Assessment of BER Research in Low-Dose Radiation

Report from the BER Advisory Committee

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Subcommittee

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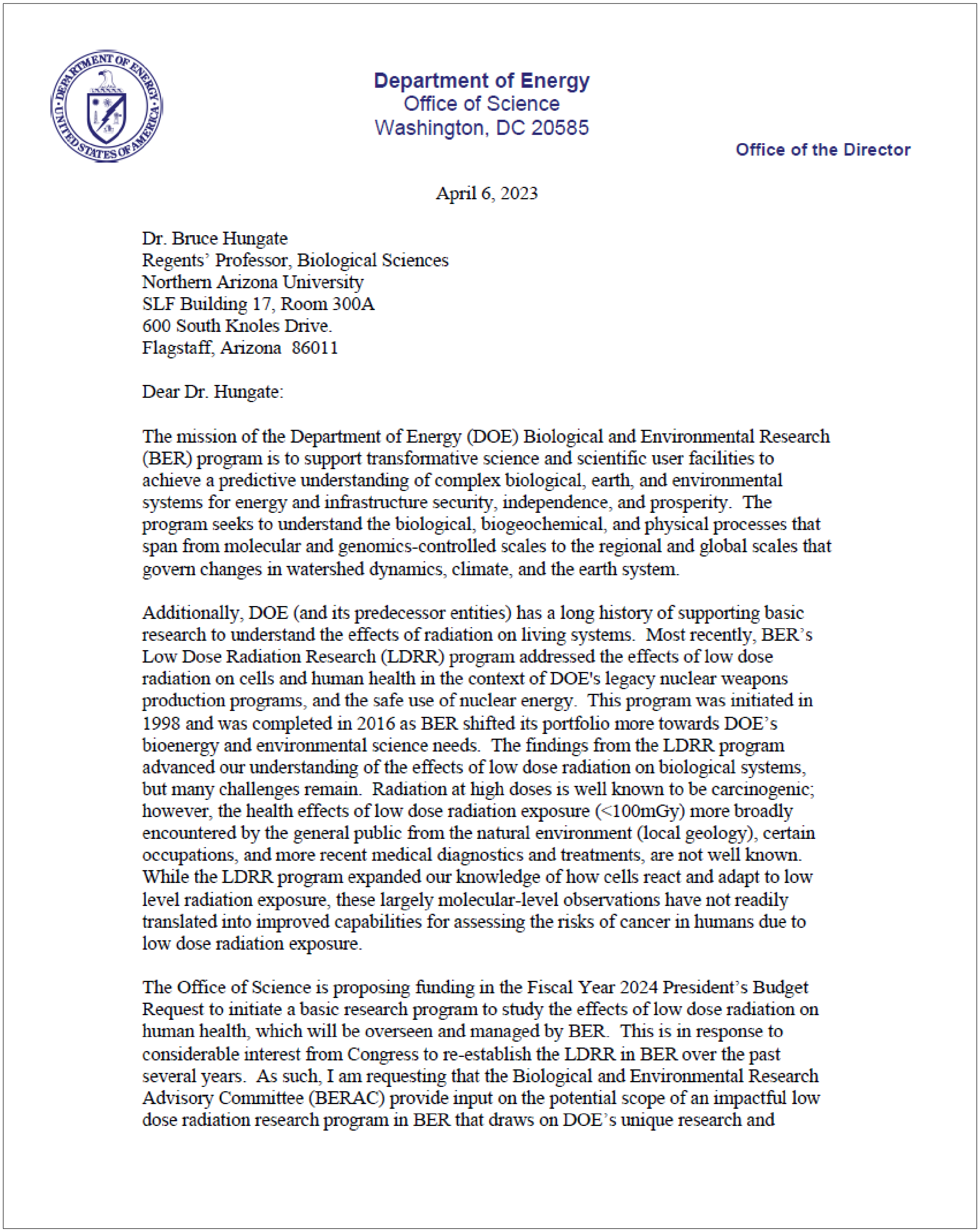
About BERAC

The Biological and Environmental Research Advisory Committee (BERAC) provides advice on a continuing basis to the U.S. Department of Energy's (DOE) Office of Science Director on the many complex scientific and technical issues that arise in developing and implementing DOE's Biological and Environmental Research program (science.osti.gov/ber/berac).

