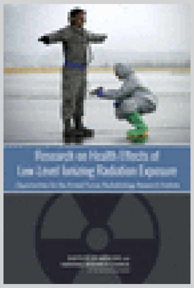

Research on Health Effects of Low-Level Ionizing Radiation Exposure: Opportunities for the Armed Forces Radiobiology Research Institute

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Nuclear and Radiation Studies Board

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

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Reviewers

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

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Richard J. Vetter, Retired; Section of Safety and Radiation Safety Officer, Mayo Foundation; Mayo Medical School

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 **Chris G. Whipple,** Principal, ENVIRON. Appointed by the National Research Council and the Institute of Medicine, he was responsible for making certain 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 authoring committee and the institution.

Contents

Abbreviations and Acronyms

AAPM	American Association of Physicists in Medicine
AFRRI	Armed Forces Radiobiology Research Institute
ARS	acute radiation syndrome
ATSDR	Agency for Toxic Substances and Disease Registry
BARDA	Biomedical Advanced Research and Development Authority (HHS)
BAT	Biodosimetry Assessment Tool
BEIR	biological effects of ionizing radiation
BNL	Brookhaven National Laboratory
CARR	Center for Acute Radiation Research
CAMI	Civil Aerospace Medical Institute
CBMN	cytokinesis-blocked micronucleus assay
CBRN	Division of Chemical, Biological, Radiological and Nuclear
CBRNE	Chemical, Biological, Radiological, Nuclear, and Explosives
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMCR	Centers for Medical Countermeasures against Radiation
CT	computed tomography
DARPA	Defense Advanced Research Projects Agency (DoD)
DASA	Defense Atomic Support Agency
DCA	dicentric chromosome assay
DDREF	dose and dose-rate effectiveness factor

DHS	U.S. Department of Homeland Security
DNA	deoxyribonucleic acid
DoD	U.S. Department of Defense
DOE	U.S. Department of Energy
DoReMi	Low Dose Research Towards Multidisciplinary Integration
DTP	Developmental Therapeutic Program
DTRA	Defense Threat Reduction Agency (DoD)
DU	depleted uranium
EPA	U.S. Environmental Protection Agency
EPR	electron paramagnetic resonance
FAA	Federal Aviation Administration
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
FSR&M	facilities sustainment, restoration, and modernization
HHS	U.S. Department of Health and Human Services
HJF	Henry M. Jackson Foundation for the Advancement of Military Medicine
HPS	Health Physics Society
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IND	improvised nuclear device
IOM	Institute of Medicine
ISN	Bureau of International Security and Nonproliferation
LBNL	Lawrence Berkeley National Laboratory
LET	linear energy transfer
LINAC	linear accelerator
LNT	linear no-threshold
LSS	Life Span Study
MCM	medical countermeasure
MEIR	medical effects of ionizing radiation
MELODI	Multidisciplinary European Low Dose Initiative
MRAT	Medical Radiobiology Advisory Team
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NCES	National Center of Education Statistics

NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements
NIAID	National Institute of Allergy and Infectious Diseases (NIH)
NIH	National Institutes of Health (HHS)
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council (of the U.S. National Academy of Sciences)
NRF	National Response Framework
NRIA	Nuclear/Radiological Incident Annex
NSBRI	National Space Biomedical Research Institute
NSF	National Science Foundation
NSRSS	NASA Space Radiation Summer School
O&M	operations and maintenance
OCET	Office of Counterterrorism and Emerging Threats
ORISE	Oak Ridge Institute for Science and Education (ORNL)
ORNL	Oak Ridge National Laboratory
OSCC	Oxford Survey of Childhood Cancer
OSTP	Office of Science and Technology Policy (Executive Office of the President)
PCC	premature chromosome condensation
PI	principal investigator
PNNL	Pacific Northwest National Laboratory
RadCCORE	Radiation Countermeasures Center of Research Excellence
RBE	relative biological effectiveness
RDD	radiological dispersal device ("dirty bomb")
RDT&E	research development testing and evaluation
REB	Radiation Epidemiology Branch (NCI)
RRP	Radiation Research Program (NCI)
RRS	Radiation Research Society
SED	Survey of Earned Doctorates
SES	socioeconomic status
STEM	science, technology, engineering, and mathematics
TRIGA	training, research, isotopes, general atomics
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
U.S. NRC	U.S. Nuclear Regulatory Commission

USAF	U.S. Air Force
USTUR	U.S. Transuranium and Uranium Registry
USUHS	Uniformed Services University of the Health Sciences (DoD)
VA	U.S. Department of Veterans Affairs
WMD	weapon of mass destruction

Summary

It is probably only a matter of time before we witness the next event in which large numbers of people are exposed to ionizing radiation. In the past, planning a response to such an occurrence would have likely focused on the management of casualties from high-dose exposure. However, more recently, a different threat has come to the fore: accidental (through a containment breach in a nuclear power plant, for example) or intentional (via a "dirty bomb") releases of radioactivity resulting in low-dose exposure to a population.

The magnitude of the health risks arising from low-dose radiation exposure is uncertain, and this uncertainty has significant economic implications for public health decision making. U.S. Department of Energy estimated the FY 2013–FY 2090 cost of cleanup at the radioactively contaminated Hanford Site in Washington State to be $114.8 billion (DOE, 2013). Three years after the March 11, 2011, Fukushima nuclear accident, nearly half of the evacuated populations is not able or willing to return to their homes (IAEA, 2011; WNA, 2014). The challenges of dealing with such situations are due in part to the difficulties associated with understanding and communicating radiation-exposure risks and solutions. For these reasons and others, it is important to improve the scientific understanding of biological effects of exposure to low-dose radiation.

The U.S. military has a particular interest and stake in understanding the effects of exposure to ionizing radiation. Response to nuclear threats has been a critical part of its planning process since the Trinity atomic test detonation in 1945, and U.S. Department of Defense (DoD) has long recognized the importance of maintaining a health-effects research program as part of this process. To that end, it established the Armed Forces Radiobiology Research Institute (AFRRI) in 1961 and gave it the mission to "preserve the health and performance of the U.S. military personnel and to protect humankind through research that advances understanding of the effects of ionizing radiation." AFRRI conducts research on the prevention, assessment, and treatment of injuries resulting from the effects of ionizing radiation and provides education on medical and emergency response to radiation-exposure incidents.

INTENT AND GOALS OF THE STUDY

In 2012, the Uniformed Services University of the Health Sciences (USUHS)—the DoD organization that exercises organizational responsibility for AFRRI—requested that the Institute of Medicine (IOM), in concert with the Nuclear and Radiation Studies Board of the National Research Council (NRC), examine recent scientific knowledge about the human effects of exposure to low-dose radiation from medical, occupational, and environmental ionizing-radiation sources, focusing on the work of and opportunities for the Institute. They asked that the study

1. Identify current research directions in radiobiological science related to human health risks from exposure to low-dose ionizing radiation.
2. Assess how AFRRI programs are advancing research along these directions.
3. Identify opportunities for AFRRI to advance its mission for understanding human health risks from exposure to low-dose ionizing radiation with special emphasis on DoD military operations and personnel.
4. Assess the demand for radiobiology researchers and examine workforce projections. If workforce projections are inadequate to meet demand, suggest ways to accelerate training and investigator development.

This report, prepared by the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation, answers that request.

FRAMEWORK AND ORGANIZATION

The committee organized its approach to responding to its tasks into four primary chapters addressing the following topics:

- An introduction to the topic of human health effects from exposure to ionizing radiation; an explanation of the committee's statement of task; the methodologic considerations that informed the committee's evaluation of the literature; and summary information on earlier National Academy of Sciences reports addressing such related topics as the health effects of exposure to low-level ionizing radiation; military radiation exposure concerns; radiation exposure in other populations, including civilians; and the research workforce (Chapter 1).

- Background on the current directions in radiobiology research, with a focus on the cancer and noncancer health effects associated with exposure to low levels of radiation and the tools available to researchers to study them; the different methods used to analyze biological markers of dose or effect; and the factors that influence the risks associated with exposure (Chapter 2).
- The state of the radiobiology research workforce, including a description of the field of study and information on the supply of and demand for professionals in the discipline (Chapter 3).
- Details on AFRRI's organization and its role in radiobiology research: the history of the Institute; its physical plant, staff, budget, and capabilities; its research priorities and portfolio; its education, training, and emergency response responsibilities; and its interactions with the broader research community (Chapter 4).

These chapters contain the details and analysis that build the foundation for the findings, conclusions, and recommendations presented in Chapter 5. Chapter 5 puts forward a series of proposals for how AFRRI might build on its strengths and advance its mission while contributing to the body of scientific knowledge on the health effects of exposure to low-dose ionizing radiation.

THE COMMITTEE'S EVALUATION

Current Directions in Radiobiology Research

The health effects of exposure to high doses of ionizing radiation (1 gray [Gy] and above) are generally well understood; when they are not, research methods exist to address unanswered questions. Research opportunities in this dose range exist for the study of genetic and epigenetic effects on future generations, although these may be of less significance to the military than acute outcomes that affect its ability to carry out missions.

Less well established, even at high doses, are the effects of radiation dose modifiers, such as radiation quality, dose rate, individual sensitivity, and combined injury.[1] Studies of the significance of these modifiers at high doses are often feasible with current methods, but their results are typically dependent on the assumptions made to model effects.

At lower radiation doses, data interpretation is more challenging because it becomes increasingly difficult to distinguish effects attributable to exposure from other causes. Most of the epidemiological data to date at dose levels less than 1 Gy are for carcinogenesis, cardiovascular effects, and cataracts. Other radiation-induced endpoints may be present at lower doses but masked by confounding factors.

Methods for lower-dose studies are much less well established than those for high-dose research. Epidemiological studies are currently quite limited, and laboratory models do not directly relate to radiation-induced carcinogenesis in humans. There are theoretical models for extrapolating risks from higher to lower doses, but these have yet to be validated.

Scientific advances are providing new opportunities to understand the effects of ionizing radiation at subcellular levels and to translate this understanding to whole organisms. For example, new molecular biology tools enable the study of radiation effects at doses that are below those considered amenable to study using traditional epidemiological methods. These tools can be used to investigate chemical changes to DNA molecules that affect their signaling capacity and alter molecular expression in the absence of DNA structural damage, thus yielding information that might inform the evaluation of more subtle and long-term health effects in coordination with targeted epidemiological studies.

There are thus a number of unanswered questions regarding the human health effects of low-dose ionizing radiation exposures and, although scientific advances provide opportunities to address them, significant challenges are associated with moving forward.

For many years, the United States has been the world leader in understanding the health consequences of radiation exposure, but more recently, research in this area has slowed down, and the country lacks a long-term milestone-driven strategic plan for better understanding effects and risks of low doses. Sixteen nations—under the aegis of the Multidisciplinary European Low Dose Initiative and its low dose research towards multidisciplinary integration (DoReMi) research integration effort—are already pursuing the development and implementation of such a plan, and the United States would benefit from undertaking similar action.

[1] A combined injury is "physical, thermal, and/or chemical trauma combined with radiation exposure at a dose sufficient to diminish the likelihood of overall survival or functional recovery" (HHS, 2014).

The Radiobiology Workforce

Radiobiology, the study of the effects of ionizing radiation on living things, is a diverse field whose workforce includes individuals who were trained in various disciplines and who engage in varied areas of practice, including clinical care, monitoring of radiation exposure, research, and teaching. As such, it is difficult to evaluate the supply of and demand for professionals because there is no uniformity in the name given to their degree program or their self-identification. Professional societies have some data on their membership, but such information presents an incomplete picture.

Although it does not appear that there is currently an acute shortage of researchers in radiobiology and related disciplines, available information suggests that the number of professionals leaving the field through retirement and other means exceeds the number entering and that this trend will continue. Assuming a continuing demand for radiobiology research, it is reasonable to conclude that the supply of professionals will not meet the demand in the coming years. When this committee completed its work, the congressionally chartered National Council on Radiation Protection and Measurements was engaged in an effort to better characterize the magnitude of the problem and offer recommendations for addressing it on a national level.

AFRRI Programs, Research, and Resources

AFRRI is the only DoD entity dedicated to ionizing-radiation health-effects research. Its unique infrastructure boasts a 1-Megawatt TRIGA® Mark F reactor that is one of the few dedicated to radiobiology research. It also houses X-ray, cesium-137 (^{137}Cs), and cobalt-60 (^{60}Co) exposure sources and a vivarium that maintains rodents, minipigs, and nonhuman primates for studies. The Institute's research portfolio principally comprises work addressing biodosimetry, combined injury, internal contamination and metal toxicity, and countermeasure development. Some projects are supported by and in some cases conducted at the behest of government or private-sector funders, whereas the remainder are initiated by its principal investigators and supported internally. AFRRI also fulfills its mission by producing manuals and protocols on radiation-exposure response, conducting education and training in these areas, supplying nuclear and radiological emergency response assistance, and providing advice to the federal government.

Although AFRRI has conducted a small number of studies at low doses, low-dose radiation exposure was not a specifically defined research area at the time this report was written. In the dose range 1 Gy and below, studies include the development of models to study carcinogenesis and non-targeted effects at the molecular level. Late effects of radiation (including internal and external contamination from depleted uranium [DU]), countermeasures to prevent those late effects, and associated biomarkers are also being studied. Areas of research that address both low- and high-level exposure include the tissue and cellular effects of combined injuries on the skeletal system, countermeasures to the effects of low dose-rate gamma radiation encountered in nuclear fallout, and some of the Institute's biodosimetry and exposure characterization work.

The Institute's current portfolio of studies is focused almost exclusively on exposures above 1 Gy—a range that the research community and international organizations classify as moderately high and high dose. This work is consonant with AFRRI's mission and yields information that is vital to managing the consequences of nuclear and radiological material releases as a result of armed conflicts, terrorist actions, and accidents. It does not, though, generate knowledge that would help answer the questions identified as being important to understanding the health risks of low-dose radiation exposure. The committee thus concludes that while AFRRI carries on a robust program of research on the biological and health effects of high-dose ionizing radiation exposure, it is not currently substantively advancing low-dose research.

THE COMMITTEE'S FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

In the course of its work, the committee examined the full range of AFRRI's activities. Although its statement of work was focused on low-level radiation, it also offers observations applicable to the full range of AFRRI's activities and on organizational issues because the success of a low-level radiation program depends on the viability of the Institute's entire research enterprise.

AFRRI'S SCIENTIFIC PROGRAM AND OUTREACH ACTIVITIES

AFRRI as a Unique National Asset

DoD has tasked AFRRI to conduct research in the field of radiobiology and related matters essential to the operational and medical support of the U.S. military and has given it responsibilities that include operating a radiobiology- and ionizing-radiation-bioeffects research facility; cooperating with other military components, federal agencies, and outside investigators on relevant studies; providing training in radiobiology, medical and emergency response, and related fields; and consulting with the services and government in their areas of expertise. There is no other DoD-level organization whose mission is so comprehensive and has such a broad scope in radiological health and protection.

AFRRI's programs and outreach activities provide the nation with important fundamental research, basic knowledge, practical applications, tools, and guidance associated with radiobiology and related matters essential to the operational and medical support of DoD and the Military Services as well as civilian and emergency responders. The Institute's unique infrastructure, which would be difficult to reproduce elsewhere, positions it to contribute to research on the health effects of low-level ionizing radiation.

Opportunities for Additional or Expanded Roles for AFRRI

AFRRI's research currently focuses on issues related to high-dose radiation exposure. Although some low-dose work is conducted, and other existing initiatives either have low-dose applications or could presumably be extended into this exposure range, the Institute appears likely to remain oriented toward high-dose work for at least the short term because that is where the experience and practical knowledge of its personnel are centered. For these reasons, the committee concludes that it is not appropriate to propose a specific low-dose research agenda as indicated in its statement of task. Performing substantive work in this area will first require changes in institutional culture and a reorienting of staff expertise. Nevertheless, the committee believes that there may be opportunities for AFRRI to contribute to the understanding of human health risks from exposures to low-dose ionizing radiation in a manner that is consistent with its mission; that take advantage of its current expertise, its infrastructure, and its position within the DoD; and that put it on the pathway toward making greater contributions to this area of research in the future.

AFRRI has opportunities for additional or expanded work in the following areas: nuclear- and radiological-emergency response; treatment and management of psychological injuries after a nuclear or radiological event; development and evaluation of field radiation instrumentation; training of radiation-research and -response professionals; and support of radiation epidemiology and risk research. Some of these entail cooperation with outside investigators to facilitate their low-dose research; others extend existing Institute initiatives to cover low-dose exposures.

Preparedness and Response to Nuclear or Radiological Emergencies

AFRRI has been primarily concerned with the effects of nuclear weapons on the battlefield and the survival of military personnel in such environments. Much of this knowledge is directly applicable to emergency response and protective actions for the civilian population in the aftermath of a low-level nuclear or radiation-release event. AFRRI has developed and disseminates data-gathering instruments that are needed in the event of such an emergency. However, **an opportunity exists for AFRRI to make its nuclear and radiological incidents response educational materials, forms, and tools—which are already amenable to civilian applications—more useful to both the military and civilians by adapting them to modern digital devices such as tablets and smartphones and assuring their applicability to low-level exposure incidents.**

Another potential area is in the training, equipping, and standardizing of the multiple DoD radiological response teams. Currently, the U.S. Army, Navy, and Air Force have their own response teams that were originally chartered to respond to a nuclear weapon accident but whose missions now include radiological accidents and spills. Despite the commonality of their responsibilities, they have different procedures, instrumentation, sample collection and analysis capabilities, and command structures.

An opportunity exists for AFRRI to have a coordinating role within the services to facilitate standardization of their radiological response teams, and to ensure they are well trained and equipped to deal with low-level radiation incidents.

If DoD chooses to tap the Institute's expertise, AFRRI's coordinating role could extend to supporting the procurement of radiation-detecting and -analysis instrumentation (addressed below), contamination control materials, health physicist and technician training, command and control, field procedures, external and internal dosimetry, computer projection models, and sample collection and analysis methods.

Management of Psychological Effects Associated with a Nuclear or Radiological Emergency

Nuclear and radiological exposure incidents pose special challenges because the stressor is invisible and cannot be sensed or avoided like other threats. The management of psychological effects related to a nuclear or radiological event falls under AFRRI's mission to preserve the health and performance of U.S. military personnel, but the Institute does not currently have psychologists, psychiatrists, risk-communication specialists, or professionals in related fields as members of its research staff. USUHS, however, is well positioned to help implement information dissemination, training programs, and research intended to give military health care providers and first responders the tools and techniques to treat psychological injuries and deal with other issues resulting from release incidents.

Thus, **an opportunity exists for AFRRI to serve as a source of information, training, and research on the response to psychological issues raised**

by low-level nuclear and radiological release incidents if an institutional decision is made to collaborate with USUHS staff for this purpose. This in-house expertise will be helpful in crafting the psychological-injury component of AFRRI's incident-response training responsibilities.

Development and Management of DoD Radiation-Protection Instrumentation

DoD has a long history of designing, acquiring, and testing environmentally rugged radiation-protection instruments designed to withstand the harsh environments in which they operate.

Despite the fact that all three branches of Military Services have some common radiation-detection and measurement needs, the branches develop their own instrument performance specifications and acquire the instruments independently, leading to the use of different equipment designs to detect essentially the same radiation(s). Resulting interservice operability problems compound military responder training and equipment field maintenance. DoD has recently undertaken to establish a joint acquisition effort to provide personnel with instrumentation that would enable the services to effectively conduct joint operations with interoperable equipment.

An opportunity exists for AFRRI to aid in the integration and coordination of DoD purchases, commissioning, acquisition, testing, maintenance, and use of radioactivity detection instruments and to help ensure that such instruments will be useful in low-level exposure circumstances.

AFRRI is well suited to support this DoD initiative because it has the qualified staff (health physicists), facilities (calibration-exposure rooms), and dosimetry experience needed to help develop instrument-performance specifications and perform acceptance testing. Investments may need to be made in staff training and for exposure chambers needed for environmental testing of candidate devices should DoD choose to take advantage of this opportunity.

Radiation Professionals Workforce Education

AFRRI has the necessary infrastructure to help support graduate education in several radiation specialties greatly needed within DoD and the civilian sector, including radiobiology, health physics, medical physics, radioepidemiology, and radioecology.

As of January 2014, the USUHS website stated its intent to establish a Radiation Biology track within the school's Molecular and Cell Biology program. It also listed an acting chair of the department (an AFRRI investigator who holds an appointment in the university) and nine faculty members, some of whom are AFRRI investigators and all of whom have adjunct appointments. In response to a question from the committee, AFRRI indicated that although USUHS planned to begin granting degrees in radiation biology in 2013, funding shortages have delayed implementation of the program.

Other degree programs that USUHS does not offer currently—for example, in health and medical physics[2]—could be built around the advantages of its proximity to AFRRI. The Institute's laboratory and reactor facilities are an asset not shared by many universities with graduate health-physics programs and are well suited to train military health physicists, who face some unique challenges not encountered by their civilian counterparts; these include potential exposure to nuclear weapons, reactors used to power ships and submarines, military equipment that uses radioactive sources, and nuclear battlefield operations. Each year the service branches send junior officers to attend civilian universities to earn graduate degrees in health and medical physics because equivalent graduate-level programs do not exist at DoD service academies or institutes.

An opportunity exists for AFRRI to contribute to the education of radiation professionals through better integration and coordination with USUHS so that the university's degree programs support AFRRI needs and, in turn, AFRRI's research facilities support degree candidates' research. Specifically, implementation of the nascent USUHS program in Radiation Biology would help accelerate training in that field, address concerns over coming shortages of professionals, and facilitate the recruitment of new researchers for the Institute, including those with low-dose radiation expertise.

The success of a USUHS program in radiation biology or in other radiation health–related fields will depend critically on the active support of the Military Services, which determine which programs their personnel may be sent to for advanced training, and on the availability of research and graduate education funding.

Support of Radiation Epidemiology and Risk Research

To date, AFRRI has had relatively little involvement in epidemiology research and risk projections, and its staff does not have expertise in these areas. Should the Institute wish to extend into such work, it would be well positioned to support studies conducted by others that are consonant with its current expertise by, for example, providing information on biologic changes induced by radiation exposure and on military populations who have experienced DU exposure or combined injuries, which would feed into

[2] An accredited health physics M.S. and Ph.D. program formerly existed at USUHS but is not currently active, so it is unclear whether this is considered a priority by DoD.

research on health outcomes in targeted subpopulations. Further, the study of radiation-induced carcinogenesis will benefit from the identification of biomarkers and bio-indicators of radiation-associated disease that could be used in population studies.

Therefore, **an opportunity exists for AFRRI to contribute to research on low-level effects through molecular and cellular studies of radiation-induced alterations that could be employed in epidemiologic and risk assessment studies, and by extending its work in areas like DU exposure and combined injuries to generate information for use in such investigations.** To implement this, AFRRI will need to collaborate with outside subject-matter experts to define hypotheses to be tested.

AFRRI's location in DoD may also allow it to facilitate certain other investigations. The potential exists to link DoD radiation-exposure data with health information gathered by the military health system and the Department of Veterans Affairs and to use "big-data" techniques to conduct studies, thus avoiding the expense of collecting information directly from subjects. In addition, AFRRI could take advantage of its position within USUHS to collaborate with the faculty and students in the graduate programs in biomedical sciences and public health. Another source is the National Cancer Institute's (NCI's) Radiation Epidemiology Branch, which also has interests in the health effects of low-dose exposures and in dosimetry.

Opportunities for Expanded and Additional Outside Collaborations

Federal Agency Collaborations

AFRRI's responsibilities overlap with those of three other federal bodies with which it would seem to have natural affinities because of their common interests in the consequences of nuclear and radiological material releases: the Defense Threat Reduction Agency (DTRA) and the U.S. Department of Homeland Security (DHS)—which also conduct nuclear and radiation-event response training—and the Defense Advanced Research Projects Agency (DARPA), which is interested in technologies that mitigate radiation health risks. However, it currently conducts rather little work with these governmental bodies, and the efforts that have taken place have focused on high-dose questions. **An opportunity exists for AFRRI to advance its mission by actively pursuing low-level exposure research funding and collaborations with DTRA, DARPA, and DHS.** Further, **an opportunity exists for AFRRI to better integrate itself into the national nuclear and radiological response mechanism by expanding coverage of low-level exposure topics in their existing training courses and materials and adapting these to civilian emergency responders and international audiences.**

Opportunities to Facilitate Research by Outside Investigators

DoD has specific interests and needs in the low-level realm that may not be priorities for civilian entities, and the committee believes that there are ways for AFRRI to advance these interests without acquiring new staff. Notably, the Institute's radiation facilities are underused—with the TRIGA reactor free 79% of its operating days and the cobalt-60 source free for 50.5%—and their low-level source is virtually unused. Thus, **an opportunity exists for AFRRI to expand its participation in low-level radiation health effects research by making its facilities more open to use by outside investigators interested in conducting research consistent with its mission.** Allowing outside investigators to take advantage of the dead time to conduct DoD-relevant studies would not only increase the productivity of these assets but would also create new collaborations and additional sources of support for AFRRI staff. The committee understands that such work is currently possible but that associated logistical and administrative challenges represent a significant barrier to conducting such collaborative research. Facilitating the use of AFRRI facilities by outside investigators, including animals managed by its vivarium, would thus require a change in culture within the organization. Nevertheless, the committee believes that ways could and should be identified to achieve greater openness while preserving the security of the site and meeting other AFRRI and DoD requirements.

AFRRI ORGANIZATION AND ADMINISTRATION

Scientific Leadership

AFRRI's management structure formerly included a Scientific Director, a civilian who, along with the Director and Chief of Staff, comprised the senior leadership of the organization within an Office of the Director. This position, however, has not been filled since 2012. There is currently a Scientific Advisor who reports to the Director, but whose duties do not include supervision of senior research staff.

The committee believes that having a Scientific Director in a leadership position helps to achieve several goals that are important for AFRRI if it wishes to pursue a more extensive program of research on the human health risks from exposures to low-level ionizing radiation and, more generally, to promote its standing and visibility in the radiobiology research community—goals that would not necessarily be fulfilled by someone serving in an advisory role. If this person is well-respected in the low-dose scientific community, it would greatly facilitate AFRRI's efforts to establish an influential research program, attract new investigators with expertise in low-dose questions, and obtain funding for such work.

The committee believes that AFRRI will strengthen its position as an ionizing-radiation health-effects research organization when the position of Scientific Director is filled. The key roles of this person in new research projects that "advance the understanding of human health risks from exposures to low-level ionizing radiation, with a special emphasis on Department of Defense military operations and personnel" will be to

- **Develop institutional low-dose research capacity by facilitating collaborations with outside subject-matter experts and, where needed, recruiting new personnel; and**
- **Identify and implement low-dose initiatives that are responsive to DoD needs with milestones and deliverables (for accountability, promotion, and direction) while building on AFRRI's existing strengths.**

External Program Evaluation

At present, almost all of AFRRI's research initiatives are assessed on a project-specific basis, with the sponsor's review mechanisms and program managers performing the evaluation function. The intramural research program is reviewed by a panel of outside experts along with AFRRI scientific leadership, but this work accounts for only about 20% of the Institute's portfolio. AFRRI does not currently have a long-term research plan, although it indicates that one is under preparation.

The committee believes that **AFRRI's existing and new research on human health risks from exposures to low-level ionizing radiation, along with the rest of its scientific enterprise, would benefit from a strong, continuing external program evaluation that examined the totality of the Institute's work.** The purposes of such oversight would be to provide input on the quality and usefulness of current work and to assist in defining and setting reasonable and achievable research directions and priorities on the basis of the collective radiobiology knowledge base and AFRRI's mission(s). It would further promote a closer working relationship with outside organizations for the purpose of research collaboration and facilitation of greater use of AFRRI's physical plant assets.

There are also other means of facilitating external evaluation of AFRRI's prospective low-dose and other research activities. Possible means include supporting more of the Institute's research through a funding mechanism that requires such oversight. Operations and maintenance (O&M) research funding represented more than 70% of all research support and more than half of the total budget in FY 2013. AFRRI's O&M funding, however, does not have a direct connection to a funding source that expects to see an outcome at the end of the project: it often comes with no specific milestones or expectations other than the conduct of some type of radiobiologically related research. Most military-related research conducted in other DoD laboratories is supported by research development testing and evaluation (RDT&E; also known as Program 6.X) funding sources, which require a client or sponsor for the research. The sponsor specifies the research topic, defines the desired outcome measures, and tracks the research organization's progress toward the desired outcome. In this funding scenario, projects are driven by the customer, so there is no disconnect between what the client (typically the military, in the case of AFRRI) needs and what the researcher provides. Prior to 2005, AFRRI research was exclusively supported by RDT&E funds, but this has changed in recent years (AFRRI, 2013).

Thus, AFRRI may benefit if more of its radiobiology research were supported by RDT&E funds, leaving O&M research funding to support exploratory studies and educational program costs. This alternative, if pursued by DoD, would increase the accountability of investigators and better tie their work to demonstrable research outcomes.

External evaluation—and outreach to the greater research community—would also be facilitated by two other steps. One of these is the resumption of the practice of producing an annual report. A yearly accounting of the Institute's research initiatives, the accomplishments of its staff and effect of their work, and the ways in which its funds were spent would permit DoD sponsors and outside parties to gain a better understanding of AFRRI's contributions in radiation research and health. The other step would be to make the seminars conducted by AFRRI staff more accessible to researchers outside of the Institute. Although security considerations will limit access to some of the Institute's work, making the unrestricted seminars more open—by, for example, webcasting them and allowing viewers to actively participate in the proceedings—would permit the kind of informal peer review that improves research products.

REFERENCES

AFRRI (Armed Forces Radiobiology Research Institute). 2013. Responses to supplementary questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, October 31, 2013.

DOE (U.S. Department of Energy). 2013. *2013 Hanford Lifecycle Scope, Schedule and Cost Report*. http://www.hanford.gov/files.cfm/2013%20Fact%20Sheet%20Final%20_1-29-13_.pdf (accessed January 27, 2014).

HHS (U.S. Department of Health and Human Services). 2014. *Radiation + Trauma (Combined Injury)*. http://www.remm.nlm.gov/radtrauma.htm (accessed May 25, 2014).

IAEA (International Atomic Energy Agency). 2011. *Fukushima Nuclear Accident Update Log—Updates of 12 March 2011*. Vienna, Austria: International Atomic Energy Agency. http://www.iaea.org/newscenter/news/2011/fukushima120311.html (accessed February 20, 2014).

WNA (World Nuclear Association). 2014. *Fukushima Accident—Updated 26 February 2014*. London, United Kingdom: World Nuclear Association. http://www.world-nuclear.org/info/Safety-and-Security/Safety-of-Plants/Fukushima-Accident (accessed February 27, 2014).

1

Introduction and Background

This chapter provides basic information about the motivation for and the conduct of the study summarized in this report, beginning with an overview of the issues related to the health effects of exposure to low-dose ionizing radiation and the interest of the organization that requested the report—the Uniformed Services University of the Health Sciences (USUHS) of the U.S. Department of Defense (DoD)—on this subject. It then presents the statement of task for the committee responsible for conducting the study and discusses the committee's approach to its task. Summary information on related reports from the National Academy of Sciences (NAS) is presented, and the chapter concludes with a description of this report's organization.

THE ISSUE OF LOW-DOSE IONIZING RADIATION HEALTH EFFECTS

Any discussion of low-dose radiation health effects requires defining what *low* means. Although often a relative term, major national and international advisory bodies such as the International Commission on Radiological Protection (ICRP) (2007), United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2010), and the National Research Council (NRC) (2006) have defined low doses as those in the range of 100 mGy and below. This definition is intended to roughly describe the dose below which there is scientific uncertainty about the associated radiation health effects. However, for the nonspecialized public, *low-dose* often corresponds to doses equal to or about the radiation received from natural background and could therefore range from about 1–5 mGy.[1] On the other hand, for the health professional who treats cancer patients and aims to kill cancer cells with radiation, a low-dose procedure would utilize radiation of several Gy.

This report is intended to provide advice to the Armed Forces Radiobiology Research Institute (AFRRI) about its role in low-dose radiation health effects research. When the committee asked for guidance on what "low-dose" means for AFRRI, which has traditionally focused on radiation doses high enough to cause acute radiation syndrome, it was told that low-dose radiation was generally interpreted to mean doses that produce no observed acute radiation effects—that is, doses lower than approximately 1 Gy (Huff, 2013).

For consistency with ICRP, UNSCEAR, and NRC literature, the report uses their definition of a low dose: 100 mGy and below. However, to fully address its statement of task (detailed later in this chapter) and provide useful advice to AFRRI, its discussions cover a broader range of doses where appropriate. Doses on the order of 1 Gy are referred to as *moderately high*; doses of 10 mGy and below, *very low*.

Human health effects from exposure to ionizing radiation were first noted in the late 1800s and have received a great deal of attention from researchers and the public since World War II (Inkret et al., 1995). Recent events have served to heighten this interest: concerns about terrorist attacks involving improvised nuclear devices and dirty bombs, releases of radioactive materials into the environment from major nuclear accidents in Ukraine (Chernobyl) and Japan (Fukushima Daiichi), increasing exposure to radiation from diagnostic medical procedures, and increasing exposures to radiation arising from the rapid proliferation of radiation-based imaging devices for homeland security.

At high doses (several Gy), health concerns relate primarily to acute radiation syndromes that may lead to death or severe injury. These high-dose effects are reasonably well characterized, although information is still lacking for many realistic situations, such as mixed radiation fields (for example, those involving a combination of X-rays, neutrons, and alpha particles), combined injuries (radiation plus burns plus traumatic injury), and individual variations in radiosensitivity. Active areas of research on high-dose exposures include countermeasures to respond to such insults, biodosimetry to estimate doses, and pharmacologically based radiation mitigators (Pellmar et al., 2005).

The 2011 Fukushima Daiichi accident drew attention to shortcomings in the understanding of the health effects of exposure to low-dose ionizing

[1] The average natural background radiation in the United States is about 3 millisieverts (mSv) (NCRP, 2009).

radiation (Dauer et al., 2011). This confusion arises in part because regulatory agencies assume that there is no radiation dose below which the health risk is zero when, in reality, there are insufficient data and understanding to know whether this is actually the case (Brenner et al., 2013).

Although a large-scale radiological event is perhaps the most obvious exposure of concern, other important exposures, such as cleanup of radioactively contaminated sites and the rapid increase in radiation-based medical procedures, require an understanding of low-dose radiation risks that is currently unavailable. Apart from human health issues, these topics have major economic consequences for the nation. For example, the current cost of cleanup at the Hanford Site[2] in Washington State is estimated to be $114.8 billion (Cary, 2013), a figure that is the result of exposure limits and cleanup criteria that are based on science that is characterized by large uncertainties.

The U.S. military has a particular interest and stake in understanding the effects of exposure to ionizing radiation. Response to nuclear threats has been a critical part of its planning process since the Trinity atomic test detonation in 1945, and DoD has long recognized the importance of maintaining a strong health-effects research program. The U.S. Navy Bureau of Medicine and Surgery proposed in 1958 that a bionuclear research facility be established to study such issues (DTRA, 2002; Tenforde, 2011). Public Law 86-500 (June 8, 1960) authorized construction of a laboratory and vivarium under the auspices of the Defense Atomic Support Agency (DASA) and, on December 2, 1960, the three surgeons general of the armed services and DASA approved a charter to create AFRRI (DTRA, 2002). DoD Directive 5154.16, issued May 12, 1961, formally established the Institute. AFRRI was given the mission to "preserve the health and performance of U.S. military personnel and to protect humankind through research that advances understanding of the effects of ionizing radiation" (AFRRI, 2013a).[3]

Service members may encounter low doses of ionizing radiation from many sources, including situations similar to those found in industry, medicine, nuclear power, and research settings in addition to the exposures resulting from military operations (Blake and Komp, 2014). The U.S. Department of Veterans Affairs (VA) recognizes that some of these may have health consequences and provides health care and other benefits to exposed persons. Currently, those circumstances include service in response to the Fukushima accident; occupational exposures to weapons technicians

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[2] The Hanford Site is a former nuclear weapons production facility created in the 1940s as part of the Manhattan Project. Operations at the site generated large amounts of waste contaminated with radionuclides and other hazardous substances. Cleanup of the site is considered one of the most complex remediation projects in the history of U.S. weapons production (DOE, 2013).

[3] Chapter 4 gives a more complete history of AFRRI.

and medical and dental technicians; and exposure to depleted uranium from explosions, tank armor, or bullet fragments. The VA also recognizes ionizing radiation exposures from work associated with nuclear weapons testing; the occupation of Hiroshima and Nagasaki, Japan; service at McMurdo Station, Antarctica, where the U.S. Navy operated a nuclear power plant that experienced a leak; service at LORAN (Long Range Navigation) stations, which formerly used high-voltage vacuum tubes that generated X-ray radiation; and pilots, submariners, divers, and other service members who received nasopharyngeal radium irradiation treatments from 1940 until the 1960s to prevent damage from pressure changes (VA, 2013).

Because the use of radioactive materials in medical, industrial, power, and military technology is likely to continue; and because military personnel may need to operate in environments contaminated by accident or hostile action, the DoD has a clear interest in understanding the health effects of exposure to low-dose ionizing radiation.

STATEMENT OF TASK

In 2012, USUHS—which currently holds organizational responsibility for AFRRI—requested that the Institute of Medicine (IOM), in concert with the Nuclear and Radiation Studies Board of the NRC,[4] examine recent scientific knowledge about the human effects of exposure to low-dose radiation from medical, occupational, and environmental ionizing-radiation sources, focusing on the work of and opportunities for AFRRI. The committee convened to conduct this examination was asked to address four items.

1. Identify current research directions in radiobiological science related to human health risks from exposures to low-level ionizing radiation.
2. Assess how Armed Forces Radiobiological Research Institute programs are advancing research along these directions.
3. Identify opportunities for the Armed Forces Radiobiological Research Institute to advance its mission for understanding human health risks from exposures to low-level ionizing radiation, with special emphasis on Department of Defense military operations and personnel.
4. Assess the demand for radiobiology researchers and examine workforce projections. If workforce projections are inadequate to meet demand, suggest ways to accelerate training and investigator development.

[4] The Institute of Medicine and the National Research Council are, along with the National Academy of Engineering, operating components of the National Academy of Sciences.

The committee understood its task to encompass a consideration of the organizational structure and funding mechanisms that would promote the successful conduct of low-dose ionizing radiation research by the Institute.

THE COMMITTEE'S APPROACH TO ITS TASK

NAS convened a committee of twelve experts in radiobiology, health physics, medical physics, epidemiology, statistics, risk science, and workforce and training issues to respond to the statement of task. The committee partitioned their assessment into four research areas: countermeasures, dosimetry and biodosimetry, combined injury, and epidemiology. Their examination was focused on information published since major comprehensive reviews by other scientific bodies: the NRC's *Health Risks from Exposure to Low Levels of Ionizing Radiation* (known as the "BEIR VII" report [NRC, 2006]) and UNSCEAR's *2008 Report to the General Assembly* (UNSCEAR, 2010). The committee conducted an extensive examination of relevant research in the course of its work. It did not review all such literature but attempted to cover the work that it believed to have been influential in shaping policy and practice at the time it completed its task in late 2013.

The committee and staff also engaged in other information-gathering activities. AFRRI leadership presented their charge to the committee in May 2013 and answered their questions regarding the elements of the statement of task, the operation of the Institute, and the guidance that would be most useful to it (Huff, 2013). A subcommittee toured the AFRRI facilities in Bethesda, Maryland, in July 2013 to better understand the organization's capabilities and discuss current research with its investigators. The tour also gave the attendees the opportunity to familiarize themselves with the Institute's physical plant and its capabilities. Additional information was obtained in AFRRI's responses to three sets of questions submitted by the committee (AFRRI, 2013b,c,d). Staff and committee members attended meetings of professional associations[5] and educational sessions[6] related to the topics under consideration to learn about the latest research developments and engage with other experts. The committee also considered information presented at a series of open sessions held in conjunction with

[5] (NCRP) National Council on Radiation Protection and Measurements. 2013. 49th annual meeting, *Radiation Dose and the Impacts on Exposed Populations*, March 1–12, Bethesda, MD.

[6] NCRP. 2013. Workshop: *Where Are the Radiation Professionals?*, July 17, Arlington, VA; Radiation Injury Treatment Network and Centers for Medical Countermeasures Against Radiation. 2013. Workshop: *Mitigation and Treatment of Radiation Damage*, July 31–August 2; AFRRI. 2013. Conference: *Military Radiobiology Research in the 21st Century: Threats, Triage, and Treatment*, August 26–28, Bethesda, MD.

its meetings, at which experts were invited to offer their views and engage in colloquy with them. Agendas from these events are contained in Appendix A. Materials submitted by members of the public were also considered.

NAS REPORTS ADDRESSING RELATED TOPICS

A number of the IOM and the NRC reports have addressed topics relevant to the issues under consideration here: the health effects of exposure to low-dose ionizing radiation; military radiation-exposure concerns, notably depleted uranium (DU); radiation exposure in other populations, including civilians; and the scientific research workforce. Salient publications are summarized below.

Health Effects of Exposure to Low-Dose Ionizing Radiation

Committees on the Biological Effects of Ionizing Radiation (BEIR) of the NRC have advised the U.S. government on the health consequences of ionizing radiation in a series of reports that began in the 1950s.[7] The most recent publication, *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII: Phase 2,* focuses on the development of risk estimates for low linear energy transfer (LET), radiation doses less than 100 mSv. That report includes a comprehensive literature review of the relevant epidemiological evidence and in-depth descriptions of other biological effects. This committee concluded that the then current scientific evidence was consistent with the hypothesis that a linear dose-response relationship exists between exposure to low-LET radiation and cancer in humans, even at low doses, but that more information is needed to understand noncancer and heritable radiation effects (NRC, 2006).

Military Radiation Exposure Concerns

At the request of the Surgeon General of the U.S. Army, the Committee on Battlefield Radiation Exposure Criteria examined the technical and ethical aspects of military radiation protection and safety in instances of exposure to radiation doses too low to elicit acute effects but associated with long-term cancer risk. That effort focused on radiation doses up to 700 mSv. The initial, interim report—*An Evaluation of Radiation Exposure Guidance for Military Operations*—reviewed draft North Atlantic Treaty Organization (NATO) radiation-protection guidance on dose limits, documentation, and control measures (IOM, 1997). Among its recommenda-

[7] Earlier reports in the series were written under the aegis of the committees on the Biological Effects of Atomic Radiation (BEAR) (NAS, 2014).

tions were that the Army develop specific protocols for managing low-dose exposure situations and that they

> [r]eview and revise doctrine and procedures on dosimetry to ensure individual doses are monitored and recorded for all soldiers exposed to radiation, whether from routine occupational exposure or as a consequence of uniquely military missions. (p. 7)

Potential Radiation Exposure in Military Operations: Protecting the Soldier Before, During, and After was released 2 years later. This report considered the ethical questions surrounding the decision to put individuals at risk of harm; methods to protect soldiers while meeting military objectives; policies for recording, maintaining, and using individual dose information; and programs to identify potential adverse health effects appearing long after exposure. It recommended that "[m]ilitary personnel should receive appropriate training in both radiation effects and protection in a way that neither inappropriately minimizes effects nor creates unwarranted fear" (IOM, 1999, p. 2).

After the 1991 Persian Gulf War, a number of returning veterans began reporting health problems that they believed to be associated with their service. Under a congressional mandate, the IOM initiated a report series reviewing a wide array of biological, chemical, and physical agents present in the theater of operations to evaluate whether exposure might be responsible for particular health outcomes. DU, a weakly radioactive and toxic heavy metal, has been used in both munitions and protective armor for tanks since the 1980s because its high density has desirable offensive and defensive armor-penetration characteristics. As a result, military personnel have inhaled or swallowed DU particulates and suffered injuries from DU shrapnel and fragments during combat.

