon tetrachloride at the plant.

UNITED NUCLEAR CORPORATION, CONNECTICUT

The United Nuclear Corporation fabricated nuclear fuels at a plant in Connecticut for many years; the 4,106 workers during 1956-1978 were followed for both mortality and cancer incidence through 1979 by Hadjimichael et al. (1983). A subset of 2,613 men called industrial employees sustained most of the uranium exposure. Their cancer incidence showed no statistically significant increases in risk. There was a statistically significant excess of nonmalignant respiratory diseases, but it was based on small numbers.

ATOMIC WEAPONS ESTABLISHMENT, UNITED KINGDOM

Several studies of uranium workers in the United Kingdom have been conducted. Beral et al. (1988) examined mortality among 22,552 workers with various exposures employed at the UK Atomic Weapons Establishment during 1951-1982. A total of 3,044 were monitored for uranium exposure. Most of the SMRs for the uranium-exposed group were unremarkable, but there was a statistically significant excess of prostatic cancer (SMR, 2.81; 95% CI, 1.14-5.84; 6 cases observed) and a marginally increased rate of renal cancer (SMR, 4.30; CI, 0.89-12.6; 3 cases observed). It should be noted that many workers were exposed to more than one radionuclide, so the apparent increases in risk may be associated partly with other exposure. In particular, the excess prostatic cancers were accounted for by workers who had had multiple radionuclide exposures, and two of the three people with renal cancer had also been monitored for polonium.

BRITISH NUCLEAR FUELS CAPENHURST PLANT

McGeoghegan and Binks (2000b) documented mortality and cancer incidence in a cohort of 12,540 employees at the Capenhurst plant of British Nuclear Fuels or its predecessors during 1946-1995. The plant mainly performed ^{235}U enrichment, beginning in 1953. The gaseous-diffusion process was used

exclusively until 1977, when the changeover to the gas-centrifuge process was begun; in 1983, it was completed. Workers at a small tritium-production plant in the complex also were included in the cohort. The mean cumulative external radiation dose to the 3,244 radiation workers was 9.85 mSv. Radiation doses from internally deposited radionuclides were not reported. The mean followup for mortality was 26.7 y. Cancer incidence was ascertained for 1971-1991.

The SMRs for the cohort were generally less than unity except for weak suggestions of increases in risk of lymphoma and of brain and central nervous system (CNS) malignancies. The findings on cancer incidence were qualitatively similar to the cancer-mortality data except that there was a small deficit of incident lymphoma (SIR, 0.59) and no indication of an increase in brain or CNS malignancies (SIR, 1.03). Of nonmalignant diseases, there was a nominal but not statistically significant excess of chronic renal failure (4 cases observed, 2.2 expected).

BRITISH NUCLEAR FUELS SPRINGFIELDS PLANT

The other UKstudy was of the Springfields plant of British Nuclear Fuels (McGeoghegan and Binks 2000a). The main activities at the plant were uranium-fuel fabrication and uranium hexafluoride production. The plant received yellowcake containing about 75% uranium. The yellowcake was dissolved in nitric acid to produce uranyl nitrate, which was purified and concentrated and then converted to uranium tetrafluoride by a process that included reacting at a high temperature with air and then with hydrogen fluoride. Some uranium tetrafluoride was converted to uranium metal, and some was reacted with fluorine to produce uranium hexafluoride, which was then sent for enrichment before being converted to uranium oxide fuel.

The Springfields study consisted of 19,454 workers during 1946-1955, of whom 13,960 were radiation workers. The mean external radiation dose was 22.8 mSv when one method of calculation of pre-1953 doses was used and 20.5 mSv when an another method was used. Doses from internal radionuclides were not available. On the average, the workers were followed for mortality for 24.6 y. Cancer incidence was examined for 1971-1991. It is notable that this was the largest study of uranium workers, in whom there were 971 cancer deaths. There were no indications of excess cancer mortality or incidence in the radiation workers compared with the general population, and there was no excess of chronic renal failure.

NONSPECIFIC STUDIES OF URANIUM AND OTHER RADIONUCLIDE EXPOSURES

Two epidemiologic studies have examined mortality in workers exposed to uranium or other radionuclides. Carpenter et al. (1998) examined cancer-mortality risk in UK workers exposed to plutonium, tritium, and other radionu-

clides, including uranium, but they did not report any results specific to uranium exposure. Similarly, a study of cancer mortality was conducted at Rocketdyne (Ritz et al. 2000), where workers were exposed primarily to uranium and mixed fission products but also to strontium, plutonium, and other radionuclides. No analyses of a specifically uranium-exposed group were reported.

FLORIDA PHOSPHATE-PRODUCTION WORKERS

Several studies of phosphate-fertilizer production workers have been conducted. The earliest reported an excess of lung cancer in blacks (SMR, 1.82; 95% CI, 0.7-4.0; 5 cases observed, 2.74 expected) at a fertilizer-production plant (Stayner et al. 1985). The risk was found in those with 20 y or more of employment and 20 y or more of observation (SMR, 12.5; 95% CI, 1.5-45; 2 cases observed, 0.16 expected), but no excess was observed in whites (SMR, 0.85; CI, 0.4-2.9; 5 cases observed). Phosphate-fertilizer production involves likely exposure to chromium, arsenic, and radon daughters in addition to uranium. A larger study was based on 18,466 white and 4,546 nonwhite men at 16 fertilizer plants in Florida (Checkoway et al. 1985, 1996). The SMRs did not differ appreciably between the white and nonwhite cohorts, so the committee combined the two cohorts in its assessment. The men had worked in the industry for an average of 9 y and were followed for mortality for a median of 22 y. The findings were unremarkable with two exceptions: there were statistically significant deficits of hepatic cancer and lymphoma, but there was an excess of lung cancer (SMR, 1.18; CI, 1.1-1.3). In white men, there were significant lung-cancer excesses for less than 5 y of employment (SMR, 1.23; CI, 1.05-1.4) and for 30 y or more (SMR, 1.94; CI, 1.13-3.1). The former may reflect smoking patterns in short-term workers, and the latter might reflect exposure to uranium or other contaminants.