Radiology

REVIEWS AND COMMENTARY • REVIEW

Proposed Priorities for Low-Dose Radiation Research and Their Relevance to the Practice of Radiology

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Conflicts of interest are listed at the end of this article.

Radiology 2023; 309(2):e222590 • https://doi.org/10.1148/radiol.222590 • Content codes: SQ HP

Because ionizing radiation is widely used in medical imaging and in military, industry, and commercial applications, programmatic management and advancement in knowledge is needed, especially related to the health effects of low-dose radiation. The U.S. Congress in partnership with the U.S. Department of Energy called on the National Academies of Sciences, Engineering, and Medicine (NASEM) to develop a long-term strategic and prioritized agenda for low-dose radiation research. Low doses were defined as dose amounts less than 100 mGy or low-dose rates less than 5 mGy per hour. The 2022 NASEM report was divided into sections detailing the low-dose radiation exposure and health effects, scientific basis for radiation protection, status of low-dose radiation research, a prioritized radiation research agenda, and essential components of a low-dose radiation research program, including resources needed and recommendations for financial recourse. The purpose of this review is to summarize this report and examine the recommendations to assess how these pertain to the practice of radiology and medicine.

Radiation is essential in military, industrial, and commercial settings, and the number of individuals exposed to radiation is increasing worldwide. Additionally, medical ionizing radiation (hereafter, radiation) exposures have become increasingly common due to the diagnostic value of medical imaging. However, uncertainty remains in our understanding of the radiation-related health effects at the dose levels encountered in all these settings. For these reasons, the U.S. Congress in partnership with the U.S. Department of Energy called on the National Academies of Sciences, Engineering, and Medicine (NASEM) to develop a long-term strategic and prioritized agenda for low-dose radiation research. Low doses were defined as dose amounts less than 100 mGy or low dose rates less than 5 mGy per hour (1).

NASEM appointed an expert committee to define the essential components and set priorities for a broad low-dose radiation research agenda. The result is the consensus study report, *Leveraging Advances in Modern Science to Revitalize Low-dose Radiation Research in the United States* (2). This report contains a detailed summary of current low-dose radiation research programs in the United States and provides specific recommendations for the future of low-dose radiation research. The purpose of this review is to examine the recommendations of the report as they pertain to the practice of radiology.

Understanding Effects of Radiation on Humans

Medical radiation exposures, when justified and optimized (3,4), yield individual health benefits and overall societal benefits (5). However, these benefits must be balanced with the potential for adverse effects on human health. Whereas adverse effects of high-dose radiation are generally well known (6–8), knowledge about the risks from low doses of radiation mainly come from epidemiologic studies of exposed populations including survivors of the 1945 atomic bombing in Japan, medically exposed individuals, and radiation workers (9). Such studies have primarily focused on radiation-related cancer risks, demonstrating the potential for increased risk in certain organs or tissues, dependent on various factors including radiation type, dose rate, organ-absorbed dose, tissue radiosensitivity, age at exposure, and sex, among others (7). For radiation protection purposes, it is assumed that exposure to 100 mSv could result in an increased cancer mortality risk of about 0.5% (4,7). Although there are uncertainties (including a lack of a full mechanistic understanding), some recent epidemiologic studies have suggested that low-dose radiation (perhaps as low as 0.5 Gy) correlates with increased risks of cardiovascular diseases (6–10), neurologic disorders (6,11,12), immune dysfunction (8,13), and cataracts (14,15).

Unknown Aspects regarding Radiation Effects on Humans

The NASEM report (2) appropriately points out three unknowns relevant to low-dose radiation effects on humans. First, in addition to a lack of statistical power in the studies of low-dose radiation health effects (eg, the doses typically involved in imaging and medical occupational settings), the exact biologic mechanisms impacted by different low-dose and dose-rate radiation sources and their direct or indirect effects on human health are not well understood (16). Second, the committee noted that the current radiation protection framework assumes that the cancerous effects observed at high radiation doses also exist at low doses, despite little to no direct evidence for

Abbreviation

NASEM = National Academies of Sciences, Engineering, and Medicine

Summary

This review discusses contents relevant to medical imaging in the broad-reaching and ambitious 2022 National Academies of Science, Engineering, and Medicine report, *Leveraging Advances in Modern Science to Revitalize Low-Dose Radiation Research in the United States*, and its value to the imaging profession.