Charge Letter



Department of Energy
Office of Science
Washington, DC 20585

Office of the Director

April 6, 2023

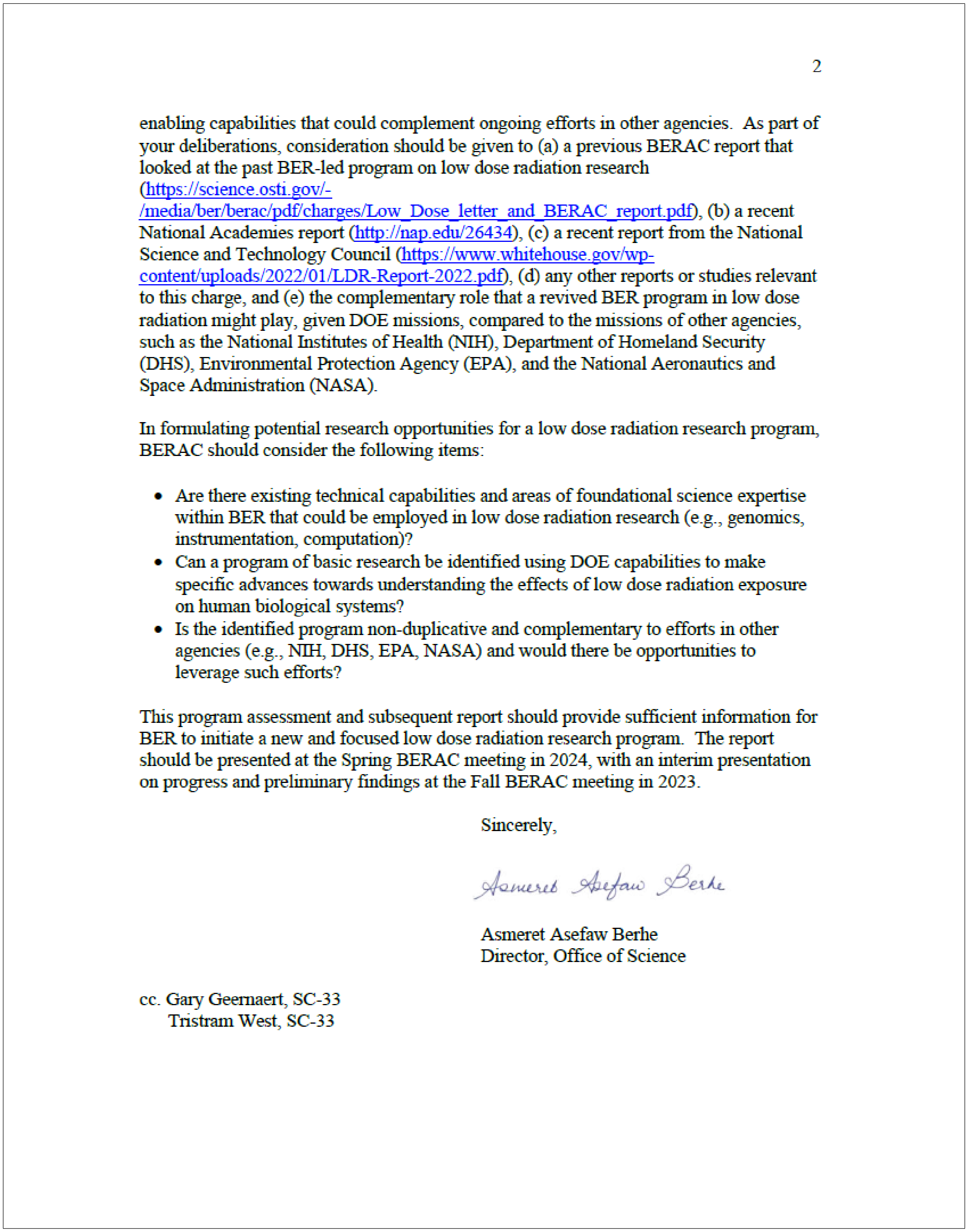
Dr. Bruce Hungate
Regents' Professor, Biological Sciences
Northern Arizona University
SLF Building 17, Room 300A
600 South Knoles Drive.
Flagstaff, Arizona 86011

Dear Dr. Hungate:

The mission of the Department of Energy (DOE) Biological and Environmental Research (BER) program is to support transformative science and scientific user facilities to achieve a predictive understanding of complex biological, earth, and environmental systems for energy and infrastructure security, independence, and prosperity. The program seeks to understand the biological, biogeochemical, and physical processes that span from molecular and genomics-controlled scales to the regional and global scales that govern changes in watershed dynamics, climate, and the earth system.

