Ionizing radiation occurs in a wide range of medical, industrial, military, and commercial settings and the number of individuals exposed or potentially exposed to radiation in these settings is increasing. There are longstanding concerns that exposures in these settings, even at low doses (defined as doses below 100 milligray [mGy]) or low dose-rates (delivered at rates below 5 mGy per hour), can adversely affect human health. Today, these concerns influence patient acceptance of medical diagnostic procedures; U.S. government decisions related to the future of nuclear power and clean energy policies; continuing efforts to assess the full range of radiogenic health outcomes of legacy exposures to fallout from nuclear weapons production, testing, and waste sites; management of nuclear waste; and plans for responding to radiological threats. They also raise questions as to whether the public and workers are adequately protected from current environmental and occupational radiation exposures and from potential new sources of exposure such as rare earth element and lithium mining to support green energy and long-term energy policies in the United States.

Low-dose and low-dose-rate radiation effects on human health outcomes and the biological mechanisms of these effects are not fully understood. Cancer is the health outcome most commonly studied for its association with low doses of radiation, and heritable genetic effects are assumed to be associated with low-dose exposures despite minimal evidence to-date of such effects in humans. There is also increasing evidence that low dose radiation exposure may be associated with non-cancer health outcomes such as cardiovascular disease, neurological disorders, immune dysfunction, and cataracts. For some of these health outcomes, experts rely on risk estimates from studies of individuals who were primarily exposed to higher doses, which introduces considerable uncertainty assessing risks at low doses.

Advances in epidemiological study design and analysis, radiation biology research, and biotechnology and research infrastructure make it possible to obtain more direct information on health effects that result from exposures to low-dose and low-dose-rate radiation. The increasing low-dose radiation exposures and the improved capabilities to quantify health risks and study the underlying mechanisms make it both urgent and feasible to improve understanding of the adverse human health effects from exposures to doses and dose rates of relevance to the U.S. population.

Today, research in low-dose and low-dose-rate radiation in the United States is limited and fragmented, and lacks leadership and an overarching prioritized strategic research agenda. This report defines the essential components and
sets priorities to guide research for a multidisciplinary coordinated low-dose radiation program.

**IMPACT OF A MULTIDISCIPLINARY LOW-DOSE RADIATION PROGRAM**

A coordinated multidisciplinary low-dose radiation research program in the United States can improve understanding of adverse human health effects from exposures to radiation at doses and dose rates of relevance to the U.S. population. Specific goals for such a program include identifying mechanisms for induction of these health effects, developing improved risk models for doses and dose rates at which direct measurement of risks is not currently possible, and, ultimately developing more individualized risk estimates. Reaching those goals will enable better assessment of whether current risk estimates (primarily for cancer) at low doses and low dose rates are accurate, underestimated, or overestimated and provide improved risk estimates for other adverse health outcomes. Improved risk assessments, in turn, may affect current regulatory efforts to protect human health, supporting either more restrictive or less restrictive regulations and guidance.

**PROPOSED RESEARCH AGENDA PRIORITIES**

Epidemiological and biological research of low-dose and low-dose-rate radiation faces several challenges. These arise because the effects of low-dose and low-dose-rate radiation exposures are assumed to be subtle and difficult to distinguish from those caused by other stressors or “spontaneous” changes that adversely affect the normal functions of cells, tissues, and organs. Moreover, a full understanding of possible effects may be complicated by change in the magnitude of observed effect with dose, dose rate, type of radiation, and duration of exposure.

Agencies responsible for the management of the multidisciplinary low-dose radiation program should fund low-dose and low-dose-rate radiation research on the 11 high-priority research topics identified in this report. These research priorities are broadly classified as epidemiological research, biological research, and research infrastructure and are of equal importance. Criteria used to identify these priorities for low-dose and low-dose-rate research included existing human, laboratory model, and cellular evidence for adverse health effects resulting from radiation exposure; limitations in the current radiation protection system in the United States; feasibility of improving low-dose and low-dose-rate risk estimation models given newly available technologies and resources as well as increased understanding of human disease mechanisms; and issues of concern for exposed populations. Integration across the research lines is needed for the most impactful research projects, including work in more than one research line and work being conducted by multidisciplinary teams.

**Priorities for Epidemiological Research**

Epidemiological studies have played a crucial role in identifying risks (primarily for cancer) from medical, occupational, and environmental radiation exposures at low doses. Existing epidemiological studies are unable to address a number of outstanding questions of low-dose and low-dose-rate exposures of concern to the U.S. population including the full range of potential adverse health effects, risks associated with doses around 10 milligray, and the potential impacts of genetic, lifestyle, environmental, and other factors that may also affect radiation-related risk estimates. Priorities for improving epidemiological studies include:

1. Develop and deploy analytical tools for radiation epidemiology.
2. Improve estimation of risks for cancer and non-cancer health outcomes from low-dose and low-dose-rate external and internal radiation exposures.
3. Determine factors that modify the low-dose and low-dose-rate radiation-related adverse health effects.