Essentials

- Medical imaging is the main source of nonnatural (human-made) radiation exposure in populations both in the United States and globally.
- Low doses are defined as dose amounts less than 100 mGy or low-dose rates less than 5 mGy per hour in a 2022 report from the National Academies of Sciences, Engineering, and Medicine (NASEM).
- Applying a simple linear no-threshold model to data from individuals exposed to moderate to high doses of radiation to extrapolate risk for those exposed to lower doses leads to uncertainties in dose response and an ambiguous understanding of the potential impacts of low-dose radiation on human health.
- The NASEM report introduces a set of recommendations for the development of a long-term strategy for low-dose radiation research in the United States.
- In recommending a prototype research program composed of interactive multidisciplinary hubs with significant funding, there remains a need for additional detail about the challenges and likelihood of implementation and management.

this (2). This assumption mainly comes from studies that applied the linear no-threshold model to data from individuals exposed to moderate to high doses of radiation to extrapolate risk for individuals exposed to lower doses. Importantly, this extrapolation may not accurately reflect dose response and may lead to an ambiguous understanding of the impact of these lower radiation doses on human health. Third, whereas the report recognized that the linear no-threshold model is currently the most accepted model for radiation-related cancer risk for the purpose of radiation protection, it also noted that this model is relatively generic and highlighted research on other sex-specific and cancer-specific linear and nonlinear models of risk, such as linear-quadratic model, supralinear, hormesis, and threshold, that are likely more appropriate for examining low-dose radiation biology.

Main Theme of the Report

The report (2) provides background information on the various sources of low-dose radiation exposures to the U.S. population and summarizes the current understanding of the health effects associated with such exposures. It introduces a set of recommendations for the development of a long-term strategy for low-dose radiation research in the United States. It sets priorities to guide research and recommends essential elements for a successful multidisciplinary coordinated low-dose radiation program. The proposed program involves the broader U.S. research enterprise, including universities and national laboratories, with coordination between several federal and international agencies.

Agencies in the United States have radiation protection responsibilities with varying and often disconnected jurisdiction and regulatory limits that will benefit from coordinated long-term research on low-dose effects on humans (2). Following the termination of the former low-dose research program managed by the U.S. Department of Energy in 2016, the breadth of the programs with direct involvement in low-dose radiation research have been managed by the National Institutes of Health and, to a much lesser extent, the National Aeronautics and Space Administration, Centers for Disease Control and Prevention, Department of Defense, and National Science and Technology Council.

Although a strong scientific basis is critical to ensure appropriate protection from the use of radiation, the radiation protection framework in the United States is based on several assumptions that rely on risk estimates extrapolated from higher doses such as the current linear no-threshold model. Federal agencies have been challenged about the use of the linear no-threshold assumptions because they use the current best-available data for minimizing risks of radiation exposure. The committee states that advancements in epidemiologic study design, biologic understanding of disease occurrence, improved capabilities to quantify health risks, and computational technologies can be leveraged to provide better evidence and improve our understanding of the risks of health effects resulting from exposures to low-dose and low-dose-rate radiation.

The report authorship also noted that new knowledge gained from a revitalized low-dose radiation research program can help address concerns raised by members of the public, radiation workers, patients exposed to radiation, and down-wind communities exposed involuntarily to radiation, such as during the nuclear weapons program operations. It will also be useful to inform federal agencies and assess whether current radiation protection policies and regulations sufficiently protect human health. Findings from the program may impact the decision-making frameworks in the federal regulatory systems, potentially supporting either more or less restrictive regulations, thereby providing agencies with data to update radiation protection standards on a sound basis of evidence about radiation health effects.

Recommendations of the Report

The committee identified challenges in epidemiologic and biologic research in low-dose radiation, including difficulty in distinguishing low-dose and low-dose-rate effects from other confounding factors, and the lack of understanding of the cellular and molecular processes affected by low-dose and low-dose-rate exposure. These challenges led the committee to define 11 research priorities divided into three approaches: epidemiologic research, biologic research, and research infrastructure (Table).