Additionally, DOE (and its predecessor entities) has a long history of supporting basic research to understand the effects of radiation on living systems. Most recently, BER's Low Dose Radiation Research (LDRR) program addressed the effects of low dose radiation on cells and human health in the context of DOE's legacy nuclear weapons production programs, and the safe use of nuclear energy. This program was initiated in 1998 and was completed in 2016 as BER shifted its portfolio more towards DOE's bioenergy and environmental science needs. The findings from the LDRR program advanced our understanding of the effects of low dose radiation on biological systems, but many challenges remain. Radiation at high doses is well known to be carcinogenic; however, the health effects of low dose radiation exposure (<100mGy) more broadly encountered by the general public from the natural environment (local geology), certain occupations, and more recent medical diagnostics and treatments, are not well known. While the LDRR program expanded our knowledge of how cells react and adapt to low level radiation exposure, these largely molecular-level observations have not readily translated into improved capabilities for assessing the risks of cancer in humans due to low dose radiation exposure.

The Office of Science is proposing funding in the Fiscal Year 2024 President's Budget Request to initiate a basic research program to study the effects of low dose radiation on human health, which will be overseen and managed by BER. This is in response to considerable interest from Congress to re-establish the LDRR in BER over the past several years. As such, I am requesting that the Biological and Environmental Research Advisory Committee (BERAC) provide input on the potential scope of an impactful low dose radiation research program in BER that draws on DOE's unique research and



enabling capabilities that could complement ongoing efforts in other agencies. As part of your deliberations, consideration should be given to (a) a previous BERAC report that looked at the past BER-led program on low dose radiation research (https://science.osti.gov/-/media/ber/berac/pdf/charges/Low_Dose_letter_and_BERAC_report.pdf), (b) a recent National Academies report (http://nap.edu/26434), (c) a recent report from the National Science and Technology Council (https://www.whitehouse.gov/wp-content/uploads/2022/01/LDR-Report-2022.pdf), (d) any other reports or studies relevant to this charge, and (e) the complementary role that a revived BER program in low dose radiation might play, given DOE missions, compared to the missions of other agencies, such as the National Institutes of Health (NIH), Department of Homeland Security (DHS), Environmental Protection Agency (EPA), and the National Aeronautics and Space Administration (NASA).

In formulating potential research opportunities for a low dose radiation research program, BERAC should consider the following items:

- Are there existing technical capabilities and areas of foundational science expertise within BER that could be employed in low dose radiation research (e.g., genomics, instrumentation, computation)?
- Can a program of basic research be identified using DOE capabilities to make specific advances towards understanding the effects of low dose radiation exposure on human biological systems?
- Is the identified program non-duplicative and complementary to efforts in other agencies (e.g., NIH, DHS, EPA, NASA) and would there be opportunities to leverage such efforts?

This program assessment and subsequent report should provide sufficient information for BER to initiate a new and focused low dose radiation research program. The report should be presented at the Spring BERAC meeting in 2024, with an interim presentation on progress and preliminary findings at the Fall BERAC meeting in 2023.

Sincerely,

Asmeret Asefaw Berhe

Asmeret Asefaw Berhe
Director, Office of Science

cc. Gary Geernaert, SC-33
Tristram West, SC-33

BERAC Subcommittee

Gemma Reguera*,* Chair, Michigan State University

Michael Bellamy, Memorial Sloan Kettering Cancer Center

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Executive Summary

On April 6, 2023, Dr. Asmeret Asefaw Berhe, director of the U.S. Department of Energy (DOE) Office of Science, charged the Biological and Environmental Research (BER) program's advisory committee with "**formulating potential research opportunities for a low-dose radiation research program**." Her charge letter (see p. 3) asked the committee to consider three questions:

1. Are there existing technical capabilities and areas of foundational science expertise within BER that could be employed in low-dose radiation research (e.g., genomics, instrumentation, and computation)?
2. Can a program of basic research be identified using DOE capabilities to make specific advances toward understanding the effects of low-dose radiation exposure on human biological systems?
3. Is the identified program non-duplicative and complementary to efforts in other agencies (e.g., the National Institutes of Health, U.S. Department of Homeland Security, U.S. Environmental Protection Agency, and NASA), and would there be opportunities to leverage such efforts?

Subcommittee Formation and Process

In response to the charge, the BER Advisory Committee (BERAC) established a subcommittee (see p. 5) to discuss potential research opportunities for BER in low-dose radiation (LDR). They also set out to produce a report with sufficient information for BER to initiate a new and focused LDR research program that addresses major uncertainties in health projections related to low-dose/low-dose rate radiation.