Health effects possibly associated with exposure to DU have been considered in multiple volumes in the IOM report series. In a 2000 report, *Gulf War and Health, Volume 1: Depleted Uranium, Sarin, Pyridostigmine Bromide, and Vaccines*, a committee concluded that there was not enough evidence to draw conclusions as to whether long-term health problems were associated with DU exposure (IOM, 2000). The IOM updated its review in 2008, focusing on literature published since the first effort. That report, *Gulf War and Health: Updated Literature Review of Depleted Uranium,* determined that there continued to be inadequate or insufficient evidence to determine whether an association exists between in-theater exposure and the cancer and noncancer health outcomes examined. However, the report noted that "[t]he period of followup in several studies might have been too short to detect some diseases that are typically characterized by long latency" and that exposure characterization was inadequate in many of the studies reviewed by the committee (IOM, 2008a, p. 5). A subsequent report, *Gulf War and Health, Volume 8: Update of Health Effects of Serving in the Gulf War* (IOM, 2010), did not identify any new literature that would change these conclusions.

Two additional reports released in 2008 also addressed DU. The first, *Epidemiologic Studies of Veterans Exposed to Depleted Uranium: Feasibility and Design Issues,* examined several options for conducting such research and concluded that the lack of accurate and complete individual-level exposure information on military personnel would make it difficult to design a retrospective study of DU-related health outcomes but that a prospective study might yield useful information should future military operations entail exposure to the substance (IOM, 2008b). The second report, *Review of Toxicologic and Radiologic Risks to Military Personnel from Exposure to Depleted Uranium During and After Combat,* was produced by an NRC committee. On the basis of their review of epidemiological, radiological, and toxicokinetic data, the committee found that the kidneys are the most sensitive target of uranium toxicity but that "[e]vidence on the risk of cancer or other chronic diseases after exposure to DU in Gulf War soldiers is inadequate" (NRC, 2008a, p. 4).

Radiation Exposure in Other Populations

The report *Managing Space Radiation Risk in the New Era of Space Exploration* examined factors influencing the exposure of astronauts to ionizing radiation and offered a strategic plan for developing appropriate mitigation capabilities. The study concluded that the lack of knowledge about biological effects of radiation encountered in space is the single most important factor limiting the prediction of risk associated with human space exploration and recommended that the National Aeronautics and Space Administration (NASA) invest in research on that topic (NRC, 2008b).

Technical Evaluation of the NASA Model for Cancer Risk to Astronauts Due to Space Radiation (NRC, 2012d) considers the components, input data (for the radiation types, estimated doses, and epidemiology), and associated uncertainties in a model developed to assess health risks for current and potential future missions. The report also identifies gaps in NASA's current research strategy for reducing the uncertainties in cancer induction risks. It concludes that, although many aspects of the space radiation environments are now relatively well characterized, important uncertainties still exist regarding biological effects and thus regarding the level and types of risks faced by astronauts.

Assessing Medical Preparedness to Respond to a Terrorist Nuclear Event summarizes a workshop conducted by the IOM under the sponsorship of the U.S. Department of Homeland Security that assessed medical preparedness to respond to the detonation of an improvised nuclear device. The workshop included a presentation by COL John Mercier, Ph.D.—then Senior Health Physicist at AFRRI and Director of Military Medical Operations—on the U.S. military's approach to prompt treatment of personnel with combined injuries in the event of a nuclear attack and how this approach might be adapted to the civilian setting (IOM, 2009).

In 2010, the U.S. Nuclear Regulatory Commission (U.S. NRC) requested that the NAS provide an update of a 20-year-old assessment of cancer risks in populations near U.S. NRC–licensed nuclear facilities that use or process uranium for the production of electricity. *Analysis of Cancer Risks in Populations Near Nuclear Facilities: Phase 1* focuses on issues related to conducting a scientifically valid epidemiological study. Prominent among these were the challenge of assessing risks at low doses, weak exposure characterization for the populations of interest, and the uncertainties surrounding low-dose health effects (NRC, 2012a). Phase 2 of the study, which is planning a pilot study of cancer risks, was in progress at the time that this report was completed in late 2013.

Research Workforce

Advancing Nuclear Medicine Through Innovation (NRC and IOM, 2007) reported on a number of issues related to the practice of nuclear medicine, including the state of the workforce. It concluded that there are shortages of both clinical and research personnel in all nuclear medicine disciplines (chemists, radiopharmacists, physicists, engineers, clinician-scientists, and technologists) and that training of the next generation of professionals has not kept up with current demands (p. 129).

In 2012, the NRC released *Assuring a Future U.S.-Based Nuclear and Radiochemistry Expertise*. The authoring committee had been charged with examining the demand for nuclear chemistry expertise and the supply of incoming skilled experts. The committee noted that although the demand for nuclear chemistry expertise was unlikely to decrease, the current labor force is approaching retirement age, with fewer incoming students in the field. To avoid a gap between supply and demand, the committee recommended ways to increase student interest through such steps as on-the-job training opportunities (NRC, 2012b).

Nuclear Physics: Exploring the Heart of the Matter (NRC, 2013) reported that labor-supply problems have been building for several decades, and they affect all areas of applied nuclear science. It stated that "there is an increasing decline in the percentage of physics Ph.D.s graduating with expertise in nuclear physics at a time when workforce demands are growing" and that "the workforce shortage will become acute unless a coordinated and integrated plan is implemented to build and sustain an appropriately sized workforce, coupled with the necessary research facilities" (p. 219). Among the report's recommendations is that fellowships should be established to support postdoctoral researchers interested in the field.

The committee responsible for the report *Assuring the U.S. Department of Defense a Strong Science, Technology, Engineering, and Mathematics (STEM) Workforce* found that STEM activities in DoD are a small and diminishing part of the nation's overall science and engineering enterprise. The report presents five principal recommendations for attracting, retaining, and managing highly qualified STEM talent within the department, on the basis of an examination of the current DoD labor force and the defense industrial base. The recommendations include a call for DoD to upgrade education and training for its civilian STEM workforce and to focus investments to ensure that STEM competencies in all potentially critical emerging topical areas are maintained at least at a basic level within the department and its industrial and university bases (NRC, 2012c).

ORGANIZATION OF THIS REPORT

The remainder of this report is divided into five chapters plus three supporting appendixes. Chapter 2 sets the stage for the remaining chapters by providing background on the current directions in radiobiology research. It describes the cancer and noncancer health effects associated with exposure to low doses of radiation and the tools available to researchers to study them. The chapter also outlines the different methods used to analyze biological markers of dose or effect and the factors that influence the risks associated with exposure.

Chapter 3 examines the state of the radiobiology research workforce by first defining the field of study and then summarizing the literature on the supply of and demand for professionals in the discipline. A listing of academic programs in the United States that focus on radiobiology is also presented.

Chapter 4 centers on AFRRI's organization and its role in radiobiology research. It gives the history of the Institute and describes its infrastructure, staff, budget, and capabilities. This chapter also elucidates AFRRI's current (2013) research priorities and portfolio; their education, training, and emergency response responsibilities; and their interaction with the broader research community through collaborations and representation in scientific groups.

The concluding chapter of the report, Chapter 5, builds on the foundation of the previous chapters and offers the committee's primary findings, conclusions, and recommendations. It puts forward a series of proposals for how AFRRI might build on its strengths and advance its mission while contributing to the body of scientific knowledge on the health effects of exposure to low-dose ionizing radiation.

Agendas of the public meetings held by the committee are provided in Appendix A. Appendix B comprises a brief summary of research programs concerning low-dose ionizing radiation health effects under way in the United States. Biographical information on the committee members and staff responsible for this study are contained in Appendix C.

REFERENCES

AFRRI (Armed Forces Radiobiology Research Institute). 2013a. *About AFRRI*. http://www.usuhs.edu/afrri/organiza/about_afrri.htm (accessed December 27, 2013).

AFRRI. 2013b. Responses to questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, July 12, 2013.

AFRRI. 2013c. Responses to supplementary questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, October 31, 2013.

AFRRI. 2013d. Responses to supplementary questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, January 10, 2014.

Blake, P. K., and G. R. Komp. 2014. Radiation exposure of U.S. military individuals. *Health Physics* 106(2):272-277.

Brenner, D. J., J. Boice, W. F. Morgan, J. E. Cleaver, T. K. Hei, H. Hricak, S. J. Adelstein, and J. M. Samet. 2013. Letter to John P. Holdren, Director of the White House Office of Science and Technology Policy, on the future of low-dose radiation research in the U.S. New York. http://www.radres.org/?page=HoldrenLetter&hhSearchTerms=%22holdren%22 (accessed February 27, 2014).

Cary, A. 2013. Estimated cost to finish Hanford cleanup now at $114.8B. *TriCity Herald*, February 22, 2013. http://www.tri-cityherald.com/2013/02/22/2284650/estimated-cost-to-finish-hanford.html (accessed December 19, 2013).

Dauer, L. T., P. Zanzonico, R. M. Tuttle, D. M. Quinn, and H. W. Strauss. 2011. The Japanese tsunami and resulting nuclear emergency at the Fukushima Daiichi power facility: Technical, radiologic, and response perspectives. *Journal of Nuclear Medicine* 52(9):1423-1432.

DOE (U.S. Department of Energy). 2013. *Hanford overview and history*. http://yosemite.epa.gov/r10/cleanup.nsf/sites/Hanford (accessed April 22, 2014).

DTRA (Defense Threat Reduction Agency). 2002. *Defense's nuclear agency 1947-1997*. DTRA History Series. Washington, DC: U.S. Department of Defense.

Huff, L. A. 2013. *Armed Forces Radiobiology Research Institute*. Presentation to the Committee on Research Directions in Human Biological Effects of Low-Level Radiation. Washington, DC, May 3, 2013.

Inkret, W. C., J. C. Taschner, and C. B. Meinhold. 1995. A brief history of radiation protection standards. *Los Alamos Science* 23:116-123.

IOM (Institute of Medicine). 1997. *An evaluation of radiation exposure guidance for military operations: Interim report*. The Compass Series. Washington, DC: National Academy Press.

IOM. 1999. *Potential radiation exposure in military operations: Protecting the soldier before, during, and after.* The Compass Series. Washington, DC: National Academy Press.

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

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

IOM. 2008b. *Epidemiologic studies of veterans exposed to depleted uranium: Feasibility and design issues*. Washington, DC: The National Academies Press.

IOM. 2009. *Assessing medical preparedness to respond to a terrorist nuclear event: Workshop report*. Washington, DC: The National Academies Press.

IOM. 2010. *Gulf War and health, volume 8: Update of health effects of serving in the Gulf War.* Washington, DC: The National Academies Press.

NAS (National Academy of Sciences). 2014. *Organized collections. Committees on Biological Effects of Atomic Radiation, 1954-1964*. http://www.nasonline.org/about-nas/history/archives/collections/cbear-1954-1964.html (accessed April 23, 2014).

NRC (National Research Council). 2006. *Health risks from exposure to low levels of ionizing radiation: BEIR VII: Phase 2*. Washington, DC: The National Academies Press.

NRC. 2008a. *Review of toxicologic and radiologic risks to military personnel from exposure to depleted uranium during and after combat*. Washington, DC: The National Academies Press.

NRC. 2008b. *Managing space radiation risk in the new era of space exploration*. Washington, DC: The National Academies Press.

NRC. 2012a. *Analysis of cancer risks in populations near nuclear facilities: Phase 1*. Washington, DC: The National Academies Press.

NRC. 2012b. *Assuring a future U.S.-based nuclear and radiochemistry expertise*. Washington, DC: The National Academies Press.

NRC. 2012c. *Assuring the U.S. Department of Defense a strong science, technology, engineering, and mathematics (STEM) workforce*. Washington, DC: The National Academies Press.

NRC. 2012d. *Technical evaluation of the NASA model for cancer risk to astronauts due to space radiation*. Washington, DC: The National Academies Press.

NRC. 2013. *Nuclear physics: Exploring the heart of the matter.* Washington, DC: The National Academies Press.

NRC and IOM. 2007. *Advancing nuclear medicine through innovation*. Washington, DC: The National Academies Press.

Pellmar, T. C., S. Rockwell, and the Radiological/Nuclear Threat Countermeasures Working Group. 2005. Priority list of research areas for radiological nuclear threat countermeasures. *Radiation Research* 163:115-123.

Tenforde, T. S. 2011. *Tribute to AFRRI on its 50th anniversary and perspectives on the history and future of radiation biology and health protection*. Presented at AFRRI Golden Jubilee Banquet. http://www.ncrponline.org/PDFs/2011/AFRRI_TST_05-12-11.pdf (accessed December 27, 2013).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2010. *Sources and effects of ionizing radiation. Report to the General Assembly, with scientific annexes*. New York: United Nations.

VA (U.S. Department of Veterans Affairs). 2013. *Exposure to radiation during military service.* http://www.publichealth.va.gov/exposures/radiation/sources/index.asp (accessed April 7, 2014).

2

Current Directions in Radiobiological Research

The committee's statement of task directed it to "identify current research directions in radiobiological science related to human health risks from exposures to low-dose ionizing radiation." This chapter fulfills that directive by presenting an overview of the state of the science, major challenges and uncertainties, and research being pursued when the committee's work concluded in late 2013. It is not a systematic literature review—a task beyond the scope of this study—but is instead a discussion of some recent developments in the field that highlight research directions. The focus is on research findings released after publication of two comprehensive reviews on the effects of low-level ionizing radiation: the National Research Council's *Health Risks from Exposure to Low Levels of Ionizing Radiation* (known as the Biological Effects of Ionizing Radiation VII or the "BEIR VII" report (NRC, 2006) and the United Nations Scientific Committee on the Effects of Atomic Radiation's (UNSCEAR's) 2008 report to the General Assembly (UNSCEAR, 2010).

As discussed in Chapter 1, this report defines low doses to be those in the range of 100 milligray[1] (mGy) and below, an approach consistent with that used by International Commission on Radiological Protection (ICRP, 2007), the BEIR VII report (NRC, 2006), and UNSCEAR (2010). Doses on the order of 1 Gray (Gy) are referred to as moderately high; those on the order of 10 mGy, as very low. Discussions in the chapter focus primarily on low linear energy transfer (LET) ionizing radiation unless otherwise stated.

[1] Gray (Gy) is the International System of Units name for the unit of absorbed dose; 1 Gy is equal to 1 joule per kg or 100 rad.

INTRODUCTION

Low levels of radiation can induce DNA damage. Cells respond to the direct radiogenic damage to DNA by attempting to repair it. If that repair is not perfect, the modifications induced may be transmitted to daughter cells and may lead to uncontrolled cell growth and consequently cancer. More recent experiments have challenged the view that genetic alterations are restricted to directly irradiated cells by demonstrating that radiogenic damage can also be observed in cells that are not themselves irradiated (nontargeted effects) but are the progeny of an irradiated cell (radiation-induced genomic instability) or have received the damaging signal from the irradiated cell within the tissue microenvironment (radiation induced bystander effects). The exact mechanisms by which these nontargeted responses result in adverse health effects are not yet understood. However, the best understood bystander effect arises in a setting of chronic inflammation where the production of reactive oxygen species results in damage in adjacent cells (Kadhim et al., 2013; Morgan, 2003).

Radiation effects at low doses are often described as stochastic—there appears to be no threshold below which an effect does not occur and the greater the exposure the higher the probability that an effect will occur, but the severity of the effect is independent of the dose received. This is in contrast to tissue reactions[2] (formerly called deterministic effects), which are based on tissue damage and whose severity increases as the dose increases. A deterministic effect typically has a threshold (of the order of magnitude of 100 mGy or higher) below which the effect does not occur. Although much is known about the risk of health effects after exposure to radiation at the 100 mGy–1 Gy dose range and high dose rates, there is greater uncertainty about the risk of those associated with exposure to low doses of radiation. Nevertheless, it is low doses that are of primary interest for radiation-protection purposes, such as making decisions on the dose limit for occupational exposure or the resettlement of populations after a radiological release event. Brenner and colleagues (2013) assert that setting radiation-protection standards too stringently in this dose range could have severe economic consequences, whereas setting them too low would present an unacceptable health burden.

Low-dose radiation research involves observational studies of populations and experimental studies of radiation effects on molecules, cells, tissues, and animal models. Epidemiological studies provide information about possible associations between exposure to low-dose radiation and disease in humans. Experimental studies improve our understanding of the

[2] The term "tissue reaction" has been adopted because some of these effects can be modified post irradiation rather than being solely determined at the time of irradiation (ICRP, 2012).

mechanisms by which low-dose ionizing radiation causes damage and how cells and tissues respond to that damage.

As noted in Appendix B, the U.S. Department of Energy (DOE) Low Dose Radiation Research Program began work in 1999 to investigate radiation effects on genomes and cells to better understand outcomes in living organisms and develop radiation protection standards based on risk. The original plan called for a 10-year effort funded at $22.4M/year in years 1–3, $25.6M/year in years 4–6, and $18.6M/year in years 7–10 (PNNL, 2012). More recently, however, the program's funding has been reduced. It no longer has its own line in DOE's proposed budget; instead, low-dose research activities are now included in the Radiological Sciences/Radiobiology line of the Office of Biological and Environmental Research's budget. The DOE FY 2015 Congressional Budget Request notes that overall funding for radiobiology was ~$6.2M for FY 2013, that the enacted total for FY 2014 was $3.2M, and that the FY 2015 request was for $2.4M (DOE, 2014). The accompanying text indicates that low-dose radiobiology research will "emphasize a systems biology approach to understanding the effects of low dose radiation on cellular processes and epidemiological studies to uncover statistically significant effects of low dose radiation in large populations" (DOE, 2014, p. 102). It goes on to state that "[d]ecreases in radiobiology reflect a shift towards bioenergy and environmental research within the Biological Systems Science portfolio" (DOE, 2014, p. 102).

Research on low-dose radiation in the United States lacks a strategic agenda aiming to address a common set of scientific questions (Brenner et al., 2013). An assessment of important scientific questions and research priorities, with emphasis on questions of greatest policy relevance for regulators involved in radiation protection, was developed over several years by the European Commission's High Level and Expert Group (EC, 2009). This effort led to programs such as the Multidisciplinary European Low Dose Initiative (MELODI, 2014) and its Low Dose Research Towards Multidisciplinary Integration (DoReMi) research-integration component (DoReMi, 2014). A 2012 workshop conducted as part of this effort assessed the state of the art in research into the risk of low-dose radiation exposure and offered recommendations for updating its research agenda and a work plan for future research activities (Salomaa et al., 2013). When this report was completed, the most current update to the MELODI strategic research agenda was its fourth draft, published in March 2013 (Averbeck, 2013).

In this chapter, discussions of scientific gaps and recent developments in the low-dose radiation research parallel the lines of research that the MELODI consortium believes to be the most promising in better understanding low-dose radiation health effects (Averbeck, 2013). First, the committee addresses some of the key factors that may modify low-dose radiation health effects. It then discusses the primary approaches used to answer questions about such health effects—experimental studies and epidemiological studies—and provides insights on current research directions.

LOW-DOSE RADIATION–RISK MODIFIERS

The Shape of the Dose-Response Curve

In the absence of a detailed understanding of human biological effects at low doses (less than 100 mGy) and low dose rates, radiation-protection standards and exposure limits that require an assessment of risks are set by assuming that there is a linear relationship between exposure and effect and by extrapolating from the outcomes observed at higher radiation levels. This is called the linear no-threshold (LNT) model (ICRP, 1977; NCRP, 2001).[3] Whether the risk of cancer actually diverges from the predictions made by using this model at low doses is disputed.

Although U.S. and international bodies consider using the LNT approach to be prudent in the absence of direct evidence, the possibility of other shapes for dose-response curves at doses less than 100 mGy cannot be ruled out. As simplistically illustrated in Figure 2-1, various potential extrapolations may be consistent with the data but would result in different risk estimates at low doses. For example, compared with an LNT extrapolation (curve ***a***), a threshold (curve ***d***) or beneficial-effect (termed "hormetic"; curve ***e***) extrapolation would result in decreased risk at doses less than 100 mGy, whereas a downward-curving extrapolation (curve ***b***) would result in increased risk. With the exception of scenarios ***d*** and ***e***, risk estimates assume that for any dose, no matter how low, there is a corresponding risk. In scenario ***b***, the assumption of linearity would underestimate the risk, whereas in scenarios ***c*** and ***d***, the assumption of linearity would overestimate the risk.[4]

National and international scientific groups such as the International Commission on Radiological Protection (ICRP), the National Council on Radiation Protection and Measurements (NCRP), BEIR, and UNSCEAR regularly review and currently endorse the use of the LNT model for assessing risk in a radiation-protection context. However, other institutions, such as the French Academy of Sciences, rejected the LNT at low doses (Aurengo et al., 2005) on the basis of evidence for protective postirradiation cellular responses such as activation of DNA-repair systems and programmed cell death of damaged cells. This disagreement highlights the need for more

[3] The biophysical argument for the model is described later in this chapter in the "Mechanistic Models" section.

[4] The logic and evidence underlying these extrapolations are described by Brenner and colleagues (2003).

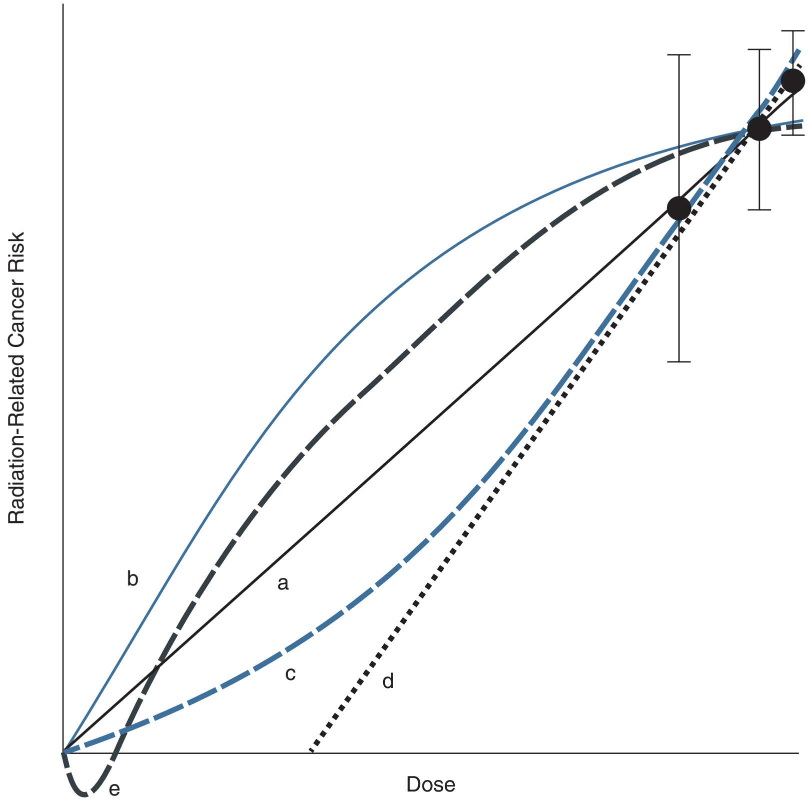

FIGURE 2-1 Potential extrapolated radiation risks at low doses in five different scenarios: curve ***a***, linear extrapolation; ***b***, downward curving (decreasing slope); ***c***, upward curving (increasing slope); ***d***, threshold; ***e***, hormetic.
SOURCE: Reprinted from Brenner et al., 2003. Copyright 2003, with permission from the National Academy of Sciences, U.S.A.

research to characterize the health risks at low radiation doses with more certainty.

Biological Effectiveness

The biological effect of radiation differs by type, even when the absorbed dose is the same. High (i.e., densely ionizing) LET radiation has been shown to have different relative biological effectiveness (RBE) than low (i.e., sparsely ionizing)-LET radiation has. RBE, which is defined as the inverse of the dose of test radiation compared with the dose of reference radiation

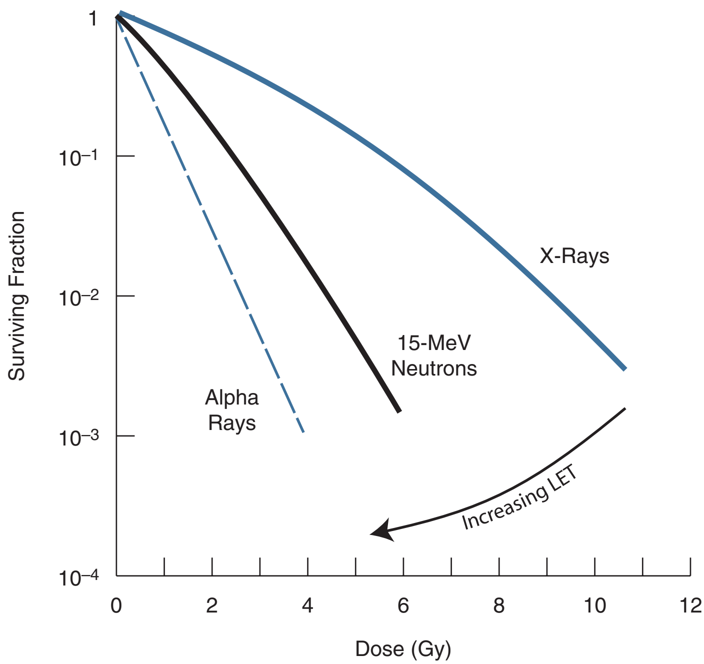

FIGURE 2-2 Relative biological effectiveness as a function of surviving fraction.
SOURCE: Hall and Giaccia, 2005.

required to produce the same effect, is dependent on the dose level and the endpoint measured. For radiation-protection purposes, the relative effectiveness of each type of radiation is represented by a weighting factor that is used to convert the tissue-absorbed dose into the equivalent dose. These values, published by the ICRP, were last revised in 2007 (ICRP, 2007).

One endpoint that may be considered is cell killing. Figure 2-2 illustrates RBE as a function of surviving fraction.[5] The primary difference between the high- and low-LET radiation dose-response curves is the reduction of the curve's so-called shoulder region with increasing LET. In the low-dose region of low-LET radiation, damage is due primarily to single tracks' acting independently, and it is relatively easier for cells to repair this form of damage. In the high-dose region of the low-LET radiation curve, damage from multiple tracks more likely contributes to the nonlinear shape of the curve. For high-LET radiation, the dose-response curve is more linear

[5] Surviving fraction is defined as the ratio of the number of viable cells (or cell colonies) after a given exposure to the number of cells or colonies irradiated.

because the damage is complex and less reparable than that from low-LET radiation.

Figure 2-3 illustrates RBE as a function of LET. For cell killing, the RBE is easily quantified at high doses; differences in effects at low doses are more difficult to determine with confidence. In addition, the frequency of events in most cells is zero at low mean doses of high-LET radiation, with a few cells having only one event and the rare cell having more than one event. This leads to large differences in energy-deposition distribution, which have been correlated to differences in RBE (UNSCEAR, 2000). In this case, non-targeted effects, particularly genomic instability, are of greater importance. High-LET radiation has been shown to be more effective at inducing transmissible instability than low-LET radiation is (UNSCEAR, 2012).

For low-LET radiation, the energy deposition remains fairly homogeneous at doses ranging about 10–100 mGy. However, it is still difficult to measure biological effects at doses lower than that. With respect to the induction of genomic instability, however, there appears to be a threshold of about 0.5 Gy for low-LET radiation (Koterov et al., 2005; Zyuzikov et al., 2011), indicating that this would not contribute to the development of health effects.

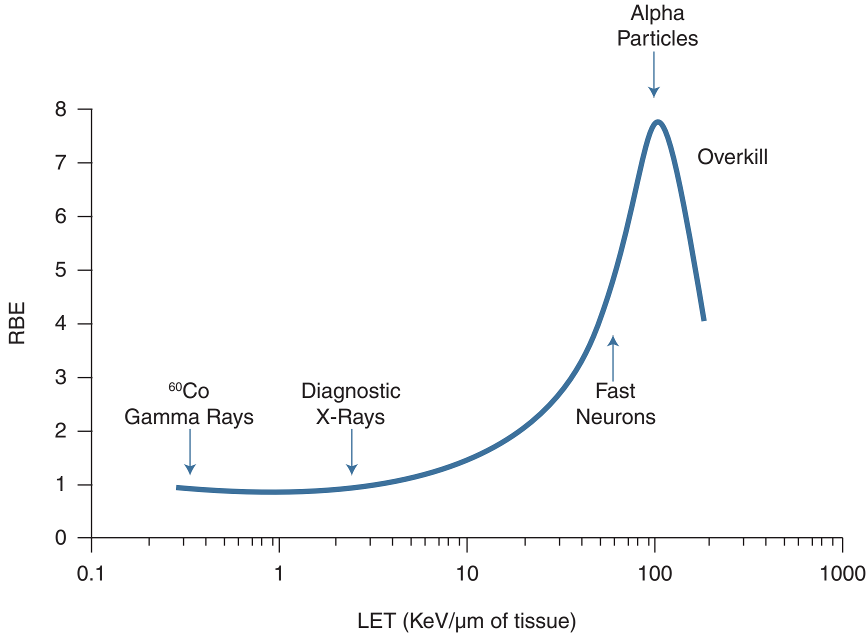

FIGURE 2-3 Relative biological effectiveness as a function of linear energy transfer.
SOURCE: Bushberg et al., 2002.

It is clear that high-LET radiation is more effective at causing cellular effects such as chromosome aberrations and mutations per unit dose. However, the number of DNA breaks produced per Gy is not very different for high- and low-LET radiation (UNSCEAR, 2000). The differences are in the efficiency and fidelity of the DNA double strand–breaks repair and in the spatial distribution of the breaks.

Thus, there is still much to be understood about the RBE at low doses of radiation and about how the RBE changes with decreasing dose.

Dose and Dose-Rate Effects

The role of dose rate in the biological effects of radiation is also a subject of much debate. Considerable evidence exists from molecular, cellular, tissue, and animal studies that induced damage decreases as the dose rate decreases, at least for X-rays and gamma rays (NCRP, 1980); however, epidemiological data do not consistently support this conclusion.

Current radiation-protection practices often assume that cancer risks are lower at low doses and low dose rates than they are at high doses and high dose rates by a factor known as the DDREF (dose and dose-rate effectiveness factor). For many years, the recommended DDREF ranged between 2 and 10 (NRC, 1990). More recently, the BEIR VII report (NRC, 2006) recommended a distribution of DDREF values with a modal value of 1.5, whereas ICRP's 2007 guidance on the control of exposure from radiation sources recommended a modal value of 2.0 (ICRP, 2007).

Animal studies at low dose rates or with internally deposited radionuclides have clearly demonstrated that protracted low-dose radiation exposure to tissues has fewer detrimental effects than the same dose delivered as an acute exposure (Brooks, 2011; NCRP, 1980; Vares et al., 2011). Studies of dogs and mice exposed daily to either low doses or equal doses given in a single exposure revealed that animals given the high dose-rate exposure were more likely to develop cancer compared to those that received the low dose-rate exposures (Carnes and Fritz, 1991; Carnes et al., 1998; Haley et al., 2011; Shin et al., 2011). In addition, gene expression studies in mice showed large variation in expression levels depending on exposure dose rates, suggesting that there are significant differences in the biological consequences of dose-rate factors (Uehara et al., 2010). For radiation-induced carcinogenesis in humans, however, the data are limited (Brenner, 1999), although recent studies in chronically exposed workers suggest a DDREF of about 1.0 (Jacob et al., 2009)

At high LET, there is insufficient evidence of a diminution in cancer risk with decreasing dose rate. Indeed, for exposure to radon and its progeny (through alpha particles), evidence exists that radiation-induced cancer risks actually increase at low dose rates (Lubin et al., 1995; NRC, 1999).

The dose-rate effect is an important variable for understanding radiation risk. Reconciling the more than 60 years of radiation biology research with the epidemiological data remains a significant challenge for the future.

External Versus Internal Sources of Radiation

Scientific uncertainty also exists about the differences in tissue effects and therefore the risks from external versus internal radiation sources. Although currently, for radiation-protection purposes, an assumption is made that the effect is the same, independent of source location, it is understood that internal deposition of radionuclides is not as uniform as external irradiation is. The need for improved biokinetic and dosimetric models is crucial for making progress with this scientific question (EC, 2009). This issue is particularly salient for the military because of the potential for personnel to be wounded by depleted uranium (DU), a component of certain munitions and armor.

EXPERIMENTAL STUDIES—CURRENT WORK AND RESEARCH DIRECTIONS

Laboratory Studies

Cancer development is a complex process. In vitro studies have been valuable in the understanding of how radiation causes DNA damage, including changes in gene expression, DNA strand breaks, mutations, or chromosomal aberrations. However, no credible in vitro model exists yet for radiation-induced cancer.[6] In addition, low-dose radiation studies that use DNA damage endpoints have not established the quantitative connection between any of these endpoints and radiation-induced cancer, which occurs long after exposure (Goodhead, 2009).

Using Radiation Biology to Augment Radiation Epidemiological Studies

Although experimental radiation biology cannot currently provide direct models for estimating low-dose radiation health risks in humans, there is much interest in using radiobiology to augment epidemiological studies (Preston et al., 2013). One example is the search for a "molecular

[6] A credible model would provide convincing quantitative and mechanistic evidence of an association between radiation-induced cancer and an endpoint such as gene expression changes, DNA strand breaks, or mutations. Brenner (2014) asserts that the most plausible in vitro model for radiation-induced cancer is oncogenic transformation but notes that it is not feasible to conduct studies of this effect at levels less than 1 Gy. Further, evidence in this exposure range comes primarily from animal models (Mancuso et al., 2008).

fingerprint" of radiation-induced cancer within tumors: If radiation-induced cancers could be definitively identified, then stochastic models would be unnecessary, and the problems of statistical estimation of radiation risks might be largely eliminated. Suggestions have been made in this regard (Boltze et al., 2009; Dom et al., 2012; Hess et al., 2011; Taylor et al., 1994; Vahakangas et al., 1992), but none have been validated convincingly, although new high-throughput evaluation techniques show clear promise (Besaratinia et al., 2012).

A second example focuses on sensitive subpopulations. Plausible evidence suggests that in an exposed population, a significant proportion of radiation-induced cancers may occur in genetically sensitive subpopulations (Flint-Richter and Sadetzki, 2007; Land et al., 1993). If this is the case and if rapid screening techniques could be developed to identify these radiation-sensitive individuals, epidemiological studies of low doses would be greatly facilitated. Efforts to identify individuals who are genetically susceptible to the effects of ionizing radiation are ongoing. Not surprisingly, research to date indicates that carriers of adverse mutations in genes involved in the DNA-repair and cell cycle–control pathways may play an important role. However, thus far only rather rare mutations have been shown to have an appreciably heightened radiation effect.

Given the role of *BRCA1* and *BRCA2* genes in the repair of DNA double-strand breaks and the high prevalence of breast cancer among women carriers, for example, investigators have hypothesized and observed that mutations in these genes enhance the radiation-associated increase in breast cancer after exposure to ionizing radiation from diagnostic X-rays (Andrieu et al., 2006). The Women's Environment, Cancer, and Radiation Epidemiology (WECARE) study examined the effect of radiation exposure on the etiology of second breast cancers in women treated with radiation for an initial breast cancer (Malone et al., 2010). The investigators found that women carriers of the *BRCA1* and *BRCA2* mutations had 4.5- and 3.4-fold increased risks of contralateral breast cancer, respectively, compared with noncarrier women.

Biomarkers of Dose or Effect

A large range of biological marker assays can be used to determine the dose received by an individual. These assays have the advantage of measuring the biological effect of the doses that can take individual susceptibility into account. The most widely accepted techniques are cytogenetic, with the dicentric chromosome assay (DCA) currently the technique of choice in the case of recent acute exposures (IAEA, 2011). In general, cytogenetic assays tend to be the most widely used because of their sensitivity and specificity to ionizing radiation. Other techniques, each having advantages in different scenarios (IAEA, 2011), include cytokinesis-blocked micronucleus assay (CBMN), fluorescence in situ hybridization (FISH), and premature chromosome condensation (PCC).

One limitation of cytogenetic assays (except the PCC) is the requirement to culture cells for at least 48 hours before preparing the samples for an analysis that is itself laborious and requires expertise. When analyzed on microscopy, these assays give accurate dose estimates, but they cannot be performed quickly enough to be useful after a mass-casualty radiation event in which the dose may need to be determined for hundreds to thousands of exposed individuals. Over the years, many efforts have been made to automate the existing cytogenetic assays using metaphase-finding platforms, flow cytometry, imaging cytometry, and other high-throughput systems; for example, the Rapid Automated Biodosimetry Tool (RABiT) (Vaurijoux et al., 2009). Many other biomarkers of radiation exposure have also been examined with the hope of developing a faster biodosimeter that could be used in the field. These can be grouped as genetic markers, hematological markers, protein markers, and physical markers.

Many of the methods in use today, along with their respective lowest measurable doses, strengths, and limitations, are presented in Table 2-1.

Systems Biology

Systems biology and systems radiation biology are young but rapidly evolving fields that investigate the complex interactions of cells within tissues and within organisms in the context of the whole irradiated system rather than the response of the individual cell. The ultimate goal is to provide a mathematical description of radiation-induced carcinogenesis across all dose levels.

Biological systems are by nature complex, and current radiation modeling is limited to simplistic models that do not fully reflect the inherent biological diversity of humans or the mechanisms that underlie risks to the population (Barcellos-Hoff, 2008). Indeed, the fate of irradiated cells within a tissue is strongly modulated by their interactions with one another and with the tissue microenvironment (Barcellos-Hoff, 2005). Linking mechanisms of cellular and molecular responses to radiation exposure with macroscopic processes at the tissue, organ, and whole-organism levels would improve our ability to predict cancer risk in response to irradiation (Dauer et al., 2010).

Although much is known about the DNA damage induced by the deposition of energy from exposure to ionizing radiation and the subsequent cellular responses, a significant gap exists in the understanding of how these might lead to detrimental health effects years after exposure. Recent

TABLE 2-1 List of Existing Biodosimetry Methods

Method	Sensitivity (Gy)	Strengths	Limitations
Cytogenetic			
DCA	0.1	Partial body; sensitivity and specificity to radiation	48-h culture time; 3-month half-life of dicentrics
CBMN	0.2	Easy to score and automate	72-h culture time; cannot identify partial body exposures
FISH	0.25	Retrospective	High background, expensive
PCC	1	High dose range	Poor sensitivity
Genetic			
Glycophorin A	1	Fast (3 h for dose estimate)	Present in 50% of population
Gene expression	0.1	Fast	Transient response
Hematological			
Cell counts	1	Fast (<1 h/test)	Requires serial tests
Protein			
γ-H2Ax	0.5	Fast (3 h for dose estimate)	Short half-life (days)
C reactive protein	1	Fast (within hours)	Poor specificity
Serum amylase	1	Fast (within hours)	Requires dose to salivary gland
Physical			
EPR	0.1	Fast (min)	Invasive; not useful for partial-body exposures
Neutron activation	0.0001	Neutron specific	Not for partial-body exposures

SOURCE: Adapted from Ainsbury et al., 2011. Review of retrospective dosimetry techniques for external ionising radiation exposures. *Radiation Protection Dosimetry* 147(4):573-592, by permission of Oxford University Press.

advances in high-throughput "-omics"[7] technologies, however, enable interrogation of radiation-induced effects at the genomic, transcriptomic, proteomic, and metabolomic levels. The systems biology-level challenge is to integrate these -omics platforms to understand radiation dose and dose-rate effects in a complex tissue as a function of time and then to relate these effects to observable functional physiological or physical changes in that tissue after irradiation. Addressing this problem requires knowledge of the biological processes involved, such as the molecular and biochemical signaling pathways, and computational-modeling capabilities to organize this information in a way that it can be integrated with radiation-risk models.

Mechanistic Models

At present, the only approach to risk estimation at low doses involves models for interpolation across a range of observed doses to derive estimates of risk at lower doses. Risk estimates at low doses may be highly sensitive to model choice.

At doses greater than 1 Gy, cells are typically hit by many tracks of radiation, whereas for low doses of low-LET radiation (i.e., at doses less than 100 mGy), most cells are hit by a single track; the lower the dose within the low-dose region the smaller the number of cells hit. That is, in the low dose region the damage to cells hit remains essentially the same (i.e., a single radiation track passing through a cell). What changes is the number of cells that are subjected to this damage, which decreases proportionally with decreasing dose. This is the biophysical argument for the LNT model.

Many caveats are associated with this biophysical argument. Examples include the potential effects of phenomena such as intercellular communication and immunosurveillance and the possibility of different radiobiological processes at very low doses (less than 10 mGy), compared with doses at the 10–100 mGy range (Brenner, 2009; Tubiana et al., 2006). However, currently there is no scientific knowledge as to whether or how these phenomena and processes would deviate cancer risks at very low doses from those predicted by linear extrapolation from low doses (Brenner et al., 2003).

[7] The suffix "-omics" refers to the study of the genome, proteome, or metabolome; hence genomics, proteomics, and metabolomics. Typically, -omics involves analysis of large databases of information and requires that investigators with different areas of expertise (e.g., computer scientists and biologists) work together to best interpret the data.

EPIDEMIOLOGICAL STUDIES— CURRENT WORK AND RESEARCH DIRECTIONS

Epidemiological radiation studies become increasingly impractical at low doses because of the large sample sizes required, because the background cancer rate is high enough that the study's signal-to-noise ratio becomes prohibitively low. To estimate cancer risks at low doses (and potentially more chronic exposures), one then needs to extrapolate radiation-related risks from epidemiological studies at higher doses (Puskin, 2008).

In any epidemiological study, investigators need to carefully examine whether an observed association is real or results from bias.[8] Well-designed epidemiological studies aim to minimize bias problems or at least to characterize their potential influence. The approaches taken to minimize bias in low-dose radiation epidemiology vary, in part depending on decisions about the study design, statistical methods, and opportunities available to investigators for data collection.

Studies aiming to estimate risks at low radiation doses deal with challenging problems related to design, analysis, and interpretation of the study findings. These include

- Measurement errors related to estimation of radiation doses and uncertainties in dosimetric models,
- Confounding, which is related to factors other than radiation that cause the outcome of interest, and
- Model uncertainty in selection of dose-response models.

The NCRP (2012) and others have provided comprehensive reviews of the sources of bias and uncertainty in radiation epidemiological studies.

The three most commonly used types of epidemiological studies designed to answer questions about low-dose radiation are cohort studies, case-control studies, and ecological studies. The following sections discuss those and risk-projection models.

Epidemiological Study Designs

Cohort Studies

Cohort studies typically follow a group of exposed and a group of unexposed individuals over time to determine disease occurrence in relation to radiation exposure. Much of what we know about cancer risks at lower radiation levels comes from the study of the atomic-bombing survivors of

[8] Bias is an error in the measurement of a factor that can arise, for example, from choosing study subjects that are not representative of the overall population (i.e., selection bias) or from inaccurate or incomplete information on the disease or exposure (i.e., information bias).

Hiroshima and Nagasaki, Japan. The Life Span Study (LSS) cohort, the main cohort of these survivors, includes about 94,000 atomic-bombing survivors who were within 10 km of the bombs' hypocenter and about 26,000 individuals who were not in either of these two cities at the times of the bombings. The Radiation Effects Research Foundation and its predecessor, the Atomic Bomb Casualty Commission, tracked cancer incidence (Preston et al., 2007), cancer mortality (Ozasa et al., 2012), and non-cancer-related mortality (Neriishi et al., 2012; Ozasa et al., 2012; Shimizu et al., 2010) rates in the LSS cohort. Estimates of doses to cohort members reflect major efforts to retrospectively collect data on survivors' locations and degree of shielding at the time of the bombings (Cullings et al., 2006). Dosimetry systems have been recently revised to derive exposure estimates for many (but not all) members of the cohort.

Since the inception of the LSS, the investigators involved have been concerned with issues of confounding, measurement error, and selection bias. To be part of the LSS, individuals must have survived for at least five years after the bombings, an inclusion criterion that may be related to the ability to survive acute effects (Pierce et al., 2007). Exposure was determined in part by each person's location and shielding conditions, and one concern is confounding of the radiation effect by other disease risk factors related to each individual's location and shielding conditions at the time of the bombing. Proximity to the hypocenter in Hiroshima, for example, was not only related to radiation exposure from the bomb but also potentially related to each individual's occupation, socioeconomic status (SES), and other independent risk factors for mortality that simultaneously can be correlated with dose. Another concern is exposure misclassification caused by uncertainty in determining the survivors' location and shielding. Studies have varied in their use of self-reported information to classify survivors with respect to distance from the hypocenter, level of shielding, and the presence of acute radiation effects such as hair loss.