These goals are of equal importance and complementary to each other, with the expectation that the most important research projects will be performed by multidisciplinary teams. The report provides a prototype research program composed of interactive multidisciplinary hubs (Figure 1) to justify an estimated initial funding of \$30–\$40 million for 2023–2024 (Congress attributed \$20 million to the U.S. Department of Energy office of Biologic and Environment Research for 2023) followed by an annual budget of \$100 million thereafter through 2037. The cost and time

Research Priorities for Low-Dose and Low-Dose-Rate Radiation Research

Epidemiologic Research	Biologic Research	Research Infrastructure
E1. Develop and deploy analytical tools for radiation epidemiology	B1. Develop appropriate model systems for study of low-dose and low-dose-rate radiation-induced health effects	I1. Develop tools for sensitive detection and precise characterization of aberrant cell and tissue states
E2. Improve estimation of risks for cancer and noncancer health outcomes from low-dose and low-dose-rate external and internal radiation exposures	B2. Develop biomarkers for radiation-induced adverse health outcomes	I2. Harmonize databases to support biologic and epidemiologic studies
E3. Determine factors that modify the low-dose and low-dose-rate radiation-related adverse health effects	B3. Define health-effect dose-response relationships below 10 mGy and below 5 mGy/hour	I3. Dosimetry for low-dose and low-dose-rate exposures
	B4. Identify factors that modify or confound estimation of risks for radiation-induced adverse health outcomes	I4. Facilities for low-dose and low-dose-rate exposures

Note.—Adapted, with permission, from reference 2.

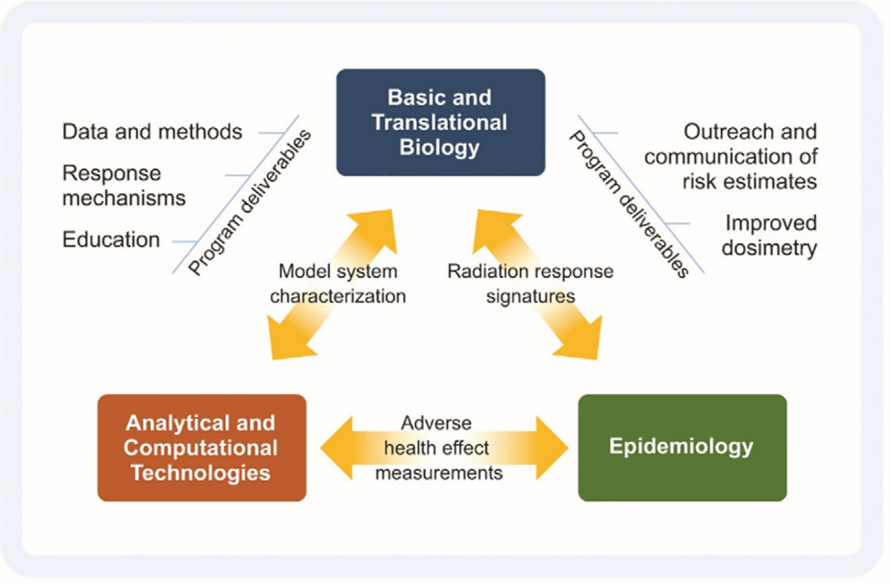

Figure 1: Illustration of the interactive hubs of the low-dose radiation multidisciplinary program and overall program deliverables. Reprinted, with permission, from reference 2.

line involve the creation of a nation-wide infrastructure that would include: a basic and translational biology hub; an epidemiology hub; a hub dedicated to education, outreach, and policy; and a program administration component focused on the coordination of all hubs, grants management, and the operation of an external advisory committee.