To address the charge, subcommittee members held four meetings to coordinate efforts (meeting 1) and discuss each of the three charge questions (meetings 2-4):

- **Meeting 1** – Introduction [*Deliver the charge*]
- **Meeting 2** – Charge question #1 [*BER capabilities*]
- **Meeting 3** – Charge question #2 [*Program scope*]
- **Meeting 4** – Charge question #3 [*Effort complementarity*]

The subcommittee chair drafted a preliminary report that captured the subcommittee meeting discussions and revised it based on written feedback from the subcommittee members. Additionally, the chair provided an interim presentation on progress and preliminary findings at the BERAC meeting in fall 2023. Feedback received during this meeting and additional input from the subcommittee members was added to the report.

Conclusions

Based on the meeting discussions, written feedback from subcommittee members, and input from BERAC at the Fall 2023 meeting, there is consensus to conclude that:

- BER's **LDR research program** could leverage DOE facilities and experience in radiation research as well as capabilities in systems biology and computational research to advance radiation biology in the low-dose range.
- The **program's scope** could emphasize links between LDR physics and biology, ensuring well-defined dosimetry, a broad spectrum of biological systems for investigation, and integrated technologies and computational analysis tools to correlate LDR physics and biology.
- BER is well suited to **coordinate international, multiagency efforts** that enhance the capabilities of a potential LDR program to address outstanding questions in low-dose science.

Final Report

This final report was completed for presentation at the BERAC meeting in spring 2024. Ch. 1: Background and Rationale, p. 9, provides overview information about ionizing radiation, LDR, and common sources, and describes the most widely applied model for projecting radiation risk. It also presents the rationale for a BER-managed LDR research program. The rest of the report outlines the subcommittee's findings in response to the three charge questions: BER capabilities (see Ch. 2, p. 14), program scope (see Ch. 3, p. 17), and effort complementarity (see Ch. 4, p. 23).

1. Background and Rationale

1.1 Ionizing Radiation

The electromagnetic (EM) spectrum covers the range of radiation from below visible light (lower energy) to above visible light (higher energy; see Fig. 1.1, this page). Above visible light, a wavelength shortens progressively while frequency increases along with the photon energy of the radiation wave proportionally. At the highest energy range of gamma rays, X-rays, and extreme ultraviolet rays, radiation is ionizing; that is, the rays penetrate atoms and cause the removal of electrons (ionization). The major sources of ionizing radiation are cosmic rays, which may be significant for frequent air travelers, and radiation derived from the decay of radioactive isotopes (e.g., radon gas). However, exposure is also possible from:

- Man-made devices, particularly those used in medical diagnostics, such as X-rays; computerized tomography (CT), computed axial tomography (CAT), and positron emission tomography (PET) scans and fluoroscopy.
- Nuclear power sources or nuclear weapons testing and accidents.
- Various consumer products, such as smoke detectors, luminous paints, and clock dials.

Exposure is either external (e.g., skin exposure) or internal (e.g., via inhalation, ingestion, or direct injection into the bloodstream or through wounds)[1]. The type, dose, and rate of radiation exposure ultimately dictate its impact on human health.

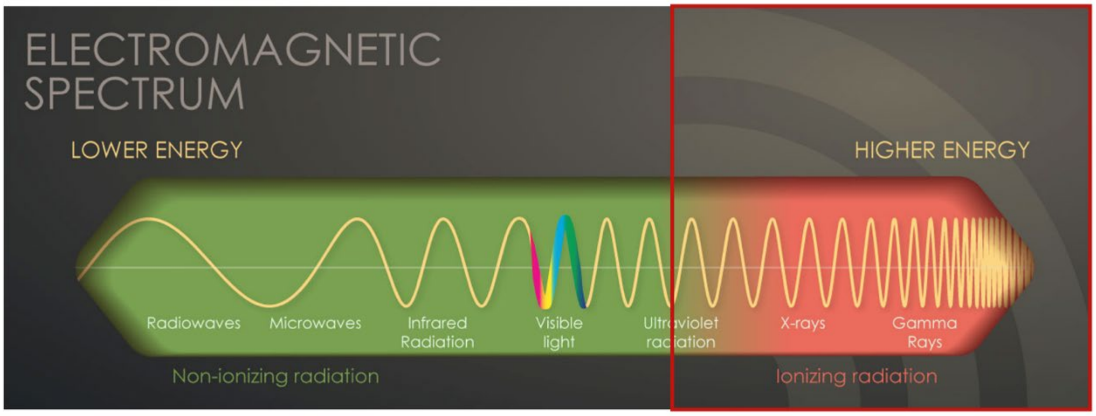

Fig. 1.1 Energy Range of Radiation Within the Electromagnetic Spectrum. *Ionizing radiation is shown in red box. [Modified from Centers for Disease Control and Prevention, www.cdc.gov/nceh/radiation/ionizing_radiation.html]*