Selection bias may arise because of the effect of conditioning on survival; this may induce associations between location (and therefore exposure) and risk factors that were not confounders in the base population. Selection bias may also influence generalizability if the survivors differ. Further, in an observational study, the exposure may be seen to have both direct and indirect effects; for example, the experience of surviving the atomic-bomb blast may not simply have direct effects related to the radiation dose but may also have indirect effects because the experience could lead to changes in health-related behaviors.

Case-Control Studies

Case-control studies aim to determine whether the frequency of exposure is higher in the group of people with the disease of interest (the cases) than it is in the group without the disease (the controls). As in the case of cohort designs, confounding, measurement error, and selection bias are concerns in case-control designs.

In some situations, case-control designs allow collection of more detailed information on covariates than would be feasible to assemble for a large cohort; this may help to address concerns about confounding by ascertaining information on a longer list of potential confounders of concern. A disadvantage of case-control designs is the potential for different recall of exposure information by case and control subjects. In studies in which self-reported exposure information is used as the basis for classifying people with respect to exposure, this may introduce bias. Such concerns were raised with respect to interpretation of findings from the Oxford Survey of Childhood Cancer (OSCC), a highly influential case-control study on low-dose ionizing radiation effects (Doll and Wakeford, 1997; NCRP, 2013). One way to address these concerns is to rely on information recorded before diagnosis of the case or symptom onset. For example, OSCC investigators were able to draw on medical records as an alternative to self-reporting as a source of information about in utero X-ray exposure for many of the case and control subjects.

Differences in participation between the cases and controls may also lead to bias. This would occur, for example, if most cases agreed to participate in a study but most lower SES controls did not, and SES was related to the distribution of exposure in the study population.

Ecological Studies

Ecological studies (also called geographical studies) are those in which exposures and outcomes are assessed for groups of individuals within neighborhoods, counties, or other geographical units rather than at the individual level. Ecological designs have been used for the study of protracted low-level exposure to ionizing radiation (Little et al., 2010b). As with other study types, problems of confounding, measurement error, and selection bias are important considerations. A unique problem of inference arises with ecological studies, compared with cohort studies: the possibility of errors when the findings from ecological designs are used to draw conclusions about the existence of causal associations at the individual level. This is referred to as ecological fallacy.[9]

[9] The ecological fallacy arises when the relationships observed for groups are used to draw conclusions about individuals. For example, it has been shown that countries with high fat intake also have high rates of breast cancer. This does not necessarily imply that women with high fat intake are at higher risk of developing breast cancer (Holmes et al., 1999).

Risk-Projection Models

Risk-projection models are used to predict excess cancer risks by combining population-dose estimates with existing risk coefficients, thus transferring risks across populations with different baseline rates. Recent applications of risk-projection modeling have increased for two main reasons: their provision of timely estimates by making use of the risk estimates for U.S. populations published in the BEIR VII report (NRC, 2006) and the increasing acceptance of the limitations of epidemiological studies of low-dose radiation exposures (Berrington et al., 2011).

However, this approach may lead to erroneous conclusions in several ways. First, the insights drawn from a historical epidemiological study may provide a distorted, or biased, model for projecting an exposure's effect on disease occurrence in the study population. This is called a problem of internal validity. Such problems might result from confounding of the estimate due to an imbalance in the distribution of disease risk factors other than radiation, errors in historical estimates of radiation exposures, or health-related selection into the exposure groups.

Second, the population that one wishes to draw inferences about may not be comparable with the historical population that was studied; this is considered to be a problem of external validity. Differences in susceptibility, exposure to other hazards (for example, smoking), or access to medical and preventive care may work against a valid extrapolation of radiation-risk estimates from a historical study population to the contemporary population of interest because of differences in baseline cancer rates.

Cancer Risk at Low Doses

A common comment about the atomic-bombing survivors' LSS cohort is that it is a high-dose group, and one thus needs to extrapolate radiation-risk estimates to address questions about the effects of lower doses. In fact, Preston and colleagues (2007) noted that about 85% of the cohort received estimated radiation doses to the colon less than 200 mGy.

When one focused only on the cohort members exposed to low doses, there was evidence of increased solid-cancer incidence when the analysis was restricted to LSS cohort members who received doses of 150 mGy or less (Preston et al., 2007). Evidence was less strong when the analysis was restricted to cohort members who received doses of 100 mGy or less. Similar results were seen for cancer mortality. Epidemiological studies on populations exposed to still lower doses (with presumably correspondingly lower radiation risks) are likely to yield more uncertain results. An approach to epidemiological assessment of risks at such lower doses is to focus on scenarios in which the signal-to-background ratio is likely to be higher. One example is the study of childhood cancers after in utero medical diagnostic imaging. Here, the excess relative risk among the exposed subjects (the signal) is expected to be high because they were exposed at a critical point in their development, and the background is expected to be low because childhood cancers are rare. Indeed, the OSCC detected a significant increase in childhood cancer risk for a mean dose of ~10 mGy (Doll and Wakeford, 1997).[10] The results from this large study and others showing an association between in utero exposure and cancer risk in childhood (IARC, 2012) are widely accepted and have changed medical practice related to exposure of pregnant women to ionizing radiation. However, NCRP (2013) questioned whether the relationship is causal.

The same logic—focusing on subgroups of the population in which the excessive relative risk of cancer after radiation exposure is posited to be largest—applies to two more recently published epidemiological studies of cancer risks associated with pediatric exposure to computed tomography (CT) scans, both of which had a relatively short mean follow-up of ~10 years (Mathews et al., 2013; Pearce et al., 2012). The relatively short follow-up after pediatric exposure permits detection of radiation-induced cancers with short latency while excluding investigation of those cancers that may appear at later ages. Both of these studies had large cohorts, and both showed a statistically significant association between the number of CT scans and increased cancer risk. Pearce and colleagues concluded that in children, the use of CT scans that deliver cumulative doses of ~50 mGy might triple the risk of leukemia, and doses of ~60 mGy might triple the risk of brain cancer. Mathews and colleagues reported finding a statistically significant dose-response relationship over the range of zero to more than three CT scans, and the cancer incidence–rate ratio increased by 0.16 (95% confidence interval [CI]: 0.13–0.19) for each additional scan.

One concern that has been raised is the possibility of confounding by indication (NCRP, 2012); i.e., a factor that prompted the CT scanning might itself also be a risk factor for the subsequent cancer (reverse causality). For example, an undiagnosed brain tumor might have brought about the symptoms that led to the need for CT scanning and is itself a cause of later increased risk of brain cancer. The investigators of both studies acknowledged this potential for confounding and attempted to address it by conducting analyses that discounted cancers in the period 5 or 10 years immediately after the CT scanning. The fact that associations between CT radiation dose and childhood cancer were observed many years after scanning diminishes the plausibility that latent disease led to the need for CT scanning. However, confounding by indication remains a concern that has been raised about potential bias in these studies. Other CT-specific issues

[10] Note that the absolute risk of childhood cancer is low, even among those exposed in utero.

include the potential for undocumented rescans necessitated by patient movement during the initial examination[11] (NCRP, 2012).

Of course, radiation-related excess cancer risks may persist for many decades after exposure (Preston et al., 2007). To date, studies of cancer development after pediatric CT scanning have not encompassed sufficient follow-up time to permit estimates of lifetime excessive cancer risks.

Recently, Boice and colleagues launched a study that aims to provide information on risks when a radiation dose is received gradually over many years (Boice, 2012). The study, known as the One Million U.S. Radiation Worker Study, focuses on the following occupational groups with differing radiation exposure patterns: uranium workers at multiple DOE locations (196,000); DOE plutonium workers (155,000 participants); nuclear weapons test participants (atomic veterans) (120,000 participants); nuclear power plant workers (236,000 participants); and industrial radiographers, radiologists, and other medical practitioners (300,000 participants) (Boice, 2011). Still at its initial stages, the study may help inform radiation protection standards for chronic exposure.

Other Health Consequences

Radiation exposure at doses higher than 1 Gy is associated with many noncancer health effects, but little existing evidence addresses such effects at doses less than 1 Gy. Many questions remain about biological mechanisms operating at moderately high to low (i.e., at the 100 mGy–1 Gy range) doses and below that might affect the risk of disease. For example, the association between low-dose radiation exposure and circulatory diseases is increasingly gaining attention (ICRP, 2012). However, the fact that established risk factors for circulatory disease (such as smoking, diet, obesity, diabetes, and elevated blood pressure) that could act as confounding influences prevents confident interpretation of the reported statistical associations (Little et al., 2008, 2010a; Ozasa et al., 2012). Recent studies of cohorts including atomic-bombing survivors (Shimizu et al., 2010), the Mayak radiation workers[12] (Azizova et al., 2012), Chernobyl emergency workers (Ivanov et al., 2006), and nuclear workers (McGeoghegan et al., 2008) have shown an increase in circulatory disease at doses higher than

[11] Before more modern technology was implemented, individual CT scan exposures could last for several seconds, leading to high exposures on repeated scans.

[12] The Mayak worker cohort is a collaborative American–Russian study of workers employed in the plutonium and reprocessing plants in the Chelyabinsk region of the Russian Federation that started in the late 1940s. Workers in the reactors and in the plutonium and radiochemical plants were exposed to external gamma radiation during their employment at Mayak and the radiochemical plants (Shilnikova et al., 2003).

0.5 Gy. Informed by the results of these recent studies, ICRP listed circulatory disease as a radiation health effect (ICRP, 2012).

Additionally, the eye lens is relatively radiosensitive, and cataract formation has been associated with exposure to ionizing radiation for decades (ICRP, 1991). Recent studies provided a strong scientific basis for ICRP's revision of standards for protection of the eye, which lowered the allowable acute dose to the eye from 5 Gy to 0.5 Gy (ICRP, 2012).

A reanalysis of atomic-bombing survivor data suggests a linear dose response for cataract induction, with an estimated threshold of 0.1 Gy (Neriishi et al., 2007) and a radiation effect for vision-impairing cataracts—that is, clinically significant cataracts that require surgery—at doses less than 1 Gy (Neriishi et al., 2012). Data from the U.S. radiological technologists study, one of the largest undertaken to date on cataract risk, suggested an increased risk of cataracts arising from cumulative doses of a few tenths of milligray (Chodick et al., 2008). Further support for cataract formation after exposure to less than 1 Gy comes from studies of commercial airline pilots and Chernobyl clean-up workers (Worgul et al., 2007).

SUMMARY AND OBSERVATIONS

The committee's examination of current directions in radiobiological science related to the human health risks from exposure to ionizing radiation led it to several findings and conclusions.

Although much is known about the health effects after exposure to radiation at the 100 mGy–1 Gy dose range and high dose rates, the scientific uncertainty concerning the effects of low-dose radiation is considerable. Debate continues about how to extrapolate radiation risks at low doses, the biological effectiveness of low-dose radiation, and the effects of dose rate and external versus internal exposure.

Nevertheless, it is exposures at low doses that are of primary interest for radiation-protection purposes, and decisions are needed for use in setting standards for protection of individuals against the adverse effects of low-dose radiation. The health effect of primary concern in the context of low-level radiation is cancer. However, recent data suggest that other effects, such as cardiovascular diseases and cataracts, may occur after exposure at lower doses than previously thought, and this has led to changes in international recommendations for radiation protection.

Low-dose radiation research involves both experimental studies of radiation effects on molecules, cells, tissues, and animal models and observational studies on populations (i.e., epidemiological studies). Although epidemiological studies can provide the most direct evidence of associations between exposure to low-dose radiation and disease in humans, experimental studies are essential to improving our understanding of the mechanisms by which low-dose ionizing radiation causes damage and how the cells and tissues respond to that damage.

For many years, the United States has been the world leader in understanding the health consequences of radiation exposure, but more recently, research in this area has slowed down, and the country lacks a long-term milestone-driven strategic plan for better understanding effects and risks of low doses. Sixteen nations—under the aegis of MELODI and its DoReMi research integration effort—are already pursuing such a plan. The United States would benefit from undertaking similar action.

There are thus a number of unanswered questions concerning the human health effects of low-dose ionizing radiation exposures and, although scientific advances provide opportunities to address them, there are also significant challenges associated with moving forward. Chapter 5 discusses opportunities for AFRRI to contribute to the body of knowledge on the health effects of low-dose ionizing radiation in ways relevant to its mission and offers recommendations on possible courses of action.

REFERENCES

Ainsbury, E. A., E. Bakhanova, J. F. Barquinero, M. Brai, V. Chumak, V. Correcher, F. Darroudi, P. Fattibene, G. Gruel, I. Guclu, S. Horn, A. Jaworska, U. Kulka, C. Lindholm, D. Lloyd, A. Longo, M. Marrale, O. Monteiro Gil, U. Oestreicher, J. Pajic, B. Rakic, H. Romm, F. Trompier, I. Veronese, P. Voisin, A. Vral, C. A. Whitehouse, A. Wieser, C. Woda, A. Wojcik, and K. Rothkamm. 2011. Review of retrospective dosimetry techniques for external ionising radiation exposures. *Radiation Protection Dosimetry* 147(4):573-592.

Andrieu, N., D. F. Easton, J. Chang-Claude, M. A. Rookus, R. Brohet, E. Cardis, A. C. Antoniou, T. Wagner, J. Simard, G. Evans, S. Peock, J. P. Fricker, C. Nogues, L. Van't Veer, F. E. Van Leeuwen, and D. E. Goldgar. 2006. Effect of chest X-rays on the risk of breast cancer among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study: A report from the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. *Journal of Clinical Oncology* 24(21):3361-3366.

Aurengo, A., D. Averbeck, A. Bonnin, B. Le Guen, R. Masse, R. Monier, M. Tubiana, A.-J. Valleron, F. de Vathaire. 2005. *Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation*. Paris, France: Académie des Sciences, Académie nationale de Médecine. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.126.1681&rep=rep1&type=pdf (accessed March 3, 2014).

Averbeck, D. 2013. MELODI—*Multidisciplinary European Low Dose Initiative: 4th draft of Strategic Research Agenda (SRA)*. March 21, 2013 (updated version). http://www.melodi-online.eu/doc/SRA4.pdf (accessed April 10, 2014).

Azizova, T. V., C. R. Muirhead, M. B. Moseeva, E. S. Grigoryeva, E. V. Vlasenko, N. Hunter, R. G. Haylock, and J. A. O'Hagan. 2012. Ischemic heart disease in nuclear workers first employed at the Mayak Production Association in 1948-1972. *Health Physics* 103(1):3-14.

Barcellos-Hoff, M. H. 2005. Integrative radiation carcinogenesis: Interactions between cell and tissue responses to DNA damage. *Seminars in Cancer Biology* 15(2):138-148.

Barcellos-Hoff, M. H. 2008. Cancer as an emergent phenomenon in systems radiation biology. *Radiation and Environmental Biophysics* 47(1):33-38.

Berrington de Gonzalez, A., A. Brenner, P. Hartge, C. Lee, L. Morton, and P. Rajaraman. 2011. Evolving strategies in epidemiologic research on radiation and cancer. *Radiation Research* 176(4):527-532.

Besaratinia, A., H. Li, J. I. Yoon, A. Zheng, H. Gao, and S. Tommasi. 2012. A high-throughput next-generation sequencing-based method for detecting the mutational fingerprint of carcinogens. *Nucleic Acids Research* 40(15):e116.

Boice, J. D. 2011. *The One Million U.S. Radiation Worker Study*. Department of Energy Low Dose Radiation Research Program Investigators' Workshop. Bethesda, MD. http://lowdose.energy.gov/pdf/2011/boice_j.pdf (accessed April 11, 2014).

Boice, J. D. 2012. A study of one million U.S. radiation workers and veterans (The Boice Report #6). *Health Physics News*. Pp. 7-10. http:\\www.ncrponline.org/PDFs/BOICE-HPnews/Nov-2012_Million_Worker.pdf (accessed April 11, 2014).

Boltze, C., A. Riecke, C. G. Ruf, M. Port, H. Nizze, C. Kugler, C. Miethke, N. Wiest, and M. Abend. 2009. Sporadic and radiation-associated papillary thyroid cancers can be distinguished using routine immunohistochemistry. *Oncology Reports* 22(3):459-467.

Brenner, D. J. 1999. Does fractionation decrease the risk of breast cancer induced by low-LET radiation? *Radiation Research* 151:225-229.

Brenner, D. J. 2009. Extrapolating radiation-induced cancer risks from low doses to very low doses. *Health Physics* 97(5):505-509.

Brenner, D. J. 2014. What we know and what we don't know about cancer risks associated with radiation doses from radiological imaging. *British Journal of Radiology* 87(1035).

Brenner, D. J., R. Doll, D. T. Goodhead, E. J. Hall, C. E. Land, J. B. Little, J. H. Lubin, D. L. Preston, R. J. Preston, J. S. Puskin, E. Ron, R. K. Sachs, J. M. Samet, R. B. Setlow, and M. Zaider. 2003. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. *Proceedings of the National Academy of Sciences of the United States of America* 100(24):13761-13766.

Brenner, D. J., J. Boice, W. F. Morgan, J. E. Cleaver, T. K. Hei, H. Hricak, S. J. Adelstein, and J. M. Samet. 2013. Letter to John P. Holdren, Director of the White House Office of Science and Technology Policy, on the future of low-dose radiation research in the U.S. New York. http://www.radres.org/?page=HoldrenLetter&hhSearchTerms=%22holdren%22 (accessed February 27, 2014).

Brooks, A. L. 2011. Is a dose and dose-rate effectiveness factor (DDREF) needed following exposure to low total radiation doses delivered at low dose-rates? *Health Physics* 100(3):262.

Bushberg, J. T., J. A. Seibert, and E. M. Leid. 2002. *The essential physics of medical imaging, second edition.* Philadelphia, PA: Lippincott Williams & Wilkins.

Carnes, B. A., and T. E. Fritz. 1991. Responses of the beagle to protracted irradiation. I. Effect of total dose and dose rate. *Radiation Research* 128(2):125-132.

Carnes, B. A., S. J. Olshansky, and D. Grahn. 1998. An interspecies prediction of the risk of radiation-induced mortality. *Radiation Research* 149(5):487-492.

Chodick, G., N. Bekiroglu, M. Hauptmann, B. H. Alexander, D. M. Freedman, M. M. Doody, L. C. Cheung, S. L. Simon, R. M. Weinstock, A. Bouville, and A. J. Sigurdson. 2008. Risk of cataract after exposure to low doses of ionizing radiation: A 20-year prospective cohort study among US radiologic technologists. *American Journal of Epidemiology* 168(6):620-631.

Cullings, H. M., S. Fujita, S. Funamoto, E. J. Grant, G. D. Kerr, and D. L. Preston. 2006. Dose estimation for atomic bomb survivor studies: Its evolution and present status. *Radiation Research* 166(1):219-254.

Dauer, L. T., A. L. Brooks, D. G. Hoel, W. F. Morgan, D. Stram, and P. Tran. 2010. Review and evaluation of updated research on the health effects associated with low-dose ionising radiation. *Radiation Protection Dosimetry* 140(2):103-136.

DOE (U.S. Department of Energy). 2014. *Department of Energy FY 2015 Congressional Budget Request. Volume 4. Science. Advanced Research Projects Agency–Energy*. March 2014. Washington, DC: U.S. Department of Energy, Office of Chief Financial Officer. http://www.energy.gov/sites/prod/files/2014/03/f12/Volume_4.pdf (accessed April 3, 2014).

Doll, R., and R. Wakeford. 1997. Risk of childhood cancer from fetal irradiation. *British Journal of Radiology* 70:130-139.

Dom, G., M. Tarabichi, K. Unger, G. Thomas, M. Oczko-Wojciechowska, T. Bogdanova, B. Jarzab, J. E. Dumont, V. Detours, and C. Maenhaut. 2012. A gene expression signature distinguishes normal tissues of sporadic and radiation-induced papillary thyroid carcinomas. *British Journal of Cancer* 107(6):994-1000.

DoReMi (Low Dose Research Towards Multidisciplinary Integration). 2014. *DoReMi—Integrating low dose research*. http://www.doremi-noe.net (accessed February 16, 2014).

EC (European Commission). 2009. *High Level and Expert Group report—European low dose risk research radiation protection*. EUR 23884 ERC. http://ec.europa.eu/research/energy/pdf/hleg_report_-_january_2009.pdf (accessed February 16, 2014).

Flint-Richter, P., and S. Sadetzki. 2007. Genetic predisposition for the development of radiation-associated meningioma: An epidemiological study. *Lancet Oncology* 8(5):403-410.

Goodhead, D. T. 2009. Fifth Warren K. Sinclair keynote address: Issues in quantifying the effects of low-level radiation. *Health Physics* 97(5):394-406.

Haley, B., Q. Wang, B. Wanzer, S. Vogt, L. Finney, P. L. Yang, T. Paunesku, and G. Woloschak. 2011. Past and future work on radiobiology mega-studies: A case study at Argonne National Laboratory. *Health Physics* 100(6):613-621.

Hall, E. J., and A. J. Giaccia. 2005. *Radiobiology for the radiobiologist: Sixth edition.* Philadelphia, PA: Lippincott Williams & Wilkins.

Hess, J., G. Thomas, H. Braselmann, V. Bauer, T. Bogdanova, J. Wienberg, H. Zitzelsberger, and K. Unger. 2011. Gain of chromosome band 7q11 in papillary thyroid carcinomas of young patients is associated with exposure to low-dose irradiation. *Proceedings of the National Academy of Sciences of the United States of America* 108(23):9595-9600.

Holmes, M. D., D. J. Hunter, G. A. Colditz, M. J. Stampfer, S. E. Hankinson, F. E. Speizer, B. Rosner, and W. C. Willett. 1999. Association of dietary intake of fat and fatty acids with risk of breast cancer. *Journal of the American Medical Association* 281(10):914-920.

IAEA (International Atomic Energy Agency). 2011. *Cytogenetic dosimetry: Applications in preparedness for and response to radiation emergencies*. Vienna: International Atomic Energy Agency.

IARC (International Agency for Research on Cancer). 2012. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 100D. *A review of human carcinogens: Radiation*. Lyon, France: International Agency for Research on Cancer.

ICRP (International Commission on Radiological Protection). 1977. Recommendations of the ICRP. Publication 26. Oxford, UK: Pergamon, Elsevier Science. *Annals of the ICRP* 1(3).

ICRP. 1991. 1990 Recommendations of the ICRP. Publication 60. Oxford, UK: Pergamon, Elsevier Science. *Annals of the ICRP* 21(1-3).

ICRP. 2007. The 2007 recommendations of the ICRP. Publication 103. Oxford, UK: Pergamon, Elsevier Science. *Annals of the ICRP* 37(2-4).

ICRP. 2012. ICRP statement on tissue reactions: Early and late effects of radiation in normal tissues and organs—Threshold doses for tissue reactions in a radiation protection context. Publication 118. Oxford, UK: Pergamon, Elsevier Science. *Annals of the ICRP* 41(1-2).

Ivanov, V. K., M. A. Maksioutov, S. Y. Chekin, A. V. Petrov, A. P. Biryukov, Z. G. Kruglova, V. A. Matyash, A. F. Tsyb, K. G. Manton, and J. S. Kravchenko. 2006. The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Physics* 90(3):199-207.

Jacob, P., W. Ruhm, L. Walsh, M. Blettner, G. Hammer, and H. Zeeb. 2009. Is cancer risk of radiation workers larger than expected? *Journal of Occupational and Environmental Medicine* 66(12):789-796.

Kadhim, M., S. Salomaa, E. Wright, G. Hildebrandt, O. V. Belyakov, K. M. Prise, M. P. Little. 2013. Non-targeted effects of ionising radiation—Implications for low dose risk. *Mutation Research* 752(2):84-89.

Koterov, A.N. 2005. Genomic instability at exposure of low dose radiation with low LET. Mythical mechanism of unproved carcinogenic effects. *International Journal of Low Radiation* 1(4):376-451.

Land, C. E., M. Tokunaga, S. Tokuoka, and N. Nakamura. 1993. Early-onset breast cancer in A-bomb survivors. *Lancet* 342(8865):237.

Little, M. P., D. G. Hoel, J. Molitor, J. D. Boice, Jr., R. Wakeford, and C. R. Muirhead. 2008. New models for evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 report. *Radiation Research* 169(6):660-676.

Little, M. P., E. J. Tawn, I. Tzoulaki, R. Wakeford, G. Hildebrandt, F. Paris, S. Tapio, and P. Elliott. 2010a. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. *Radiation and Environmental Biophysics* 49(2):139-153.

Little, M. P., R. Wakeford, J. H. Lubin, and G. M. Kendall. 2010b. The statistical power of epidemiological studies analyzing the relationship between exposure to ionizing radiation and cancer, with special reference to childhood leukemia and natural background radiation. *Radiation Research* 174(3):387-402.

Lubin, J. H., J. D. Boice, Jr., C. Edling, R. W. Hornung, G. Howe, E. Kunz, R. Kusiak, H. Morrison, E. Radford, and J. M. Samet. 1995. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Physics* 69:494-500.

Malone, K. E., C. B. Begg, R. W. Haile, A. Borg, P. Concannon, L. Tellhed, S. Xue, S. Teraoka, L. Bernstein, M. Capanu, A. S. Reiner, E. R. Riedel, D. C. Thomas, L. Mellemkjaer, C. F. Lynch, J. D. Boice, Jr., H. Anton-Culver, and J. L. Bernstein. 2010. Population-based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 or BRCA2. *Journal of Clinical Oncology* 28(14):2404-2410.

Mancuso, M., E. Pasquali, S. Leonardi, M. Tanori, S. Rebessi, V. Di Majo, S. Pazzaglia, M. P. Toni, M. Pimpinella, V. Covelli, and A. Saran. 2008. Oncogenic bystander radiation effects in *Patched* heterozygous mouse cerebellum. *Proceedings of the National Academy of Sciences of the United States of America* 105(34):12445-12450.

Mathews, J. D., A. V. Forsythe, Z. Brady, M. W. Butler, S. K. Goergen, G. B. Byrnes, G. G. Giles, A. B. Wallace, P. R. Anderson, T. A. Guiver, P. McGale, T. M. Cain, J. G. Dowty, A. C. Bickerstaffe, and S. C. Darby. 2013. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: Data linkage study of 11 million Australians. *British Medical Journal* 346:f2360.

McGeoghegan, D., K. Binks, M. Gillies, S. Jones, and S. Whaley. 2008. The non-cancer mortality experience of male workers at British Nuclear Fuels PLC, 1946-2005. *International Journal of Epidemiology* 37(3):506-518.

Morgan, W. F. 2003. Is there a common mechanism underlying genomic instability, bystander effects and other nontargeted effects of exposure to ionizing radiation? *Oncogene* 22(45):7094-7099.

MELODI (Multidisciplinary European Low Dose Initiative). 2014. *Multidisciplinary European Low Dose Initiative*. http://www.melodi-online.eu (accessed February 16, 2014).

NCRP (National Council on Radiation Protection and Measurements). 1980. *Influence of dose and its distribution in time on dose-response relationships for low-LET radiations*. Bethesda, MD: National Council on Radiation Protection and Measurements.

NCRP. 2001. *Evaluation of the linear-nonthreshold dose-response model for ionizing radiation*. Report No. 136. Bethesda, MD: National Council on Radiation Protection and Measurements.

NCRP. 2012. *Uncertainties in the estimation of radiation risks and probability of disease causation*. NCRP Report No. 171. Bethesda, MD: National Council on Radiation Protection and Measurements.

NCRP. 2013. *Preconception and prenatal radiation exposure: Health effects and protective guidance*. Report No. 174. Bethesda, MD: National Council on Radiation Protection and Measurements.

Neriishi, K., E. Nakashima, A. Minamoto, S. Fujiwara, M. Akahoshi, H. K. Mishima, T. Kitaoka, and R. E. Shore. 2007. Postoperative cataract cases among atomic bomb survivors: Radiation dose response and threshold. *Radiation Research* 168(4):404-408.

Neriishi, K., E. Nakashima, M. Akahoshi, A. Hida, E. J. Grant, N. Masunari, S. Funamoto, A. Minamoto, S. Fujiwara, and R. E. Shore. 2012. Radiation dose and cataract surgery incidence in atomic bomb survivors, 1986-2005. *Radiology* 265(1):167-174.

NRC (National Research Council). 1990. *Health effects of exposure to low levels of ionizing radiation: BEIR V*. Washington, DC: National Academy Press.

NRC. 1999. *Potential radiation exposure in military operations: Protecting the soldier before, during, and after*. Washington, DC: National Academy Press.

NRC. 2006. *Health risks from exposure to low levels of ionizing radiation: BEIR VII: Phase 2*. Washington, DC: The National Academies Press.

Ozasa, K., Y. Shimizu, A. Suyama, F. Kasagi, M. Soda, E. J. Grant, R. Sakata, H. Sugiyama, and K. Kodama. 2012. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. *Radiation Research* 177(3):229-243.

Pearce, M. S., J. A. Salotti, M. P. Little, K. McHugh, C. Lee, K. P. Kim, N. L. Howe, C. M. Ronckers, P. Rajaraman, A. W. Craft, L. Parker, and A. Berrington de Gonzalez. 2012. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *Lancet* 380(9840):499-505.

Pierce, D., M. Vaeth, and Y. Shimizu. 2007. Selection bias in cancer risk estimation from A-Bomb survivors. *Radiation Research* 167(6):735-741.

PNNL (Pacific Northwest National Laboratory). 2012. *Original research program plan: Biological effects of low dose and dose rate radiation*. http://lowdose.energy.gov/about_originalplan.aspx (accessed April 3, 2014).

Preston, D. L., E. Ron, S. Tokuoka, S. Funamoto, N. Nishi, M. Soda, K. Mabuchi, and K. Kodama. 2007. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiation Research* 168(1):1-64.

Preston, R. J., J. D. Boice, Jr., A. B. Brill, R. Chakraborty, R. Conolly, F. O. Hoffman, R. W. Hornung, D. C. Kocher, C. E. Land, R. E. Shore, and G. E. Woloschak. 2013. Uncertainties in estimating health risks associated with exposure to ionising radiation. *Journal of Radiological Protection* 33(3):573-588.

Puskin, J.S. 2008. What can epidemiology tell us about risks at low doses? *Radiation Research* 169(1):122-124.

Salomaa, S., K. M. Prise, M. J. Atkinson, A. Wojcik, A. Auvinen, B. Grosche, L. Sabatier, J. R. Jourdain, E. Salminen, S. Baatout, U. Kulka, H. Rabus, E. Blanchardon, D. Averbeck, and W. Weiss, 2013. State of the art in research into the risk of low dose radiation exposure—Findings of the fourth MELODI workshop. *Journal of Radiological Protection* 33(3):573-588.

Shilnikova, N. S., D, L. Preston, E. Ron, E. S. Gilbert, E. K. Vassilenko, S. A. Romanov, I. S. Kuznetsova, M. E. Sokolnikov, P. V. Okatenko, V. V. Kreslov, and N. A. Koshurnikova. 2003. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiation Research* 159(6):787-798.

Shimizu, Y., K. Kodama, N. Nishi, F. Kasagi, A. Suyama, M. Soda, E. J. Grant, H. Sugiyama, R. Sakata, H. Moriwaki, M. Hayashi, M. Konda, and R. E. Shore. 2010. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *British Medical Journal* 340:b5349.

Shin, S. C., K. M. Lee, Y. M. Kang, K. Kim, S. A. Lim, K. H. Yang, J. Y. Kim, S. Y. Nam, and H. S. Kim. 2011. Differential expression of immune-associated cancer regulatory genes in low- versus high-dose-rate irradiated AKR/J mice. *Genomics* 97(6):358-363.

Taylor, J. A., M. A. Watson, T. R. Devereux, R. Y. Michels, G. Saccomanno, and M. Anderson. 1994. p53 mutation hotspot in radon-associated lung cancer. *Lancet* 343(8889):86-87.

Tubiana, M., A. Aurengo, D. Averbeck, and R. Masse. 2006. The debate on the use of linear no threshold for assessing the effects of low doses. *Journal of Radiological Protection* 26(3):317-324.

Uehara, Y., Y. Ito, K. Taki, M. Nenoi, K. Ichinohe, S. Nakamura, S. Tanaka, Y. Oghiso, K. Tanaka, T. Matsumoto, T. Paunesku, G. E. Woloschak, and T. Ono. 2010. Gene expression profiles in mouse liver after long-term low-dose-rate irradiation with gamma rays. *Radiation Research* 174(5):611-617.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2000. *Sources and effects of ionizing radiation. Report to the General Assembly, with scientific annexes*. New York: United Nations.

UNSCEAR. 2010. *Sources and effects of ionizing radiation. Report to the General Assembly, with scientific annexes*. New York: United Nations.

UNSCEAR. 2012. *Biological mechanisms of radiation actions at low doses. A white paper to guide the scientific committee's future programme of work*. New York: United Nations. http://www.unscear.org/docs/reports/Biological_mechanisms_WP_12-57831.pdf (accessed March 3, 2014).

Vahakangas, K. H., J. M. Samet, R. A. Metcalf, J. A. Welsh, W. P. Bennett, D. P. Lane, and C. C. Harris. 1992. Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. *Lancet* 339(8793):576-580.

Vares, G., Y. Uehara, T. Ono, T. Nakajima; B. Wang, K. Taki, T. Matsumoto, Y. Oghiso, K. Tanaka, K. Ichinohe, S. Nakamura, S. Tanaka, and M. Nenoi. 2011. Transcription factor-recognition sequences potentially involved in modulation of gene expression after exposure to low-dose-rate gamma-rays in the mouse liver. *Journal of Radiation Research (Tokyo)* 52(2):249-256.

Vaurijoux, A., G. Gruel, F. Pouzoulet, E. Gregoire, C. Martin, S. Roch-Lefevre, P. Voisin, P. Voisin, and L. Roy. 2009. Strategy for population triage based on dicentric analysis. *Radiation Research* 171:541-548.

Worgul, B. V., Y. I. Kundiyev, N. M. Sergiyenko, V. V. Chumak, P. M. Vitte, C. Medvedovsky, E. V. Bakhanova, A. K. Junk, O. Y. Kyrychenko, N. V. Musijachenko, S. A. Shylo, O. P. Vitte, S. Xu, X. Xue, and R. E. Shore. 2007. Cataracts among Chernobyl clean-up workers: Implications regarding permissible eye exposures. *Radiation Research* 167(2):233-243.

Zyuzikov, N. A., P. J. Coates, J. M. Parry, S. A. Lorimore, and E. G. Wright. 2011. Lack of nontargeted effects in murine bone marrow after low-dose in vivo X irradiation. *Radiation Research* 175(3):322-327.

3

The Radiobiology Workforce

This chapter examines the available information about the supply of and demand for radiobiology researchers—a part of the fourth element of the committee's statement of task. It identifies the wide range of scientists who study radiation health and biology and summarizes the available studies of workforce issues, including data from professional associations in the field. The chapter also notes other efforts to foster training and development of investigators.

THE COMMITTEE'S APPROACH

The committee encountered several challenges in gathering data to support its evaluation of the supply of and demand for radiobiology researchers, difficulties that have also complicated the analysis of workforce issues in related fields like radiochemistry (NRC, 2012). Notably, "radiobiology" is not among the Bureau of Labor Statistics' Standard Occupational Classification categories and—as a result—the bureau does not gather information on employment or make projections regarding it. Further, although educational institutions grant graduate degrees in radiobiology and radiation biology, not everyone who conducts research in the field holds a degree with that name, and not everyone who earns such a degree conducts radiobiology research, complicating the evaluation of supply. And finally, a number of foreign institutions—for which no data are available—grant radiobiology degrees and some of their graduates practice in the United States. For these reasons, it was not feasible to conduct a quantitative analysis with any certainty.

The committee thus took a broad-based approach to assembling information, including qualitative information. As detailed in this chapter, it reviewed material on education, and on workforce supply and demand in related fields; requested and summarized data from professional societies whose members address radiation health issues; searched funding databases for radiation health- and biology-related research opportunities; and examined the available journal and grey literature on the topic. The committee also solicited opinions from prominent professionals in the field and consulted stakeholders concerned with these issues. Additional detail on these issues is provided in the remaining sections of the chapter.

RADIOBIOLOGY AS A FIELD OF STUDY

Radiobiology, the study of the effects of ionizing radiation on living things, is a diverse field that addresses basic research, medicine, public health, and national security needs. Ionizing radiation is found in many environments and used in various ways; as a result, the people who study or apply radiobiology come from a variety of disciplines. Physicians and other health professionals use ionizing radiation for procedures such as diagnostic imaging, accurate placement of medical devices, and therapeutic purposes such as killing cancerous cells. In the nuclear power industry, health physicists and radiological engineers are responsible for preventing and detecting accidental releases that might expose employees or the surrounding communities. Workers who may be exposed occupationally when mining radioactive ores or when manufacturing, repairing, or operating equipment that uses ionizing radiation are monitored by industrial hygienists and other occupational health specialists. Radon, a gas formed naturally from the decay of radioactive elements found in the environment, is a source of concern for public health professionals. Basic research scientists investigate the genetic, molecular, immunological, cancer, cardiovascular, ophthalmologic, and other effects of radiation on a variety of animal models, tissues, and cells. Epidemiologists and biostatisticians are now using biomarker and other information generated by radiobiology research to identify and distinguish populations for study. Military health, science, and command personnel need to control or manage the effects of ionizing radiation emitted by nuclear weapons, depleted uranium munitions, certain monitoring and detection devices, and the nuclear power sources used in submarines and aircraft carriers.

Given that these applications typically require different areas of expertise, the educational backgrounds of these professionals are also diverse. Radiobiology is taught through dedicated academic programs but also through specialized tracks in other fields (for example, nuclear engineering and health physics programs). This diversity of disciplines and specializations is evidenced in graduate training programs that make primary use of faculty in several departments and with several different areas of expertise, such as biology, engineering, medicine, or physics. In addition to Ph.D. scientists who traditionally conduct research, physician-scientists who have earned an M.D. or an M.D./Ph.D. and completed appropriate postdoctoral research training may also conduct independent research. Also, individuals who pursue a Ph.D. often have earned their bachelor's and master's degrees in fields akin to but outside of radiobiology.

The task of assessing the supply of and demand for researchers in radiobiology as well as the adequacy of current research training efforts necessitates recognition of this diversity. Accordingly, the committee adopted an expansive working definition of radiobiology and examined literature from related fields when appropriate. Although personnel in radiobiology are engaged in a variety of roles, including clinical care, radiation-exposure monitoring, radiation protection, and teaching, the committee was charged to focus on researchers. Because a research or professional doctorate-level education[1] typically requires the conduct of scientific investigations, this chapter targets the subset of people with such training and the academic programs that educate them. Individuals and training programs primarily involved in applied roles such as nuclear medicine technology and radiation therapy were not included.

STUDIES OF THE RADIATION HEALTH AND BIOLOGY RESEARCH WORKFORCE

During the last decade, increasing attention has been paid to issues related to the radiation health and biology workforce. The Health Physics Society (HPS)[2] has repeatedly examined the radiation workforce in the energy, health, and security sectors (HPS, 2005, 2008; Nelson, 2004; ORISE, 2009). Taking into account all degree levels and roles, the HPS produced what was described as a conservative estimate of approximately 6,700 radiation-protection professionals working in the United States as of 2004. On the basis of a 55% decline in the number of bachelor's, master's, and Ph.D. degrees, as well as a drop from 20 to 7 in the number of health physics programs graduating at least five students annually between 1995 and 2002, the HPS expressed concern over whether the pipeline in health physics could actually replenish the pool of radiation professionals in the future. Its conclusion was, "[T]he critical human capital shortage in radiation safety is overwhelming the Society's efforts to help respond to this

[1] Ph.D. and Sc.D. are typical doctoral-level research degrees; M.D. is a typical doctoral-level professional degree.

[2] HPS is an independent, nonprofit scientific organization of professionals who specialize in radiation safety. It comprises ~5,000 members (HPS, 2013).

crisis" (HPS, 2008, p. 4). A report published by the Oak Ridge Institute for Science and Education (ORISE) in 2009 on workforce trends for health physicists through 2012 reiterated this concern. It stated, "[I]t is highly likely that the number of job openings for new graduate health physicists will continue to exceed the number of new graduates available in the labor supply through 2012" (ORISE, 2009, p. 5). A 2013 update stated that the number of graduate enrollments in health physics programs was the lowest reported since the early 1970s and anticipated that there would be decreases in master's and doctoral degree recipients in 2014 and 2015 (ORISE, 2014).

A survey by Rosenstein and colleagues (2009) of faculty members employed in radiation biology in U.S. and Canadian residency programs revealed similar concerns over the declining numbers of radiobiologists in this sector. Those data showed both that the faculty members who are responsible for teaching radiation biology to radiation-oncology residents are aging (average age, ~58 years) and that faculty members whose degree is in radiation biology are scarce. Consequently, the investigators concluded, "[T]he declining numbers of radiobiologists has the potential to threaten the quality of the didactic radiation biology education that radiation oncology residents receive and could also affect research mentoring for residents" (Rosenstein et al., 2009, p. 904). This also has implications for the radiobiology research workforce—particularly the pool of physician-scientists involved in clinical and translational research related to radiation oncology.

Stating that "[c]urrent and potential shortfalls in the number of radiation scientists stand in sharp contrast to the emerging scientific opportunities and the need for new knowledge to address issues of cancer survivorship and radiological and nuclear terrorism," the Radiation Research Program (RRP), the National Cancer Institute (NCI), and the National Institute of Allergy and Infectious Diseases (NIAID) held a workshop in 2003 titled "Education and Training for Radiation Scientists" (Coleman et al., 2003). Several recommendations resulted from this effort, two of which specifically addressed the Armed Forces Radiobiology Research Institute (AFRRI). One of those called for the Institute to continue its coordination with other federal agencies engaged in radiation research and biodefense, and the other advised that AFRRI, in collaboration with other agencies and institutions, "[a]ccelerate plans to develop an educational program in radiation sciences within the Uniformed Services University for [sic] Health Sciences [USUHS] in collaboration with neighboring regional programs" (Coleman et al., 2003, p. 735).

Wogman and colleagues (2005) addressed issues related to the workforce of nuclear scientists and engineers, including those conducting radiobiology research, at the Pacific Northwest National Laboratory (PNNL) of the U.S. Department of Energy (DOE). Their assessment noted that the United States is facing serious attrition of nuclear scientists and engineers and their capabilities through the effects of aging. On the basis of the number of personnel eligible to retire by 2010, the investigators estimated that a significant loss of senior nuclear science and technology staff at PNNL would occur by 2015 and concluded that the maintenance and replenishment of the human capital needed to support PNNL nuclear science and technology programs were key issues that required immediate attention.

In 2012, Vichare and colleagues (2013) surveyed all members of eight specialty societies to examine the characteristics of currently practicing radiation oncology professionals. In contrast to Wogman and colleagues, these investigators found that respondents[3] believed that the overall supply of and demand for the radiation workforce in that field was balanced but that there was a perception of an oversupply of professionals in certain disciplines, including medical physicists (Vichare et al., 2013). However, the meaningfulness of those conclusions is ambiguous, given that only 19% of those surveyed completed the questionnaire and that the assessment of undersupply or oversupply was derived from respondents' self-perceptions, which may be based more on their own experiences than on objective data on the workforce across all employment sectors.

In July 2013, the National Council on Radiation Protection and Measurements (NCRP)—a congressionally chartered private corporation (Public Law 88-376) charged with advising the U.S. government on radiation-protection issues—hosted a workshop titled "National Crisis: Where Are the Radiation Professionals? (WARP)." The workshop was attended by representatives from federal and governmental agencies, universities, professional societies, and the private sector. Partly on the basis of reports from the National Academy of Sciences (NAS) Committee on the Assessment of and Outlook for Nuclear Physics (NAS, 2013) and the American Physical Society (APS, 2008), participants concluded that the human capital crisis (in radiation sciences) continues to deepen. They identified four basic needs and recommendations for action (Pryor, 2013):

1. Collect data on an ongoing basis to monitor current and future supply and demand.
2. Improve coordination among the government, academic, and private sectors to ensure national capability to manage radiological incidents and maintain the radiation sciences enterprise.
3. Continue federal support of academic education programs and basic research in radiobiology, medical countermeasures, improved detection capability, and nuclear forensics.
4. Cultivate radiation professionals who can develop the new science required for the future, ensure the safe use of radiation for the

[3] About 15% of the 35,204 surveys distributed yielded responses that could be analyzed.

health and welfare of the U.S. population, and respond to radiological incidents.