The report (2) discusses its proposed research agenda priorities to overcome limitations, quantify effects, and inform on risk assessment models. The scope of the proposed research agenda will require coordination across several agencies, for which the committee recommends the U.S. Department of Energy to lead the program with shared coordination with National Institutes of Health. This joint coordination optimizes the development of low-dose research capabilities from current U.S. Department of Energy strategic resources and relies on the demonstrated expertise and reputation of the National Institutes of Health to run cross-institutional research efforts successfully. The report also issues two formal recommendations and addresses eight essential elements that should be considered in the development of a successful low-dose radiation research program (Fig 2).

Why Is This Important for Medical Imaging?

The assessment in the report (2) regarding funding and organizational needs to support multidisciplinary low-dose radiation research is relevant to medical imaging. First, low-dose radiation exposure found in diagnostic radiologic imaging is of concern for health care providers, the public, patients, caregivers, and regulatory bodies because of the uncertainties about health effects. Anxiety may be amplified because of lack of information or disinformation from both the lay press and medical communications. A national low-dose research program will help educate the medical community and patients about radiologic risks and will improve public trust in the benefits provided by medical imaging. Medical imaging that depends on ionizing radiation (eg, CT, fluoroscopy, radiography, and nuclear imaging) is valued for the diagnosis and treatment of a variety of medical disorders, which is demonstrated by the increased use of radiologic imaging over the past decades (17,18). As noted in the Consensus Study Report (2), medical imaging is the main source of nonnatural (human-made) radiation exposure in populations in the United States and globally.

A working knowledge of radiation levels from medical imaging examinations and potential health risks should be provided to the medical imaging community. This community is wide, encompassing all those that use medical radiation beyond

Recommendation #1: Agencies responsible for the management of the multidisciplinary low-dose radiation program should fund low-dose and low-dose-rate radiation research in the 11 high-priority research topics identified by the committee and address the scopes outlined in Table 1. These research priorities are broadly classified as epidemiologic research, biologic research, and research infrastructure and are of equal importance

Recommendation #2: Agencies responsible for the management of the multidisciplinary low-dose radiation program should incorporate the following elements:

1. Programmatic commitment to develop and maintain a sustainable program that leverages the advances in United States 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 with transparent peer review.
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 (nonradiation) research.

Figure 2: Specific recommendations for a low-dose radiation research program. Adapted, with permission, from reference 2.

radiology, such as cardiologists, radiation oncologists, surgeons, gastroenterologists, chiropractors, and dentists (19). Results from the low-dose radiation program will help reduce uncertainties in estimations of radiologic risk for patients and facilitate a more informed justification for the use of ionizing radiation by medical providers. Occupational exposures are also relevant for this research paradigm because, as the report states, "uncertainties in low-dose radiation risks raise questions about whether dose limits and guidance levels are set appropriately or whether they are set too high and therefore do not sufficiently protect workers and members of the public or too low and therefore result in unnecessary costs to reduce radiation exposure" (2).

The medical field in general can benefit from the multidisciplinary coordinated research program proposed by NASEM. Evidence-based clarification of low-dose radiation sources, doses, and risks will enable improved risk-benefit dialogues in the clinical domain as well as establishment of research approaches. Further clarification of the appropriateness of the linear no-threshold model for different cancers and in different populations, such as women, the fetus, and children, or in settings with genetic susceptibility for cancer can inform research efforts. Improved understanding of low-dose radiation can potentially enhance technology development and application in medicine. This includes appropriate biologic markers for radioprotectants for radiation effects in diagnostic and therapeutic medical radiation use (eg, micronuclei, or γ-H2AX), radiation monitoring technology, such as with individual organ doses for an examination, or in leveraging focused efforts with artificial intelligence radiation exposure reduction tools. Moreover, impact includes assisting regulatory and health authorities with respect to policies, recommendations, and guidelines.

Is the Report Sufficient to Answer Prevailing Questions?

The Consensus Study Report (2) provides a valuable detailed context of the historical and current organizational structure of low-dose radiation research, providing both successes as well as challenges. The report also details leveraging opportunities for advancing multidisciplinary low-dose radiation research. Whereas there is discussion of the current state, including gaps toward developing a more global research approach, the authors acknowledged that these would need to be clearly identified and have adequate resources. The committee is unable to quantify the economic impact of the low-dose radiation program due to a lack of comprehensive estimates of the financial costs with complying with current radiation protection standards and guidelines. It also states costs to federal agencies and society will depend on new knowledge of human health effects gained by the research program. Nevertheless, measures to assess the future economic impact need to be developed and fiscally supported early in the research program because this is an inherent accountability for any resource-requiring proposal. There is a requisite accountability in how the low-level radiation research will improve the lives of the nation's citizens, and at what cost.