1.2 Low-Dose Radiation

Low-dose radiation (LDR) generally refers to exposure to ionizing radiation at levels significantly lower than 100 mSv (0.1 Gy[2]). In addition, exposures can be acute or chronic, with a low-dose rate considered <5 mSv/h. Furthermore, LDR may originate from many common sources, including natural background

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[1] www.epa.gov/radiation/radiation-sources-and-doses

[2] One Gray (Gy) is the amount of absorbed radiation (dose) required to deposit 1 joule of energy in 1 kilogram of matter. One sievert (Sv) is the radiation dose equivalent of 1 Gy of high-penetration X-rays adsorbed by living matter.

radiation, medical and dental procedures, occupational exposures, consumer products, environmental contaminants, military and industrial facilities, and nuclear weapons testing and detonation.

Radiation dose from most of these sources is typically low. However, the cumulative effects of long-term exposure need to be considered as does the fact that potential health risks depend on various factors, including the type of radiation, the dose received, and individual sensitivity.

Natural Background Radiation

- **Cosmic Radiation —** Cosmic rays from space interact with the Earth's atmosphere, contributing to background radiation.
- **Terrestrial Radiation —** Radioactive materials in the Earth's crust, such as uranium and thorium, emit radiation.
- **Radon Gas —** Radon is a naturally occurring radioactive gas that can enter homes through the ground. It is a significant source of background radiation in some geographic locations.
- **Food and Water —** Some foods and natural water sources can contain trace amounts of radioactive materials.

Medical and Dental Procedures

- **X-rays —** Diagnostic X-ray procedures, such as dental X-rays, chest X-rays, fluoroscopic imaging, and mammograms, expose patients to low doses of ionizing radiation.
- **CT Scans —** CT scans reconstruct detailed images of the body and its organs or tissues by reconstructing X-ray images collected at different angles, thus requiring higher doses of radiation compared to standard X-rays.
- **Nuclear Medicine —** Certain medical procedures, like PET scans, involve the use of radioactive tracers that emit LDR.
- **Radiation Therapy —** Radiation therapy is used to treat cancer. While it delivers high doses to the tumor, surrounding healthy tissue may receive lower doses.

Occupational Exposures

Workers in certain industries may be exposed to LDR, including:

- Radiologic technologists and healthcare professionals who work with X-ray equipment.
- Employees at nuclear power plants.
- Airport security personnel.
- Military pilots, as well as airline crew members and passengers, who receive slightly higher radiation doses due to cosmic rays at higher altitudes.

These workers are subject to strict safety regulations to minimize exposure and health risks.[3]

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[3] In medical settings, the "ALARA" principle (As Low As Reasonably Achievable) is followed to minimize radiation exposure during diagnostic procedures. Strict safety guidelines and regulations are in place to protect both patients and healthcare workers.

Consumer Products

Some consumer products, such as smoke detectors and certain luminous paints or clock dials, may contain small amounts of radioactive materials.

Environmental Contaminants

Radioactive contaminants from nuclear accidents, like Chernobyl or Fukushima, can lead to long-term LDR exposure in affected areas.

Military and Industrial Facilities

Some military and industrial activities involve the use of radioactive materials, which can result in LDR exposure for workers and nearby communities.

Nuclear Weapons Testing and Detonation

Historical nuclear weapons testing, both above- and belowground, released radioactive fallout into the atmosphere, contributing to background radiation levels. The potential for purposeful or accidental use of a nuclear weapon must also be considered. The U.S. military has programs investigating high-dose radiation exposure and the development of acute radiation syndrome (ARS). However, long-term LDR exposure is likely to be significant after a nuclear detonation and will affect both military and civilian populations.