A working committee formed as part of this effort was charged with gathering additional information and developing a position statement on workforce issues. The April 2014 edition of the HPS's *Health Physics News* contained an update on this effort. Among the observations offered were that a coordinated, broad-based, and comprehensive effort should be undertaken to address the dwindling number of radiation professionals, that "continued data gathering to monitor supply and demand is needed" and that "increased federal support of academic education programs and basic research in radiobiology, medical countermeasures, improved detection capability, and nuclear forensics is essential" (Boice, 2014, p. 22).

In summary, the radiation health and biology workforce has gained repeated attention from researchers and professional societies, most of whom have concluded that that workforce may soon be inadequate to meet the multiple roles it occupies in the academic, medical, energy, and defense sectors. Anecdotally, Dr. Tom K. Hei, a former president of the Radiation Research Society (RRS),[4] expressed the belief that demand for research professionals will outstrip supply because of the growing need for research on radiation and the dearth of graduate training programs to train future independent investigators (Hei, 2013). Others have noted that attrition in the existing workforce will exacerbate shortfalls in the number of new professionals entering the field. Specific information on the subset of professionals who pursue research careers is lacking.

CHARACTERISTICS OF THE RADIATION HEALTH AND BIOLOGY RESEARCH WORKFORCE

To better understand the characteristics of the radiation health and biology research workforce, the committee solicited input from three professional associations: the HPS, the American Association of Physicists in Medicine (AAPM),[5] and the RRS.

[4] The RRS is a professional society whose objectives are to encourage advancement of radiation research in all areas of the natural sciences; to facilitate cooperative research between the disciplines of physics, chemistry, biology, and medicine in the study of the properties and effects of radiation; and to promote dissemination of knowledge. The RRS numbers approximately 1,600 members (RRS, 2013).

[5] The AAPM describes itself as "a scientific and professional organization, founded in 1958, composed of more than 8,000 scientists whose clinical practice is dedicated to ensuring accuracy, safety, and quality in the use of radiation in medical procedures such as medical imaging and radiation therapy" (AAPM, 2013).

TABLE 3-1 HPS Member-Reported Employment Specialties in 2012

Employment Specialty	Number of Members	Employment Specialty	Number of Members
Not identified	1,702	Instrumentation	200
Applied health physics	844	Nuclear medicine	199
Radiation safety/survey	766	Research	164
Radiological assessment	450	Other	119
Medical physics	439	Accelerators	104
Regulations/standards	398	Nuclear fuel cycle	100
Dosimetry	355	Radiochemistry	98
Reactors, power	311	Radiation biology	97
Environmental monitoring	299	Personnel monitoring	75
Waste management	263	Nonionizing radiation	60
Administration	237	Reactors, other	46
Education	208		

SOURCE: Hamrick, 2013.

The HPS requests employment information both when an applicant joins and when a member renews membership. Table 3-1 presents data suggesting that about 4% (261 individuals) of HPS members are involved in "research" or "radiation biology," even though the organization primarily attracts radiation-safety and radiation-protection practitioners. In contrast, RRS members span several scientific disciplines and are more explicitly focused on research; the proportions of its members with ties to radiobiology-related fields are much greater: biology, 43%; medicine, 25%; physics or biophysics, 16%; chemistry, 5%; and multidisciplinary, 11% (Cucinotta, 2013).

One difficulty in interpreting such data is the large percentage of missing responses: that about half of the HPS members did not identify a specialty raises the possibility of response bias if the nonresponders are distributed differently across the various specialties. Another difficulty is that many radiobiology and health physics researchers may not be members of the HPS, given that its focus is on radiation-protection professionals. If this is the case, then these data may not accurately represent the workforce in radiobiology research.

EDUCATION AND TRAINING OF THE RADIATION HEALTH AND BIOLOGY RESEARCH WORKFORCE

As already noted, radiobiology research typically requires a doctoral degree. Examining the literature on the number of doctoral degrees awarded in radiobiology and related disciplines may thus provide some insight on the supply of future investigators, although not all individuals with such credentials will participate in radiation health and biology research. Information on master's degrees is also included because such degrees may be awarded during the pursuit of a Ph.D.

The two traditional sources on Ph.D. and research-based degrees—the National Center of Education Statistics (NCES) and the Survey of Earned Doctorates (SED)—have only recently reported relevant data on earned degrees. NCES began collecting information on health and medical physics and radiobiology in 2003, and the SED first incorporated a separate code for health and medical physics and radiological sciences in 2010. The NCES *Digest of Education Statistics* draws information from various sources, including surveys of degree-granting institutions (NCES, 2013a; NSF, 2014).

In contrast, the SED[6] annually collects information from individuals receiving research doctoral degrees from all accredited U.S. institutions. Every person receiving a doctoral degree is asked to participate, and many institutions require completion of the questionnaire before the degree is awarded. A doctoral degree[7] is described as follows: "(1) Requires the completion of an original intellectual contribution in the form of a dissertation or an equivalent culminating project (e.g., musical composition) and (2) Is not primarily intended as a degree for the practice of a profession" (NSF, 2014).

These data, however, have limited ability to estimate the flow of new investigators into the radiobiology workforce. First, they pertain only to degrees awarded by U.S. universities; however, many radiobiology researchers have been trained by institutions outside of the United States. Second, these data may include foreign citizens who may or may not remain and work in the United States after their graduation. For example, 28% of the doctoral degrees awarded in medical physics or radiological science in 2011 were to holders of temporary visas (NSF, 2013a). Data on M.D.s trained in radiobiology research are also not readily available. Consequently, although this information gives one indication of the supply of potential future researchers, it should be interpreted with caution.

Table 3-2 shows the total number of master's and doctoral degrees awarded in "health or medical physics" and "radiation biology or radiobiology" from 2003 through 2012, according to NCES.[8] SED data on doctoral degrees in "medical physics or radiological science" from 2010

[6] The SED is sponsored by National Science Foundation (NSF), National Institutes of Health (NIH), U.S. Department of Education, U.S. Department of Agriculture, National Endowment for the Humanities, and National Aeronautics and Space Administration and conducted by the National Opinion Research Center at the University of Chicago (NSF, 2014).

[7] Generally, this refers to degrees such as a Ph.D. or Sc.D.; professional degrees such as an M.D. are not included in the SED (NSF, 2014).

[8] NCES Classification of Instructional Programs (CIP) codes 26.0209 for Radiation Biology or Radiobiology and 51.2205 for Health or Medical Physics.

TABLE 3-2 Earned Degrees in Health and Medical Physics and Radiation Biology or Radiobiology in the United States by Type of Degree, 2003 Through 2012

	Health/Medical Physics		Radiation Biology/ Radiobiology		Medical Physics/ Radiological Science
Year	Master's	Doctorate	Master's	Doctorate	Doctorate*
2003	28	3	17	9	
2004	15	2	12	9	
2005	25	1	16	4	
2006	36	1	21	8	
2007	51	1	20	8	
2008	52	2	22	8	
2009	109	16	12	4	
2010	110	15	4	2	61
2011	120	12	13	7	74
2012	79	51	9	8	81

*Data are from NSF. All other data are from NCES.
SOURCES: NCES, 2005a,b, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013a,b; NSF, 2013b,c,d.

through 2012 are also displayed.[9] The combined number of doctoral degrees awarded for health or medical physics and radiation biology or biology awarded each year as reported by NCES is small, ranging from 5 in 2005 to 59 in 2012. In all, NCES reported a total of 171 doctoral degrees—104 in health or medical physics and 67 in radiation biology or radiobiology—granted from 2003 through 2012 (NCES, 2005a,b, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013b).[10] However, the total number of doctoral degrees for medical physics or radiological science as assessed by the SED for a much shorter period (2010–2012) is much higher: 61 in 2010; 74 in 2011; and 81 in 2012—a total of 216 degrees awarded over 3 years (NSF, 2013b,c,d). The reasons for this disparity are not clear. For example, they could be a methodological artifact resulting from institutions' reporting on degree fields (the NCES surveys) versus individuals' choosing what their degree field was (the SED surveys). Further, some degree recipients earned their Ph.D.s in disciplines other than radiobiology (e.g., physics) but chose to report the track as medical physics. In some cases, the institution may

[9] SED code 577 for Medical Physics or Radiologic Science. Prior to 2010, most respondents who wrote in "medical physics" selected the "physics, other," "biophysics," "applied physics," or "health sciences, other" designation (Latter, 2013).

[10] In comparison, the overall number of biological and biomedical sciences doctoral degrees conferred by postsecondary institutions increased from 5,268 in 2003 to 7,935 in 2012 (NCES, 2013c).

have classified their degree as physics for the NCES survey whereas the individual degree recipient may have chosen medical physics or radiologic sciences for the SED survey.

The number of master's degrees in radiation biology or radiobiology awarded over the 2003–2012 period remained relatively unchanged while the number of health or medical physics master's degrees graduates increased. The latter result may be a consequence of the significant growth in medical physics (both diagnostic and therapy tracks) training programs in the United States. For example, the number of Ph.D. degree programs—including those that may also award master's degrees—has expanded from 21 in 2009 to 29 in 2012 (Jackson, 2012). Although the primary purpose of medical physics training is to prepare people to perform clinical service and consultation and to help fulfill the demand for technological advances in devices used in radiation therapy and diagnostic imaging, some of that training can be applied to research questions in the field of radiobiology.

Academic Programs

Universities offer radiobiology education within schools of medicine and medical centers as residencies or specialty training for residents; degrees are also awarded through schools of engineering or life sciences. A handful of programs in the United States are dedicated to doctoral and postdoctoral training focused on researching the biological effects of radiation (Purdue University, 2013; University of Iowa, 2013; The University of Texas Health Science Center, 2013; Yale School of Medicine, 2013). However, the number of training facilities for radiological workers around the nation is decreasing, and some of the centers that trained the current leaders in the radiation research community have either been closed or are struggling (Hei, 2013).

An important note is that there are also several important educational opportunities and institutions outside of the United States that contribute to the domestic supply of doctoral-level researchers. Data describing the number of persons with doctorates from foreign institutions entering the U.S. radiobiology workforce are not available, although the committee suspects it may be substantial. As Chapter 4 notes, for example, 7 of AFRRI's 19 principal investigators received their doctorates outside of the United States (India [3], China, Germany, Italy, and Russia [1 each]) (AFRRI, 2013).

Radiobiology Training Programs

It is difficult to quantify the availability of support for training and for training programs for those wishing to study radiobiology. A program need not have the words "radiation biology" or "radiobiology" in it in order provide education or funding, and not all those who end up conducting research in radiation biology do their graduate training in that field. That said, some programs focused on training radiobiologists or improving research skills are available, and a few examples of efforts that assist in investigator development follow. In addition to these, organizations provide training grants to researchers working in related areas like radiation epidemiology (NCI, n.d.-a) and health physics (HPS, 2014), and on specific health issues like cancer that radiobiologists may study (ASTRO, 2014; NCI, n.d.-b).

NASA Space Radiation Summer School (NSRSS)

Offered each summer since 2005, the NSRSS program consists of approximately 3 weeks of intensive courses primarily focused on high-LET (linear energy transfer) radiation, taught by National Aeronautics Space Administration (NASA) biologists and physicists. Eligible participants include graduate students, postdoctoral fellows, and faculty members. NSRSS aims to provide a pipeline of researchers to tackle the challenges of radiation exposure to humans who will travel on space exploration missions (NASA, 2014). The program is administered at the DOE's Brookhaven National Laboratory (BNL) and is sponsored by NASA's Space Radiation Program, BNL, and the NASA–BNL Space Radiation Biology Program.

DOE Scholars Program

The DOE Scholars Program was created to engage undergraduate, graduate, and postdoctoral students in DOE programs and research to allow them to explore a career at the DOE and to better understand the DOE's functions. The program sponsors paid internships that include opportunities for research and development of individuals with potential for DOE employment. The internship lasts for approximately 10 weeks. Many disciplines related to the DOE's operations, from scientific to management, including radiation biology, are considered. The program is managed by ORISE (DOE, 2014).

MELODI (Multidisciplinary European Low Dose Initiative)

MELODI, a collaborative European research agenda on low-dose radiation risk, emphasizes the need for developing and training investigators; to accomplish this, all MELODI programs are required to have an educational or training component. DoReMi (Low Dose Research Towards Multidisciplinary Integration), the programmatic arm of MELODI, is designed to "develop an integrated support system for Education and Training both within the research effort in the other work packages, and more broadly within the low-dose radiation-risk research community as a whole" (DoReMi, 2014a). Annual education and training workshops and a series of short courses have been developed to support the continued stream of scientists dedicated to researching the effects of low-dose ionizing radiation. DoReMi also sponsors conferences and other educational events (DoReMi, 2014b).

WE-Heraeus Physics School on Ionizing Radiation and the Protection of Man

This 10-day seminar, funded by the WE-Heraeus Foundation and held in Bad Honnef, Germany, aims to teach and engage graduate students and postdoctoral fellows in the field of radiation protection. Lectures are given by interdisciplinary experts. Several topics are covered: basics of radiation physics, radiation biology, and statistics; basics of radioecology and radio-epidemiology; natural and anthropogenic radiation exposure; radiation effects from various sources; ionizing radiation in medicine; and practical aspects of radiation protection (Helmholtz Zentrum München, 2012).

EVALUATING THE DEMAND FOR AND SUPPLY OF RADIOBIOLOGY RESEARCHERS

Current Demand

Skipperud and colleagues (2009) carried out a stakeholder needs assessment of several fields that address radiological protection and related health issues as part of a European effort to assess whether educational institutions were meeting the demand for professionals by industry, government, and research entities (Skipperud, 2011). The researchers noted that aging faculty, outdated facilities, inadequate course offerings, and lack of student interest were all contributing to a lack of scientists being trained. The authors concluded that there is

> a significant and constant need for post-graduates with skills in radiochemistry, radioecology, radiation dosimetry, and environmental modelling and a smaller, but still important, demand for radiobiologists and bio-modelers. (Skipperud et al., 2011, p. 1013)

The effort to meet radiobiology needs was being driven by government and research institution stakeholders.

Similarly, the supply of and demand for radiobiology researchers are affected by available research funding. For example, the size of doctoral programs may be driven primarily by departmental needs for teaching assistants and research assistants, the latter of whom are largely supported by research grants (Massy and Goldman, 1995). A search of several databases for government contracting and sources of funding conducted by the committee in early 2013 showed a range of sponsors, research institutions, and interests involved in radiation health- and biology-related research. Those databases indicate the number of solicitations, grants, and length and topical areas, but they provide incomplete information about funding amounts and workforce requirements. However, they do indicate the contracting and grant activity, important stakeholders, and interests in the field, which are at least indirectly related to the current demand for radiobiology researchers. A compilation of this information is presented in Table 3-3.

Drivers of Future Demand

As it is with many efforts to construct valid workforce projections, it is difficult to accurately estimate the future need for radiobiology researchers. However, certain trends in the use of radiological materials and information gaps in the science suggest that demand will continue and may increase. Those trends include increased use of radiation for diagnostic imaging, the emergence of new forms of radiation therapy, and a resurgence of interest in nuclear energy (Hei, 2013).

Chapter 2, which addresses current directions in radiobiology research, identifies a number of unanswered questions about the human health effects of low-dose ionizing radiation exposures that require attention. Answers to these questions are needed to better quantify radiological risks and derive exposure guidance that can be used when making public health decisions (for example, shelter in place versus evacuation versus long-term relocation) in the wake of a release incident or accident.

The Current and Future Workforce

The available data are insufficient to determine whether the supply of radiobiology researchers will be adequate to satisfy demand, and the information that is available is potentially complicated by a lessening of demand due to weak economic conditions and diminished support for research. Information suggests, however, that although the current supply may be meeting the demand, shortages could occur as the current workforce reaches retirement.

As already noted, DOE and its national laboratories are facing serious attrition of nuclear scientists and engineers and their capabilities through the effects of aging staff. In 2010, three-quarters of the radiological professionals within the DOE laboratories were eligible to retire (Wogman et al.,

TABLE 3-3 U.S. Sources of Funding for Radiation Health- and Biology-Related Research in Early 2013

Source / *Website*	Topics
Government contracts *FBO.gov*	Research on countermeasures; research on Mayak Techa River, Hiroshima, and Nagasaki cohorts; services for radiation monitoring
Government grants *Grants.gov*	Fellowships, scholarships, and other education; biodosimetry; study of space radiobiology; food safety after a nuclear event
Government-sponsored clinical trials *ClinicalTrials.gov*	Exposure[s]: fluoroscopy, cosmic radiation, occupational radiation, computed tomographic (CT) examinations; protective devices; radiation injury Outcomes: cancer (lung, prostate, ovarian, brain, leukemia, breast, angiosarcoma, colorectal, liposarcoma, colon, testicular, neuroblastoma); behavior and cognitive performance disorders; chromosomal aberrations; renal insufficiency; well-being; immune function; meningococcal meningitis; aortic valve stenosis; cataracts and lens opacities; myeloid progenitor cells; coronary heart disease and vascular access complication
NIH research portfolio NIH Report *report.nih.gov/index.aspx*	
Department of Defense Congressionally Directed Medical Research Programs *cdmrp.army.mil*	Predoctoral and postdoctoral training; idea development; new investigator and investigator-initiated research One award to AFRRI in 2005 to study the carcinogenicity of embedded tungsten alloys in mice

SOURCES: DoD, 2013; FBO.gov, 2013; HHS, 2013; NIH, 2013a,b.

Sponsors	Research Institutions
Biomedical Advanced Research and Development Authority (BARDA), NIAID, U.S. Department of Homeland Security (DHS), U.S. Department of Health and Human Services (HHS), DOE, and NCI	
Defense Advanced Research Projects Agency (DARPA), DOE, National Geospatial Intelligence Agency, National Research Council (NRC), NASA, and National Institute of Food and Agriculture	
Various U.S. government agencies	NIH Clinical Center; NCI; National Heart, Lung, and Blood Institute (NHLBI); Memorial Sloan Kettering Cancer Center (MSKCC); U.S. Department of Veterans Affairs (VA); University of Aarhus, Aalborg University; NIOSH; Ministry of Health (France); Health Protection Agency (United Kingdom); Novartis Vaccines; Institut de Radioprotection et de Sûreté Nucléaire; Instituto de Cardiologia do Rio Grande do Sul; Group Health Cooperative; University of California, San Francisco; Baptist Health South Florida; Total Cardiovascular Solutions; Centre Oscar Lambret; CINECORS–Hospital Ernesto Dornelles
NIH	AHRQ, FIC, NCI, NEI, NHLBI, NIA, NIAID, NIAMS, NIBB, NIDCR, NIDDK, NIEHS, NIGMS, NIMH, NIMHD, NINDS, NINR, NIOSH, NLMOD, VA with investigator affiliations at universities, for-profit companies, hospitals, medical schools, and university hospitals; other governmental agencies
DoD	Yale; Virginia Commonwealth University; University of California, San Diego, and San Francisco; Cornell Medical College; University of Arizona; Stanford University

2005). A 2014 U.S. Government Accountability Office report notes that this is a widespread problem in the federal civilian workforce that could produce mission-critical skill gaps if left unaddressed (GAO, 2014).

Figure 3-1 illustrates age distributions for the memberships of the HPS and AAPM professional associations who chose to provide this information. These distributions are both heavily skewed toward older members: in the HPS, more than 50% are 50 or older, and more than 80% are 40 or older; in the AAPM, more than one-third are 50 and older and nearly two-thirds are 40 or older. Further, this characteristic is becoming more pronounced with time. In 2000, 46% of HPS members were at least 50 years old. In 2005, that proportion rose to 53% and, in 2013, to 57%. The respective declines in the 30–39-year-old group were 18% to 15% to 14% (Hamrick, 2013). However, note that because age information is available for less than half of the HPS membership, these figures must be treated with caution.

No information was available on the changes in age distribution of the AAPM members over time. Additionally, it is unknown what percentage of members engage in research and what in other activities. Data reflecting the age distribution of the RRS members were not available.

Different interpretations of these age-distribution data are possible. One is that, in time, there is likely to be a deficit of radiation professionals across all specialties. This interpretation is consistent with the recent decline in U.S. students' interest in science, technology, engineering, and mathematics (STEM) curricula and the viewpoints of many federal and professional organizations (Martin, 2014). Another interpretation is that professional-society membership in general is on the decline; this trend has been experienced by many other professional societies as well (NCF, 2012; Putnam, 2000). It may thus be the case that millennial-generation radiobiology researchers,

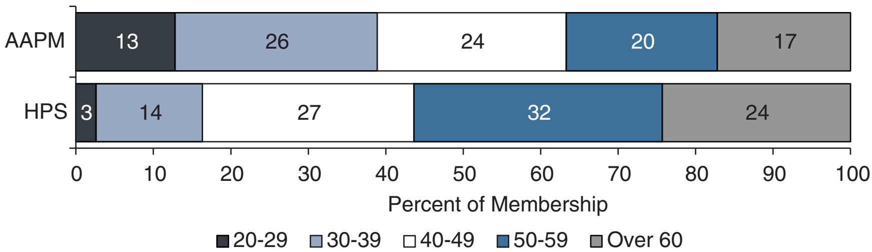

FIGURE 3-1 Age distribution of the members of the AAPM (2013) and the HPS (2013).
NOTE: Percentages are based on available data: Age was reported by about 95% of the AAPM members and 41% of the HPS members. The RRS does not track members' age groups.
SOURCES: Fairobent, 2013; Hamrick, 2013.

health physicists, and medical physicists are simply not joining professional societies at the rates seen in previous generations. Therefore, using society-membership demographics to assess the pipeline of future researchers could be misleading.

More generally, the number of retiring society members cannot be directly linked to the number of graduating master's and doctoral students in radiation-related disciplines because that connection assumes that graduates will become members and that individuals from other fields and educational backgrounds do not join these societies. But as described early in this chapter, radiobiology researchers come from a variety of disciplines.

Even though these data cannot describe a portion of the workforce that does not belong to professional societies and inferences are limited by available data, it is evident that the radiation health workforce is changing. This supports the sentiment of leaders in the field who note the inevitable aging of the radiology-researcher workforce and express concerns over the effects of projected retirements in the coming years (Hei, 2013).

SUMMARY AND CONCLUDING COMMENTS

Although it does not appear that an acute shortage of researchers in radiobiology and related disciplines exists currently, available information suggests that the number of professionals leaving the field through retirement and other means exceeds the number entering and that this trend will continue. Assuming a continuing need for radiobiology research, it is reasonable to conclude that the supply of professionals will not meet the demand in the coming years. When this committee completed its work, the NCRP was engaged in an effort to better characterize the magnitude of this problem and to offer recommendations for addressing it on a national level.

In Chapter 5, the committee provides recommendations for actions that AFRRI could undertake to help ensure that the military can meet its needs for radiobiology professionals.

REFERENCES

AAPM (American Association of Physicists in Medicine). 2013. *Welcome to the AAPM website*. http://www.aapm.org/default.asp (accessed December 30, 2013).

AFRRI (Armed Forces Radiobiology Research Institute). 2013. Responses to questions provided by the National Academy of Sciences regarding the statement of work for the committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, July 12, 2013.

APS (American Physical Society). 2008. *Readiness of the U.S. nuclear workforces for 21st century challenges*. APS Panel on Public Affairs Committee on Energy and Environment, June 2008.

ASTRO (American Society for Radiation Oncology). 2014. *ASTRO supported grants*. https://www.astro.org/Research/Funding-Opportunities/ASTRO-Supported-Grants/Index.aspx (accessed April 15, 2014).

Boice, J. D. 2014. WARP—Where are the radiation professionals? (The Boice Report #23). *Health Physics News*, p. 22. http://www.ncrponline.org/PDFs/BOICE-HPnews/23_WARP_Apr2014.pdf (accessed April 11, 2014).

Coleman, C. N., H. B. Stone, G. A. Alexander, M. H. Barcellos-Hoff, J. S. Bedford, R. G. Bristow, J. R. Dynlacht, Z. Fuks, L. S. Gorelic, R. P. Hill, M. C. Joiner, F. F. Liu, W. H. McBride, W. G. McKenna, S. N. Powell, M. E. C. Robbins, S. Rockwell, P. B. Schiff, E. G. Shaw, D. W. Siemann, E. L. Travis, P. E. Wallner, R. S. L. Wong, and E. M. Zeman. 2003. Education and training for radiation scientists: Radiation Research Program and American Society of Therapeutic Radiology and Oncology Workshop, Bethesda, MD, May 12-14, 2003. *Radiation Research* 160(6):729-737.

Cucinotta, F. A. 2013. Personal communication, responses to request posed by the Institute of Medicine Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation to the Radiation Research Society by Francis A. Cucinotta, President of the Radiation Research Society. Las Vegas, NV, November 26, 2013.

DoD (U.S. Department of Defense). 2013. *CDMRP (Congressionally Directed Medical Research Programs)*. http://cdmrp.army.mil (accessed March 19, 2013).

DOE (U.S. Department of Energy). 2014. *DOE Scholars Program*. http://orise.orau.gov/doescholars (accessed January 14, 2014).

DoReMi (Low-Dose Research Towards Multidisciplinary Integration). 2014a. *WP3 News*. http://www.doremi-noe.net/pdf/WP3_news/WP3_News.pdf (accessed January 14, 2014).

DoReMi. 2014b. *Training and education*. http://www.doremi-noe.net/training_and_education.html (accessed January 14, 2014).

Fairobent, L. 2013. Personal communication, responses to questions posed by the Institute of Medicine Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation to the Center for American Association of Physicists in Medicine by Lynne A. Fairobent, Manager of Legislative and Regulatory Affairs of American Association of Physicists in Medicine, College Park, MD, November 21, 2013.

FBO.gov (Federal Business Opportunities). 2013. *FedBizOps.gov: Homepage*. http://www.fbo.gov (accessed January 28, 2013).

GAO (U.S. Government Accountability Office). 2014. *Federal workforce—Recent trends in federal civilian employment and compensation*. Publication No. GAO-14-215. Washington, DC: U.S. Government Accountability Office.

Hamrick, B. 2013. Personal communication, responses to questions posed by the Institute of Medicine Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation to the Health Physics Society by Barbara Hamrick, JD, CHP. Irvine, CA, November 15, 2013.

Hei, T. K. 2013. Personal communication, responses to questions posed by the Institute of Medicine Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation to the Radiation Research Society by Tom K. Hei, Associate Director for the Center for Radiological Research, New York City, NY, September 22, 2013.

Helmholtz Zentrum München. 2012. *WE-Heraeus Physics School on "Ionizing radiation and protection of man."* http://iss-kurse.helmholtz-muenchen.de/heraeus-school/index.php (accessed January 14, 2014).

HHS (U.S. Department of Health and Human Services). 2013. G*rants.gov: Home*. http://www.grants.gov (accessed February 19, 2013).

HPS (Health Physics Society). 2005. *Human capital crisis in radiation safety: Position statement of the Health Physics Society*. http://hps.org/documents/HumanCapitalCrisis05.pdf (accessed December 30, 2013).

HPS. 2008. *Human capital crisis in radiation safety: Position statement of the Health Physics Society.* http://hps.org/documents/humancapital_ps015-2.pdf (accessed December 30, 2013).

HPS. 2013. *About the Health Physics Society*. http://hps.org/aboutthesociety (accessed December 30, 2013).

HPS. 2014. *Scholarships and grants*. http://hps.org/students/scholarships.html (accessed April 15, 2014).

Jackson, E. 2012. Preliminary report: CAMPEP/SDAMPP Graduate Program Survey results, E. Jackson, Ph.D., Chair, SDAMPP Outcome and Statistics Committee (2012). http://www.sdampp.org/documents/Graduate_Program_Survey_2011_Final.pdf (accessed March 5, 2014).

Latter, M. A. 2013. Personal communication, Mary Ann Latter, Project Director for the Survey of Earned Doctorates, to Cary Haver, Chicago, IL, March 19, 2013.

Martin, J. 2014. STEM interest declining among teens. *CBS News*. http://www.cbsnews.com/news/stem-interest-declining-among-teens (accessed January 14, 2014).

Massy, W. F., and C. A. Goldman. 1995. *The production and utilization of science and engineering doctorates in the United States*. Stanford Institute for Higher Education Research discussion paper, Stanford, CA.

NAS (National Academy of Sciences). 2013. *Nuclear physics: Exploring the heart of matter.* Washington, DC: The National Academies Press.

NASA (National Aeronautics and Space Administration). 2014. *NASA space radiation summer school at the Brookhaven National Laboratory*. http://spaceradiation.usra.edu/nsrss (accessed January 14, 2014).

NCES (National Center for Education Statistics). 2005a. *Digest of education statistics 2004: Table 253. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and field of study: 2002–03*. http://nces.ed.gov/programs/digest/d04/tables/dt04_253.asp (accessed February 3, 2014).

NCES. 2005b. *Digest of education statistics 2005: Table 252. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and field of study: 2003–04*. http://nces.ed.gov/programs/digest/d05/tables/dt05_252.asp (accessed February 3, 2014).

NCES. 2006. *Digest of education statistics 2006: Table 258. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and field of study: 2004–05*. http://nces.ed.gov/programs/digest/d06/tables/dt06_258.asp (accessed February 3, 2014).

NCES. 2007. *Digest of education statistics 2007: Table 265. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and field of study: 2005–06*. http://nces.ed.gov/programs/digest/d07/tables/dt07_265.asp (accessed February 3, 2014).

NCES. 2008. *Digest of education statistics 2008: Table 275. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2006–07*. http://nces.ed.gov/programs/digest/d08/tables/dt08_275.asp (accessed February 3, 2014).

NCES. 2009. *Digest of education statistics 2009: Table 275. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2007–08*. http://nces.ed.gov/programs/digest/d09/tables/dt09_275.asp (accessed February 3, 2014).

NCES. 2010. *Digest of education statistics 2010: Table 286. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2008–09*. http://nces.ed.gov/programs/digest/d10/tables/dt10_286.asp (accessed February 3, 2014).

NCES. 2011. *Digest of education statistics 2011: Table 290. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2009–10*. http://nces.ed.gov/programs/digest/d11/tables/dt11_290.asp (accessed February 3, 2014).

NCES. 2012. *Digest of education statistics 2012: Table 317. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2010–11*. http://nces.ed.gov/programs/digest/d12/tables/dt12_317.asp (accessed February 3, 2014).

NCES. 2013a. *Digest of education statistics 2013: Table 318.30. Bachelor's, master's, and doctor's degrees conferred by degree-granting institutions, by sex of student and discipline division: 2011–12*. http://nces.ed.gov/programs/digest/d13/tables/dt13_318.30.asp (accessed February 3, 2014).

NCES. 2013b. *Digest of education statistics 2013: Table 324.10. Doctor's degrees conferred by postsecondary institutions, by field of study: Selected years, 1970–71 through 2011–12*. http://nces.ed.gov/programs/digest/d13/tables/dt13_324.10.asp (accessed April 8, 2014).

NCES. 2013c. Appendix A.2. *Integrated postsecondary education data system*. Institute of Education Sciences. http://nces.ed.gov/programs/digest/d12/app_a2_11.asp (accessed January 31, 2014).

NCF (National Chamber Foundation). 2012. *The millennial generation research review.* Washington, DC: U.S. Chamber of Commerce.

NCI (National Cancer Institute). n.d.-a. *Research training opportunities in radiation epidemiology*. Division of Cancer Epidemiology and Genetics. http://dceg.cancer.gov/fellowship-training/research-training-opportunities/reb-training (accessed April 15, 2014).

NCI. n.d.-b. *Training cancer researchers for the 21st century*. The Center for Cancer Training. http://www.cancer.gov/researchandfunding/cancertraining (accessed April 15, 2014).

Nelson, K. 2004. Human capital crisis report. *Health Physics News,* September, pp. 18-19.

NIH (National Institutes of Health). 2013a. http://clinicaltrials.gov (accessed February 19, 2013).

NIH. 2013b. *RePORT (Research Portfolio Online Reporting Tools)*. http://report.nih.gov/index.aspx (accessed March 19, 2013).

NRC (National Research Council). 2012. *Assuring a future U.S.-based nuclear and radiochemistry expertise*. Washington, DC: The National Academies Press.

NSF (National Science Foundation). 2013a. *Survey of earned doctorates: Table 22. Doctorate recipients, by citizenship, race/ethnicity, and subfield of study: 2011*. http://www.nsf.gov/statistics/sed/2011/data_table.cfm (accessed April 2013).

NSF. 2013b. *Survey of earned doctorates: Table 16. Doctorate recipients, by sex and subfield of study: 2010.* https://www.apsanet.org/media/dsp/doctorate%20recipients%20by%20sex%20and%20subfield%202010.pdf (accessed April 2013).

NSF. 2013c. *Survey of earned doctorates: Table 16. Doctorate recipients, by sex and subfield of study: 2011*. http://www.nsf.gov/statistics/sed/2011/pdf/tab16.pdf (accessed April 2013).

NSF. 2013d. *Survey of earned doctorates: Table 16. Doctorate recipients, by sex and subfield of study: 2012*. http://www.nsf.gov/statistics/sed/2012/pdf/tab16.pdf (accessed April 2013).

NSF. 2014. *Survey of earned doctorates*. http://www.nsf.gov/statistics/sed/2012/survey.cfm (accessed February 3, 2014).

ORISE (Oak Ridge Institute for Science and Education). 2009. *Labor market trends for health physicists through 2012*. http://hps.org/documents/orise_hp-labor-market-trends_1010.pdf (accessed December 30, 2013).

ORISE. 2014. *ORISE: Number of health physics degrees up for undergrads, down for grads*. http://oakridgetoday.com/2014/04/02/orise-number-health-physics-degrees-2013-increased-undergrads-declined-grads (accessed April 3, 2014).

Pryor, K. 2013. The WARP initiative: Where are the radiation professionals? *Health Physics News* September.

Purdue University. 2013. *Radiation biology graduate program*. http://www.healthsciences.purdue.edu/academics/graduate/radiationbiology (accessed December 2013).

Putnam, R. 2000. *Bowling alone: The collapse and revival of American community*. New York: Simon & Schuster.

Rosenstein, B. S., K. D. Held, S. Rockwell, J. P. Williams, and E. M. Zeman. 2009. American Society for Radiation Oncology (ASTRO) survey of radiation biology educators in U.S. and Canadian radiation oncology residency programs. *International Journal of Radiation Oncology, Biology, Physics* 75(3):896-905.

RRS (Radiation Research Society). 2013. *Governance general information and objectives*. http://www.radres.org/?page=Governance (accessed December 30, 2013).

Skipperud, L., B. Salbu, H. Garelick, N. Priest, C. Tamponnet, and P. Mitchell. 2009. *Stakeholder Needs for Recruitment—EU ENE-II Project on MSc in Nuclear Sciences*. Paper presented at Nuclear Energy for New Europe International Conference; Bled, Slovenia, September 14-17, 2009.

Skipperud, L., B. Salbu, N. Priest, H. Garelick, C. Tamponnet, A. Abbott, and P. Mitchell. 2011. European MSc programs in Nuclear Sciences—To meet the need of stakeholders. *Nuclear Engineering and Design* 241:1013-1017.

University of Iowa. 2013. *Welcome to the free radical and radiation biology program at the University of Iowa*. http://www.uiowa.edu/~frrbp (accessed December 13, 2013).

The University of Texas Health Science Center. 2013. *The radiobiology program*. http://radonc.uthscsa.edu/Divisions/radiobiology.asp (accessed December 13, 2013).

Vichare, A., R. Washington, C. Patton, A. Arnone, C. Olsen, C. Y. Fung, S. Hopkins, and S. Pohar. 2013. An assessment of the current U.S. radiation oncology workforce: Methodology and global results of the American Society for Radiation Oncology 2012 Workforce Study. *International Journal of Radiation Oncology • Biology • Physics* 87(5):1129-1134.

Wogman, N. A., L. J. Bond, A. E. Waltar, and R. E. Leber. 2005. The nuclear education and staffing challenge: Rebuilding critical skills. *Journal of Radioanalytical and Nuclear Chemistry* 263(1):137-143.

Yale School of Medicine. 2013. *Radiobiology and radiotherapy*. http://medicine.yale.edu/cancer/research/programs/radio/index.aspx (accessed December 13, 2013)

4

AFRRI Programs, Research, and Resources

This chapter addresses the second element of the committee's statement of task, assessing how Armed Forces Radiobiology Research Institute (AFRRI) programs are advancing research in radiobiological science related to human health risks from exposures to low-dose ionizing radiation. The chapter presents a brief history of AFRRI and its role within the Military Services. The Institute's physical plant, staff, budget, current research, collaborations, and educational efforts are also described.

Material in this chapter is derived in part from a presentation to the committee by AFRRI Director L. Andrew Huff, Col. USAF, MC, SFS (Huff, 2013a) and on responses that AFRRI provided to questions posed by the committee (AFRRI, 2013a,b; Huff, 2013b, 2014). Citations for these and other sources are made as appropriate.

AFRRI HISTORY AND BACKGROUND

The Department of Defense (DoD) has been interested in the health effects of exposure to radiological agents since at least the initiation of the Manhattan Project. That interest became operational in 1958 when the U.S. Navy Bureau of Medicine and Surgery proposed that a bionuclear research facility be established to study such issues (DTRA, 2002; Tenforde, 2011). Public Law 86-500 (June 8, 1960) subsequently authorized construction of a laboratory and vivarium under the auspices of the Defense Atomic Support Agency (DASA) and, on December 2, 1960, the Military Services surgeons general and DASA approved a charter for AFRRI (DTRA, 2002;

Solyan, 2004). The Institute was formally established on May 12, 1961, when DoD Directive 5154.16 was issued.

Research at AFRRI began in January 1962, although the laboratory was not fully operational until September 1963 (DTRA, 2002; Solyan, 2004). At that time, the research facility included a Training, Research, Isotopes, General Atomics (TRIGA®) Mark F nuclear reactor, laboratory space, and an animal facility. The TRIGA reactor, a unit specifically designed for research, teaching, and commercial applications, allowed studies of radiation characteristics relevant to nuclear weapons that were not available at other DoD or Department of Energy facilities at that time. A high-dose cobalt-60 (^{60}Co) facility, a 54-megaelectron volt (MeV) linear accelerator (LINAC), and a low-level ^{60}Co irradiation facility were subsequently added (Solyan, 2004).

The Institute operated as a joint agency of the U.S. Army, Navy, and Air Force under the command and administrative control of the Office of the Secretary of Defense. In July 1964, responsibility for AFRRI was assigned to DASA, and the Chief of DASA was designated as the chair of its Board of Governors. AFRRI was identified as an operational field element of DASA while essentially functioning as an independent institute (AFRRI, 1968).

In the 1960s, the Institute's research enterprise was partitioned into five departments—Experimental Pathology, Behavioral Sciences, Physical Sciences, Chemistry, and Radiation Biology—and focused on biological responses, with an emphasis on high doses of external radiation. Animal studies were an integral part of this work and were used to establish the effects of radiation on the central nervous and circulatory systems and on other tissues and organs (DTRA, 2002). AFRRI collaborated through memoranda of understanding and interagency agreements with universities, government agencies, and corporations (DTRA, 2002).

DASA was disestablished in 1971, and its responsibility for AFRRI was assumed by the newly formed Defense Nuclear Agency (DTRA, 2002). At around the same time, concerns were emerging about the possible relationship between exposure to radiation during military service and the occurrence of cancer. AFRRI was involved in the process that resulted in the establishment of the Nuclear Test Personnel Review program in January 1978. This program, which is still in operation, determines or estimates the radiation dose of veterans who participated in U.S. atmospheric nuclear tests or in the occupation forces of Hiroshima and Nagasaki, Japan, immediately after the atomic bombings, information that is used in compensation determinations for long-term radiation-related illnesses (DTRA, 2010). The experience and expertise developed by AFRRI in dealing with accidents, hazardous materials, and radiological cleanup issues were used in the international arena when AFRRI staff formed part of the International Chernobyl Site Restoration Assistance Team after the 1986 accident. They also provided assistance to the environmental cleanup efforts at the closed Soviet test site at Semipalatinsk, Kazakhstan (DTRA, 2002).

The Defense Nuclear Agency transferred control of AFRRI to the Uniformed Services University of the Health Sciences (USUHS) in 1993 (DTRA, 2002). As the Cold War wound down, resources shifted to concentrate on peaceful activities, including social and nondefense programs. AFRRI's funding and personnel levels diminished, and proposals were made to close the facility. However, military leaders indicated that there were no alternative sources for the information that the Institute developed, and these proposals were not acted on (Solyan, 2004).

U.S. interest in nuclear preparedness again increased in the late 1990s in response to India's and Pakistan's nuclear testing and the suspected development of nuclear weapons by Iraq and North Korea. AFRRI's mission became more important to DoD in part because private companies lacked the incentive to develop radioprotectants and countermeasures for the military (Solyan, 2004). In response to this renewed interest, funding for AFRRI increased in 2000 (Assistant Secretary of Defense, 2004).

Increased awareness of terrorist threats in the wake of the attacks on U.S. sites on September 11, 2001, also stimulated support for the Institute (AFRRI, 2009). These events helped shape a change in AFRRI's scope of work to include minimizing the effects of radiological dispersal devices (RDDs), terrorist access to radiation sources, and sabotage of nuclear reactors (Solyan, 2004). However, AFRRI's readiness and capabilities were limited by their facilities and staffing level. At the time, the Institute faced the challenge of deteriorating mechanical and structural systems. Extra support granted in 2003–2004 allowed for infrastructural upgrades and the development of a radioprotective drug (5-androstenediol, HE 2100).

Today, AFRRI is DoD's only medical research and development initiative dedicated to nuclear and radiological defense. It serves the military by performing medical research and development, education, and advisory and consultative functions for the purposes of understanding, preventing, preparing for, and responding to releases of ionizing radiation (AFRRI, 2011a). Box 4-1 delineates AFRRI's mission, responsibilities, and assigned functions.

Management Structure

AFRRI functions as a joint entity of the Military Services under the authority, direction, and control of the president of USUHS, the Assistant Secretary of Defense for Health Affairs, and the Under Secretary of Defense for Personnel and Readiness (DoD, 2006). DoD Initiative 5105.33 (§4.2) specifies that it is to be led by a director who is a military officer with a doctoral degree in one of the life sciences. The director is nominated by the

BOX 4-1
AFRRI's Mission, Responsibilities, and Functions as Delineated in DoD Instruction 5105.33, Issued on March 29, 2006

Mission (§3)

The mission of the AFRRI shall be to conduct research in the field of radiobiology and related matters essential to the operational and medical support of the Department of Defense and the Military Services. The AFRRI may provide services and perform cooperative research with other Federal and civilian agencies and institutions with the approval of the Assistant Secretary of Defense for Health Affairs.

Responsibilities and Functions (§5.1)

- Operate research facilities for the study of radiobiology and ionizing radiation bioeffects and for the development of medical countermeasures against ionizing radiation, and the results shall be disseminated.
  - — The scope of this research shall reflect requirements identified by the DoD Components for support of military operational planning and employment (current and future), and shall put special emphasis on individual and organizational performances under nuclear and radiological combat conditions in realistic operational and force protection scenarios.
  - — The AFRRI program shall consider present and projected threats, Service and joint operational concepts and weapons, and defense systems developments.
- Provide analysis, study, and consultation on the impact of the biological effects of ionizing radiation on the organizational efficiency of the Military Services and their members.
- Conduct cooperative research with the Military Medical Departments in those aspects of military operational and medical support considerations related to nuclear weapons effects and the radiobiological hazards of space operations.
- Conduct advanced training in the field of radiobiology and the biological effects of nuclear and radiological weapons to meet the internal requirements of the AFRRI, the Military Services, and other DoD Components and organizations.
- Participate in cooperative research and other enterprises, consistent with the AFRRI mission and applicable authorities, with other Federal agencies involved in homeland security and emergency medical preparedness.
- Perform such other functions as may be assigned by the Assistant Secretary of Defense for Health Affairs.

SOURCE: DoD, 2006.

surgeons general of the U.S. Army, Navy, and Air Force and appointed for a 4-year term. It is the director's responsibility (§6.1) to act as liaison to the heads of DoD's components and other governmental and nongovernmental agencies and to ensure that the DoD components are informed of AFRRI's activities. No scientific duties are assigned to the post.