**Priorities for Radiation Biology Research**

Radiation biology studies have contributed to the mechanistic understanding of the effects of radiation on molecular pathways and intra- and extra-cellular processes. The application of novel and developing technologies will enable more precise definition of the cellular and molecular processes that are affected by low-dose and low-dose-rate exposures. Integration of this information with that from epidemiological studies will enable better quantification of the adverse health effects from low-dose and low-dose-rate exposures.
relevant to the U.S. population, increase understanding of the involved mechanisms, and inform on the most appropriate risk assessment models to be used. Priorities for improving radiation biology studies include:

4. Develop appropriate model systems for study of low-dose and low-dose-rate radiation-induced health effects.
5. Develop biomarkers for radiation-induced adverse health outcomes.
6. Define health effect dose-response relationships around 10 mGy and 5 mGy/h.
7. Identify factors that modify or confound estimation of risks for radiation-induced adverse health outcomes.

Priorities for Research Infrastructure
Advances in biotechnology and research infrastructure have been driven by the vast research and development enterprise in the United States. These include new observational and experimental systems, tools for measurement and genetic manipulation, increased computational power, improved interpretative algorithms, and shared data access systems. These advances have enabled innovation and breakthroughs in many scientific areas including cancer research and treatment, environmental health effects research, and vaccine production. A revitalized low-dose radiation research program can likewise leverage and further develop these capabilities to enable scientific innovation and breakthroughs in radiation biology and epidemiology. Priorities include:

8. Tools for sensitive detection and precise characterization of aberrant cell and tissue states.
9. Harmonized databases to support biological and epidemiological studies.

Elements of a Successful Low-Dose Radiation Research Program
Long-term commitment to the low-dose radiation program is needed to address the research priorities identified in this report and to take advantage of the continuing technological and biological advances. Significant investments over a sustained period spanning several decades are necessary to develop and maintain a multidisciplinary low-dose radiation research program in the United States that leverages existing and developing research infrastructure. The research agenda laid out in this report extends for 15 years. Funding needed for the program is on par with the congressionally authorized funds for 2023 and 2024 ($30 million and $40 million, respectively) but needs to rise at the level of $100 million annually thereafter and remain at that level through 2037 (i.e., 15 years from now).

Low Dose Radiation Research Leadership
The Department of Energy’s (DOE’s) Office of Science has a long history leading and supporting radiation research at national laboratories and universities to advance knowledge of radiation health effects and mechanisms of these effects. However, since about 2016, the Office’s focus has been directed away from radiation health effects research, resulting in a lack of leadership and scientific activity in this area.

The only entity at this point that Congress has tasked with a focused low-dose radiation program is DOE; therefore, DOE has a role in coordinating low-dose radiation research within the United States. However, members of impacted communities have raised concerns about DOE’s inherent conflicts with leading low-dose radiation research and also regulating radiation exposures and members of the research community have cited DOE’s shortcomings related to management of the previous low-dose radiation program. In addition, the research agenda proposed extends beyond any single agency’s capabilities, and a partnership with an agency whose mission is to enhance health would be warranted.

Among various federal agencies with missions to enhance or protect health, the National Institutes of Health (NIH) is widely trusted by the scientific community and members of the public and does not have any regulatory responsibilities related to setting or implementing radiation protection standards; therefore, it has no perceived conflict of interest with leading low-dose radiation research through a cross-institutional effort.
In addition, it has well-established and transparent processes for soliciting, reviewing, and funding research. Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) Radiation and Nuclear Countermeasures Program (RNCP) could be suitable to support low-dose radiation research through a cross-institutional effort. Although RNCP currently supports research in moderate and high doses starting at about 1 gray and supports limited research on cancer (which is the primary focus of the National Cancer Institute (NCI)), the committee was impressed with the program management’s commitment and transparency as well as engagement with its stakeholder communities. NCI has processes similar to NIAID’s and by virtue of its mission it focuses on cancer research. The Advanced Research Projects Agency for Health (ARPA-H), a proposed agency tasked with building high-risk, high-reward capabilities to drive biomedical breakthroughs, could also contribute to innovative low-dose radiation research leadership.

Agencies responsible for the management of the multidisciplinary low-dose radiation program should incorporate the following elements:

1. Programmatic commitment to developing and maintaining a long-term multidisciplinary low-dose radiation research program that leverages the advances in U.S. research infrastructure and health effects research.

2. Independent scientific advice and program evaluation by a trusted entity.

3. Transparent management of the research process.

4. A prioritized strategic research agenda developed with input from all relevant scientific, regulatory, and impacted stakeholder communities nationally and internationally.

5. Research sponsorship mechanisms that support competitive research and infrastructure development projects and employ transparent peer review to select projects that are aligned with the program’s strategic research agenda.

6. Training and research support for scientists of all career levels and relevant disciplines that promote equity, diversity, and inclusion.

7. Commitment to engagement and communication with all relevant stakeholder communities.

8. Coordination across federal agencies and other national and international organizations that carry out low-dose radiation research or have relevant expertise and entities that carry out relevant (non-radiation) research.

DOE could implement most of the essential elements identified above within about 2 years given adequate funding. DOE’s progress with implementing the essential elements needs to be formally and transparently assessed by Congress. If Congress finds that DOE failed to adopt the recommended research agenda and implement the essential elements, it may consider alternatives for placement and management of the low-dose radiation program, for example within NIH, likely as a cross-institutional effort, for example, by NIAID and/or NCI and/or the newly conceptualized ARPA-H.

**COMMITTEE ON DEVELOPING A LONG-TERM STRATEGY FOR LOW-DOSE RADIATION RESEARCH IN THE UNITED STATES**

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To read the full report, please visit http://nap.nationalacademies.org/author/nrsb

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