1.3 Linear No-Threshold Model

The potential health risks associated with LDR exposure have an associated uncertainty, and their predicted impact remains the subject of ongoing debate. While research clearly links high-dose radiation exposure to an increased risk of cancer and other health problems, the projected risks from LDR are much smaller and generally harder to quantify than those from higher doses. Individuals working in settings with frequent exposure to LDR are typically monitored to ensure they do not exceed recommended exposure limits. In the case of medical diagnostics, the potential risks associated with LDR are weighed against the benefits of the procedure. Assessing the potential risks remains challenging, though, because the overall observed health effects of LDR are not well established.

The most widely applied model for radiation risk projections is the Linear No-Threshold (LNT) model (see Fig. 1.2, p. 12). As its name states, this model assumes a linear correspondence between the dose of ionizing radiation (e.g., X-rays and gamma rays) and the associated cancer risk across all possible doses. The LNT model, therefore, posits that there is no safe dose below which radiation exposure poses no cancer risk. This model, however, cannot predict other potential health impacts of radiation exposure that may be nonlinear.

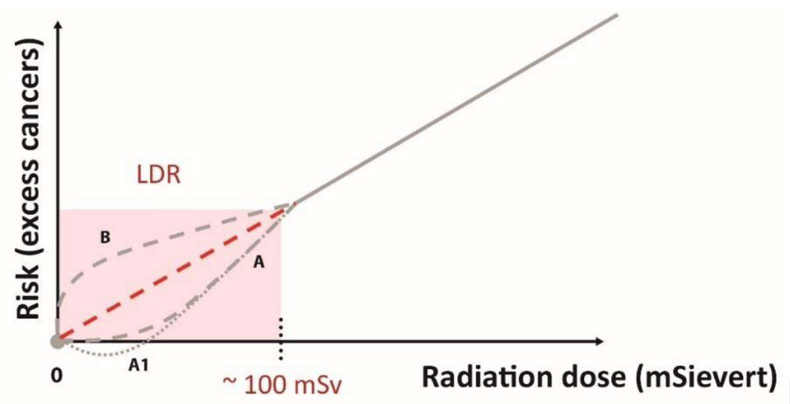

Fig. 1.2. The Linear No-Threshold (LNT). *This model assumes a linear correspondence between radiation dose exposure and excess cancer risk in the LDR region (<100 mSv; shaded in red). Alternative models assume that the risk is greater (B) or lower (A) or has no effect (A1) in this region. [Modified with permission from the Swiss Federal Nuclear Safety Inspectorate ENSI, www.ensi.ch/en/2022/02/10/radiation-biology-3-5-low-doses-and-their-damage-potential/]*

The LNT model has significantly influenced radiation protection standards and public policy. Many radiation protection agencies and organizations, such as the U.S. Environmental Protection Agency (EPA) and the International Commission on Radiological Protection (ICRP), use the LNT model as a basis for setting dose limits and guidelines. Epidemiological studies typically focus on higher radiation levels. Furthermore, research on the health impacts of radiation doses in the lower region are inconclusive. This uncertainty has led to ongoing debate and controversy within the scientific and medical communities about the health outcomes of individuals within the low-dose range of exposure. These communities have presented the following arguments:

- **Underestimation of Risk —** The linear correlation between cancer risk and radiation dose in the LNT model is an approximation. In the absence of experimental validation, it cannot be concluded that the risk increases in this low-dose region. This risk may, in fact, may be underestimated.
- **Overestimation of Risk —** The body has mechanisms to repair or adapt to low-level radiation exposure. Hence, the LNT model may overestimate low-dose risks and lead to overly conservative regulations.
- **Alternative Models —** The LNT assumption in the low-dose region has been challenged by alternative proposals, such as the threshold model, which suggests that there is a dose threshold below which radiation exposure has no significant effect. The hormesis model suggests that LDR might even have some beneficial effects (see Fig. 1.2, this page).

The scientific literature extensively explores the topic of dose-response forms at low doses. Resolving these uncertainties is a significant component of any low dose/low dose rate research program.

1.4 Rationale for a BER-Managed LDR Research Program

There is broad consensus that the LNT model is appropriate for the field of radiation protection. Yet, an incomplete understanding of the underlying science limits its interpretation. Indeed, neither radiobiology nor epidemiology provides evidence of this model's accuracy at low doses. It is this uncertainty that motivated the subcommittee to meet and discuss current research in the field to address the three charge questions:

1. Are there existing technical capabilities and areas of foundational science expertise within BER that could be employed in LDR research (e.g., genomics, instrumentation, and computation)?
2. Can a program of basic research be identified using DOE capabilities to make specific advances toward understanding the effects of LDR exposure on human biological systems?
3. Is the identified program non-duplicative and complementary to efforts in other agencies (e.g., National Institutes of Health, U.S. Department of Homeland Security, EPA, and the National Aeronautics and Space Administration), and would there be opportunities to leverage such efforts?