Scientific leadership is exercised by a scientific director, who is tasked with the administration and supervision of the Institute's research-oriented departments, overall scientific and technical planning of the research program, and service as the scientific liaison with the outside world (AFRRI, 1968). However, this position has not been filled since 2012. There is, at present, a scientific advisor, who counsels the director and acts as a liaison with outside agencies but is not a part of the chain of command (Huff, 2013b). Box 4-2 lists AFRRI's directors and scientific directors since its inception.

AFRRI is currently made up of Radiation Sciences, Scientific Research, Military Medical Operations, Veterinary Sciences, Facilities Management, Good Laboratory Practice/Test Facility, and Administration Support departments, which are led by department heads or managers (see Figure 4-1). Four primary research areas are identified on the Institute's website: biodosimetry, combined injury (radiation with other insults), internal contamination and metal toxicity, and countermeasure development (AFRRI, 2014g).

Capability and Infrastructure

AFRRI's dedicated radiation sources and specialized facilities are summarized in Table 4-1 and are described in the following sections.

TRIGA Reactor

AFRRI's TRIGA reactor is 1 of 66 worldwide (General Atomics, 2014). These research reactors are used in university and government laboratories and medical centers for applications that include production of radioisotopes for medicine and treating tumors, nondestructive testing, basic science research, education, and training. They operate at thermal power levels of <0.1–16 megawatts (MW) and may be pulsed up to 22,000 MW.

The reactor is licensed by the U.S. Nuclear Regulatory Commission (License R-84). As of 2005, it was 1 of 18 TRIGA reactors in the United States and the only one dedicated to applied medical radiobiology research (Dix, 2005). It is a medium-sized unit that generates neutrons and gamma rays for radiation experiments. The reactor can produce a controlled, self-sustaining fission chain reaction in the reactor core which, in addition to the fuel elements and control rods (containing boron carbide), includes a neutron start-up source (americium/beryllium). It is suspended under 16 feet (~4.9 m) of water within a pool (an effective radiation shield) in a

BOX 4-2
AFRRI Leadership

AFRRI Directors

1961–1966: James T. Brennan, COL, MC, USA
1966–1967: Joseph S. Burkle, CAPT, MC, USN
1967–1971: Hugh B. Mitchell, Col, MC, USAF
1971–1975: Myron I. Varon, CAPT, MC, USN
1975–1977: LaWayne R. Stromberg, Col, MC, USAF
1977–1979: Darrell W. McIndoe, Col, MC, USAF
1979–1982: Paul E. Tyler, CAPT, MC, USN
1982–1985: Bobby R. Adcock, COL, MSC, USA
1985–1986: James J. Conklin, Col, MC, USAF
1986–1987: Richard I. Walker, CAPT, MSC, USN
1987–1991: George W. Irving III, Col, BSC, USAF
1991–1995: Robert L. Bumgarner, CAPT, MC, USN
1995–1997: Eric E. Kearsley, CAPT, MSC, USN
1997–2003: Robert R. Eng, COL, MS, USA
2003–2006: David G. Jarrett, COL, MC, USA
2006–2010: Patricia K. Lillis-Hearne, COL, MC, USA
2010–2012: Mark A. Melanson, COL, MSC, USA
2012–present: L. Andrew Huff, Col, MC, SFS, USAF

AFRRI Scientific Directors

1966–1971: Harold O. Wyckoff, Ph.D.
1982–1987: Lawrence S. Myers, Ph.D.
1987–1989: Richard I. Walker, Ph.D., CAPT, MSC, USN
1989–1998: E. John Ainsworth, Ph.D.
2002–2008: Terry C. Pellmar, Ph.D.
2008–2012: Christopher R. Lissner, Ph.D.

NOTE: This position was not filled in some periods.

SOURCES: AFRRI, 2010, 2013b; Solyan, 2004.

carriage assembly that allows movement of the core between two exposure rooms for experimental work with large-animal or other studies (Dix, 2005). The advantages of such a movable reactor core are that the quantity and character of the radiation that reaches the exposure facilities can be controlled, and more than one exposure facility can be used during reactor operations.

The reactor can operate in steady-state as well as pulse mode. The maximum allowed steady-state power level is 1.0 MW. Its pulse mode can produce a short peak (from a prompt critical excursion) of up to 2,500 MW occurring in about 0.1 second. The neutrons and gamma rays produced

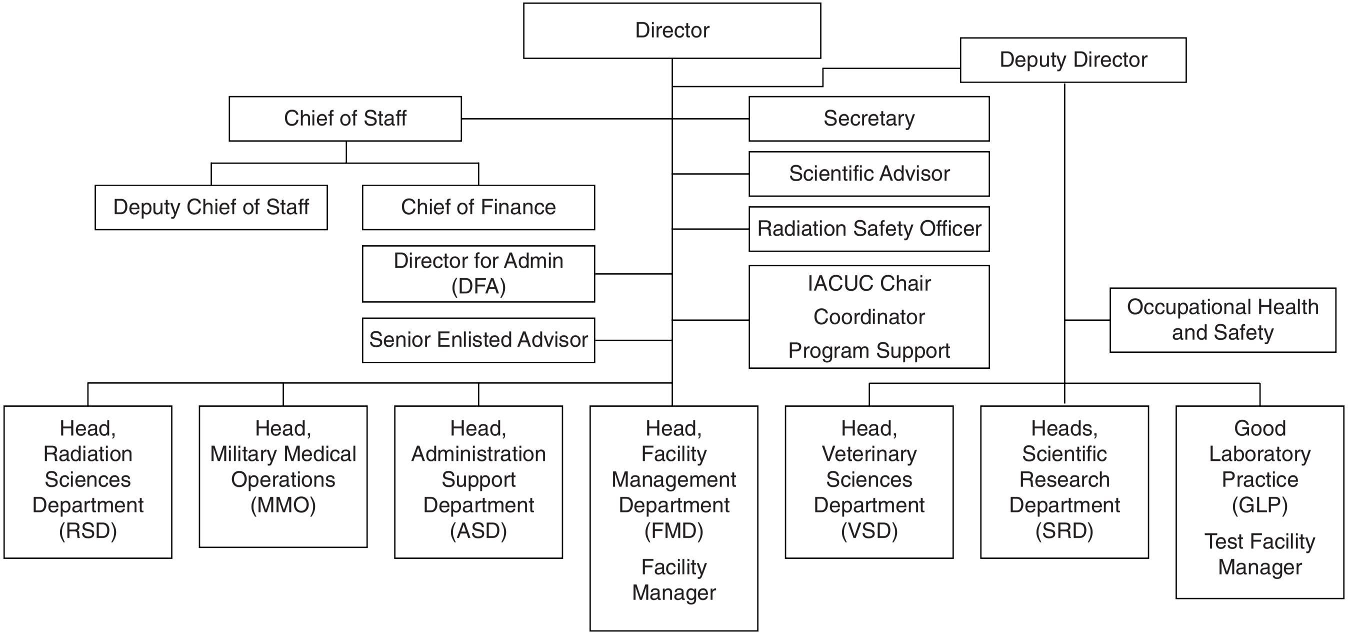

FIGURE 4-1 AFRRI chain of command and organizational structure.
NOTE: IACUC = Institutional Animal Care and Use Committee.
SOURCES: Derived from AFRRI, 2013c, and Huff, 2013b.

TABLE 4-1 AFRRI Radiation Sources

Source	Activity or Energy
TRIGA® Mark F reactor	1-megawatt (MW) steady-state or 2,500-MW pulse, mixed beam—neutron, photon
^{60}Co facility (panoramic irradiator)	450,000-Curie (Ci) ^{60}Co source
Chronic irradiation facility	100-Ci ^{60}Co source
Philips industrial X-ray machine*	40-320 peak kilovoltage (kVp)
Cesium (Cs) calibration facility	100-Ci ^{137}Cs source
Elekta Infinity™ linear accelerator (LINAC) with Synergy® image-guided workflow and Philips Brilliance CT Big Bore	LINAC operations up to 15 megaelectron volt (MeV) System was acquired in August 2012 but was not operational as of January 2014

* This source was replaced by an Xstrahl Small Animal Radiation Research Platform in 2014. SOURCES: AFRRI, 2011a; Huff, 2014; Kang et al., 2011.

in the reactor pass (as a unique mixed field) to exposure facilities, where biological systems are irradiated for studies. The facilities include two large exposure rooms and a core experiment tube, each with a distinctive radiation field and setup characteristics that allow for studies of a variety of conditions. The gamma:neutron ratio can be varied from 1:20 to 20:1 through the use of shields and absorbers placed in the exposure rooms (AFRRI, 1993). Special setups (in-pool portable beam tubes, a pneumatic transfer system, and in-core grid-location tubes) and custom radiation beams are also available. Exposure rates can be varied from about 0.1 rad/min (0.06 gray [Gy]/hr) to 1,000 rad/min/pulse (600 Gy/hr/pulse). Although primarily used for biological studies, the unit may also be used for transient radiation–electronic effects (TREE) studies and the production of isotopes.

Cobalt-60 Facility

The ^{60}Co facility at AFRRI first opened in 1969. The facility is located below ground in the AFRRI complex, with shielding provided by massive reinforced concrete and earth fill. Its panoramic irradiator is a wet-source storage unit consisting of a 450,000 Ci (at installation) ^{60}Co source, water trench, source and storage racks, elevator mechanism, and associated equipment. The exposure room is 35 ft × 35 ft and 25 ft, 8 in. high (10.7 m × 10.7 m × 7.6 m = 870 m^3) (AFRRI, 1993). The irradiator produces monoenergetic gamma rays at variable dose rates with flexible configurations in both unilateral and bilateral irradiation modes and may be used for acute and chronic studies of materials, biologic specimens, and small and large animals (Carter and Verrelli, 1973; Naquin et al., 2001). It has been employed in a variety of applications, including investigations of the effects of ionizing radiation exposure on cells (McKinney et al., 1998), prognostic indicators of survival in a variety of mammals (Moroni, et al. 2011), and the efficacy of radioprotective agents (Landauer et al., 2001; Singh et al., 2010).

In 2013, AFRRI contracted to replace the facility's existing, decaying sources with new ^{60}Co sources (FedBizOps.gov, 2013).

Chronic-Irradiation Facility

AFRRI has a second ^{60}Co radiation source that provides low-dose rate gamma-photon radiation to simulate chronic exposure to low doses and is used to study early and late effects in biological samples. This 100-Ci chronic-irradiation facility (Dix, 2005) is sometimes called the low-level irradiation facility (Solyan, 2004).

Earlier AFRRI reports (AFRRI, 1993; Zeman and Dooley, 1984) describe a 4,200-Ci therapeutic irradiator (AECL Theratron-80) capable of providing from 1 to several hundred rad/hr (0.01 to several Gy/hr) over limited field sizes, and a uniform field. It was primarily used to conduct cellular studies. However, this source was decommissioned in the 1990s.

Linear Accelerator

AFRRI's first LINAC was designed and assembled between 1965 and 1968; it provided a powerful, flexible source of high-energy electrons, high-energy bremsstrahlung (X-rays), and neutrons (AFRRI, 1993). It was used for a broad range of applications, including radiobiology and radiochemistry studies (AFRRI, 1993). Various machine configurations were used to provide electron energies continuously variable from 10 to 54 MeV (Dix, 2005).

This device was retired and, in August 2012, AFRRI acquired a new LINAC and computed tomography (CT) unit: an Elekta Infinity LINAC capable of operations up to 15 MV and a Philips Brilliance CT Big Bore (Huff, 2014). These devices will be used for research purposes only. Neither was operational at the time the committee completed its work in late 2013.

Other Radiation Sources

AFRRI also has a Philips industrial X-ray machine that is a water-cooled device with peak kilovoltage (kVp) that ranges from 40 to 320 kVp (AFRRI, 2011a).[1] This machine is used mainly for cellular work and, depending

[1] After the report was completed, the committee learned that this source has been replaced by an Xstrahl Small Animal Radiation Research Platform.

on the field size, the output can be varied from a few to 7,000 rad/min (4,200 Gy/hr). The machine also serves as a backup for the ^{60}Co facility (AFRRI, 1993).

The Institute also maintains a cesium (Cs) calibration facility that consists of a 100-Ci ^{137}Cs source and associated equipment.

Usage of Radiation Facilities

The committee asked AFRRI to delineate how often its radiation facilities are being used by AFRRI investigators and by any outside investigators or collaborators.[2] AFRRI's response, dated October 15, 2013, is summarized in Table 4-2 (AFRRI, 2013b).

Animal Facility

An animal-research facility is an important resource for understanding basic radiobiology and for developing medical countermeasures against radiation injuries. AFRRI's facility is organized within its Veterinary Science Division. The 28,565 ft^2 (~2,650 m^2) space is designed to support radiation and surgical studies and includes environmental controls and monitoring, histopathology, microbiology, and clinical pathology laboratories. It comprises

- Two large-animal surgery suites,
- One radiology suite,
- One large-animal treatment room,
- One large-animal necropsy room,
- Ultrasound and electrocautery equipment for diagnostic and surgical purposes, and
- Two rodent-procedure rooms.

AFRRI is one of the few DoD laboratories capable of housing a variety of animals. In response to an inquiry from the committee, AFRRI indicated that the facility commonly maintains 4,000–5,000 mice and rats, 8–20 minipigs, and 60–80 nonhuman primates (rhesus macaques) (AFRRI, 2013b).

In late 2013, the Veterinary Sciences Department comprised 26 staff members: 5 veterinarians (Department Head, Deputy Head, Contract Clinical Veterinarian, Veterinarian, and Veterinary Pathologist), 6 veterinary technicians (5 military and 1 civilian), 11 government animal-husbandry

[2] Outside investigators may use the facilities for studies performed in collaboration with an AFRRI project or other projects funded by a government agency.

TABLE 4-2 Usage and Availability of AFRRI Radiation Sources, January 2012–October 2013

Device	Usage	Availability*
TRIGA reactor *Accessible 293 days total*	51 days training; 17% of available time 10 days in-house use; 3% of available time	79% unused
Cobalt-60 facility *Accessible 2,300 hr total*	1,058 hr in-house use; 46% of available time 82 hr outside use; 4% of available time	50% unused
Chronic-irradiation (low-level) facility	"Several days"	Nearly 100% unused

* These numbers include time when sources were unavailable due to equipment failure or maintenance.
SOURCE: AFRRI, 2013b.

personnel, 3 pathology lab staff (2 military and 1 civilian), and 1 administrative person (military, on loan) (AFRRI, 2013b).

The Veterinary Sciences Department has maintained an American Association for Accreditation of Laboratory Animal Care–accredited animal care and use program since 1984. All research protocols require review and approval from the organization's Institutional Animal Care and Use Committee. The program supports not only AFRRI research but also USUHS and Walter Reed National Military Medical Center studies.

CURRENT RESEARCH PRIORITIES AND PORTFOLIO

AFRRI's research agenda has evolved over time with U.S. defense needs, changes in funding, and scientific advancements. In the 1960s, the focus was on the effects of high doses of external radiation and the development of causality criteria for radiation illnesses. However, as military and defense priorities changed, it has expanded to include nuclear-weapons effects, trauma, toxicology, nonionizing-radiation effects, cancer markers, and drug toxicity, as well as specific needs for solutions to casualty problems that may be associated with multiple insults from exposure to radiation and other battlefield hazards such as biological and chemical agents as well as wounds, infection, and diseases (Solyan, 2004).

AFRRI's current efforts concentrate on minimizing the health effects of exposure to high-dose ionizing radiation in combat and military environments through prevention of hazards, assessment, and medical treatments of injuries relating to radiation both alone and with other chemical or biological hazardous agents. These efforts are summarized in the following sections.

Radiobiology Research

In accordance with its charter, AFRRI conducts research in the field of radiobiology and related matters essential to the operational and medical support of DoD and the Military Services. This includes evaluation of threats (the threat spectrum, defining the source and risk, operating in a contaminated environment, consequence management, modeling and decision support, and the like); triage (methods, tools, techniques, and biodosimetric models); and treatment (both prophylactic and mitigative, as well as evaluating off-label and investigative drug use in DoD). AFRRI research has concentrated on military concerns such as preparation, consequence management, and mitigation, and it extends from acute event–response readiness to actual radiation exposures of DoD personnel. Such work is also relevant to civilian exposures resulting from accidents, terrorist activities, or war.

The AFRRI research program is aimed directly at current research gaps in medical preparedness for responding to such events. For example, current countermeasures (amifostine, the only U.S. Food and Drug Administration [FDA]-approved radioprotectant) may have effects that make them inappropriate for military use. Available biodosimetric tools for triage are limited in speed and physiological predictive power. There is also a need for mitigation and therapeutic agents approved for radiation-induced hematopoietic or gastrointestinal injury. Therefore, the AFRRI research and development goals concentrate on the following: pursuing new drugs that will prevent the life-threatening and health-degrading effects of ionizing radiation; developing methods for rapidly assessing radiation exposure to ensure appropriate medical treatment; investigating the effects of radiation injury combined with other challenges such as trauma, disease, and chemical exposures; and contributing to the radiobiological knowledge base.

Biological Dosimetry

AFRRI has been engaged in developing rapid, high-precision analytical methods that can be used to assess radiation-exposure doses from clinical samples to aid in the triage and medical management of radiological casualties. The specific objectives of this research include automating field-deployable biological dosimetry capabilities for rapid dose assessment on the battlefield, establishing reference biological dosimetry for definitive analysis of biological samples from military theater operations, and identifying and validating early-phase radiation-specific biomarkers of late-radiation effects.

AFRRI's research in the biological dosimetry arena has centered on the development of integrated biodosimetry and diagnostic systems (see Figure 4-2). Triage, clinical, and definitive radiation biodosimetry require multiple bioassays and specific analytic technologies designed for chemical,

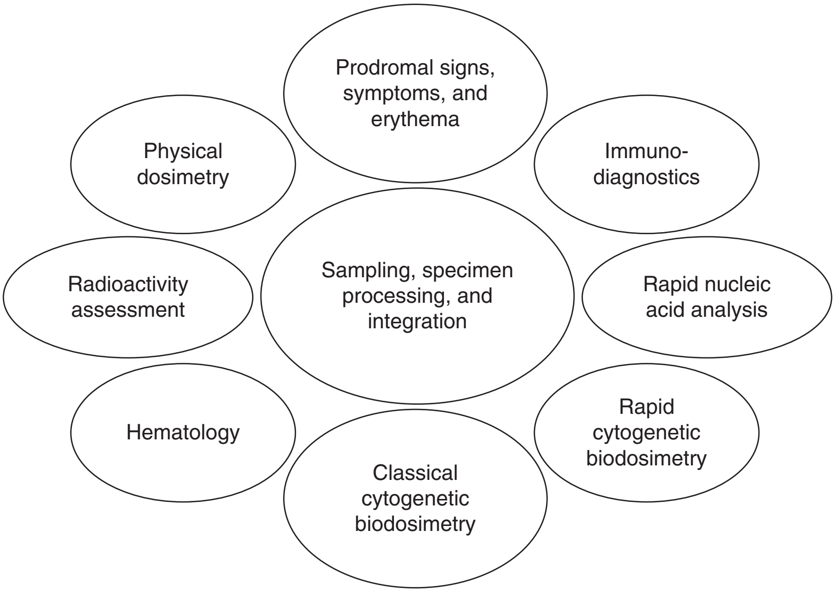

FIGURE 4-2 The components of an integrated biodosimetry and diagnostic system.
SOURCE: AFRRI, 2013d.

biological, radiological, nuclear, and explosive (CBRNE) exposures because no single assay or technique is sufficient. The aims are to create protocols and analytical systems for high-throughput applications, to identify bio-indicator assays for rapid assessment over a broad dose range, to refine hematological and molecular protocols and analytical systems, to validate the systems using in vivo model studies, and to develop software for integrated biodosimetry data management.

The appropriate use of medical resources for personnel exposed to ionizing radiation depends on timely, accurate dose information. To assist in meeting this specific and often complex need, AFRRI developed the Biodosimetry Assessment Tool (BAT) (AFRRI, 2013e), a computer-based software system for use by health care providers responding to a radiation incident. The BAT assists providers in identifying individuals who have significant radiation exposures and then in making appropriate treatment decisions using AFRRI-developed, radiation dose–predicting algorithms (single lymphocyte count, lymphocyte-depletion rate, and time from exposure to time of onset of emesis). The BAT algorithms are also available at the Radiation Event Medical Management website (www.remm.nlm.gov/ars_wbd.htm), an integrated educational and response tool supported by the U.S. Department of Health and Human Services (HHS) and the National Library of Medicine.

The AFRRI biodosimetry research program also provides assessment instrumentation, discussed later in this chapter in the section called *Publications, Guidance, and Tools*.

AFRRI is working toward integrating the various tools with a deployable laboratory system for use in the field, and it holds seminars concentrating on ongoing and future advancements in the area of biodosimetry.

Internal Contamination and Metal Toxicity

Research on the chemical and radiological toxicity of radiologic materials is applicable to a variety of battlefield scenarios and possible terrorism events. AFRRI scientists have been at the forefront of research into the health effects of embedded fragments of depleted uranium (DU), a component of some munitions and armor. A specific aim of the AFRRI internal contamination and metal toxicity program is to determine whether the short- and long-term radiological and toxicological risks of embedded metals warrant changes in the current combat and postcombat fragment-removal policies for military personnel and (in the case of internalized radiological hazards) to investigate treatment strategies to enhance elimination of these metals from the body. To that end, AFRRI is developing models for assessing the health effects of embedded metal fragments, for investigating new decorporation protocols for the elimination of internalized radionuclides, and for studying the long-term health effects resulting from exposure to DU as well as for identifying biomarkers that can distinguish this exposure from other toxic insults. Such studies are also relevant to the isotopes that could be used in RDDs.

Research conducted at AFRRI was instrumental in the formulation of the U.S. Army policy dealing with injuries from DU. As munitions developers shift away from the use of DU in armor-piercing shells, AFRRI has also examined replacement metals such as tungsten alloys. Much of the work on the development of an in vivo model for investigating the health effects of embedded fragments (and protocols for dealing with such wounds), the toxicological properties and health effects of embedded DU, the refinement of analytical procedures for determining DU levels in biological samples, and the mechanism of damage resulting from DU exposures was first conducted at AFRRI (AFRRI, 2013f).

Radiation Countermeasures

AFRRI maintains a program to study, evaluate, and develop pharmacological countermeasures to radiation injury that can be used by military personnel and emergency responders. This research program aims to develop a better understanding of the biology of radiation injury and the radiation-countermeasure drugs, to identify and assess novel drug candidates, and to collaborate with others to develop and obtain approval for such drugs for use in the field and the clinic (AFRRI, 2014b).

Possible countermeasures to ionizing radiation can be broadly categorized into three groups: drugs that prevent the initial radiation injury (for example, free-radical scavengers; antioxidant, anti-inflammatory, and anti-fibrotic agents; and hypoxia-, enzymatic detoxification-, or oncogene-targeting agents), drugs that repair the molecular damage caused by radiation (hydrogen transfer, enzymatic repair), and drugs that stimulate proliferation of surviving stem and progenitor cells (immunomodulators, growth factors, and cytokines). Nontoxic or extremely low-toxicity countermeasures to ionizing radiation are urgently needed by both military personnel and emergency responders, and much of the current focus is on drug candidates that are easy to administer and therefore suitable for use outside of specific clinics without close physician supervision.

The AFRRI radiation-countermeasures program has been involved in the development of several drugs for acute radiation syndrome (ARS) that now have FDA Investigational New Drug status, allowing their testing for safety in humans (AFRRI, 2014b). Several of the countermeasures were conceived by or initially developed at AFRRI or were developed in collaboration with AFRRI: granulocyte–colony stimulating factor (G-CSF), Neupogen®, 5-androstenediol, genistein, Ex-Rad®, and CBLB502. Other countermeasure candidates are ready for advanced development.

Besides its development work, AFRRI has an ongoing in vivo efficacy screening and mechanistic research program (ranging from standard models to a newly developed minipig large-animal model). AFRRI is also frequently approached by outside organizations requesting collaboration or consultation on their countermeasure candidates. The available radiation facilities at AFRRI—especially the mixed neutron–gamma fields that mimic those produced by nuclear detonations—has afforded AFRRI's radiation-countermeasures scientists the opportunity to assess agents for efficacy more broadly across a spectrum of possible needs and uses. In addition to evaluating the toxicity of amifostine, AFRRI's work on cytokines as a radiation countermeasure resulted in the inclusion of Neupogen® in the Strategic National Stockpile[3] (CDC, 2012).

[3] The Centers for Disease Control and Prevention's Strategic National Stockpile comprises caches of medicine and medical supplies intended for use in case of a public health emergency (for example, a terrorist attack, flu outbreak, or earthquake) that is severe enough to deplete local supplies.

Radiation Injury Combined with Other Trauma

Recognizing that combined injuries can complicate effective treatment and mitigation activities, AFRRI established a specific research program area in 2007 to address radiation injury combined with other trauma (AFRRI, 2013g). The program's aims include the development of medical treatments for irradiated personnel who also have traumatic wounds, burns, hemorrhage, or infection. AFRRI researchers seek to develop a comprehensive understanding of the biology of radiation injury combined with traumatic injury and to establish an understanding of countermeasure drugs (including novel drug candidates for prophylaxis, mitigation, or therapy). Treatment strategies under investigation include the use of biological-response modifiers, new antimicrobial agents, probiotics, and stem cells. Another aim is to collaborate proactively with other research institutions, pharmaceutical firms, and government agencies to further develop and gain approval of promising drugs for use in the field or the clinic. Little research is being conducted in this area, so AFRRI's work fills an otherwise unmet need.

Other Research Areas

AFRRI formerly conducted research on the effects of radiation on behavior (DTRA, 2002). Its Behavioral Sciences Department was responsible for investigating the psychological effects of radiation by using animal models. Studies included the effect of ionizing radiation on stimulation-response rates in rats (Mele et al., 1990) and the behavioral effects of a medication used as a radiation countermeasure (Landauer et al., 1997). AFRRI published results on behavioral effects as early as 1969 (Thorp and Germas, 1969) and released a database of its findings in primates in 1981. That department was disbanded, however, and the last publications from it are from the late 1990s.

The committee is not aware of any human epidemiological research conducted by AFRRI. However, results of studies conducted by AFRRI researchers of *Helicobacter pylori* gastric infection in rhesus monkeys were asserted to have implications for epidemiological investigations in humans (Dubois et al., 1995).

EDUCATION, TRAINING, AND EMERGENCY-RESPONSE EFFORTS

AFRRI has long maintained a mission related to education and emergency response. Some major components of this responsibility—the Institute's Medical Effects of Ionizing Radiation (MEIR) course, the Medical Radiobiology Advisory Team (MRAT), and production and dissemination of publications, guidance, and tools for managing nuclear and radiation-exposure incidents—are described in the following sections.

Medical Effects of Ionizing Radiation Course

AFRRI originally developed a course on the pathophysiology, diagnosis, and treatment of radiation effects in the 1970s. That course, then called the Medical Effects of Nuclear Weapons, was designed to enhance the capability of a military medical community that was inexperienced in radiation matters. Its content was expanded in the 1990s to include the medical response to radiation accidents, and the course took its current name.

MEIR is now offered regularly at military bases in the United States and abroad as a 3-day graduate-level course (AFRRI, 2014d). The course is presented by AFRRI subject-matter experts using up-to-date information (AFRRI, 2013h). It is available without cost to military personnel and DoD civilian employees; members of the general public may attend for a fee. A 6-hour online refresher course is also offered. Some 800–1,000 people take the course each year (Parde, 2012).

The course concentrates on the biomedical consequences of radiation exposure, the reduction of effects, and the medical management of casualties. It covers health-physics aspects, biological effects of radiation, and both the physical and psychological health effects.

Medical Radiobiology Advisory Team

DoD Directive 3150.08 specifies that AFRRI is "the DoD lead on medical and radiobiological matters for radiological-incident response and training" and that as part of this responsibility it shall maintain, in coordination with DTRA, a medical radiobiology advisory team (MRAT) "to support the medical and radiobiological aspects of the response to a U.S. nuclear-weapon incident and other nuclear or radiological incidents" (DOD, 2010a, p. 8). Depending on need, the team may be composed of radiation-medicine physicians, health physicists, radiobiologists, biodosimetrists, and other subject specialists. The MRAT may deploy either independently or as part of a larger team to provide guidance and advice on potential health hazards, decontamination, medical response, exposure modeling, population monitoring, risk assessment, and the like, and it participates in military training exercises that have a nuclear or radiological component (AFRRI, 2013i). This cadre of experts augments the on-call quick response of DTRA's Consequence Management Advisory Teams (CMATs) for dealing with worst-case nuclear- and radiological-emergency scenarios worldwide. Its personnel also support other DoD activities, including the Nuclear Weapon

Incident Response Group out of the Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs and the Joint Chiefs of Staff Joint Nuclear Accident and Incident Response Team (DoD Manual 3150.08 [DOD, 2013]).

The MRAT's emergency-response mission also extends to the domestic civilian sector under the Nuclear/Radiological Incident Annex (NRIA) of the National Response Framework (NRF) (FEMA, 2013a). The NRF defines the roles and responsibilities of different federal agencies during an emergency. It may be invoked only when that emergency overwhelms the state, local, and regional capabilities.[4] Its NRIA "describes the policies, situations, concepts of operations, and responsibilities of the federal departments and agencies governing the immediate response and short-term recovery activities for incidents involving release of radioactive materials to address the consequences of the event" (FEMA, 2013b).

Publications, Guidance, and Tools

In accordance with its charter and mission, AFRRI produces a number of products intended to educate medical and emergency-response professionals and facilitate the management of nuclear- and radiological-exposure incidents. These are compiled from the outcomes of more than five decades of research and development and experience.

One handbook, *Medical Management of Radiological Casualties,* developed by the AFRRI Military Medical Operations staff, is designed to be used by responders who may have minimal knowledge of the effects of ionizing radiation on the human body. It addresses such topics as ARS, biodosimetry, skin injury, internal contamination, psychological support, delayed effects, and decontamination. The first edition was released in 1999. At the time this report was completed, it was in its fourth edition, published in July 2013; it is available in print, PDF, and online[5] formats (AFRRI, 2014e).

In 2008, AFRRI first produced its *Pocket Guide—Emergency Radiation Medicine Response*. As the name suggests, it is intended to be a quick reference used to help assess and control an emergency situation. The guide contains a radiation patient-treatment decision tree and summarizes steps to be taken in diagnosis, treatment, decontamination, and reporting. Its most current version is dated April 2011, and it is available in both print and PDF format (AFRRI, 2011b).

As part of the DoD series, *Textbooks of Military Medicine,* AFRRI—in

[4] Robert T. Stafford Disaster Relief and Emergency Assistance Act, Public Law 100-707, signed into law November 23, 1988; amending the Disaster Relief Act of 1974, Public Law 93-288.

[5] See http://www.usuhs.edu/afrri/outreach/4thEdition.html (accessed May 15, 2014).

conjunction with the Borden Institute, U.S. Army, Office of the Surgeon General—produced the book *Medical Consequences of Radiological and Nuclear Warfare*. It was initially published in 1999 and was updated in 2012 (AMEDD, 2013). This volume addresses nuclear events and their consequences for the medical community, including ARS; triage and treatment of radiation and combined-injury mass casualties; treatment of internal radionuclide contamination; behavioral and neurophysiological consequences of radiation exposure; cytogenic dosimetry; and other related topics. One chapter is devoted to late and low-level effects of ionizing radiation.

Further, AFRRI has published several specific policy guidelines for military-specific activities. Among these are a guideline on the use of insoluble Prussian blue (Radiogardase®) for treatment of internal radiocesium contamination, and an associated worksheet has a decision tree to guide response to an RDD event that involves the dispersal of radioactive cesium or thallium (AFRRI, 2014e). Both documents are in print and PDF format and were last updated in 2005. AFRRI's guidance on the management of embedded DU and on the use of potassium iodide (KI) for the protection of U.S. service personnel and family members[6] has resulted in specific Department of the Army and DoD Health Affairs policies.

AFRRI has also produced a number of publications as part of its scientific program and guidance-and-outreach mission. These include books and book chapters, contract reports, scientific journal articles, reports and report chapters, scientific abstracts, and technical documents. The AFRRI website maintains lists of these with links to PDFs of some publications. In response to a question posed by the committee, AFRRI indicated that the lists are in various stages of completeness, with the most recently released materials being the best documented (AFRRI 2013a). Table 4-3 enumerates these publications.

A number of forms and software tools useful in the response to a nuclear or radiological emergency have also been developed and are disseminated by AFRRI (2013e). These include the following:

- AFRRI Adult/Pediatric Field Medical Record (AFRRI Form 330), a one-page form for gathering emergency medical information in the field applicable to both adult and pediatric cases.
- AFRRI Biodosimetry Worksheet (AFRRI Form 331), which provides a place for recording the facts about a case of radiation exposure, including the source and type of radiation, the extent of exposure, and the nature of the resulting injuries.

[6] Potassium iodide protects the thyroid gland against internal uptake of radioiodines that could be released in certain nuclear accidents or terrorist events (NRC, 2004).

TABLE 4-3 Publications Produced by AFRRI

Publication Type	Years Covered	Number of Publications*
Books/book chapters	1976–2013	285
Contract reports	1965–2012	44
Journal articles	1961–2014	1,585
Reports and report chapters	1993–2012	105
AFRRI scientific reports	1965–1979	264
AFRRI special publications	1965–2009	25
AFRRI technical reports	1965–1997	130

* As of April 2014, as compiled by AFRRI.
SOURCE: AFRRI, 2014f.

- AFRRI Radiocesium Worksheet (AFRRI Form 335), a flowchart, which details steps for screening patients suspected of having been or confirmed to have been exposed to radiocesium during an RDD event.
- Biodosimetry Assessment Tool (BAT), a computer-based software diagnostic tool for use by healthcare providers shortly after a radiation incident to help them identify individuals with significant radiation exposure and make appropriate treatment decisions.
- WinFRAT (First-responders Radiological Assessment Triage), a software tool that enables first responders to triage suspected radiation casualties on the basis of the initial, or prodromal, features listed in the *Emergency Radiation Medicine Response* pocket guide.

At present, the forms exist as PDFs and the software tools as Windows operating system programs. All are applicable to low-dose exposure circumstances.

AFRRI formerly provided information on its operations, research initiatives, publications, and other accomplishments in its annual reports. These contained detailed descriptions of work in each of the Institute's major research areas and of the Institute's outreach, research support and extramural activities. Annual reports were discontinued after FY 1992, but some of the same material—including a comprehensive listing of publications—is posted on the Institute's website. However, neither that material nor information on budgets, research sponsors, staff biographies, or the like is currently available in a consolidated form.

Collaborative Educational Efforts

The USUHS Department of Radiation Biology within the School of Molecular and Cell Biology has several AFRRI principal investigators (PIs) serving as primary or adjunct faculty members. The department offers graduate training and research opportunities that are complementary to AFRRI's work (USUHS, 2012). According to information gathered in July 2013, one graduate course in radiation biology is offered each spring. For more than 10 years, the course has been taught by an AFRRI PI, with four to eight students in attendance. In addition, staff members participate in teaching USUHS classes in biology, physiology, toxicology, and military response to nuclear and radiation threats and also serve on doctoral-dissertation committees. Plans for a graduate program in radiation biology as a part of the USUHS Molecular and Cell Biology Department have been developed but not implemented (AFRRI, 2013a).

AFRRI PIs also participate in educational activities outside of the Institute. They have served as experts and lecturers for the International Atomic Energy Agency (IAEA) cytogenic biodosimetry courses, the Oak Ridge Institute for Science and Education (ORISE) Radiation Emergency Assistance Center/Training Site (REAC/TS) courses, and the National Aeronautics and Space Administration (NASA) Space Radiation Summer School (AFRRI, 2013a).

Further, the Institute conducts periodic and special educational symposia, including seminars related to their research programs and overall mission, strategic plans, and objectives.

AFRRI Internships and Fellowships

In addition to the formal educational activities of its staff members, AFRRI sponsors internships and fellowships. Generally, the Institute hosts one to three postdoctoral scholars at a time through the Research Associateship Program of the National Research Council (NAS, 2014); eight participants in this program subsequently became AFRRI staff members (AFRRI, 2013a; Gamble, 2013). AFRRI has also hosted IAEA fellows studying biodosimetry. For more than a decade, AFRRI has worked with the American Society for Engineering Education's Scientist and Engineering Apprenticeship Program to encourage high school students to pursue careers in laboratory research and science and technology fields (SEAP, 2014). In 2013, the Office of Naval Research provided funding for eight summer interns within AFRRI (AFRRI, 2013a). Further, some military institutions send students to be educated at AFRRI. The Institute hosts one to two second- or third-year midshipmen from the U.S. Naval Academy for 3–4 weeks each summer and, in 2013, it trained a West Point cadet for

2 weeks. Finally, AFRRI reports that starting in 2014, it plans to host two or three undergraduate summer interns though the Naval Research Enterprise Internship Program (AFRRI, 2013a; NREIP, 2014). Overall, these efforts typically account for fewer than 10 students per year.

BUDGET

AFRRI functioned on a budget of $2–$3M/year in the 1960s (DTRA, 2002). After the Cold War years, funding decreased as national spending priorities concentrated on peacetime activities, including social and nondefense programs, in the 1990s. The budget dropped from $17.9M in FY 1992 to $10.1M in FY 1999, resulting in the loss of personnel and delays in routine facility maintenance and upgrades (Assistant Secretary of Defense, 2004).

As priorities changed to focus on radiological emergency preparedness, the Institute's budget stabilized in the early 2000s at $11.3M, with yearly supplements to address infrastructural needs and specific research opportunities (Assistant Secretary of Defense, 2004). Since 2006, it has fluctuated from year to year because of one-time investments made in the physical plant and infrastructure and variations in research funding. Table 4-4 delineates allocations and amounts for FY 2005–FY 2014 (AFRRI, 2013a).

AFRRI's DoD-supplied research funding is currently derived from two accounts: research development testing and evaluation (RDT&E)—so-called Program 6.X funding—and operations and maintenance (O&M). RDT&E funding supports basic research; applied research; technology, component, and systems development; and management support of such work (DoD, 2010b). Within DoD's Defense Health Program, O&M funding is divided into seven major areas: in-house health care, private-sector health care, information management, education and training, management activities, consolidated health support, and base operations (Defense Health Program, 2014). AFRRI also receives external research funding from other government entities and from university and private sector collaborations.

In 2005, AFRRI was funded solely through RDT&E program funding. However, in more recent years, its funding has been divided between RDT&E and O&M allocations. O&M funding represented more than 70% of all research support (including staff salaries) and more than half of the total budget in FY 2013. Additional O&M and, to a much smaller extent, RDT&E money has been devoted to facilities sustainment, restoration, and modernization (FSR&M) and infrastructure. The amount allocated for this purpose has varied considerably between FY 2005 and FY 2013, ranging between 5% and 61% of the total budget. Extramural funding has also been variable, depending on the availability of sponsored research monies and the success of investigators' applications for it.

Figure 4-3 illustrates AFRRI's budgets for FY 2005 through FY 2014, separating O&M research funding (all intramural), RDT&E intramural and extramural research funding, and FSR&M and infrastructure allocations. O&M funding after FY 2005 has remained relatively stable at ~$10M/year, whereas overall RDT&E funding has fluctuated between $6M and $22M/year. The six highest budget years depicted in the figure—FY 2006–FY 2008 and FY 2010–FY 2012—were all the result of one-time infusions of facilities-related money.

Research Grants and Contracts

In recent years, the public push for greater government transparency has given rise to several sources of information that detail grants, contracts, procurement, and other expenditures. To try to assess the support that AFRRI receives in the form of research grants or other awards, several online databases were searched in May 2013. Generally, few entries reflected research support given to AFRRI either directly or through the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF).[7]

The search indicated that AFRRI was neither the sponsor of nor the investigator on any clinical trials registered on the National Institutes of Health (NIH) website www.ClinicalTrials.gov. The Institute was also not associated with any grants accessible on the www.Grants.gov clearinghouse site, and no awards were found in the System for Award Management (SAM, 2013), a searchable database covering several federal government procurement systems.

The awards database of DoD's Congressionally Directed Medical Research Programs (CDMRP, 2013) indicates that AFRRI has received monies totaling ~$3.6M since 1995. The funded projects include two that are associated with low-dose radiation exposure: *Evaluation of the Health Risks of Embedded Depleted Uranium (DU) Shrapnel on Pregnancy and Offspring Development* in 1995 and *Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage to Offspring* in 2007.

A search of HHS's Tracking and Accountability in Government Grants System website (tags.hhs.gov) did not identify any grants directly awarded to AFRRI. However, from 2008 through 2012, HJF received awards totaling ~$1.5M for the study "Ciprofloxacin Enhances DNA Repair Capacity After Radiation Combined Injury" from the National Institute of Allergy and Infectious Diseases (NIAID).

[7] The Henry M. Jackson Foundation is a not-for-profit organization approved by Congress to support USUHS and military medical research (HJF, 2013).

TABLE 4-4 AFRRI Budgets (in $K) for Fiscal Years 2005–2014 by Funding Category, Form of Appropriation, and Source

Funding Category	Appropriation	Source
Research		
Applied Research (6.2)	RDT&E	intramural
Advanced Technology Development Research (6.3)	RDT&E	intramural
DMRDP-Guidance for Development of the Force	RDT&E	extramural
Congressional funds	RDT&E	extramural
Other DoD Components, Federal Agencies, etc.	RDT&E	extramural
		All RDT&E research
Operations & Maintenance: Direct Research Support	O&M	intramural
Operations & Maintenance: Indirect Research Support	O&M	intramural
All O&M research		
		All research related
Infrastructure and Facilities		
Research Infrastructure (one-time)	RDT&E	intramural
Facilities Sustainment, Restoration & Modernization	O&M	intramural
		All infrastructure and facilities related
		Total Budget: (Intramural and Extramural)

NOTES: DMRDP = Defense Medical Research and Development Program; DoD = Department of Defense; FY = fiscal year; RDT&E = research development testing and evaluation funds; O&M = operations and maintenance funds. FY 2013 and FY 2014 funding allocations may have been affected by cuts implemented as a result of the Budget Control Act of 2011.

* Estimated July 2013.

SOURCE: AFRRI, 2013a.

	FY05	FY06	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14*
	9,427	3,166	3,236	3,223	2,997	3,239	3,464	3,558	1,139	1,216
	2,127	783	799	797	736	699	733	739	250	304
	0	0	0	0	0	3,589	1,026	762	849	3,813
	1,350	3,352	1,682	3,705	6,975	800	0	0	0	0
	Not avail.	Not avail.	Not avail.	3,214	4,327	7,772	5,372	4,939	2,442	3,487
	12,904	**7,301**	**5,717**	**10,939**	**15,035**	**16,099**	**10,595**	**9,998**	**4,680**	**8,820**
	0	7,964	5,826	5,321	5,043	6,054	5,954	5,418	7,078	7,558
	0	1,723	3,566	4,214	4,571	4,047	4,124	4,203	4,285	4,366
	0	9,687	9,392	9,535	9,614	10,101	10,078	9,621	11,363	11,924
	12,904	**16,988**	**15,109**	**20,474**	**24,649**	**26,200**	**20,673**	**19,619**	**16,043**	**20,744**
	0	0	0	0	0	6,000	1,984	3,600	0	0
	0	26,672	17,636	17,922	1,285	19,495	13,583	8,197	4,686	6,363
	0	**26,672**	**17,636**	**17,922**	**1,285**	**25,495**	**15,567**	**11,797**	**4,686**	**6,363**
	12,904	**43,660**	**32,745**	**38,396**	**25,934**	**51,695**	**36,240**	**31,416**	**20,729**	**27,107**

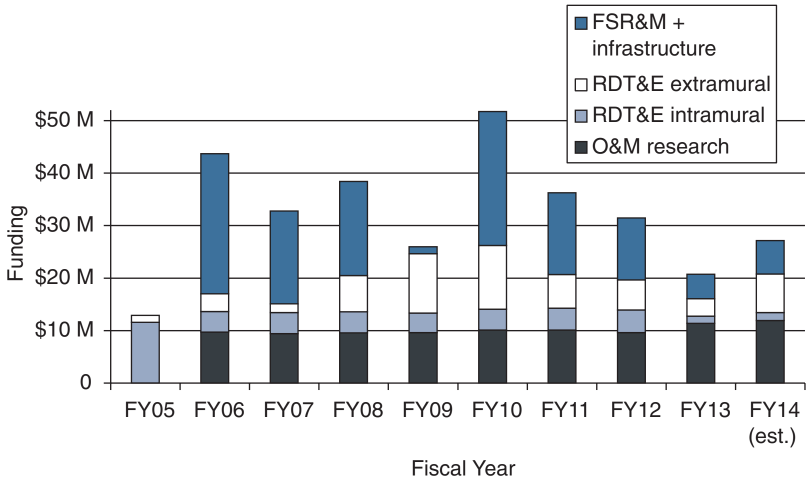

FIGURE 4-3 AFRRI funding FY 2005–FY 2014 (all sources).
NOTES: No information on extramural funding from DoD components, other federal agencies, and outside sources is available for FY 2005–FY 2007.
FSR&M: facilities sustainment, restoration, and modernization; O&M: operations and maintenance; RDT&E: research development testing and evaluation.
SOURCE: AFRRI, 2013a.