There are additional considerations relevant to the medical community represented by the diverse authorship of this report. For example, does a designated government agency have the operational capacity to handle this ambitious project as either the champion or co-champion with the Department of Energy? Would this partnership be accepted by all stakeholders? Who will decide what public voices should be included, and to what extent might they influence the direction and assessment of fund allocation? How will the various outcomes of the research be centrally managed and audited, following delegation of funds? Allocation is challenging in and of itself; the accountability arm is equally important and seems less well-defined. For example, will a decrease in medical radiation and other occupational exposures from this project be addressed by a resultant shift in both funding allocation between research corridors as well as the regulatory aspects? Is this recommendation for the time line and amount of funding realistic given challenges at the government level with approvals, changes in administration and dollars allocated, and public perception of the importance of low-dose medical radiation? How will the economic impact be determined and who is responsible for this aspect, and what stakeholder voices will be included? Will there be legal interventions by potentially unheard voices that may affect the time line of or even actual implementation of components? Although an advisory panel was suggested and justified, it will be important to identify to whom this panel will ultimately report. These questions imply that there remains a need for operational clarifications.

Need for Engaging Public Trust

Uncertainties about low-dose radiation health impacts may erode patient, caregiver, and public trust in individual settings or in medical care in general. For these populations, uncertainties regarding potential risks may overshadow the known benefits of medical imaging. A potential impact includes reluctance to perform or undergo medical imaging. Reducing the public's uncertainty surrounding low-dose radiation risk is therefore paramount to ensuring acceptance of and trust in medical imaging and therapies with radiation and radioactive materials.

Additional Items to Be Addressed

Whereas the justification for the designated research funding was well detailed in this Consensus Study Report (2), there are aspects relevant to the scientific, medical, and patient communities that were not specifically addressed. For example, irrespective of what outcomes may result from low-dose radiation research, it is important to promote the recognized broad benefits of medical imaging. Furthermore, support for patient-centered research about how the justifications for medical imaging could be communicated more effectively, such as with decision support, should parallel the other research efforts laid out in this report. Considerations regarding funding after the proposed period ends also need to be addressed and should be open to necessary modification based on important "asks" from the various relevant stakeholders, including the public. Finally, opportunities for global partnerships and methods for doing so should be considered, including integrated strategic prioritization and resource management for cost-effective research that is planned or ongoing.

Conclusion

A revitalized low-dose radiation research program, with appropriate scientific and stakeholder leadership, and a prioritized strategic research agenda is vital for the United States. This is timely and essential in addressing still-to-be resolved questions and reducing uncertainties that exist in estimation of low-dose radiation effects on humans, especially in the context of medical imaging. To that end, the report from the NASEM calls for coordinated development and oversight with substantial funding over the next 15 years, including the $30 million and $40 million already authorized by U.S. Congress for 2023 and 2024 (2), followed by $100 million annually through 2037. The development, curation, and audit of this ambitious effort would also require objective, respected, expert, and actively engaged oversight. There should be a defined anticipatory operational approach and clear metric-driven goals considering and accommodating normal fluxes (many unpredictable) over time. These fluxes include the direction and importance of competing scientific efforts, the influence of multiple stakeholder voices including those of advocacy, such as the public, and relevant global economic and regulatory and/or governmental forces. This would also help in the sufficient and accountable allocation of overall funding in meeting the goals of this effort.

Disclosures of conflicts of interest: **M.M.** No relevant relationships. **D.P.F.** Chair, Image Gently Alliance; nonvoting board member, Society for Pediatric Radiology; associate editor, *Radiology*. **S.G.** No relevant relationships. **L.D.** No relevant relationships. **I.B.** No relevant relationships. **A.J.A.** No relevant relationships.

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