While addressing these questions, the subcommittee also identified grand challenges in LDR research that could serve as focus areas for a BER or broader-based program (see Ch. 3: LDR Program Scope, p. 17. Furthermore, the subcommittee assessed the future success of such a program in the context of BER's mission, scientific progress, and program history:

- BER's mission is to support transformative science and scientific user facilities to achieve a predictive understanding of complex biological, Earth, and environmental systems for energy and infrastructure security, independence, and prosperity.
- BER programs have made remarkable progress toward advancing understanding of the biological, biogeochemical, and physical processes that range from molecular and genomics-controlled scales to the regional and global scales that govern changes in watershed dynamics, climate, and the Earth system.
- DOE and its predecessor entities have a long history in supporting basic research to understand the effects of radiation on living systems.

BER's most recent effort in this area is the LDR Research (LDRR) program (1998 to 2016). LDRR addressed the effects of LDR on cells and human health in the context of DOE's legacy nuclear weapons production programs and the safe use of nuclear energy. The end of the LDRR program marked a shift in BER's portfolio to address DOE's bioenergy and environmental science needs. LDRR efforts expanded the understanding of cellular responses and adaptations to LDR at the molecular level, but the program lacked the translational power needed to assess health risks from LDR exposure.

In 2016, Pat Dehmer, then Acting Director of the DOE Office, commissioned a report by the BER Advisory Committee (BERAC) about the sustainability of an LDR program. The report concluded that "further research into this area is unlikely to yield 'conclusive' results" and did "not align with current BER priorities (BERAC 2016)." Seven years later, this BERAC subcommittee questions whether a new BER-supported LDR program could merge advances in BER-sponsored omics technologies with recent insights suggesting links between LDR and noncancer health risks, such as Parkinson's disease, cardiovascular conditions, and immune and other disorders. This request aligns well with both Congress' interest in re-establishing such a program in BER and the President's Budget Request for Fiscal Year 2024, which includes an Office of Science funding proposal to initiate a basic research program to study the effects of LDR on human health.

2. BER Capabilities

With its support of national laboratory instrumentation and resources, advances in genome biology, computational and modeling capabilities, interdisciplinary science, and early career research, BER is well equipped to manage research in some aspects of LDR effects.

2.1 Controlled LDR Emission and Calibration Standards

Controlled emission and calibration standards are key for data reproducibility and cross-comparisons of LDR studies. LDR dose control and calibration require specialized equipment, instrumentation, and expertise available across the DOE national laboratory complex.

Key Findings

- DOE is the only federal agency with capabilities and instrumentation for LDR dose control and calibration in experiments at all scales.
- Such capabilities could enable single-cell studies that leverage BER strengths in genome science. Single-cell omics technologies are not fully developed but could be the focus of investments to support LDR and broader BER research programs, as needed to advance science on LDR effects.
- Dosimetry and calibration standards (provided by national laboratories) will enable physics–biology correlations and accurate description of the radiation dose and rate in biological systems.

2.2 Biological Capabilities

The power to translate broader biological research to LDR research ultimately depends on generating reproducible data from biological model systems. BER-supported advances in studying complex biological systems at molecular, genomics-controlled, and population-level scales could greatly benefit and accelerate LDR research in the broader scientific community. By leveraging BER advances in genome biology, an LDR focused program could expand opportunities to investigate, for example, linkages of LDR to noncancer health outcomes and address health disparities resulting from the involuntary exposure of vulnerable populations to LDR (NASEM 2022).

Key Findings

- BER capabilities in genome biology, population-based model systems, and computation could enable, in collaboration with other scientific entities, LDR studies ranging from molecular and cellular levels to mammalian systems genetics as well as epidemiological studies.
- Molecular and cellular studies could fill knowledge gaps that epidemiological studies cannot address. Using the current example of the LNT model, some suggest moving in both directions of the model from right (macroscale) to left (molecular/microscale) until collected data reveal an experimentally validated LDR plot linking radiation dose to cancer and noncancer outcomes.
- Deepening the understanding of how biological systems respond to an ionizing radiation stressor could potentially lead to biological and medical breakthroughs in other fields. Toward this goal, archiving biological research data in public databases accessible by the broader research community will prove important for the proposed LDR program.
- Internal exposure to LDR (e.g., inhalation) is a critical and unaddressed knowledge gap.