Other Agency Support

A May 15, 2013, search of USAspending.gov[8] using "AFRRI" as a keyword identified 135 contracts since 2006. These accounted for $74.9M and were contracted through the Army, Navy, TRICARE, and USUHS (see Table 4-5). Contracts were mainly awarded for maintenance, materials, and, in a few cases, staffing. The largest one reported was for building repair, contracted through the Army for $13.3M in 2006. Also included was $0.5M to the National Academy of Sciences' Research Associateship Program for 2010–2012, contracted through USUHS.

It should be noted that the accuracy of these data is subject to timely and accurate reporting by each agency and to the frequency of updates to the online database. Changes may occur as errors are corrected and more information is submitted, and contract amounts may change as modifications are made and other contracting issues occur (USAspending.gov, 2013).

[8] USAspending.gov fulfills a provision of the Federal Funding Accountability and Transparency Act of 2006 (Public Law 109-282) requiring the Office of Management and Budget to maintain a publicly accessible database of all federal contracts.

TABLE 4-5 Base and Exercised Options Contract Amounts (in $M) to AFRRI by Contracting Agency and Year

Contracting Agency	2006	2007	2008	2009	2010	2011	2012	2013	Total
Navy		1.1	0.3	0.8		0.5	1.9	0.0	4.6
Army	20.2	11.6	12.6		0.1	11.2	7.5		63.2
TRICARE							3.9	0.1	4.0
USUHS		0.3	0.4	1.1	0.7	0.5			3.1
Total	20.2	13.0	13.3	1.9	0.8	12.2	13.3	0.1	74.9

SOURCE: USASpending.gov data as of May 15, 2013.

STAFF AND CAPABILITIES

AFRRI's current and future research is dependent on its staff and resources. The Institute's labor force grew from 254 in 1965 to 285 in 1990, followed by budgetary cuts that reduced personnel in the 1990s. In 2004, the staff comprised 154 employees, 97 of whom were civilian (Assistant Secretary of Defense, 2004; Solyan, 2004), and in 2011, there were 183 employees, of whom 130 were civilian (AFRRI, 2011a).

As of July 2013, AFRRI's Scientific Research Department comprised 68 employees:

- 19 PIs: 17 civilian federal employees and 2 military personnel,
- 14 Research Associates: 13 contractors and 1 military personnel member, and
- 35 Technicians: 22 contractors, 9 civilian federal employees, and 4 military personnel.

The AFRRI scientific staff is interdisciplinary and diverse. Its PIs come from a range of educational backgrounds. Two have doctoral degrees in the field of Radiation Biology or Radiobiology, a third has a master's-level degree in the same field, and three others have received specialized training or completed postdoctoral work directly related to the field (radiation countermeasures, radiation biodosimetry, and cell radiobiology). Other fields of doctorate study among the PIs include biodefense, bioinformatics, bioinorganic chemistry, biology, chemistry, medicinal chemistry and molecular pharmacology, medicine, microbiology, nutritional chemistry, nuclear particle physics, physiology, space life sciences, toxicology, and zoology. Their specialized training includes algorithm development, programming and micro-array, cell and molecular biology, immunology, oxidative stress and cancer research, molecular biology or developmental biology, hematology, B-complex vitamins, neurophysiology or neurophamacology, neuroendocrinology, DNA radiochemistry, neurotechnology, pharmacology, toxicology, transport physiology, and image analysis and microscopy (AFRRI, 2013a).

The PIs earned their degrees from both domestic and international institutions. Seven PIs received doctoral degrees in countries other than the United States (India [3]; China, Germany, Italy, and Russia [1 each]) (AFRRI, 2013a). The most recent doctorate among the AFRRI PIs was attained in 2011; the range of years when the doctorates were received extends back to 1974, indicating that more than half of the PIs with doctoral degrees have at least 30 years' experience since completing their degree (median year of attainment, 1983) (AFRRI, 2013a).

These PIs participate in AFRRI's key research areas: six conduct biodosimetry research, eight conduct countermeasures research, four conduct research on combined injuries, two investigate internal contamination and heavy-metal toxicity; some participate in two research areas. However, not everyone fits into these categories. For example, one PI focuses on radiation neutralization to better understand radiation's effect on microbial infection and the immune system and how radiation can be an effective tool to inactivate microbial threats (sterilization, sanitation, remediation of contaminated sites, and the like) (AFRRI, 2013a). Nine PIs serve as USUHS faculty members in the Departments of Preventive Medicine and Biometrics; Radiation Biology; and Anatomy, Physiology, and Genetics (AFRRI, 2013a).

Two PIs list low-dose research topics among their interests (AFRRI, 2013a). One PI conducts work on low-dose radiation carcinogenesis models (Miller, 2011), was lead author of a literature review on late and low-level effects of ionizing radiation published in the 2013 *Textbook of Military Medicine* (Miller et al., 2013), and carries out studies on the effects of DU exposure (for example, Miller et al., 2010). A second PI notes an interest in the effects of low-dose-rate radiation that models the fallout environment (AFRRI, 2014a). In addition—as noted in Chapter 5—some of the other work conducted by investigators has potential low-dose applications.

AFRRI posts on its website a list of journal articles produced by its staff (AFRRI, 2014c). Of the 127 articles published or in press from 2010 through May 15, 2014,[9] only two explicitly mention doses below 1 Gy. Both of these relate to biodosimetry: One examined the utility of giant magnetoresistive nanosensors for measuring protein concentrations in blood for medical diagnosis (Kim et al., 2013), and the other evaluated the minipig for its potential in γ-H2AX-based biodosimetry after exposure to ionizing radiation from ^{137}Cs and ^{60}Co sources (Moroni et al., 2013).

As already noted, the Veterinary Sciences Department, which manages the animal facility, is staffed with specially trained individuals, including

[9] This averages to nearly two papers per year per PI over this time period, including papers authored by more than one PI.

veterinarians, veterinary technicians, animal husbandry personnel, pathology staff, and administrators, who are Army, Air Force, federal, and contract employees.

COLLABORATIONS AND REPRESENTATION IN SCIENTIFIC GROUPS

As of July 2013, AFRRI listed a number of current and recent collaborations on various research projects, listed in Box 4-3. Collaborative projects reflect all of the Institute's key areas: radiation biology, countermeasures, biodosimetry, combined injury, and heavy-metal toxicity (AFRRI, 2013a).

Three of the projects are specified as investigations of low-dose radiation exposure. Two of these three are with USUHS investigators—one on the development of a low-dose radiation-induced skin cancer model and the other on low-dose radiation cancer risks; the third is a collaboration with a NASA researcher on low-dose-rate radiation effects.

Earlier, AFRRI collaborated with various other academic and governmental organizations for DU research: Columbia University, NIH and NCI, University of Paris, United Kingdom Medical Research Council, French Institute of Nuclear Security, Memorial Sloan Kettering Cancer Center, New York University, University of Maine, Armed Forces Institute of Pathology, and the University of Maryland School of Medicine (Kalinich et al., 2005).

AFRRI seeks extramural support for a portion of its research. In July 2013, the Institute reported 21 extramural projects. Sponsors include the Biomedical Advanced Research and Development Authority (BARDA) (three awards), Cleveland BioLabs (to evaluate a countermeasure), the Defense Medical Research and Development Program (DMRDP) (four awards, all for countermeasures research), DTRA (six awards: five for countermeasures research and one for triage biodosimetry), NASA (the previously mentioned low-dose-rate study), NIAID (five awards for countermeasures, one to develop a pediatric radiation injury model), and Xavier University (for a countermeasures study). These extramural awards sponsor the research of 10 different AFRRI PIs (AFRRI, 2013a).

AFRRI personnel also participate in a number of committees and working groups associated with DoD, the Military Services, other government agencies (including HHS, U.S. Department of Homeland Security, Environmental Protection Agency, National Institute of Standards and Technology, and Office of Science and Technology Policy), and national and international organizations (including the National Council on Radiation Protection and Measurements, International Atomic Energy Agency, International Organization for Standardization, North Atlantic Treaty Organization, and World Health Organization) (AFRRI, 2013a).

BOX 4-3
Current and Recent AFRRI Research Collaborators as of Mid-2013

Governmental Agencies

Army Research Labs, Department of Veterans Affairs, Lawrence Berkeley National Laboratory, NASA, National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), Sandia National Laboratory

Medical and Academic Institutions

Albert Einstein College of Medicine, Columbia University Center for Radiological Research, Indiana School of Medicine, National Space Biomedical Research Institute, New York University Medical School, Roswell Park Cancer Institute, Sloan Kettering Institute, Southwest Research Institute, Stanford University, Tulane University, University of Arkansas, University of California, Los Angeles, University of Maryland School of Medicine, University of New Hampshire, University of New Mexico, USUHS, Wake Forest University, Xavier University

Private-Sector Entities

Cellerant Therapeutics, Cleveland BioLabs, Eukarion, Hollis-Eden Pharmaceuticals, Humanetics Pharmaceuticals, LaMotte Corporation, Meso Scale Diagnostics, Tech Micro Services

International Collaborations

Commonwealth Scientific and Industrial Research Organization (Australia), Defence Research and Development Canada, Health Canada, University of Western Ontario (Canada), Commission of Atomic Energy (France), University of Paris (France), Hannover Medical School (Germany), Bhabha Atomic Research Centre (India), Institute of Nuclear Medicine and Allied Sciences (India), ENEA National Institute of Ionizing Radiation Metrology (Italy), Hirosaki University (Japan), National University of Singapore, World Health Organization

The Institute indicates that "[a]dditionally, more than 200 companies and researchers have engaged AFRRI in collaborations or discussions regarding novel radiation countermeasure candidates."

SOURCE: AFRRI, 2013a.

SUMMARY, FINDINGS, AND CONCLUSIONS

AFRRI's Programs, Research, and Resources

AFRRI is the only DoD entity dedicated to ionizing-radiation health-effects research. Its unique infrastructure includes a number of radiation sources that may be used to study acute and chronic effects on cells and animals, and it maintains a vivarium that houses mammals, including non-human primates, used in studies. The Institute's research portfolio principally comprises work addressing biodosimetry, combined injury, internal contamination and metal toxicity, and countermeasure development. It disseminates the results of these studies in refereed journal papers, reports, books and book chapters, and other publications. Some projects are supported by and in some cases conducted at the behest of government or private-sector funders, and the remainder are initiated by PIs and supported internally. AFRRI also fulfills its mission by producing manuals and protocols on radiation-exposure response, conducting education and training in these areas, supplying nuclear and radiological emergency response assistance, and providing advice to the federal government. Approximately a third of the Institute's 19 PIs hold appointments (primarily adjunct) at the USUHS, teaching classes or lecturing there, and mentor students. USUHS and other graduate students can perform research at the Institute. AFRRI hosts participants in fellowship programs and participates in science, technology, engineering, and mathematics outreach. Its budget—which was ~$21M in FY 2013—has fluctuated in recent years, including some large infusions to maintain and upgrade the physical plant, but overall it and the Institute's staffing levels are lower than they were in the early 1990s.

Findings and Conclusions

AFRRI contributes to ionizing-radiation health-effects research by providing specialized expertise and abilities for evaluating, modeling, and countering the consequences of exposure to nuclear and radioactive agents. Assessing risks and creating models to predict casualties from combined injuries and internal contamination (radiation or metal poisoning resulting from embedded shrapnel made of DU or tungsten alloys) permits better military decision making. Developments in biological dosimetry increase the speed and accuracy of radiation dose assessment; these developments include assays that use blood, urine, or hair for screening, and improvements in equipment design that aid in the triage, medical management, and treatment of radiation-exposed personnel. Researchers at AFRRI continue to investigate the mechanisms of radiation damage and pursue the development of treatments for persons exposed to harmful doses of ionizing radiation by using molecular and cellular approaches and animal models. These scientific advancements are also applicable to the aerospace industry and flight personnel exposed to cosmic and solar radiation and to the civilian population in cases of terrorism and industrial accidents that result in radiation exposure.

The second element of the statement of task called on the committee to assess how AFRRI programs are advancing research in radiobiological science related to human health risks from exposures to low-dose ionizing radiation. Although AFRRI has conducted a small number of studies at low doses, low-dose radiation exposure was not a specifically defined research area at the time this report was written. In the dose range 1 Gy and below, studies include the development of models to study carcinogenesis and non-targeted effects at the molecular level. Late effects of radiation (including internal and external contamination from DU), countermeasures to prevent those late effects, and associated biomarkers are also being studied. Areas of research that address both low- and high-level exposure include the tissue and cellular effects of combined injuries on the skeletal system (for example, bone marrow and bone loss), countermeasures to the effects of low-dose-rate gamma radiation encountered in nuclear fallout, and some of the Institute's biodosimetry and exposure characterization work.

As noted in this chapter, the Institute's current portfolio of studies is focused almost exclusively on exposures above 1 Gy—a range that the research community and international organizations classify as moderately high and high dose. This work is consonant with AFRRI's mission and yields information that is vital to managing the consequences of nuclear and radiological material releases as a result of armed conflicts, terrorist actions, and accidents. It does not, though, generate knowledge that would help answer the questions identified in Chapter 2 as being important to understanding the health risks of low-dose radiation exposure. The committee thus concludes that, although AFRRI carries on a robust program of research on the biological and health effects of high-dose ionizing radiation exposure, it is not currently substantively advancing low-dose research.

Chapter 5 draws on the material presented here to offer findings, conclusions, and recommendations about opportunities for AFRRI to advance its mission for understanding human health risks from exposures to low-level ionizing radiation, with special emphasis on DoD military operations and personnel.

REFERENCES

AFRRI (Armed Forces Radiobiology Research Institute). 1968. *Organization. AFRRI Staff Memorandum 10-1.* https://www.osti.gov/opennet/servlets/purl/16004533-h9b0K3/16004533.pdf (accessed February 10, 2014).

AFRRI. 1993. *Annual report on AFRRI research for fiscal year 1992*. Bethesda, MD. http://www.dod.mil/pubs/foi/operation_and_plans/NuclearChemicalBiologicalMatters/910.pdf (accessed February 10, 2014).

AFRRI. 2009. *Former AFRRI Scientific Director was pioneer in radiation research*. http://www.usuhs.edu/afrri/news/pioneer.htm (accessed December 30, 2013).

AFRRI. 2010. *Ceremony welcomes new AFRRI director*. http://www.usuhs.edu/afrri/news/new_director2010.htm (accessed March 2, 2014).

AFRRI. 2011a. *AFRRI: A unique national resource*. Presented at the 2011 Society of American Federal Medical Laboratory Scientists (SAFMLS) annual meeting, New Orleans, LA, March 31. http://www.safmls.org/2011/2011%20Presentations/ST%2014/AFRRI%20-%20A%20Unique%20National%20Resource.pdf (accessed March 2, 2014).

AFRRI. 2011b. *Pocket guide—emergency radiation medicine response*. http://www.usuhs.edu/afrri/outreach/pdf/AFRRI-Pocket-Guide.pdf (accessed December 30, 2013).

AFRRI. 2013a. Responses to questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, July 12, 2013.

AFRRI. 2013b. Responses to supplementary questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, October 31, 2013.

AFRRI. 2013c. *About AFRRI*. http://www.usuhs.edu/afrri/organiza/about_afrri.htm (accessed October 8, 2013).

AFRRI. 2013d. *Biodosimetry*. http://www.afrri.usuhs.mil/research/biodos.htm (accessed February 12, 2013).

AFRRI. 2013e. *Biodosimetry Assessment Tool*. http://www.usuhs.edu/afrri/outreach/pdf/BAT_brochure.pdf (accessed December 30, 2013).

AFRRI. 2013f. *Internal contamination and metal toxicity*. http://www.usuhs.edu/afrri/research/metal-tox.htm (accessed December 30, 2013).

AFRRI. 2013g. *Combined injury: Radiation with other insults*. http://www.usuhs.edu/afrri/research/combined-injury.htm (accessed December 30, 2013).

AFRRI. 2013h. *Medical effects of ionizing radiation (course brochure)*. November 2013. http://www.usuhs.edu/afrri/outreach/pdf/MEIR_brochure.pdf (accessed April 12, 2014).

AFRRI. 2013i. *The Medical Radiobiology Advisory Team*. http://www.usuhs.edu/afrri/outreach/pdf/describeMRAT.pdf (accessed February 2, 2014).

AFRRI, 2014a. *Biography, Dr. Mark H. Whitnall, AFRRI Scientific Advisor*. http://www.usuhs.edu/afrri/organiza/Bio-DrWhitnall2014.pdf (accessed May 15, 2014).

AFRRI. 2014b. *Countermeasures*. http://www.usuhs.edu/afrri/research/rcp.htm (accessed February 12, 2014).

AFRRI. 2014c. *Journal articles 2010–2019*. http://www.usuhs.edu/afrri/outreach/journal2010s.htm (accessed May 15, 2014).

AFRRI. 2014d. *Medical effects of ionizing radiation (in-person) course*. http://www.usuhs.edu/afrri/outreach/meir/meir.htm (accessed February 5, 2014).

AFRRI. 2014e. *Medical/operational guidance for managing radiation casualties*. http://www.usuhs.edu/afrri/outreach/guidance.htm (accessed February 10, 2014).

AFRRI. 2014f. *Product quick list*. http://www.usuhs.edu/afrri/outreach/infoprod.htm (accessed April 7, 2014).

AFRRI. 2014g. *Research programs*. http://www.usuhs.edu/afrri/research/research.htm (accessed February 10, 2014).

AMEDD (Army Medical Department). 2013. *Medical consequences of radiological and nuclear warfare*. http://www.cs.amedd.army.mil/borden/Portlet.aspx?id=b3cb37ed-08e7-4617-a40c-f148ee3d2303 (accessed December 30, 2013).

Assistant Secretary of Defense. 2004. *Report to Congress: Armed Forces Radiobiology Research Institute (AFRRI)*. Washington, DC, September 20, 2004.

Carter, R. E., and D. M. Verrelli. 1973. *AFRRI cobalt whole-body irradiation. Technical Note 73-3*. Bethesda, MD: Armed Forces Radiobiology Research Institute.

CDC (Centers for Disease Control and Prevention). 2012. *Strategic National Stockpile (SNS)*. http://www.cdc.gov/phpr/stockpile/stockpile.htm (accessed December 30, 2013).

CDMRP (Congressionally Directed Medical Research Programs). 2013. *Search awards*. http://cdmrp.army.mil/search.aspx (accessed December 30, 2013).

Defense Health Program. 2014. *Fiscal year (FY) 2014 budget estimates: Appropriation highlights*. http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2014/budget_justification/pdf/09_Defense_Health_Program/VOL_I/VOL_I_Sec_1_PBA-19_Introductory_Statement_DHP_PB14.pdf (accessed May 14, 2014)

Dix, M. A. 2005. The Armed Forces Radiobiology Research Institute. *Uniformed Services University of the Health Sciences Journal 2004/5 Edition*. Pp. 461-496.

DoD (Department of Defense). 2006. *Instruction: Armed Forces Radiobiology Research Institute. Directive number 5105.33*. http://www.dtic.mil/whs/directives/corres/pdf/510533p.pdf (accessed December 30, 2013).

DoD. 2010a. *DoD response to nuclear radiological incidents*. Department of Defense Directive 3150.08. January 20, 2010.

DoD. 2010b. *Financial management regulation, Volume 2b: Budget formulation and presentation (Chapters 4–19)*. Department of Defense Directive 7000.14-R. September 2010. http://comptroller.defense.gov/Portals/45/documents/fmr/current/02b/Volume_02b.pdf (accessed May 14, 2014).

DoD. 2013. *Nuclear Weapon Accident Response Procedures (NARP)*. Department of Defense Manual 3150.08. August 22, 2013. www.dtic.mil/whs/directives/corres/pdf/315008m.pdf (accessed February 2, 2014).

DTRA (Defense Threat Reduction Agency). 2002. *Defense's Nuclear Agency 1947–1997*. Washington, DC: U.S. Department of Defense, DTRA History Series.

DTRA. 2010. *Nuclear Test Personnel Review (NTPR) program fact sheet*. http://www.dtra.mil/documents/ntpr/factsheets/NTPR_Program.pdf (accessed February 5, 2014).

Dubois, A., N. Fiala, R. H. Weichbrod, G. S. Ward, M. Nix, P. T. Mehlman, D. M. Taub, G. I. Perez-Perez, and M. J. Blaser. 1995. Seroepizootiology of *Helicobacter pylori* gastric infection in nonhuman primates housed in social environments. *Journal of Clinical Microbiology* 33(6):1492-1495.

FedBizOps.Gov. 2013. *Cobalt-60, remove and replace. Solicitation number: HT9404-13-Q-0020*. https://www.fbo.gov/?s=opportunity&mode=form&tab=core&id=614ea9482f61dd43ae19febece66f2e1&_cview=1 (accessed February 11, 2014).

FEMA (Federal Emergency Management Agency). 2013a. *The national response framework*. http://www.fema.gov/media-library/assets/documents/32230?id=7371 (accessed February 2, 2014).

FEMA. 2013b. *The Nuclear/Radiological Incident Annex*. http://www.fema.gov/media-library/assets/documents/25554 (accessed February 2, 2014).

Gamble, R. 2013. Personal communication, H. Ray Gamble, Director, Fellowships Office, National Research Council, May 5, 2013.

General Atomics. 2014. *TRIGA nuclear reactors*. http://www.ga.com/triga (accessed February 11, 2014).

HJF (Henry M. Jackson Foundation). 2013. *About HJF*. http://www.hjf.org/about (accessed December 30, 2013).

Huff, L. A. 2013a. *Armed Forces Radiobiology Research Institute*: Presentation to the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation.Washington, DC, May 3, 2013.

Huff, L. A. 2013b. Personal communication, e-mail to the committee, Washington, DC, November 1, 2013.

Huff, L. A. 2014. Personal communication, e-mail to the committee, Washington, DC, January 10, 2014.

Kalinich, J. F., C. A. Emond, T. K. Dalton, S. R. Mog, G. D. Coleman, J. E. Kordell, A. C. Miller, and D. E. McClain. 2005. Embedded weapons-grade tungsten alloy shrapnel rapidly induces metastatic high-grade rhabdomyosarcomas in F344 rats. *Environmental Health Perspectives* 113(6):729-734.

Kang, A., D. Gibson, and M. Dempsey. 2011. *AFRRI: A unique national resource*. Presented at the 2011 Society of American Federal Medical Laboratory Scientists (SAFMLS), New Orleans, LA, March 31, 2011.

Kim, D., F. Marchetti, Z. Chen, S. Zaric, R. J. Wilson, D. A. Hall, R. S. Gaster, J. R. Lee, J. Wang, S. J. Osterfeld, H. Yu, R. M. White, W. F. Blakely, L. E. Peterson, S. Bhatnagar, B. Mannion, S. Tseng, K. Roth, M. Coleman, A. M. Snijders, A. J. Wyrobek, S. X. Wang. 2013. Nanosensor dosimetry of mouse blood proteins after exposure to ionizing radiation. *Science Reports* 3(2234).

Landauer, M. R., D. G. McChesney, and G. D. Ledney. 1997. Synthetic trehalose dicorynomycolate (S-TDCM): Behavioral effects and radioprotection. *Journal of Radiation Research* 38(1):45-54.

Landauer, M. R., C. A. Castro, K. A. Benson, J. B. Hogan and J. F. Weiss. 2001. Radioprotective and locomotor responses of mice treated with nimodipine alone and in combination with WR-151327. *Journal of Applied Toxicology* 21:25-31.

McKinney, L. C., E. M. Aquilla, D. Coffin, D. A. Wink, and Y. Vodovotz. 1998. Ionizing radiation potentiates the induction of nitric oxide synthase by IFN-g and/or LPS in murine macrophage cell lines: Role of TNF-α. *Journal of Leukocyte Biology* 64(4):459-466.

Mele, P. C., C. G. Franz, and J. R. Harrison. 1990. Effects of ionizing radiation on fixed-ratio escape performance in rats. *Neurotoxicology and Teratology* 12(4):367-373.

Miller, A. C. 2011. Development of models to study radiation-induced late effects. In *RTG 033 Subgroup 1: Radiobiology mechanisms and late effects. HFM Panel-099 RTG-033 Activity: Radiation bioeffects and countermeasures*. Bethesda, MD. http://ftp.rta.nato.int/public/PubFullText/RTO/TR/RTO-TR-HFM-099/$$TR-HFM-099-Pre-Release-ALL.pdf (accessed May 15, 2014).

Miller, A. C., M. Stewart, R. Rivas. 2010. Preconceptional paternal exposure to depleted uranium: Transmission of genetic damage to offspring. *Health Physics* 99(3):371-379.

Miller, A. C., M. Satyamitra, S. Kulkarni, T. Walden. 2013. Late and low-level effects of ionizing radiation. In *Medical Consequences of Radiologicial and Nuclear Weapons*, edited by A. B. Mickelson. Fort Detrick, MD: Office of the Surgeon General. Pp. 195-215.

Moroni, M., E. Lombardini, R. Salber, M. Kazemzedeh, V. Nagy, C. Olsen, M. Whitnall. 2011. Hematological changes as prognostic indicators of survival: Similarities between gottingen minipigs, humans, and other large animal models. *PLoS ONE* 6:e25210.

Moroni, M., D. Maeda, M. H. Whitnall, W. M. Bonner, C. E. Redon. 2013. Evaluation of the gamma-H2AX assay for radiation biodosimetry in a swine model. *International Journal of Molecular Science* 14:14119-14135.

Naquin, T. D., R. C. Bhatt, G. R. Kahles, and D. M. McKown. 2001. A low gamma dose rate cobalt-60 facility. *Radiation Protection Management* 18(2):31-36.

NAS (National Academy of Sciences). 2014. *Associateship programs at Armed Forces Radiobiology Research Institute*. http://nrc58.nas.edu/RAPLab10/Opportunity/Program.aspx?LabCode=15&ReturnURL=%2fRAPLab10%2fOpportunity%2fPrograms.aspx%3fLabCode%3d15 (accessed February 12, 2014).

NRC (National Research Council). 2004. *Distribution and administration of potassium iodide in the event of a nuclear incident*. Washington, DC: The National Academies Press.

NREIP (Naval Research Enterprise Internship Program). 2014. *Participating labs: Armed Forces Radiobiology Research Institute*. https://nreip.asee.org/labs/armed_forces_radiobiology_research_institute__bethesda__md_ (accessed February 12, 2014).

Parde, N. 2012. AFRRI: A global authority on ionizing radiation. *The Journal (official newspaper for Walter Reed Army Medical Center)*. http://www.dcmilitary.com/ARTICLE/20120906/NEWS11/709069953/AFRRI-A (accessed February 6, 2014).

SAM (System for Award Management). 2013. *System for Award Management*. http://www.sam.gov (accessed December 30, 2013).

SEAP (Scientist and Engineering Apprenticeship Program). 2014. *Participating labs: Armed Forces Radiobiology Research Institute*. https://seap.asee.org/participating_labs/armed_forces_radiobiology_research_institute_bethesda_md (accessed February 12, 2014).

Singh, V. K., D. S. Brown, T.-C. Kao. 2010. Alpha-tocopherol succinate protects mice from gamma-radiation by induction of granulocyte-colony stimulating factor. *International Journal of Radiobiology* 86(1):12-21.

Solyan, D. K. 2004. Armed Forces Radiobiology Research Institute. In *The Uniformed Services University of the Health Sciences: First Generation Reflections*, edited by K. E. Kinnamon, pp. 309-315.

Tenforde, T. S. 2011. *Tribute to AFRRI on its 50th anniversary and perspectives on the history and future of radiation biology and health protection*. Presented at AFRRI Golden Jubilee Banquet, Bethesda, MD, May 12, 2011.

Thorp, J. W., and J. E. Germas. 1969. *Performance of monkeys after partial body irradiation*. AD699127. Bethesda, MD: AFRRI. http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=AD0699127 (accessed February 10, 2014).

USAspending.gov. 2013. *USA spending*. http://usaspending.gov (accessed December 30, 2013).

USUHS (Uniformed Services University of the Health Sciences). 2012. *Uniformed Services University of the Health Sciences: Learning to care for those in harm's way*. 2012 Report, 40th Anniversary Edition.

Zeman, G. H., and M. A. Dooley. 1984. *Performance and dosimetry of theratron-80 cobalt-60 unit at Armed Forces Radiobiology Research Institute*. Technical report. Accession Number: ADA142770. Bethesda, MD: AFRRI.

5

Opportunities for AFRRI

This final chapter of the report brings together the information presented in the previous chapters and responds to the third element of the committee's statement of task, putting forward findings, conclusions, and recommendations regarding opportunities for the Armed Forces Radiobiology Research Institute (AFRRI) to advance its mission for understanding human health risks from exposures to low-level[1] ionizing radiation, with special emphasis on U.S. Department of Defense (DoD) military operations and personnel. In so doing, the chapter highlights the unique resources associated with the Institute and how they might be better used, identifies possibilities for expanded and additional responsibilities, discusses AFRRI's role in fostering the next generation of radiation-research professionals, and offers perspectives on the scientific oversight of programs.

In the course of its work, the committee examined the full range of AFRRI's activities. Although its statement of work focuses on low-dose radiation, it also offers observations applicable to the full range of AFRRI's activities and on organizational issues, because the success of a low-dose program depends on the viability of the Institute's entire research enterprise.

[1] The committee's statement of task references "low-level" ionizing radiation; that terminology is retained here and in other places where the report is presenting responses to these directives.

AFRRI'S SCIENTIFIC PROGRAM AND OUTREACH ACTIVITIES

AFRRI as a Unique National Asset

As delineated in Chapter 4, DoD has tasked AFRRI with conducting research in the field of radiobiology and related matters essential to the operational and medical support of the U.S. military. DoD has also given AFRRI responsibilities that include operating a radiobiology and ionizing radiation–bioeffects research facility; cooperating with other military components, federal agencies, and outside investigators on relevant studies; providing training in radiobiology, medical and emergency response, and related fields; and consulting with the Military Services and government in their areas of expertise.

No other DoD-level organization has such a comprehensive and broad-scoped mission in radiological health and protection. The threat spectrum that AFRRI is concerned with, illustrated in Figure 5-1, is wide ranging, and the Institute additionally concerns itself with such nonmilitary issues as civilian radiological-accident response and the safety of astronauts exposed to high linear energy transfer (LET) cosmic radiation.

AFRRI's physical plant boasts a 1-megawatt (MW) TRIGA® Mark F reactor that is the only such unit in the United States dedicated to radiobiology research. It also houses X-ray, cesium-137 (^{137}Cs), and cobalt-60 (^{60}Co) exposure sources and a vivarium that maintains rodents, minipigs, and nonhuman primates (rhesus macaques) for studies.

AFRRI's research and development goals and collaborations with other government facilities, academic institutions, and civilian laboratories in the United States and throughout the world cover areas that receive relatively little attention elsewhere. Such areas include the pursuit of new drugs to prevent the life-threatening and health-degrading effects of high-dose ionizing radiation, the development of methods for rapidly assessing radiation exposure to ensure appropriate medical treatment, and the investigation of the effects of radiation injury combined with other insults, such as trauma, disease, and chemical exposures.

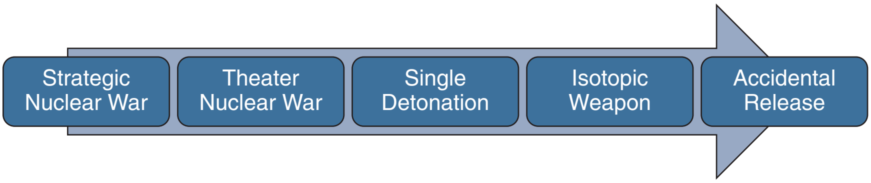

FIGURE 5-1 The ionizing radiation exposure threat spectrum.
SOURCE: Adapted from Kang et al., 2011.

The Institute has DoD's lead on medical and radiobiological matters for radiological-incident response, maintaining a deployable team of subject experts to support actions taken in military and civilian nuclear or radiological incidents. It trains military and civilian health care providers, disaster-preparedness personnel, and operational planners on the effects of ionizing radiation and the logistical and medical responses to exposures; it disseminates data collection instruments to help manage such events; and it develops biodosimetry tools.

Taken individually, none of the facilities, capabilities, assets, and responsibilities just listed is unique; the fact that all of them are under a single roof and managed by the same command structure is what makes AFRRI unique.

AFRRI's programs and outreach activities provide the nation with important fundamental research, basic knowledge, practical applications, tools, and guidance associated with radiobiology and related matters essential to the operational and medical support of DoD and the Military Services as well as civilian and emergency responders. The Institute's unique infrastructure, which would be difficult to reproduce elsewhere, positions it to contribute to research on the health effects of low-level ionizing radiation.

Opportunities for Additional or Expanded Roles for AFRRI

As documented in Chapter 4, AFRRI's research currently focuses on issues related to high-dose radiation exposure. Although some low-dose work is conducted, and other existing initiatives either have low-dose applications or could presumably be extended into this exposure range, the Institute appears likely to remain oriented toward high-dose work for at least the short term because that is where the experience and practical knowledge of its personnel are centered. For these reasons, the committee concludes that it is not appropriate to propose a specific low-dose research agenda as indicated in its statement of task. Performing substantive work in this area will first require changes in institutional culture and a reorienting of staff expertise. Nevertheless, the committee believes that there may be opportunities for AFRRI to contribute to the understanding of human health risks from exposures to low-dose ionizing radiation in a manner that is consistent with its mission that takes advantage of its current expertise, its infrastructure, and its position within the DoD; and that puts it on the pathway toward making greater contributions to this area of research in the future.

The committee's review of AFRRI's mission and assets led it to conclude that there are opportunities for an expanded or additional role in the following areas: nuclear- and radiological-emergency response; treatment and management of psychological injuries after a nuclear or radiological event; development and evaluation of field radiation instrumentation; training of radiation-research and -response professionals; and support of radiation epidemiology and risk research. Some of these entail cooperation with outside investigators to facilitate their low-dose research; others extend existing initiatives to cover low-dose exposures. Specific recommendations are addressed below.

Preparedness and Response to Nuclear and Radiological Emergencies

AFRRI has been primarily concerned with the effects of nuclear weapons on the battlefield and the survival of members of the Military Services in such environments. On the nuclear battlefield, mortality and morbidity are not limited to radiation injuries; they also include thermal burns, overpressure and underpressure (blast) injuries, and puncture wounds, often involving radiological contamination of the wound. During the 1960s, the Institute emerged as the lead U.S. agency in the assessment of combined-injury triage and medical management, and it still conducts research to develop medical treatments for irradiated personnel whose exposure is compounded by traumatic wounds, burns, hemorrhage, or infection.

This work is directly transferable to other areas, including preparedness and response to low-dose, noncombat nuclear and radiological emergencies, a responsibility that AFRRI exercises through its Medical Radiobiology Advisory Team (MRAT)—experts who provide health-physics, medical, and radiobiological advice to military and civilian command and control operations worldwide (AFRRI, 2013a). As Chapter 4 details, the Institute produces guidance for physicians and emergency-response personnel deployed to nuclear and radiological incidents, and it disseminates forms and software tools intended to make screening routine and assess the exposure of potential casualties. At present, the guidance and forms exist as PDFs and the software tools as Windows operating system programs.

An opportunity exists for AFRRI to make its nuclear and radiological incidents response educational materials, forms, and tools—which are already amenable to civilian applications—more useful to both the military and civilians by adapting them to modern digital devices such as tablets and smartphones and assuring their applicability to low-level exposure incidents.

For example, the U.S. Department of Health and Human Services has in recent years implemented its Radiation Emergency Medical Management (REMM) software tool as an application for iPhone/iPad, Android, and BlackBerry platforms (HHS, 2014).

Another area in which AFRRI could potentially lead is the training, equipping, and standardizing of the multiple DoD radiological response teams. Currently, the U.S. Army,[2] Navy, and Air Force[3] have their own teams that were originally chartered to respond to a nuclear-weapon accident but that now have expanded missions, including nuclear and radiological accidents and other events. Since 2006, these teams have been listed as part of the federal response assets available under the Nuclear/Radiological Incident Annex (FEMA, 2008) of the National Response Framework, a set of policies that guide how the nation responds to emergencies and disasters. All Military Services take part in U.S. Department of Homeland Security (DHS) and DoD exercises. Despite the commonality of the service teams' missions, though, they have different procedures, instrumentation, sample-collection and analysis capabilities, and command structures.

An opportunity exists for AFRRI to have a coordinating role within the services to facilitate standardization of their radiological response teams, and to ensure they are well trained and equipped to deal with low-level radiation incidents.

If DoD chooses to tap the Institute's expertise, AFRRI's coordinating role could extend to supporting the procurement of radiation-detecting and -analysis instrumentation (addressed below), contamination-control materials, health-physicist and technician training, command and control, field procedures, external and internal dosimetry, computer projection models, and sample collection and analysis methods. AFRRI is well suited for this role as a triservice organization with the required in-house expertise.

Management of Psychological Effects Associated with a Nuclear or Radiological Event

Nuclear and radiological exposure incidents pose special challenges because the stressor is invisible and cannot be sensed or avoided like other threats (Vyner, 1988). The psychological effects of such incidents have been demonstrated on numerous occasions, including nuclear power plant accidents such as the 1986 Chernobyl and 2011 Fukushima events. They are often caused by fear of developing cancer in the future without regard to the actual dose of radiation received (Bromet, 2011).

Prompt treatment of psychological effects after radiological or nuclear accidents is crucial to the long-term well-being and combat effectiveness of military services personnel. The same is true for the persons who are called on to operate and maintain the civilian infrastructure after an incident and the populations affected by the event (AFRRI, 2010).

The management of psychological effects related to a nuclear or radiological event falls under AFRRI's mission to preserve the health and perfor-

[2] Radiological Advisory Medical Team (RAMT) (U.S. Army, 2012).
[3] Air Force Radiation Assessment Team (AFRAT) (U.S. Air Force, 2011).

mance of U.S. military personnel (AFRRI, 2013b), but the Institute does not currently have psychologists, psychiatrists, risk-communication specialists, or professionals in related fields as members of its research staff.[4] However, the Uniformed Services University of the Health Sciences (USUHS) is well positioned to support training programs to give military health care providers and first responders the tools and techniques to communicate with service members and other responders who operate in potentially contaminated areas, treat psychological injuries, and deal with other issues raised in response to nuclear and radiological incidents. Its Center for the Study of Traumatic Stress has a broad mission that includes "trauma exposure from the consequences of combat, operations other than war, terrorism, natural and human-made disasters, and public health threats" (CSTS, 2014). The Center produced white papers on radiological-incident response in 1999 (Pastel et al., 1999) and 2005 (CSTS, 2005) but does not appear to have conducted work in the area since then. AFRRI's interest in the topic is evinced by the "Psychological Issues in a Radiological or Nuclear Attack" chapter of the 2013 publication *Medical Consequences of Radiological and Nuclear Warfare*, a text that the Institute was intimately involved in producing (AMEDD, 2013).

An opportunity exists for AFRRI to serve as a source of information, training, and research on the response to psychological issues raised by low-level nuclear and radiological release incidents if an institutional decision is made to collaborate with USUHS staff for this purpose. This in-house expertise would additionally be helpful in crafting the psychological injury component of AFRRI's incident-response training responsibilities.

Development and Management of DoD Radiation-Protection Instrumentation

DoD has a long history of designing, acquiring, and testing radiation-protection instrumentation that is designed to withstand the harsh environments in which the military may operate. The evolution of rugged handheld radiation-detection instruments has been driven by lessons learned in responses to weapons accidents. These range from the need for a single scaler with multiple attachable probes and protection of battery supplies from extreme temperatures to on-site calibration and repair capabilities and alternative detection technologies for hard-to-detect and alpha emitters.

[4] As noted in Chapter 4, AFRRI formerly had a Behavioral Sciences Department that was disbanded in the 1990s. The current (2013) director completed a residency in psychiatry, and two principal investigators have undergraduate or master's level training in psychology (AFRRI, 2013c).

Despite the fact that all three branches of Military Services have some common radiation-detection and measurement needs,[5] the branches develop their own instrument performance specifications and acquire the instruments independently, with the result that several different equipment designs are used to detect essentially the same radiation(s). This leads to interservice operability problems that compound military-responder training and equipment field maintenance.

The problems associated with this lack of harmony were highlighted in the U.S. military's relief efforts in response to the 2011 Fukushima Daiichi nuclear plant accident—a low-dose-level radiation exposure incident for the general public. An after-action report on radiation monitoring noted that the dosimetry guidance given to personnel participating in the effort was confusing, delayed, and conflicting and that the different dosimetry systems used by the services were "[n]ot conducive to a joint operation in a radiological environment" (Sharp, 2012). The U.S. Army Peacekeeping and Stability Operations Institute concluded that

> [o]verall, all these dosimetry systems/dosimeters were adequate for their designed purpose—occupational dosimetry in a controlled environment—but they all had drawbacks when it came to using them in this particular situation

and recommended that DoD designate a single radiation dosimeter and common measurement units and reporting standards for use in joint operations in a radiological environment (PKSOI, 2013).[6]

A DoD program exists for addressing such needs. The FY 2013–18 strategic goals for the Joint Program Executive Office for Chemical and Biological Defense include combining "common requirements and [seeking] common solution sets in order to achieve interoperability across the larger [radiological/nuclear] community," championing "a truly joint acquisition effort to provide warfighters the most effective [radiological/nuclear defense] systems," and providing "enhanced personal and tactical dosimeters to detect the location, extent, and level of radiation hazards, and . . . individual and collective protection measures for our forces" (JPEO-CBD, 2012). The Office's Joint Project Manager for Radiological & Nuclear Defense released a Request for Information (RFI) in 2013 seeking input on a dosimeter that would enable the services "to effectively conduct joint operations with interoperable equipment" while meeting requirements for detection of the entire spectrum of radiological/nuclear

[5] There are also service-specific needs for radiation detection instruments.

[6] The Peacekeeping and Stability Operations Institute also offered other observations about the need for standardization across the services when responding to radiologic incidents that may be of interest to AFRRI.

hazards and threats and for operation in hostile environments (JPM-RND, 2013). The committee believes that AFRRI has the capability to contribute to such work.

An opportunity exists for AFRRI to aid in the integration and coordination of DoD purchases, commissioning, acquisition, testing, maintenance, and use of radioactivity detection instruments and to help ensure that such instruments will be useful in low-level exposure circumstances.

AFRRI is well suited to support this DoD initiative because it has the qualified staff (triservice health physicists), facilities (calibration-exposure rooms), and dosimetry experience needed to help develop instrument-performance specifications and perform acceptance testing. Investments may need to be made in staff training and for exposure chambers needed for environmental testing of candidate devices should DoD choose to take advantage of this opportunity.

Radiation Professionals Workforce Education

AFRRI has the necessary infrastructure to help support graduate education in several radiation specialties that are greatly needed within the DoD and civilian sectors. These specialties include radiobiology, health physics, medical physics, radioepidemiology, and radioecology.

As of January 2014, the USUHS website stated its intent to establish a Radiation Biology track within the school's Molecular and Cell Biology program. It also listed an acting chair of the department (an AFRRI investigator who holds an appointment in the university) and nine faculty members, some of whom are AFRRI investigators and all of whom have adjunct appointments. In response to a question from the committee, AFRRI indicated that although USUHS planned to begin granting degrees in radiation biology in 2013, funding shortages have delayed implementation of the program (AFRRI, 2013c).

Other degree programs that USUHS does not offer currently—for example, in health and medical physics[7]—could be built around the advantages of its proximity to AFRRI. The Institute's laboratory and reactor facilities are an asset not shared by many universities with graduate health-physics programs and are well suited to train military health physicists, who face some unique challenges not encountered by their civilian counterparts; these include potential exposure to nuclear weapons, reactors used to power ships and submarines, military equipment that uses radioactive sources, and nuclear battlefield operations. Each year the service branches send junior officers to attend civilian universities to earn graduate degrees

[7] An accredited health physics M.S. and Ph.D. program formerly existed at USUHS but is not currently active, so it is unclear whether this is considered a priority by DoD.

in health and medical physics because equivalent graduate-level programs do not exist at DoD Service academies or institutes.

AFRRI and USUHS have the necessary expertise, experience, infrastructure, and facilities (both classroom and laboratory) to help train and grant graduate degrees in several of the radiation specialties that are in demand within the DoD and civilian marketplace.

An opportunity exists for AFRRI to contribute to the education of radiation professionals through better integration and coordination with USUHS so that the university's degree programs support AFRRI needs and, in turn, AFRRI's research facilities support degree candidates' research. Specifically, implementation of the nascent USUHS program in Radiation Biology would help accelerate training in that field, address concerns over coming shortages of professionals, and facilitate the recruitment of new researchers for the Institute, including those with low-dose radiation expertise.

The success of a USUHS program in radiation biology or in other radiation-health-related fields will depend critically on the active support of the Military Services, which determine which programs their personnel may be sent to for advanced training, and on the availability of research and graduate education funding.

Support of Radiation Epidemiology and Risk Research

The National Cancer Institute (NCI) defines the goals of radiation-epidemiology research as identifying, understanding, and quantifying the risk of cancer in populations exposed to medical, occupational, or environmental radiation and advancing the understanding of radiation-induced carcinogenesis (somatic) and deterministic (acute) effects (NCI, 2014).

To date, AFRRI has had relatively little involvement in epidemiological research and risk projections, and its staff does not have expertise in these areas. It does, however, conduct work on the development of biodosimetry tools and on retrospective dose reconstruction for exposure assessment that could be used in studies.

As discussed in Chapter 2, there is currently much interest in using radiobiology to augment epidemiological studies (Preston et al., 2013), and AFRRI has the staff experience and qualifications to do so. Should AFRRI wish to become involved in such work, it would be well positioned to support studies that are consonant with its current expertise by, for example, providing information on biological changes induced by radiation exposure and on military populations that have experienced depleted uranium (DU) exposure or combined injuries, which would feed into research on health outcomes in targeted subpopulations. Further, the United Nations Scientific Committee on the Effects of Atomic Radiation asserts that the study of radiation-induced carcinogenesis will benefit from the identification of biomarkers and bio-indicators of radiation-associated disease that could be used in population studies (UNSCEAR, 2012).

An opportunity exists for AFRRI to contribute to research on low-level effects through molecular and cellular studies of radiation-induced alterations that could be employed in epidemiologic and risk assessment studies, and by extending its work in areas like DU exposure and combined injuries to generate information for use in such investigations.

To implement this, AFRRI will need to collaborate with outside subject-matter experts to define the hypotheses to be tested. The Institute's position within USUHS is one source of such expertise, through collaborations with the faculty and students in the graduate programs in Biomedical Sciences and Public Health. Another source is NCI's Radiation Epidemiology Branch, which also has interests in the health effects of low-dose exposures and in dosimetry.

AFRRI's location in DoD may also allow it to facilitate certain other epidemiological studies. Approximately 2% of the military workforce (~70,000 individuals) are currently monitored for occupational ionizing-radiation exposure, and repositories hold exposure records for some 2 million individuals accumulated since 1945 (Blake and Komp, 2014). Exposure to radiation via medical diagnostic procedures is also recorded. The potential exists to link these data with health information gathered by the military health system and the Department of Veterans Affairs and use so-called big-data techniques to conduct analyses of radiation exposure.

Opportunities for Expanded and Additional Outside Collaborations

Collaborations with Other Governmental Entities

AFRRI's responsibilities overlap with those of three other federal bodies with which it would seem to have natural affinities because of their common interests in the consequences of nuclear and radiological material releases.

The Defense Threat Reduction Agency (DTRA), DoD's official combat-support agency for countering weapons of mass destruction, includes consequence management and nuclear and radiological response among its major responsibilities. DTRA conducts training in this area and works with other federal agencies and international counterparts to improve global preparedness and response capabilities. AFRRI already cooperates with DTRA, notably through a standing Inter-Service Support Agreement, to provide expertise (via its MRAT) to the Agency's Consequence Management Advisory Teams (DTRA, 2013). AFRRI has also received DTRA funding for research on high-dose questions regarding radioprotective agents and dose assessment, but these contracts ended in 2013 (AFRRI, 2013c).

The Defense Advanced Research Projects Agency (DARPA) facilitates cutting-edge research to support military and other national objectives. In the past 10 years, it has undertaken three initiatives aimed at ionizing radiation and health: a 2005 effort to foster technologies to minimize the warfighter's vulnerability to high-dose radiation exposures via vaccines and novel antidotes (DARPA, 2005), a 2008 initiative to develop low-cost and minimally-invasive biodosimeters (DARPA, 2013), and a 2013 RFI seeking

> ideas, methodologies, and approaches . . . to support a potential new DARPA program to enable novel therapies for mitigating the effects of ionizing radiation exposure in military or civilian personnel in the aftermath of a large-scale release of nuclear material that may result from either a natural disaster or deliberate attack. (DARPA, 2013)

In July 2013, AFRRI did not list any current support from DARPA (AFRRI, 2013c) but it has received funding in the past (Kang et al., 2011).

The DHS came into being in 2002 when 22 different federal departments and agencies were unified and integrated into a single cabinet-level agency. Its responsibilities include health aspects of contingency planning for chemical, biological, radiological, and nuclear hazards. However, the committee could not identify any collaboration between AFRRI and DHS other than common participation in advisory committees or working groups (AFRRI, 2013c).

Thus, AFRRI currently conducts rather little work with these other governmental bodies that have similar interests, and the efforts that have taken place have focused on high-dose questions. The committee believes, however, that there are areas into which the Institute could expand its reach and pursue its interest in low-level radiation research by using its existing strengths. Two are identified below.

Given the interests that DTRA, DARPA, and DHS share and the two DoD agencies' past work with AFRRI on high-dose questions, new work on low-dose questions represents an unexploited area for expansion. **An opportunity exists for AFRRI to advance its mission by actively pursuing low-level exposure research funding and collaborations with DTRA, DARPA, and DHS.** This will entail outreach to these organizations to determine their low-dose interests and needs and how AFRRI assets can best be used to meet them.

Further, **an opportunity exists for AFRRI to better integrate itself into the national nuclear and radiological response mechanism by expanding coverage of low-level exposure topics in their existing training courses and materials and adapting these to civilian emergency responders and international audiences.** For example, the Institute's Medical Effects of Ionizing

Radiation (MEIR) course has been in existence for more than 40 years and reaches 800–1,000 people per year (Parde, 2012). Its course materials are directly applicable to first responders and first receivers, but—with a few exceptions—the course has not been exported to other domestic organizations or to international governmental organizations.[8]

Other short-course topics that AFRRI—perhaps in collaboration with USUHS—would be well suited to conduct should appeal to agencies like DTRA and DHS. Possible course areas include

- Radiological screening and decontamination of large civilian populations after an improvised nuclear device (IND) or radiological dispersal device (RDD) event,
- Triage and management of combined injuries after an IND or RDD event, and
- Dosimetric assessment of radiologically contaminated wounds.

Opportunities to Facilitate Research by Outside Investigators

DoD has specific interests and needs in the low-level realm that may not be priorities for civilian entities, and the committee believes that there are ways for AFRRI to advance these interests without acquiring new staff. As noted in Chapter 4, the Institute's radiation facilities are underused: the TRIGA reactor is free 79% of its operating days, the ^{60}Co source is free 50.5%, and the low-level source is virtually unused. Thus, **an opportunity exists for AFRRI to expand its participation in low-level radiation health effects research by making its facilities more open to use by outside investigators interested in conducting research consistent with its mission.** Allowing outside investigators to take advantage of the dead time to conduct DoD-relevant studies would not only increase the productivity of these assets but would also create new collaborations and additional sources of support for AFRRI staff. The committee understands that such work is currently possible but that associated logistical and administrative challenges represent a significant barrier to conducting such collaborative research. Facilitating the use of AFRRI facilities by outside investigators, including animals managed by its vivarium, would thus require a change in culture within the organization. Nevertheless, the committee believes that ways could and should be identified to achieve greater openness while preserving the security of the site and meeting other Institute and DoD requirements.

[8] The MEIR website indicates that "defense contractors and non-DoD civilians" may register for the course but the FY 2014 schedule only lists DoD locations for classes (AFRRI, 2014).

AFRRI ORGANIZATION AND ADMINISTRATION

The committee believes that there are steps that AFRRI can take that will promote the successful conduct of current and future low-dose ionizing radiation work by strengthening its overall research enterprise. It thus offers suggestions regarding the Institute's scientific leadership and external program evaluation for AFRRI's and DoD's consideration.

Scientific Leadership

AFRRI's management structure includes a Scientific Director in a senior leadership position. A 1968 staff memorandum (AFRRI, 1968, p. 4) defining the Institute's organization lists a "Deputy Director, Scientific" reporting to the Director and exercising the following duties:

1. Responsible for organization, effective operation, administration and supervision of assigned personnel, subject to the authority, direction and control of the Director, for the Behavioral Science, Radiation Biology, Experimental Pathology, and Physical Sciences departments and the Veterinary Support and Publications Offices.
2. Performs the scientific and technical planning of the AFRRI research program and advises the Director, AFRRI, on technical and scientific matters within the broad field of radiobiology and related scientific disciplines necessary to support radiobiological research programs.
3. Provides assistance and guidance to technical and scientific panels and committees organized within the AFRRI and serves in a scientific liaison capacity with Headquarters, Defense Atomic Support Agency (DASA), Atomic Energy Commission, National Institutes of Health, Colleges and Universities, other DOD and other Federal laboratories and the civilian scientific community.

DoD Directive 5105.33, November 25, 1987, specifies that the Scientific Director post is to be filled by a civilian.[9] A later (September 30, 1992) organizational chart identifies a Scientific Director as one of the three members—along with the Director and Chief of Staff—of the senior leadership of AFRRI within an "Office of the Director" (AFRRI, 1993, p. 124).

[9] DoD Directive 5105.33, November 25, 1987, §E1b stated that "[t]he Scientific Director shall be a civilian with professional qualifications acceptable to the Board of Governors and the Director, AFRRI." This Directive—which addressed a number of AFRRI organizational issues—was canceled and superseded by DoD Instruction 5105.33, March 29, 2006. The Instruction did not include any details regarding the "Scientific Director" position.

This position, however, has not been filled since 2012. There is currently a Scientific Advisor who reports to the Director (Chapter 4; Figure 4-1), but whose duties do not include supervision of senior research staff.

It is common for DoD organizations that have a research-based mission to have a civilian Scientific Director or Chief Scientist in a senior leadership role. A 2005 National Research Council report lists eight such organizations, including three—DARPA, DTRA, and the Naval Research Lab—that conduct or facilitate ionizing radiation research (NRC, 2005).

The committee believes that having a Scientific Director in a leadership position helps to achieve several goals that are important for AFRRI if it wishes to pursue a more extensive program of research on the human health risks from exposures to low-level ionizing radiation and, more generally, to promote its standing and visibility in the radiobiology research community—goals that would not necessarily be fulfilled by someone serving in an advisory role:

- As the scientific point person within the Institute, the Scientific Director has the standing to plan and carry out short- and long-term institutional research goals; make sure that the staff needed to achieve these goals are in place; monitor and review the performance of senior research staff; and provide continuity across the tenures of AFRRI's Directors.
- As a senior member of the USUHS faculty,[10] the Scientific Director can be influential in building and maintaining a strong graduate education program that attracts top-flight faculty, developing potential AFRRI researchers, and helping to address concerns over possible future shortfalls in the number of radiation professionals.
- As a member of the senior management of a DoD scientific organization, the Scientific Director is in a position to complement the work of the AFRRI Director, serving as a principal science and technology representative on radiobiological research and radiological-emergency response to the federal and civilian scientific communities as well as to the public at large on behalf of DoD, and interacting with DoD leadership on scientific issues regarding AFRRI's mission to fulfill military needs.
- As a recognized leader in the radiobiology research community, the Scientific Director can market AFRRI's unique capabilities and facilities to other federal and civilian agencies, helping to expand its research funding sources and serving as the local advocate for AFRRI research clients and stakeholders.

[10] Past AFRRI Scientific Directors have concurrently held faculty appointments at USUHS.

If this person is well-respected in the low-dose scientific community, it will greatly facilitate AFRRI's efforts to establish an influential research program, attract new investigators with expertise in low-dose radiation questions, and obtain funding for such work.

The committee believes that AFRRI will strengthen its position as an ionizing-radiation health-effects research organization when the position of Scientific Director is filled. The key roles of this person in new research projects that "advance the understanding of human health risks from exposures to low-level ionizing radiation, with a special emphasis on Department of Defense military operations and personnel" will be to

- **Develop institutional low-dose research capacity by facilitating collaborations with outside subject-matter experts and, where needed, recruiting new personnel; and**
- **Identify and implement low-dose initiatives that are responsive to DoD needs with milestones and deliverables (for accountability, promotion, and direction) while building on AFRRI's existing strengths.**

External Program Evaluation

At present, almost all of AFRRI's research initiatives are evaluated on a project-specific basis with the sponsor's review mechanisms and program managers performing the evaluative function. AFRRI's intramural research program is reviewed by a panel of outside experts along with senior AFRRI scientific personnel, but this work accounts for only about 20% of the Institute's portfolio. In response to a question posed by the committee, AFRRI indicated in October 2013 that the Institute did not have a long-term research plan but that the Scientific Advisor was gathering information to formulate such a plan in consultation with AFRRI leaders and other DoD agencies (AFRRI, 2013d).

The committee believes that **AFRRI's existing and new research on human health risks from exposures to low-level ionizing radiation, along with the rest of its scientific enterprise, would benefit from a strong, continuing external program evaluation that examined the totality of the Institute's work.** The purposes of such oversight would be to provide input on the quality and usefulness of current work and to assist in defining and setting reasonable and achievable research directions and priorities on the basis of the collective radiobiology knowledge base and AFRRI's mission(s). It would further promote a closer working relationship with outside organizations for the purpose of research collaboration and facilitation of greater use of AFRRI's physical plant assets.

An Institute-wide continuing program-evaluation function could be provided by members at the Scientific Director or Chief Scientist level from one or more DoD organizations (DTRA, DARPA), other federal agencies (DHS, DOE, Environmental Protection Agency [EPA], National Aeronautics and Space Administration [NASA], Nuclear Regulatory Commission), and researchers from universities and private-sector organizations who are actively engaged in radiobiological research.

There are also other means of facilitating external evaluation of AFRRI's prospective low-dose and other research activities. Possible means include supporting more of the Institute's research through a funding mechanism that requires such oversight. As noted in Chapter 4, operations and maintenance (O&M) funding represented more than 70% of all research support (including staff salaries) and more than half of the total budget in FY 2013. AFRRI's O&M funding, however, does not have a direct connection to a funding source that expects to see an outcome at the end of the project: It often comes with no specific milestones or expectations other than the conduct of some type of radiobiologically related research. Most military-related research conducted in other DoD laboratories is supported by research development testing and evaluation (RDT&E; also known as Program 6.X) funding sources, which require a client or sponsor for the research. The sponsor specifies the research topic, defines the desired outcome measures, and tracks the research organization's progress toward the desired outcome. In this funding scenario, projects are driven by the customer, so there is no disconnect between what the client (typically the military, in the case of AFRRI) needs and what the researcher provides. Prior to 2005, AFRRI research was exclusively supported by RDT&E funds, but this has changed in recent years (AFRRI, 2013c).

The Institute may have already recognized that this is an issue. In response to a question from the committee, they indicated that

> [i]n FY2013, as a result of a Board of Governors' decision, AFRRI's RDT&E resources were realigned to 1) distinguish protocol-driven research from direct and indirect research support functions, and 2) facilitate oversight of research goals and objectives by the Defense Health Program. (AFRRI, 2013b, p. 1)

Thus, AFRRI may benefit if more of its radiobiology research were supported by RDT&E funds, leaving O&M research funding to support exploratory studies and educational program costs. This alternative, if pursued by DoD, would increase the accountability of investigators and better tie their work to demonstrable research outcomes.

Should DoD decide to pursue such a change, a greater reliance on RDT&E funding would require members of the AFRRI staff and leadership to actively pursue research-marketing outreach to potential DoD and other clients. The committee believes that this role would be best led by a Scientific Director with nationally recognized credentials and good familiarity with DoD, federal agencies such as DHS, HHS, DOE, EPA, NASA, and the U.S. Nuclear Regulatory Commission, and executive branch organizations like the Office of Science and Technology Policy.

External evaluation—and outreach to the greater research community—would also be facilitated by two other steps. One of these is the resumption of the practice of producing an annual report. A yearly accounting of the Institute's research initiatives, the accomplishments of its staff and effect of their work, and the ways in which its funds were spent would permit DoD sponsors and outside parties to gain a better understanding of AFRRI's contributions in radiation research and health.

The other step would be to make the seminars conducted by AFRRI staff more accessible to researchers outside of the Institute. Currently, these presentations are conducted in AFRRI's conference room, which is located in a secure complex that requires prior clearance to enter. They are not recorded, nor is the information presented at them disseminated. All of these restrictions greatly limit the ability of radiation health experts at other institutions in the DC area and beyond to become better informed about AFRRI's work and to offer feedback on it. Although security considerations will limit access to some of the Institute's work, making the unrestricted seminars more open—by, for example, webcasting them and allowing viewers to actively participate in the proceedings—would permit the kind of informal peer review that improves research products.

REFERENCES

AFRRI (Armed Forces Radiobiology Research Institute). 1968. *Organization. AFRRI staff memorandum 10-1*. https://www.osti.gov/opennet/servlets/purl/16004533-h9b0K3/16004533.pdf (accessed February 10, 2014).

AFRRI. 1993. *Annual report on AFRRI research for fiscal year 1992*. Bethesda, MD.

AFRRI. 2010. *Medical management of radiological casualties*. Bethesda, MD.

AFRRI. 2013a. *About AFRRI*. http://www.usuhs.edu/afrri/organiza/about_afrri.htm (accessed October 8, 2013).

AFRRI. 2013b. *Emergency response resources—MRAT—Medical Radiobiology Advisory Team*. http://www.usuhs.edu/afrri/outreach/emergency_response.html#MRAT (accessed December 18, 2013).

AFRRI. 2013c. Responses to questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, July 12, 2013.

AFRRI. 2013d. Responses to supplementary questions provided by the National Academy of Sciences concerning the statement of work for the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation. Bethesda, MD, October 31, 2013.

AFRRI. 2014. *MEIR course schedule*. http://www.usuhs.edu/afrri/outreach/meir/meirschd.htm (accessed April 14, 2014).

AMEDD (Army Medical Department). 2013. *Medical consequences of radiological and nuclear warfare*. http://www.cs.amedd.army.mil/borden/Portlet.aspx?id=b3cb37ed-08e7-4617-a40c-f148ee3d2303 (accessed December 30, 2013).

Blake, P. K., and G. R. Komp. 2014. Radiation exposure of U.S. military individuals. *Health Physics* 106(2):272-278.

Bromet, E. 2011. Lessons learned from radiation disasters. *World Psychiatry* 10:83-84.

CSTS (Center for the Study of Traumatic Stress). 2005. *Psychological and behavioral issues healthcare providers need to know when treating patients following a radiation event*. http://www.cstsonline.org/wp-content/resources/CSTS_issues_radiation%20event.pdf (accessed February 6, 2014).

CSTS. 2014. *About us*. http://www.cstsonline.org/about-us (accessed February 6, 2014).

DARPA (Defense Advanced Research Projects Agency). 2005. *Bridging the gap. Powered by ideas*. http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA433949 (accessed December 30, 2013).

DARPA. 2013. *Reducing ionizing radiation—Risk request for information*. RFI DARPA-SN-13-24. https://www.fbo.gov/index?s=opportunity&mode=form&id=dfd9728586164c8cdd7a1d6391d692dd&tab=core&_cview=0 (accessed December 30, 2013).

DTRA (Defense Threat Reduction Agency). 2013. *Fiscal year 2014 budget estimates*. http://comptroller.defense.gov/Portals/45/Documents/defbudget/fy2014/budget_justification/pdf/01_Operation_and_Maintenance/O_M_VOL_1_PART_1/DTRA_OP-5.pdf (accessed February 6, 2014).

FEMA (Federal Emergency Management Agency). 2008. *Nuclear/Radiological Incident Annex*. U.S. Department of Homeland Security.

HHS (U.S. Department of Health and Human Services). 2014. *Download mobile REMM*. http://www.remm.nlm.gov/downloadmremm.htm (accessed May 14, 2014).

JPEO-CBD (Joint Program Executive Office for Chemical and Biological Defense). 2012. *Joint Program Executive Office for Chemical and Biological Defense Strategic Plan FY 13–18*. http://www.jpeocbd.osd.mil/packs/DocHandler.ashx?DocID=11924 (accessed April 17, 2014).

JPM-RND (Joint Project Manager, Radiological and Nuclear Defense). 2013. *Request for information (RFI) for radiological detection system (RDS)*. https://www.fbo.gov/index?s=opportunity&mode=form&id=75ae84d703f052f00abe024abd117b31&tab=core&tabmode=list&= (accessed April 17, 2014).

Kang, A., D. Gibson, and M. Dempsey. 2011. *AFRRI: A unique national resource*. Presented at the 2011 Society of American Federal Medical Laboratory Scientists (SAFMLS), New Orleans, LA, March 31, 2011.

NCI (National Cancer Institute). 2014. *Radiation epidemiology branch*. http://dceg.cancer.gov/about/organization/programs-ebp/reb (accessed February 3, 2014).

NRC (National Research Council). 2005. *Assessment of Department of Defense basic research*. Washington, DC: The National Academies Press.

Parde, N. 2012. AFRRI: A global authority on ionizing radiation. *The Journal (official newspaper for Walter Reed Army Medical Center)*. September 6, 2012. http://www.dcmilitary.com/ARTICLE/20120906/NEWS11/709069953/AFRRI-A (accessed February 6, 2014).

Pastel, R. H., G. R. Kahles, and J. Chiang. 1999. *The medical and psychological consequences of radiation dispersal devices. AFRRI white paper on medical and psychological effects of RDDs*. Armed Forces Radiobiology Research Institute, September 1999.

PKSOI (U.S. Army Peacekeeping and Stability Operations Institute). 2013. Strategic lesson number 15: Radiological hazards during disaster relief operations. *Strategic Lessons in Peacekeeping and Stability Operations, Volume 2* (Summer 2013), pp. 16-19.

Preston, R. J., J. D. Boice, Jr., A. B. Brill, R. Chakraborty, R. Conolly, F. O. Hoffman, R. W. Hornung, D. C. Kocher, C. E. Land, R. E. Shore, and G. E. Woloschak. 2013. Uncertainties in estimating health risks associated with exposure to ionising radiation. *Journal of Radiological Protection* 33(3):573-588.

Sharp, T. 2012. *Operation Tomodachi individual radiation monitoring*. https://www.pksoi.org/document_repository/Lessons/JFLCC_OperationTomodachi_Individual_Radiation_Monitoring_(25-Jan-12)-LMS-941.pptx (accessed February 6, 2014).

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2012. *Biological mechanisms of radiation actions at low doses*. New York: United Nations.

U.S. Air Force. 2011. *Air Force Radiation Assessment Team*. http://www.wpafb.af.mil/library/factsheets/factsheet.asp?id=18146 (accessed February 6, 2014).

U.S. Army. 2012. *Army Regulation 40-13. Medical Services. Radiological Advisory Medical Teams*. http://www.apd.army.mil/pdffiles/r40_13.pdf (accessed February 6, 2014).

Vyner, H. M. 1988. The psychological dimensions of health care for patients exposed to radiation and the other invisible environmental contaminants. *Social Science and Medicine* 27:1097-1103.

Appendix A

Public Meeting Agendas

Friday, May 3, 2013
Keck Center of the National Academies, Washington, DC

1:00 pm
Welcome | Notes on the conduct of the open session | Introduction of participants
Hedvig Hricak, M.D., Ph.D.
Committee Chair

1:05 pm
Charge to the committee and background on AFRRI—presentation[s] and Q&A
Charles L. Rice, M.D.
President, Uniformed Services University of the Health Sciences (USUHS)
and
L. Andrew Huff, M.D., M.P.H., Col, USAF, MC, SFS
Acting Director, Armed Forces Radiobiology Research Institute, USUHS

2:30 pm
Public session adjourns

Wednesday, July 17, 2013
Armed Forces Radiobiology Research Institute, Bethesda, MD

2:00 pm
Announcement on the conduct of the open session | Introduction of participants
David A. Butler, Ph.D.
Study Director

2:10 pm
Tour of the facilities conducted by AFRRI staff

4:00 pm
Tour concludes; public session adjourns

Thursday, July 18, 2013
Keck Center of the National Academies, Washington, DC

12:45 pm
Doors open to the public

1:00 pm
Welcome | Notes on the conduct of the open session | Introduction of participants
Hedvig Hricak, M.D., Ph.D.
Committee Chair

1:10 pm
European initiatives regarding research directions in human biological effects of low-level ionizing radiation
Sisko Salomaa, Ph.D.
Research Director, Radiation and Nuclear Safety Authority (STUK), Finland

2:05 pm
Countermeasures for low-level ionizing radiation exposure
David Grdina, Ph.D., M.B.A.
Professor, Department of Radiation and Cellular Oncology and the Cancer Research Center, University of Chicago

4:10 pm
Radiation exposure of U.S. military individuals
LTC Andrew L. Scott
U.S. Army Public Health Command, Aberdeen Proving Ground
(presented on behalf of *Paul K. Blake, Ph.D.*, Defense Threat Reduction Agency)

5:05 pm
General discussion
Hedvig Hricak, M.D., Ph.D., moderator

5:30 pm
Public session adjourns

Friday, July 19, 2013
Keck Center of the National Academies, Washington, DC

9:00 am
Welcome | Notes on the conduct of the open session | Introduction of participants
Hedvig Hricak, M.D., Ph.D.
Committee Chair

9:10 am
The National Council on Radiation Protection and Measurements: Where Are the Radiation Professionals? (WARP) initiative
CDR Chad Mitchell, MSC USN
Radiation Health Officer Specialty Leader, Bureau of Medicine and Surgery
accompanied by David A. Schauer, Sc.D. (WARP leader), and John L. Crapo, M.S., C.H.P. (WARP facilitator)

10:05 am
General discussion
Hedvig Hricak, M.D., Ph.D., moderator

10:35 am
Public session adjourns

Friday, November 1, 2013
J. Eric Jonsson Center of the National Academies, Woods Hole, MA

9:00 am
Welcome | Notes on the conduct of the open session | Introduction of participants
Hedvig Hricak, M.D., Ph.D.
Committee Chair

9:10 am
Gaps in ionizing radiation combined injuries research and emerging areas of study
Jacqueline Williams, Ph.D.
Professor, Department of Radiation Oncology, University of Rochester

10:00 am
Public session adjourns

Appendix B

U.S. Radiation Research Programs

This appendix provides a brief summary of low-level ionizing-radiation health-effects research programs under way in the United States and under the direction of international organizations. These include several branches of the federal government with varied interests in security, defense, preparedness and response, health, and science; private organizations; academic institutions; and nonprofit organizations.

The listing is not meant to be comprehensive but rather an overview of major efforts related to the committee's task. Websites for further information are listed in Table B-1 at the end of this appendix.

Myriad research, educational, and administrative agencies and organizations have an interest in low-level and low linear energy transfer (LET) radiation. Some are focused on national defense and the risks of nuclear weapons and the resulting public health response, others are dedicated to workers and environments affected by nuclear power generation, and still others are concerned with cosmic radiation. The following section describes U.S. federal programs and initiatives that investigate and plan responses to the effects of low-level radiation exposure. Some of these programs have broad missions, of which radiation and low-level issues are just one piece.

DEPARTMENT OF DEFENSE

The Department of Defense (DoD) sponsors research on the health effects of ionizing radiation in line with its mission to protect and preserve military-force readiness and the health of military personnel. In addition to the other work performed by the Armed Forces Radiobiology Research

Institute (AFRRI), it is involved in the efforts described in the following sections.

Defense Advanced Research Projects Agency

Established in 1958, the Defense Advanced Research Projects Agency (DARPA) is dedicated to the advancement of science and technology for the U.S. military and bridging the gap between scientific discovery and military applications (DARPA, 2009). By sponsoring and conducting investigations with multidisciplinary approaches and finite duration, DARPA seeks to advance current knowledge and create innovative solutions through applied research. The research it conducts and sponsors is intended to be cutting edge, high risk, and high payoff. Its scientific areas include biology, medicine, computer science, chemistry, physics, engineering, mathematics, material sciences, and social sciences.

The Agency has a continuing interest in the health effects of radiation and, as noted in Chapter 5, has undertaken three initiatives in the last 10 years related to ionizing radiation health effects. The first of these was a 2005 effort to develop technologies to minimize the warfighter's vulnerability to radiation exposures via vaccines and novel antidotes (DARPA, 2005). The second effort was the Radiation Bio-Dosimetry (RaBiD) program, which ran from 2008 through 2011 and whose purpose was to develop "non- or minimally invasive, portable and low-cost radiation biodosimeters, as well as novel radiation mitigation technologies that can be administered 12 or more hours after exposure and provide better than 90-percent survivability to humans" (DARPA, 2012). A 2007 solicitation indicates that AFRRI was responsible for testing biodosimeter prototypes developed under the effort (DARPA, 2007). Then, in February 2013, the Agency issued a request for information for "ideas, methodologies, and approaches . . . [that] may be used to support a potential new DARPA program to enable novel therapies for mitigating the effects of ionizing-radiation exposure in military or civilian personnel in the aftermath of a large-scale release of nuclear material that may result from either a natural disaster or a deliberate attack" (DARPA, 2013).

Defense Threat Reduction Agency

The Defense Threat Reduction Agency (DTRA) was created to ensure the safety of the United States and its allies by working to reduce, eliminate, and counter threats posed by weapons of mass destruction (WMDs), including chemical, biological, radiological, nuclear, and high-yield explosive (CBRNE) WMDs. DTRA's efforts include basic and applied research in addition to operational support and think tanks (DTRA, undated).

DTRA also acts as DoD's executive agent for the Nuclear Test Personnel Review (NTPR) Program. This program provides participation and radiation-dose information to veterans who participated in U.S. atmospheric nuclear tests, served with the American occupation forces of Hiroshima and Nagasaki, Japan, or were prisoners of war in these areas at the conclusion of World War II (DTRA, 2009).

More recently, DTRA has conducted assessments and issued reports on radiation exposure in U.S. Coast Guard veterans (DTRA, 2011) and many pertaining to radiation exposure among U.S. forces associated with the Operation Tomodachi response to the Fukushima Daiichi nuclear reactor accident in 2011 (NCRP, 2012).

DEPARTMENT OF ENERGY

The Department of Energy (DOE) participates in several initiatives supporting research and education concerning low-level and low-LET radiation through diverse programs and laboratories. Those that are most pertinent to the committee's task are discussed below.

Low Dose Radiation Research Program

DOE's Office of Science's Office of Biological and Environmental Research established the Low Dose Radiation Research Program in 1999 (DOE, 2012). The primary aims of the program were to support experimental research and to generate data that could be adapted by regulatory agencies such as the Environmental Protection Agency (EPA) and the U.S. Nuclear Regulatory Commission to set future radiation standards and develop national policy for the protection of the public and the workforce during environmental cleanup, nuclear waste storage, and use of nuclear power. Today, radiation-protection standards and operating policies, such as "as low as reasonably achievable," are derived from the conservative assumption of the linear no-threshold (LNT) model. Because most human exposures to radiation are of low dose or low dose rate, the program concentrates on studies of low-LET exposures delivered at low total doses and low dose rates.

The program was intended to take advantage of the advances in molecular biology and instrumentation that were not available during the previous 50 years of radiation-biology research (Brooks, 2012). As such, it has paid particular attention to experimental research on bystander effects, adaptive responses, genomic instability, and mathematical and risk modeling that incorporates knowledge from low-level experimental research into mechanism-based models of tissue function.

As of 2013, about 40 percent of the program's funds supported research projects at academic institutions, and the remaining 60 percent supported research at three DOE-affiliated national laboratories: Lawrence Berkeley National Laboratory (LBNL), Oak Ridge National Laboratory (ORNL), and Pacific Northwest National Laboratory (PNNL) (DOE, 2013a). However, the (March 2014) DOE fiscal year (FY) 2015 congressional budget request puts forward a substantial decrease in funding levels, from ~$6.2M for FY 2013 to a proposed $2.4M for all radiobiology research in FY 2015 (DOE, 2014).

DOE is also a cosponsor of the Million U.S. Worker Study, which is examining health outcomes in a number of cohorts occupationally exposed to low-level radiation, including "uranium and plutonium workers at DOE sites, nuclear weapons test participants, nuclear power plant workers, and industrial radiographers, radiologists, and other medical practitioners" (ORAU, 2013).

Low Energy Nuclear Physics Research

The Low-Energy subprogram studies the nuclear structure, astrophysics, and fundamental symmetry and neutrinos at two Nuclear Physics Program user facilities. The personnel at the Argonne Tandem LINAC Accelerator System (ATLAS) at Argonne National Laboratory study nuclear properties under extreme conditions and reactions of interest using high-quality beams of all the stable elements up to uranium and selected beams of short-lived nuclei. The Holifield Radioactive Ion Beam Facility at ORNL staff studies exotic nuclei that do not normally exist in nature with beams of short-lived radioactive nuclei. The future Facility for Rare Isotope Beams will have next-generation equipment to advance the understanding of rare nuclear isotopes and the evolution of the cosmos. The subprogram supports four university Centers of Excellence, three with unique low energy–accelerator facilities and one with infrastructural capabilities for developing advanced instrumentation. The subprogram also partners with the National Reconnaissance Office and the U.S. Air Force to support limited operations of the 88-inch cyclotron at LBNL for a small in-house research program and to meet national security needs. Additionally, nuclear physicists at the Spallation Neutron Source at ORNL study the properties of neutrinos and their masses (DOE, 2013b).

Workforce Development for Teachers and Scientists (WDTS)

DOE supports efforts to provide opportunities for science, technology, engineering, and mathematics (STEM) workforce development, known as Workforce Development for Teachers and Scientists (DOE, 2013c). This effort offers access to leading scientists; world-class scientific user facilities and instrumentation; and large-scale, multidisciplinary research programs unavailable in universities or industry. The laboratories also provide opportunities for science, engineering, and technology training and education for more than 250,000 K–12 students, 22,000 K–12 educators, 4,000 undergraduate interns, 3,000 graduate students, and 1,600 postdoctoral researchers annually. Although these efforts are not focused on ionizing-radiation health research, they do include opportunities for those interested in the field.

National Nuclear Security Administration

The National Nuclear Security Administration was established by Congress in 2000 to support the management and security of the nation's nuclear weapons, nuclear nonproliferation, and naval reactor programs. It is a separate agency in DOE that focuses on defense, nuclear nonproliferation, naval nuclear energy, nuclear security, and counterterrorism and counterproliferation (DOE, undated).

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

To continue to its mission of space exploration, the National Aeronautics and Space Administration (NASA) must understand and prevent risk to crew members sent into space, including the risks posed by solar and cosmic radiation. Without the protection of Earth's atmosphere, space crew may be at increased risk of acute radiation sickness, cancer, and other chronic diseases associated with radiation exposure. High-energy solar radiation from the sun, sun flare, and cosmic radiation originating in deep space pose unique challenges.

Space Radiation Health Program

NASA's Space Radiation Health Program, Office of Biological and Physical Research, and DOE jointly fund research to help understand the radiation risks associated with travel in space (NASA, 2014). Because the radiation environment in space differs from that on Earth, NASA is especially interested in the health risks associated with human exposure to low levels of the high-energy ionizing radiation (alpha particles, protons, and high-energy heavy ions) that comprise the solar wind and cosmic rays and in the resulting health risks to crew members. NASA's research focuses on characterizing the risks resulting from space radiation for cancers, acute or late central nervous system effects, degenerative tissue effects, and acute risks. Its research also seeks to develop radiation countermeasures to effectively prevent and treat potential cosmic radiation damage.

Research is carried out at several research facilities, including the Johnson Space Center, the Langley Research Center, the Ames Research

Center, and the Brookhaven National Laboratory (BNL). Efforts are focused on learning more about the radiation environments that crew members will encounter during long-duration missions to the moon and Mars.

National Space Biomedical Research Institute

The National Space Biomedical Research Institute (NSBRI), founded in 1997 by NASA, is a nonprofit science institute dedicated to ensuring safe and productive spaceflight. It comprises 12 institutions that study the health risks related to long-duration spaceflight and develop methods to reduce those risks. The NSBRI supports the investigation of several areas of medical science, one of which is radiation effects. The Radiation Effects Team supports research on health risks and mitigation strategies specifically related to cosmic radiation, with an emphasis on acute effects and on dosimetery to monitor and provide advance warning of risks inside the spacecraft and out. The NSBRI Center of Acute Radiation Research (CARR), headquartered at the University of Pennsylvania through 2013, is a central component of the Radiation Effects Team that has multiple projects assessing the effects of exposure from solar events, defining associated health risks, and developing safe and effective methods to prevent and treat acute radiation–syndrome symptoms. The CARR includes researchers from the University of Illinois, the Massachusetts Institute of Technology, and AFRRI (NSBRI, undated a, undated b).

NSBRI also includes an educational component with a robust teaching, training, and public outreach program (NSRBI, 2012).

Human Research Program

NASA's Human Research Program collects data on radiation exposure from returning crew members. Findings are used to inform guidelines for exposure and safety procedures. The Human Research Program comprises scientists and engineers dedicated to research on radiation exposure during space flights and development of solutions and technologies to reduce health risks. Most research focuses on physiology, environment, and technology study areas. Future research will explore the unique challenges and risks posed by extended space missions (NASA, 2009).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Several areas within the Department of Health and Human Services (HHS) are involved in radiation-research and public health–preparedness activities. Its institutes, centers, and agencies pursue a range of endeavors, including research, training, emergency planning and response, outreach, policy support, and regulations related to radiation exposure.

National Cancer Institute

The National Cancer Institute (NCI) Division of Cancer Epidemiology and Genetics, Radiation Epidemiology Branch (REB) conducts a number of national and international studies on populations exposed to radiation for medical, environmental, and occupational reasons. Among its international collaborations are efforts with the Research Center for Radiation Medicine in Ukraine to conduct studies of the Chernobyl-affected population, the Southern Urals Biophysics Institute for research on workers at the Mayak nuclear facility, and the University of Newcastle to evaluate the relationship between radiation exposure from computed tomography (CT) scans conducted during childhood and adolescence. REB additionally supports radiation dosimetry work to support the epidemiologic studies.

Epidemiologic study activities at REB include

- Efforts to identify and quantify the risk of cancer associated with ionizing and nonionizing radiation, especially at low-dose levels;
- Characterization of the risk of radiation-induced cancer in terms of tissues at risk, dose response, biological effectiveness, dose rate, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors;
- Methods for radiation-dose reconstruction for environmental, occupational, and medical exposures;
- Applications of dosimetry in studies of countermeasures against radiological and nuclear threats;
- Examination of biologically based models of radiation-induced carcinogenesis;
- Case-control and cohort studies of cancer risk in populations exposed to occupational, environmental, or medical diagnostic or therapeutic radiation;
- Population-based studies to examine biomarkers of radiation exposure; and
- Individual variation in radiogenic risk associated with a wide range of demographic, racial or ethnic, geographic, physiologic, hormonal and immune function, and genetic factors.

REB also advises and collaborates with other agencies and individuals involved in radiation research and regulatory activities (NCI, undated a).

The Radiation Research Program (RRP) of the Division of Cancer

Treatment and Diagnosis at NCI supports basic, translational, and clinical research in radiotherapy and radiation biology. The RRP is divided into three branches: Radiotherapy Development, Clinical Radiation Oncology, and Molecular Radiation Therapeutics. In its effort to stimulate radiotherapy and radiation-biology research, the RRP serves as an advisor to researchers, an evaluator of conducted research and future research priorities, and a liaison to the Medical Countermeasures against Radiological and Nuclear Threats Initiative of NCI, the National Institute of Allergy and Infectious Diseases (NIAID), and the Office of the Assistant Secretary for Preparedness and Response. RRP staff also review grant proposals and contracts submitted to DoD and the Biomedical Advanced Research and Development Authority (BARDA) and consult on radiation issues with program staff in NIAID (NCI, undated b).

The Developmental Therapeutic Program (DTP), which was created by Congress in 1955, serves as the focal point for research on chemotherapeutic agents within NCI. DTP facilitates the work of academic and private sector investigators and has helped to bring a number of widely used agents to market.

National Institute of Allergy and Infectious Diseases

NIAID's research focus on immunology, which includes research on adult bone marrow stem cells, transplantation, and immune reconstitution, is relevant to ionizing-radiation research because ionizing radiation can cause immunosuppression after damage to the hematopoietic cells. Its Radiation and Nuclear Countermeasures Program is a focal point for such work.

The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats is the result of an HHS request to NIAID to develop and guide a research program for the development of effective medical countermeasures against possible terrorist-attack scenarios involving radioactive materials (NIAID, 2005). This initiative was the first federal mission to develop countermeasures for civilian populations. Funding is provided through a special congressional appropriation to HHS's Office of Public Health Emergency Preparedness.

In 2005, NIAID established eight cooperative Centers for Medical Countermeasures against Radiation (CMCR). The CMCR is intended to develop radioprotectors, mitigators, and therapeutic agents to facilitate effective medical response against radiological and nuclear threats. Additionally, the CMCR supports the development of biomarkers and biodosimetry techniques and devices for rapid triage and treatment of individuals exposed to radiation after a radiological event. Another aim of the CMCR network is to provide new or expanded educational resources to improve expertise in radiation biology.

To meet its goals, NIAID works in partnership with the Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), and BARDA to develop, license, procure, and deploy effective medical countermeasures against radiation threats (NIAID, 2013).

Office of the Assistant Secretary for Preparedness and Response

The Biomedical Advanced Research and Development Authority is responsible for the development and procurement of countermeasures to prepare the nation to respond to and recover from public health emergencies. BARDA is involved in all stages of product development from development and manufacture, safety and regulatory affairs, to supply issues, including stockpiling, storage, and transportation. Within BARDA, the Division of Chemical, Biological, Radiological and Nuclear (CBRN) Medical Countermeasures (MCMs) is responsible for CBRN MCMs required by the HHS to mitigate the adverse health effects arising from public health emergencies, including anthrax, smallpox, various chemical threats, and radiation (BARDA, 2013).

FOOD AND DRUG ADMINISTRATION

Radiological Health Program

The mission of FDA's Radiological Health Program is to protect the public from hazardous or unnecessary radiation exposure from radiation-emitting electronic products. The program is carried out as a part of FDA's Center for Devices and Radiological Health (CDRH). The CDRH aims to support the mission of the radiological health program by supporting

- Awareness of new and existing radiation-emitting products, their manner of use, and their manufacturers;
- Study of the biological effects of radiation-emitting products and their potential risks to health;
- Assessment of radiation-emission levels from products in various applications;
- Direction and guidance to the general public and users of radiation-emitting products to minimize unnecessary radiation exposure; and
- Product manufacturer compliance with all applicable requirements, pursuing regulatory and enforcement actions to address public health problems.

CDRH is able to regulate radiation-emitting electronic products used for both medical and nonmedical applications under authority provided by the Electronic Product Radiation Control provisions and the Medical Device Amendments of 1976 of the Federal Food, Drug, and Cosmetic Act. It also regulates facilities performing mammography under the authority of the Mammography Quality Standards Act. Further, CDRH supports FDA's radiation emergency–response activities to protect the public and communicates with stakeholders from governmental, professional, academic, manufacturing, and consumer-advocacy groups (FDA, 2012).

Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) is responsible for ensuring the safety, effectiveness, and availability of prescription and over-the-counter drugs, including countermeasures for use in a public health emergency. Currently, CDER lists three drugs as safe and effective for the prevention and treatment of radiation effects: potassium iodide, calcium- and zinc-DTPA, and Prussian blue (FDA, 2011).

Office of Counterterrorism and Emerging Threats

The Office of Counterterrorism and Emerging Threats (OCET) coordinates the various offices and departments within the FDA to oversee the development, availability, and safety of emergency medical countermeasures and the prevention of contamination, corruption, or disruption of medical supplies in a terrorist attack. OCET also administers the Medical Countermeasures initiative (MCMi) as an effort to coordinate intraagency and interagency communication and emergency-use authorizations, giving the FDA Commissioner the authority to allow the use of unapproved medical products in an emergency (FDA, 2013).

CENTERS FOR DISEASE CONTROL AND PREVENTION

Agency for Toxic Substances and Disease Registry

The Agency for Toxic Substances and Disease Registry (ATSDR) is dedicated to protecting public health by using the best science available to provide accurate health information and prevent harm from exposure to toxic substances, including radioactive substances and ionizing radiation. ATSDR publishes Toxicological Profiles (ToxProfiles) that summarize the available information about a substance and describe its health effects. ATSDR also assesses industrial sites to determine health risks to workers, cleanup personnel, and surrounding communities. Many of the hazardous waste sites are DOE or military facilities related to nuclear-weapons development, research, and testing (ATSDR, 2013; CDC, 2010).

National Institute of Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) is the lead federal agency for research on worker injury and illness. As part of its responsibility, it conducted studies of several populations with exposure to low levels of ionizing radiation under the aegis of its Occupational Energy Research Program. This program, which is no longer active, developed exposure characterization models for and examined health outcomes in several cohorts, including those associated with the Portsmouth Naval Shipyard, Fernald Feed Materials Production Center, Hanford Site, Los Alamos National Laboratory, Mallinckrodt Uranium Works, Mound Site, Oak Ridge Facilities (K-25, X-10, Y-12), Paducah Gaseous Diffusion Plant, Portsmouth Gaseous Diffusion Plant, Rocky Flats, and Savannah River National Laboratory (NIOSH, 2011).

The Radiation Dose Reconstruction Program area of the NIOSH Division of Compensation Analysis and Support operates in support of the Energy Employees Occupational Illness Compensation Program Act, which is administered by the Department of Labor (DOL, undated). NIOSH performs radiation-dose reconstruction for DOE workers and contractors exposed to radiation in support of the nuclear weapons program for the purposes of compensation. Oversight of the dose reconstruction methods and guidelines and the classification of special exposure cohorts (groups of radiation-exposed workers) is provided by the presidentially appointed Advisory Board on Radiation and Worker Health (NIOSH, 2014).

Because few studies have been conducted to characterize the cosmic-radiation exposure and associated health effects in U.S. flight personnel working in commercial aircraft, NIOSH established the Flight Crew Research Program in collaboration with the Federal Aviation Administration (FAA), NCI, HHS Office of Women's Health, and DoD Women's Health Research Program. Studies include a variety of outcomes, including menstrual function, pregnancy outcomes, infertility, cancer, stress, respiratory symptoms, and mortality (CDC, 2012).

FEDERAL AVIATION ADMINISTRATION

Radiobiology Research Team

The Radiobiology Research Team of the FAA performs research on the effects of ionizing and nonionizing radiation on living systems, identifies radiation hazards in the aviation environment, and studies methods of protection from such hazards. As part of the FAA's aerospace medical research program, investigators focus on bioaeronautical aspects of safety and security, including forensic toxicology, functional genomics, biochemistry, radiobiology, environmental physiology, and bioinformatics, at the Civil Aerospace Medical Institute (CAMI).

The CARI-6 computer program, developed at CAMI, calculates the effective dose of cosmic radiation received by an individual (based on an anthropomorphic phantom) on an aircraft flying the shortest route (i.e., a geodesic) between any two airports in the world. The program takes into account changes in altitude and geographic location during the course of a flight, as derived from the flight profile entered by the user (FAA, 2013).

ENVIRONMENTAL PROTECTION AGENCY

Because radiation is ubiquitous in the environment at low levels and is a frequent contaminant resulting from industrial activities, EPA has many duties pertaining to it.

Radiation Protection Programs

Within EPA several offices are tasked with radiation protection activities. The Office of Air and Radiation is primarily responsible for the Radiation Protection Program, but other functions are carried out in other areas. Those areas include waste management; emergency response; air and water; source reduction and management; naturally occurring radiation; cleanup and multi-agency programs; risk assessment and federal guidance; and environmental monitoring and data. Through these programs, EPA has responsibilities to assess and monitor human health risks resulting from environmental radiation exposures; to set standards and regulations for radioactive emissions in air, water, and soil; to provide guidance for cleanup of contaminated sites; to communicate with the public about radiation risks such as radon; and to coordinate with other federal agencies for emergency response and homeland security (EPA, 2012).

DEPARTMENT OF VETERANS AFFAIRS

The interest of the Department of Veterans Affairs (VA) in radiation health effects is primarily focused on providing health care and benefits and disability compensation to veterans. Veterans who were exposed to radiation during their military career may be eligible for disability and health care benefits through the VA for specific cancers and chronic diseases. The VA offers Ionizing Radiation Registry health exams to all eligible veterans who were potentially exposed to ionizing radiation during their military service, including atmospheric nuclear tests, occupation of Hiroshima or Nagasaki, status as a prisoner of war in Japan during World War II, nasopharyngeal radium-irradiation treatments, service at a DOE gaseous-diffusion plant, or proximity to an underground nuclear test site. It also produces educational materials for veterans, their families, and physicians on these topics (VA, 2013).

Public Health Epidemiology Program

The VA's Epidemiology Program conducts the Cancer Mortality among Military Participants at U.S. Nuclear Weapons Tests study. The study aims to identify cancer risks in Cold War–era veterans who participated in atmospheric nuclear weapons tests (1946–1958) (VA, 2012).

DEPARTMENT OF STATE

The Department of State's concern for radiation-related exposures and associated health effects stems from its mission to protect and advance the freedom of the American people and its international community. This includes protection from and response to nuclear threats, specifically the proliferation of WMDs and related materials, technologies, and expertise that challenge U.S. national security. The Department of State is home to two radiation-related offices that fulfill this role. It does not conduct or foster health effects–related research, except in the policy arena.

Bureau of International Security and Nonproliferation

The Bureau of International Security and Nonproliferation (ISN) manages a broad range of U.S. nonproliferation policies, programs, agreements, and initiatives to prevent the spread of WMDs (nuclear, biological, chemical, or radiological) and delivery systems. The ISN bureau combats the threat posed by the proliferation of WMDs, and terrorist efforts to obtain them, through bilateral and multilateral diplomacy. This is one of the highest priorities of the Department of State.

Bureau of Counterterrorism

The Bureau of Counterterrorism includes several programs and initiatives to prevent and respond to terrorism (including WMDs) both domestically and internationally; these efforts include radiologic events at both levels. The Counterterrorism Preparedness Program within the Bureau of

Counterterrorism focuses on strengthening the nation's capacity to prevent, protect from, respond to, and recover from attacks involving WMDs.

U.S. NUCLEAR REGULATORY COMMISSION

The U.S. Nuclear Regulatory Commission (U.S. NRC) was created by the 1974 Energy Reorganization Act to address several broad public health and safety issues in the nuclear power industry. The commission is responsible for nuclear-reactor oversight, including regulations and licensing. The use of nuclear materials for power generation imposes the risk of radiation exposure on workers and the general public, and regulatory requirements are thus developed to protect public health.

U.S. NRC's research efforts are led by the Office of Nuclear Regulatory Research, which interfaces with all areas of the program and other government agencies (such as DOE), universities, and international partners to coordinate activities. The office recommends and conducts research pertaining to nuclear reactors, materials, and radioactive waste to improve knowledge in areas of uncertainty to inform regulatory decisions (U.S. NRC, 2013a, 2014). One such activity is an analysis of cancer risks in populations residing near nuclear power reactors that is currently being conducted by the National Research Council (U.S. NRC, 2013b).

U.S. NRC's low-level radiation interests include the management and disposal of low-level waste and the risk assessment and mitigation of releases from nuclear power facilities (U.S. NRC, 2013c).

SELECTED PRIVATE AND ACADEMIC LOW-LEVEL–RADIATION RESEARCH INITIATIVES

Lovelace Respiratory Research Institute

Research at the Lovelace Respiratory Research Institute includes elucidating the biological bases for radiation-adaptive responses in the lung and for suppressing lung cancer and using the knowledge gained to produce an improved systems biology–based risk model for lung cancer induction by low-dose, low-LET radiation. Lovelace aims to encourage development of new low-level radiation risk–benefit assessment methods for use in medicine and health, such as low-dose diagnostic radiation for cancer therapy and low-dose, low-LET radiation to prevent lung cancer in high-risk groups (heavy smokers, for example) (LRRI, 2010, 2014).

Center for High-Throughput Minimally Invasive Radiation Biodosimetry

The Center for High-Throughput Minimally Invasive Radiation Biodosimetry is a consortium of research institutions composed of Georgetown University, Lovelace Respiratory Research Institute, New York University School of Medicine, Translational Genomics Research Institute, and University of Bern, led by Columbia University (Columbia University, 2012). The center, funded by NIAID, applies modern radiation-biological techniques to detect biological changes as a measure of radiation dose. In addition to conducting and funding research and pilot projects, the center supports several training courses and workshops on biodosimetry.

U.S. Transuranium and Uranium Registry

The U.S. Transuranium and Uranium Registry (USTUR) research program is focused on the study of biokinetics, dosimetry, and biological effects of measurable and documented exposures to uranium, plutonium, americium, and thorium in humans. Data are gathered from generous partial and whole-body donations from exposed government workers who may have participated in the development and testing of nuclear weapons during the Cold War, been employed at uranium milling and mining operations, or worked at one of many DOE sites such as Hanford or Fernald. The registry includes medical, dosimetry, personal, occupational, and cause-of-death data from 335 donations, with a total of 875 individuals in the registry as of March 31, 2012. USTUR was begun in 1968 and is currently operated by the University of Washington and funded by the DOE Office of Health, Safety, and Security (USTUR, 2007).

SELECTED NONPROFIT ORGANIZATIONS

National Council on Radiation Protection and Measurements

The National Council on Radiation Protection and Measurements (NCRP) is a nonprofit organization chartered by the U.S. Congress to facilitate the dissemination of information on radiation protection and measurements significant to the public interest (NCRP, 2014). The council seeks to facilitate and encourage collaboration between other organizations involved in the scientific and related aspects of radiation protection and measurement. This bridge creates a platform for conversation between national and international programs involved in similar subjects to discuss and focus on recommendations. NCRP publications serve as guides to research in the field of radiation. As noted in Chapter 3, the organization has an interest in ensuring a robust radiation health–research workforce and has been undertaking efforts to determine whether the future supply of investigators will meet the demand (Pryor, 2013).

Electric Power Research Institute

The Electric Power Research Institute is an independent nonprofit organization dedicated to research, development, and demonstration related to power generation, delivery, and public use. Its research spans all aspects of power and is focused on both long- and short-term solutions. It includes a low-dose radiation research program that seeks to gain new knowledge about the biological effects and risks of low doses of radiation associated with the normal operation of nuclear power plants to ensure that workers and the public are adequately protected (Dauer et al., 2010; EPRI, 2009, 2011, 2014).

Radiation Countermeasures Center of Research Excellence

The Radiation Countermeasures Center of Research Excellence, or RadCCORE, is dedicated to supporting basic, translational, and applied research to further develop medical countermeasures against nuclear attacks. This multidisciplinary-research center seeks to develop and move countermeasure candidates through the regulatory process and to add them to the national stockpile. Specific program areas are dedicated to biodosimetry, drug development, therapies to treat acute radiation syndrome, and methods to modulate immune response to radiation exposure. RadCCORE also seeks to expand education resources and improve expertise in radiobiology by offering workshops and seminars and by funding graduate fellowships. The members of RadCCORE come from five universities (Duke University; University of Arkansas for Medical Sciences; University of Maryland, Baltimore; University of North Carolina; and Wake Forest University) as well as from national laboratories and private enterprises (RadCCORE, 2012).

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 2013. *About ATSDR*. http://www.atsdr.cdc.gov/about/index.html (accessed January 2, 2014).

BARDA (Biomedical Advanced Research and Development Authority). 2013. *BARDA unveils path forward in the BARDA Strategic Plan 2011-2016*. http://www.phe.gov/about/barda/Pages/2011barda-stratplan.aspx (accessed January 2, 2014).

Brooks, A. L. 2012. *A history of the United States Department of Energy (DOE) Low Dose Radiation Research Program 1998-2008* (Review Draft). http://lowdose.energy.gov/pdf/albRoughDraft/doeHistoryComplete09262012.pdf (accessed January 2, 2014).

CDC (Centers for Disease Control and Prevention). 2010. *Dose reconstruction and the Cold War*. http://www.cdc.gov/nceh/radiation/public_health_research.htm (accessed January 2, 2014).

CDC. 2012. *The Flight Crew Research Program*. http://www.cdc.gov/niosh/topics/flightcrew (accessed January 2, 2014).

Columbia University. 2012. *Center for High-Throughput Minimally-Invasive Radiation Biodosimetry*. http://cmcr.columbia.edu (accessed January 2, 2014).

DARPA (Defense Advanced Research Projects Agency). 2005. *Bridging the gap. Powered by ideas*. http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA433949 (accessed December 30, 2013).

DARPA. 2007. *Proposer information pamphlet for BAA 07-29 for the Defense Advanced Research Projects Agency (DARPA) radiation biodosimetry (RaBiD)*. https://www.fbo.gov/utils/view?id=96890b83dc24a7efa62f1c2b58d148ec (accessed April 14, 2014).

DARPA. 2009. *Bridging the gap. Powered by ideas*. Presented at the European Command and African Command Science and Technology Conference held in Stuttgart, Germany, on 8-12 Jun 2009. http://www.dtic.mil/dtic/tr/fulltext/u2/a510795.pdf (accessed January 2, 2014).

DARPA. 2012. *DARPA news: Researchers successfully treat previously lethal doses of radiation*. January 12, 2012. http://www.darpa.mil/NewsEvents/Releases/2012/01/04.aspx (accessed April 14, 2014).

DARPA. 2013. *Reducing ionizing radiation risk. Request for information*. RFI DARPA-SN-13-24. https://www.fbo.gov/index?s=opportunity&mode=form&id=dfd9728586164c8cdd7a1d6391d692dd&tab=core&_cview=0 (accessed December 30, 2013).

Dauer, L. T., A. L. Brooks, D. G. Hoel, W. F. Morgan, D. Stram, and P. Tran. 2010. Review and evaluation of updated research on the health effects associated with low-dose ionising radiation. *Radiation Protection Dosimetry* 140(2):103-136.

DOE (U.S. Department of Energy). 2012. *Low dose radiation research program*. http://lowdose.energy.gov (accessed January 2, 2014).

DOE. 2013a. *Radiobiology: Low dose radiation research. Biological systems science division (BSSD)*. http://science.energy.gov/ber/research/bssd/low-dose-radiation (accessed January 2, 2014).

DOE. 2013b. *Nuclear physics: Research*. Office of Science. http://science.energy.gov/np/research (accessed January 2, 2014).

DOE. 2013c. *Workforce Development for Teachers and Scientists (WDTS)*. Office of Science. http://science.energy.gov/wdts (accessed January 2, 2014).

DOE. 2014. *Department of Energy FY 2015 Congressional budget request. Volume 4. Science. Advanced research projects agency—Energy*. March 2014. Washington, DC: DOE, Office of Chief Financial Officer. http://www.energy.gov/sites/prod/files/2014/03/f12/Volume_4.pdf (accessed April 3, 2014).

DOE. Undated. *About us. National Nuclear Security Administration*. http://nnsa.energy.gov/aboutus (accessed January 2, 2014).

DOL (U.S. Department of Labor). Undated. *About EEOICP*. http://www.dol.gov/owcp/energy/index.htm (accessed January 2, 2014).

DTRA (Defense Threat Reduction Agency). 2009. *Radiation exposure in the U.S. atmospheric nuclear weapons testing—Fact sheet*. October 2009. http://www.dtra.mil/documents/ntpr/factsheets/Radiation_Exposure.pdf (accessed January 2, 2014).

DTRA. 2011. *Personnel radiation exposure associated with X-rays emanating from U.S. Coast Guard LORAN high voltage vacuum tube transmitter units. Technical report*. DTRA-TR-10-26. July 2011. http://www.dtra.mil/documents/pdfs/DTRA-TR-10-26%20-%20USCG%20LORAN%20Transmitter%20X-Ray%20Exposure.pdf (accessed January 2, 2014)

DTRA. Undated. *About DTRA/SCC-WMD*. www.dtra.mil/About.aspx (accessed January 2, 2014).

EPA (Environmental Protection Agency). 2012. *Radiation protection: Basic information*. www.epa.gov/radiation/basic/index.html (accessed January 2, 2014).

EPRI (Electrical Power Research Institute). 2009. *Program on technology innovation: Evaluation of updated research on the health effects and risks associated with low-dose ionizing radiation*. Final Report, 1019227. Palo Alto, CA: EPRI, Inc.

EPRI. 2011. *Strategic program: Low-dose radiation*. 1023479. Palo Alto, CA: EPRI, Inc.

EPRI. 2014. *Health and safety*. http://www.epri.com/Our-Work/Pages/Health-and-Safety.aspx (accessed January 2, 2014).

FAA (Federal Aviation Administration). 2013. *Radiobiology research team*. www.faa.gov/data_research/research/med_humanfacs/aeromedical/radiobiology (accessed January 2, 2014).

FDA (Food and Drug Administration). 2011. *Drugs: Emergency preparedness*. http://www.fda.gov/Drugs/EmergencyPreparedness/default.htm (accessed January 2, 2014).

FDA. 2012. *FDA radiological health program*. http://www.fda.gov/Radiation-EmittingProducts/FDARadiologicalHealthProgram/default.htm (accessed January 2, 2014).

FDA. 2013. *Office of Counterterrorism and Emerging Threats*. http://www.fda.gov/EmergencyPreparedness/Counterterrorism/default.htm (accessed January 2, 2014).

LRRI (Lovelace Respiratory Research Institute). 2010. Researching the highs and lows of radiation. *Breathe* 3(1):10-12. www.lrri.org/Data/Sites/1/breathe/Breathe_Magazine_Fall_10.pdf (accessed January 2, 2014).

LRRI. 2014. *Home page*. http://www.lrri.org (accessed January 2, 2014).

NASA (National Aeronautics and Space Administration). 2009. *NASA—Areas of study: Radiation. Human research program*. http://www.nasa.gov/exploration/humanresearch/areas_study/environment/enviro_radiation.html (accessed January 2, 2014).

NASA. 2014. *Space radiation research. NASA space radiation program element*. http://spaceradiation.usra.edu/research (accessed January 2, 2014).

NCI (National Cancer Institute). Undated a. *Radiation epidemiology branch: Understanding the link between radiation exposure and cancer*. http://dceg.cancer.gov/reb/about (accessed January 2, 2014).

NCI. Undated b. *Radiation research program*. http://rrp.cancer.gov (accessed January 2, 2014).

NCRP (National Council on Radiation Protection and Measurements). 2012. *SC 6-8: Operation TOMODACHI radiation dose assessment peer review*. http://www.ncrponline.org/Current_Prog/SC_6-8.html (accessed January 2, 2014).

NCRP. 2014. *Our mission*. http://www.ncrponline.org/AboutNCRP/Our_Mission.html (accessed January 23, 2014).

NIAID (National Institute of Allergy and Infectious Disease). 2005. *Radiation nuclear countermeasures introduction*. http://www.niaid.nih.gov/topics/radnuc/program/Pages/introduction.aspx (accessed January 2, 2014).

NIAID. 2013. *Radiation nuclear countermeasures*. http://www.niaid.nih.gov/topics/radnuc/Pages/default.aspx (accessed January 2, 2014).

NIOSH (National Institute for Occupational Safety and Health). 2011. *Occupational energy research program*. http://www.cdc.gov/niosh/oerp/default.htm (accessed April 10, 2014).

NIOSH. 2014. *NIOSH program area: Radiation dose reconstruction*. http://www.cdc.gov/niosh/ocas/#drrev (accessed January 2, 2014).

NSBRI (National Space Biomedical Research Institute). 2012. *NSBRI education & outreach selected program highlights*. November 2012. http://www.nsbri.org/default/Education%20and%20Training/NSBRI_EO_Overview_nov12.pdf (accessed January 2, 2014).

NSBRI. Undated a. *Radiation effects*. www.nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects (accessed January 2, 2014).

NSBRI. Undated b. *Center for Acute Radiation Research*. http://www.nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects/Team-Executive-Summary (accessed January 2, 2014).

ORAU (Oak Ridge Associated Universities). 2013. *ORAU serves as co-investigator in study of radiation effects on one million U.S. workers*. http://www.orau.org/occupational-exposure-worker-health-studies/success-stories/million-worker-study.aspx (accessed December 6, 2013).

Pryor, K. 2013. *The WARP initiative: Where are the radiation professionals*? *Health Physics News* September.

RadCCORE (Radiation Countermeasures Center of Research Excellence). 2012. *About us*. http://www.radccore.org/about-us (accessed January 2, 2014).

U.S. NRC (Nuclear Regulatory Commission). 2013a. *Research activities*. http://www.nrc.gov/about-nrc/regulatory/research.html (accessed March 27, 2014).

U.S. NRC. 2013b. *Backgrounder on analysis of cancer risk populations near nuclear facilities–Phase 2 pilot study*. http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bg-analys-cancer-risk-study.html (accessed March 27, 2014).

U.S. NRC. 2013c. *History*. http://www.nrc.gov/about-nrc/history.html (accessed January 2, 2014).

U.S. NRC. 2014. *Nuclear regulatory research*. http://www.nrc.gov/about-nrc/organization/resfuncdesc.html#funcdesc (accessed March 27, 2014).

USTUR (U.S. Transuranium & Uranium Registries). 2007. *About USTUR*. http://www.ustur.wsu.edu/AboutUs/overview.html (accessed January 2, 2014).

VA (U.S. Department of Veterans Affairs). 2012. *Research on health effects of radiation exposure*. www.publichealth.va.gov/exposures/radiation/research.asp (accessed January 2, 2014).

VA. 2013. *Radiation*. www.publichealth.va.gov/exposures/radiation/index.asp (accessed January 2, 2014).

TABLE B-1 Websites of Research Programs That Address Low-Level Radiation Questions

Entity or Program	Primary Web Address[a]
U.S. FEDERAL GOVERNMENT	
Department of Defense	
Defense Advanced Research Projects Agency	darpa.mil
Defense Threat Reduction Agency	dtra.mil
Department of Energy	
Low Dose Radiation Research Program	science.energy.gov/ber/research/bssd/low-dose-radiation
Low Energy Nuclear Physics Research	science.energy.gov/np/research
Workforce Development for Teachers and Scientists	science.energy.gov/wdts
National Nuclear Security Administration	nnsa.energy.gov
National Aeronautics and Space Administration	
Space Radiation Program	spaceradiation.usra.edu/research
National Space Biomedical Research Institute	nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects
Center of Acute Radiation Research	nsbri.org/SCIENCE-and-TECHNOLOGY/Radiation-Effects/Team-Executive-Summary
Human Research Program	nasa.gov/exploration/humanresearch/areas_study/environment/enviro_radiation.html
Department of Health and Human Services	
National Cancer Institute	
Division of Cancer Epidemiology and Genetics, Radiation Epidemiology Branch	dceg.cancer.gov/reb/about
Radiation Research Program	rrp.cancer.gov
Developmental Therapeutic Program	dctd.cancer.gov/ProgramPages/dtp/default.htm
National Institutes of Health	
National Institute of Allergy and Infectious Diseases	niaid.nih.gov/Pages/default.aspx
Radiation and Nuclear Countermeasures Program	www.niaid.nih.gov/topics/radnuc/program/Pages/introduction.aspx niaid.nih.gov/topics/radnuc/Pages/default.aspx
Centers for Medical Countermeasures against Radiation	www.niaid.nih.gov/topics/radnuc/Documents/cmcr_project_descriptions.pdf
Office of the Assistant Secretary for Preparedness and Response	
Biomedical Advanced Research and Development Authority	phe.gov/about/barda/Pages/cbrn.aspx
Division of Chemical, Biological, Radiological and Nuclear Medical Countermeasures	www.phe.gov/about/barda/Pages/cbrn.aspx

TABLE B-1 Continued

Entity or Program	Primary Web Address[a]
Food and Drug Administration	
Center for Devices and Radiological Health	fda.gov/Radiation-EmittingProducts/FDARadiologicalHealthProgram/default.htm
Center for Drug Evaluation and Research	fda.gov/Drugs/EmergencyPreparedness/default.htm
Office of Counterterrorism and Emerging Threats	fda.gov/EmergencyPreparedness/Counterterrorism/default.htm
Centers for Disease Control and Prevention	
Agency for Toxic Substances and Disease Registry	atsdr.cdc.gov
National Institute of Occupational Safety and Health	
Occupational Energy Research Program	http://www.cdc.gov/niosh/oerp/default.htm
Radiation Dose Reconstruction Program	cdc.gov/niosh/ocas/ocasdose.html
Flight Crew Research Program	cdc.gov/niosh/topics/flightcrew
Federal Aviation Administration	
Radiobiology Research Team	faa.gov/data_research/research/med_humanfacs/aeromedical/radiobiology
Environmental Protection Agency	
Radiation Protection Program	epa.gov/radiation/basic/index.html
Department of Veterans Affairs	
Public Health Epidemiology Program	publichealth.va.gov/exposures/radiation/index.asp
Epidemiology Program	publichealth.va.gov/exposures/radiation/research.asp
Department of State	
Bureau of International Security and Nonproliferation	state.gov/t/isn/index.htm
Bureau of Counterterrorism	state.gov/j/ct
Nuclear Regulatory Commission	nrc.gov/about-nrc/history.html
SELECTED PRIVATE AND ACADEMIC INITIATIVES	
Lovelace Respiratory Research Institute	lrri.org
Center for High-Throughput Minimally Invasive Radiation Biodosimetry	cmcr.columbia.edu
U.S. Transuranium and Uranium Registry	ustur.wsu.edu
SELECTED NONPROFIT ORGANIZATIONS	
National Council on Radiation Protection and Measurements	ncrponline.org
Electric Power Research Institute	epri.com
Radiation Countermeasures Center of Research Excellence	radccore.org/home

[a] Addresses valid on January 24, 2014.

Appendix C

Biographic Sketches of Committee Members and Staff

COMMITTEE MEMBERS

Hedvig Hricak, M.D., Ph.D. (IOM) (*Chair*), is Chair of the Department of Radiology at Memorial Sloan Kettering Cancer Center, Professor in the Gerstner Sloan Kettering Graduate School of Biomedical Sciences, and Professor of Radiology at the Weill Medical College of Cornell University. She also holds a senior position within the Program of Molecular and Pharmacology Therapeutics at the Sloan Kettering Institute. Dr. Hricak's research aims to advance evidence-based imaging algorithms to assist in cancer management, focusing on the development and validation of biomarkers from cross-sectional (ultrasound, MRI, CT) and molecular imaging (DCE-MRI, MR spectroscopy, and PET/CT and PET/MRI with innovative tracers) for assessing gynecological and genitourinary cancers. She has served on the advisory and editorial boards of numerous peer-reviewed journals and has published more than 345 peer-reviewed original research articles, more than 200 review articles, editorials, and book chapters, and 18 books. In recognition of her career accomplishments, she received the Marie Curie Award of the American Association of Women Radiologists (2003); the gold medals of the International Society for Magnetic Resonance in Medicine (2003), the Association of University Radiologists, the European Society of Radiology (2012), and the Asian Oceanian Society of Radiology (2012); the Béclère medal of the International Society of Radiology (2007) and Médaille Antoine Béclère of the Journées Françaises de Radiologie (2007); the Morocco Medal of Merit (2008); the Katarina Zrinska Croatian presidential award (2009); and the Schinz Medal of the

Swiss Society of Radiology (2012). The many leadership posts she has held include President, California Academy of Medicine (1999–2000), and President, Radiological Society of North America (RSNA) Board of Directors (2009–2010). Dr. Hricak earned her M.D. degree from the University of Zagreb and her Ph.D. (Dr. Med. Sc.) from the Karolinska Institute. She was elected to membership in the Institute of Medicine (IOM) in 2002.

David J. Brenner, Ph.D., is Higgins Professor of Radiation Biophysics and Director of the Center for Radiological Research at the Columbia University Medical Center. He is also Professor of Environmental Health Sciences at the University's Mailman School of Public Health. His research interests include the development of mechanistic models for the effects of ionizing radiation on living systems, at both the chromosomal and animal levels, and the effects of low-dose occupational and environmental exposure to ionizing radiation. Dr. Brenner has published more than 250 papers in the peer-reviewed scientific literature and is the author of two books on radiation risk for the layperson. He was the recipient of the 1991 Radiation Research Society Annual Research Award and the 1992 National Council on Radiation Protection and Measurements Award for Radiation Protection in Medicine. In 2011, he received the Failla Award from the Radiation Research Society at the 14th International Congress of Radiation Research. Dr. Brenner earned an M.Sc. in radiation physics from St. Bartholomew's Hospital, University of London, and a Ph.D. in physics from the University of Surrey in 1980. He was awarded an honorary D.Sc. from Oxford University in 1996.

Lawrence T. Dauer, Ph.D., CHP, is a medical health physicist specializing in radiation protection in medicine. He holds appointments as Associate Attending Physicist in both the Department of Medical Physics and the Department of Radiology at Memorial Sloan Kettering Cancer Center, and he serves as the Radiation Safety Manager and Chair of its Emergency Management Committee. Dr. Dauer has spent more than 25 years in the field of radiation protection and health physics, including radiation-protection programs for the energy and industrial sectors and operations and research in medical health physics. He is a diplomate of the American Board of Health Physics, certified in comprehensive health physics, and a Licensed Medical Physicist in New York State. He is as a member of the Radiation Injury Treatment Network, has served as chair of the Radiation Safety Committee of the American Association of Physicists in Medicine, president and executive council member of the Medical Physics Section of the Health Physics Society, president of the Greater New York Chapter of the Health Physics Society, and board member of the Radiological and Medical Physics Society of New York. He is currently a council member of the National Council on Radiation Protection and Measurements and is a member of the International Commission on Radiological Protection Committee 3—radiation protection in medicine. Dr. Dauer earned a Ph.D. in adult education from Capella University and an M.S. in health physics from the Georgia Institute of Technology.

George X. Ding, Ph.D., is Professor, Director of Medical Physics, and Chief Physicist in the Department of Radiation Oncology at Vanderbilt University School of Medicine. He is an expert in radiation dosimetry and the application of Monte Carlo techniques to radiotherapy treatment planning, and he pioneered a series of studies on the use of Monte Carlo techniques to estimate radiation exposure for patients who undergo image-guidance procedures. His research interests include Monte Carlo simulation of ionizing-radiation beams produced from medical accelerators and X-ray tubes, small-field dosimetry, development of accurate model-based dose calculation algorithms for low energy–range X-rays, and Monte Carlo dose calculations in treatment planning. In addition to his clinical, educational, and research activities, Dr. Ding is involved in many professional activities, including chairing the American Association of Physicists in Medicine (AAPM) Task Group on modeling and accounting for the imaging-guidance radiation doses to patients and serving on the International Commission on Radiation Units and Measurements Report Committee on Small-Field Photon Dosimetry and Applications in Radiotherapy, the AAPM Therapy Physics Committee, the AAPM Calibration Laboratory Accreditation Executive Committee, and the AAPM Biological Effects Subcommittee addressing biological effects of radiation therapy. Dr. Ding earned a Ph.D. in medical physics from Carleton University and the National Research Council of Canada, Ottawa. He is a fellow of the Canadian College of Physicists in Medicine (FCCPM) and a fellow of the American Association of Physicists in Medicine (FAAPM).

Francesca Dominici, Ph.D., is Professor of Biostatistics and Associate Dean for Information Technology in the Harvard School of Public Health (HSPH) at Harvard University. Her research has focused on the development of statistical methods for the integration of large data to assess and monitor health risks, including the adjustment of measured and unmeasured confounders, Bayesian hierarchical models, causal-inference methods, and missing-data methods. Dr. Dominici is the recipient of the first Walter A. Rosenblith Young Investigator Award from the Health Effects Institute, Boston, Massachusetts; of the Myrto Lefkopoulou Distinguished Lectureship Award from the HSPH Department of Biostatistics in 2007; and of the Mortimer Spiegelman Award from the Statistics Section of the American Public Health Association in 2006. Her professional activities include membership on the Biostatistical Methods and Research Design Study Section of the National Institutes of Health's (NIH's) Center for Scientific Review and service as editor of the *American Journal of Epidemiology*'s statistical methodology area. She has served on a number of National Academies committees, including the Committee to Assess Potential Health Effects from Exposures to PAVE PAWS Low-Level Phased-Array Radiofrequency Energy and the Committee on the Utility of Proximity-Based Herbicide Exposure Assessment in Epidemiologic Studies of Vietnam Veterans. Dr. Dominici earned her Ph.D. in statistics from the University of Padua, Italy.

Helen A. Grogan, Ph.D., is President and founder of Cascade Scientific, Inc., a consulting firm that specializes in independent assessment of environmental effects and health risks from radionuclides and chemicals. She previously worked with the Paul Scherrer Institute (formerly the Swiss Federal Institute for Reactor Research) as a member of the Repository Performance Assessment Group, where she was responsible for the biosphere modeling aspects of the safety assessment of both high-level radioactive waste and low- or intermediate-level waste repositories. Dr. Grogan is an expert in radioecology, dose reconstruction, and assessment of radioactive and nonradioactive hazardous wastes. Her interests include the validation of computer models developed to predict the fate and transport of radionuclides in the environment. Dr. Grogan is an advisor to the National Council on Radiation Protection and Measurements Scientific Committee and has served on the National Research Council (NRC) Committee to Review the Worker and Public Health Activities Program Administered by the U.S. Department of Energy and the U.S. Department of Health and Human Services; the U.S. Environmental Protection Agency's Radiation Advisory Committee Science Advisory Board; and the Scientific Committee on Dose Reconstruction for the National Council on Radiation Protection and Measurements. Dr. Grogan earned her Ph.D. in radioecology from Imperial College of Science and Technology, University of London.

David G. Hoel, Ph.D. (IOM), is Distinguished University Professor in the Department of Medicine at the Medical University of South Carolina. He also is a principal scientist at Exponent, Inc. Dr. Hoel was at the NIH's National Institute of Environmental Health Sciences for more than 20 years and served as director of its Division of Environmental Risk Assessment. He has particular interest in estimating the health effects of radiation exposures and spent 3 years working at the Radiation Effects Research Foundation in Hiroshima, Japan, as one of its program directors. His activities also include service on U.S. Environmental Protection Agency, International Atomic Energy Agency, and World Health Organization advisory committees and on the editorial boards of a number of journals. Dr. Hoel has been on several National Academies committees that addressed radiation exposure and other risk-assessment topics and was a member of the NRC's Nuclear and Radiation Studies Board. He earned a Ph.D. in mathematical statistics from the University of North Carolina at Chapel Hill and completed postdoctoral training in preventive medicine at Stanford University. Dr. Hoel is a member of the IOM and a fellow of the American Association for the Advancement of Science.

Edward F. Maher, Sc.D., CHP, is Associate and Senior Health Physicist for the occupational and environmental health consulting firm Dade Moeller & Associates. He is also Adjunct Lecturer on Environmental Science in the Harvard School of Public Health's Department of Environmental Health. Dr. Maher is a certified health physicist with more than 30 years of experience conducting and managing radiological, safety, and environmental-protection programs for commercial clients and federal agencies, including the U.S. Departments of Defense and Energy. He was formerly an officer in the U.S. Air Force (USAF), retiring with the rank of colonel. While there, he directed the USAF Radiation Assessment Team responsible for providing immediate and global responses to nuclear-weapon accidents, and he served as division chief of the Radiation Services Division and chief of the Dosimetry and Radioanalytical Services Branches at the Armstrong Laboratory at Brooks Air Force Base. Dr. Maher is a past president of the Health Physics Society and was chairman of the American Board of Health Physics in 2000. He earned a Sc.D. in radiological protection and health from the Harvard School of Public Health.

William F. Morgan, Ph.D., D.Sc., is Director of Radiation Biology and Biophysics in the Biological Sciences Division at Pacific Northwest National Laboratory (PNNL). In this role, he provides scientific leadership in the area of effects of radiation exposure on human health. Dr. Morgan's areas of research include the long-term biological effects of low-dose-rate radiation exposure, radiation-induced genomic instability, and nontargeted effects of ionizing radiation. He is Principal Investigator for the U.S. Department of Energy's Low Dose Radiation Research Program Scientific Focus Area at PNNL. Dr. Morgan was previously professor and director of the Radiation Oncology Research Laboratory at the University of Maryland, Baltimore, and led radiation-research laboratories at the University of California, San Francisco, and Lawrence Berkeley National Laboratory. He has served on the United Nations Scientific Committee on the Effects of Atomic Radiation and the National Academy of Sciences Board on Radiation Effect Research, and he is currently on the Main Commission of the International Commission on Radiological Protection (ICRP) and chairman of ICRP Committee 1. Dr. Morgan is a member of the National Council for Radiation Protection, along with advisory committees for a number of the European Union's Low Dose Radiation Research Program, including Multidisciplinary European Low Dose Initiative (MELODI), EpiRadBio, and low dose research towards multidisciplinary integration (DoReMi). He is on the editorial board for *Environmental and Molecular Mutagenesis and Mutation Research*. Dr. Morgan earned a Ph.D. in cytogenetics and a D.Sc. from the University of Canterbury, Christchurch, New Zealand.

Georgine M. Pion, Ph.D., is Research Associate Professor in the Quantitative Methods Program within the Department of Psychology and Human Development at the Peabody College of Vanderbilt University. Dr. Pion's research has focused on career development and research policy, particularly as it pertains to determining the effectiveness of training programs of scientists in the biomedical, behavioral, and clinical sciences. She has served as chair of the Technical Advisory Committee for the National Science Foundation's Survey of Earned Doctorates and as a member of several NRC and IOM committees involved in research and clinical training, including the effort responsible for the 2012 report *Assuring a Future U.S.-Based Nuclear Chemistry Expertise*. Dr. Pion received a Merit Award from NIH in 1999 for her survey and evaluation work and is a National Associate of the National Academy of Sciences. She earned her Ph.D. in social-environmental psychology from Claremont Graduate University and completed National Research Service Award postdoctoral traineeship in Northwestern University's Evaluation and Research Methodology Program.

David Richardson, Ph.D., M.S.P.H., is Associate Professor of Epidemiology in the School of Public Health at the University of North Carolina at Chapel Hill. His research focuses on the health effects of occupational and environmental exposures, particularly with regard to ionizing radiation. He has conducted studies of cancer among nuclear workers at several U.S. Department of Energy facilities and has studied cancer among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. Dr. Richardson has served as a visiting scientist at the World Health Organization's International Agency for Research on Cancer, the French Institute for Radiological Protection and Nuclear Safety, and the Radiation Effects Research Foundation in Hiroshima, Japan. Since 2007, he has served as Director of the National Institute of Occupational Safety and Health–funded training program in occupational epidemiology at the University of North Carolina at Chapel Hill. He is associate editor of the journals *Occupational and Environmental Medicine*, *American Journal of Epidemiology*, and *Environmental Health Perspectives*, is a member of the President's Advisory Board on Radiation and Worker Health, and serves on the U.S. Environmental Protection Agency's Science Advisory Board. His international service includes membership on the scientific advisory committee of the Centre for Research in Environmental Epidemiology in Barcelona, Spain. Dr. Richardson earned a Ph.D. and M.S.P.H., both in epidemiology, from the University of North Carolina.

Ruth C. Wilkins, Ph.D., is Chief of the Radiobiology Division in the Consumer and Clinical Radiation Protection Bureau of Health Canada. She is also Adjunct Professor in the Department of Physics at Carleton University and a lecturer at the Michener Institute (Toronto), the Ottawa Hospital Cancer Center, and St. Justine Hospital (Montreal). Dr. Wilkins is currently leading a collaboration between Defence Research and Development Canada, Atomic Energy of Canada Limited, and the McMaster Institute of Applied Radiation Sciences to further develop a National Biological Dosimetry Response Plan for large-scale exposures to ionizing radiation, along with the development of new, higher-throughput methods for biological dosimetry, one of her current research interests. She has provided advice to the International Atomic Energy Agency, the Global Health Initiatives Action Group, and the World Health Organization to develop International Radiation Dosimetry Networks. Dr. Wilkins earned a Ph.D. in physics from Carleton University in Ottawa.

NATIONAL ACADEMY OF SCIENCES STAFF

David A. Butler, Ph.D., is Scholar and Director of the Medical Follow-up Agency in the IOM. He earned his B.S. and M.S. degrees in engineering from the University of Rochester and his Ph.D. in public-policy analysis from Carnegie Mellon University. Before joining the IOM, Dr. Butler served as an analyst for the U.S. Congress Office of Technology Assessment, was research associate in the Department of Environmental Health of the Harvard School of Public Health, and conducted research at Harvard's Kennedy School of Government. He has directed several IOM studies on military health, environmental health, and risk assessment, including ones that produced *Future Uses of the DoD Joint Pathology Center Biorepository*; *Provision of Mental Health Counseling Services Under TRICARE*; *PTSD Compensation and Military Service*; *Veterans and Agent Orange: Update 1998* and *Update 2000*; *Disposition of the Air Force Health Study*; and the report series *Characterizing the Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam*. Dr. Butler was also a coeditor of *Systems Engineering to Improve Traumatic Brain Injury Care in the Military Health System*.

Ourania Kosti, Ph.D., is Senior Program Officer in the NRC's Nuclear and Radiation Studies Board. She joined the staff in January 2011. Prior to her current appointment, Dr. Kosti was a postdoctoral fellow at the Lombardi Comprehensive Cancer Center at Georgetown University Hospital in Washington, DC, where she conducted research on biomarker development for early cancer detection using case-control epidemiological study designs. She focused primarily on prostate, breast, and liver cancers and on trying to identify those individuals who are at high risk for developing malignancies. She has contributed on hypothesis generation, study design, data analysis, and management of clinical databases and biospecimen repositories. Dr. Kosti also trained at the National Cancer Institute (NCI) in the Cancer and Developmental Biology Laboratory; during the same period, she volunteered in NCI's Division of Cancer Epidemiology and Genetics. Dr. Kosti earned a B.Sc. in biochemistry from the University of Surrey, United Kingdom, an M.Sc. in molecular medicine from the University College London, and a Ph.D. in molecular endocrinology from St. Bartholomew's Hospital in London.

Cary Haver, M.P.H., is Associate Program Officer in the IOM's Board on the Health of Select Populations. As a member of the IOM staff, she has worked with the Committee on Gulf War Health: Treatment of Chronic Multisymptom Illness; the Committee to Review the Department of Labor Site Exposure Matrix; and the Committee on Long-Term Health Consequences of Exposure to Burn Pits in Iraq and Afghanistan. Before joining the IOM, Ms. Haver worked for Tetra Tech Sciences, a consulting group dedicated to a variety of environmental and occupational epidemiology and toxicology projects, including exposures to asbestos, chromium, and mercury. She earned her M.P.H. with a concentration in epidemiology from George Washington University.

Sulvia Doja, M.S.H.C.P.M., is Senior Program Assistant in the IOM Board on the Health of Select Populations. She earned her master's of science degree in health care policy and management from Carnegie Mellon University's H. John Heinz III College and her undergraduate degree in biology with a minor in chemistry from Chatham College. Before coming to the IOM, she researched the effect of national health care reform on American Indian and Alaskan Native populations and pioneered a social-media marketing outlet to increase customer visibility and enhance communication with that population.