- A broad request for applications to an LDR extramural program would enable researchers to propose novel, creative approaches to reduce uncertainties in the LDR region of the LNT model and expand knowledge beyond cancer risks.

2.3 Computational Capabilities

BER is well positioned to apply its advanced computational capabilities to support LDR research progress via improved data analysis, classical statistical modeling, machine learning (ML), and the deployment of state-of-the-art artificial intelligence (AI) technologies. Computational biologists within the DOE complex specialize in model development and ML algorithms that can generate predictive models of LDR dose responses for experimental validation. A central focus is generating novel hypotheses and previously unknown biological processes from data-driven modeling efforts.

Key Findings

- BER computational capabilities can help transform LDR research. This potential was highlighted in a recent report by the National Academies of Science, Engineering, and Medicine (NASEM 2022) and in reference to the CANcer Distributed Learning Environment (CANDLE), an interagency collaborative project between BER and the National Cancer Institute. This interagency program applies deep-learning methods on high-performance and leadership-class computing platforms to support cancer research and enable precision medicine. Similar interagency efforts could be transformational in an LDR research program.
- Such computational efforts could be expanded to advance LDR research beyond cancer topics to include, for example, noncancer endpoints such as cardiovascular and neurological outcomes. This approach would fill an existing research gap in BER's current portfolio, which supports (1) interagency collaborations on computational cancer research that is NOT low dose and (2) computational LDR research that is NOT interagency. Existing collaborations between DOE and the U.S. Department of Veterans Affairs could also be extended to integrate this important demographic group in future LDR research. Among other research areas, prior joint work focused on prostate cancer among Million Veterans program members would be important.
- Similar computational tools such as deep-learning methods and digital twins could improve the predictive value of molecular, cellular, and microbiological responses to LDR as well as epidemiological studies. For instance, biological systems, from microbes to plants to humans, could be used as biosensors to detect unexpected or anthropogenic radiation in the environment, thereby improving health and safety and providing insights into how ecosystems respond to LDR.

2.4 Interdisciplinary Research

BER encourages interdisciplinary research and collaboration across various scientific disciplines, fostering partnerships between biologists, environmental scientists, chemists, physicists, and computational scientists both within DOE and with other federal and nonfederal organizations.

Key Findings

- An interdisciplinary LDR research program could follow this same tradition.
- DOE's unique capabilities to advance LDR science could alleviate concerns noted in the public input to the 2022 NASEM report (i.e., the same agency funding the science that determines its own regulatory outcomes).

- Interagency efforts also could provide oversight to the proposed LDR program to mitigate any perceived conflicts of interest with regulatory outcomes and DOE’s own efforts in legacy waste cleanup.

2.5 Support for Early Career Scientists

BER provides opportunities and funding for early career scientists through fellowship and research grant programs which encourage innovative research in biological and environmental sciences.

Key Findings

- The LDR program affords opportunities to fund innovative projects involving early career scientists and to potentially open new areas in research at the intersection of physics and biology.
- When part of interagency efforts, such funding opportunities could promote much-needed interdisciplinary research in LDR effects.

3. LDR Program Scope and Grand Challenges

The effects of LDR exposure remain an important and evolving research field that BER capabilities could significantly advance. Throughout its discussion of such capabilities, the subcommittee identified several grand challenges and research areas considerably relevant to LDR research that define the focus area for a broad research program managed (or coordinated) by BER. These grand challenges involve dosimetry, experimental biological systems, radiation biology and epidemiology data integration, technology integration, computational integration, exposure environments, noncancer adverse LDR health effects, and dose-response correlations.

Addressing these grand challenges will lead to a better understanding of the risks and effects associated with LDR exposure and contribute to improved radiation protection standards and public health. Notably, LDR research is a global endeavor, and fostering international collaboration and data sharing is necessary for pooling knowledge and resources to address these challenges effectively.

3.1 Dosimetry

BER operates and supports a range of research facilities and user facilities that provide scientists with access to cutting-edge instrumentation and expertise. These facilities are used for genomics, proteomics, structural biology, and environmental science research, but they also include capabilities for studying physical phenomena and correlations with biological outcomes.

Key Findings

- For such studies, the specifics of an LDR dose must be defined so that a range of studies and outcomes can be correlated.
- Defining dosimetry (i.e., what needs to be reported and described) remains a grand challenge to advancing LDR research.
- A robust radiation dosimetry harmonization plan should be established.

3.2 Experimental Biological Systems

Choosing an appropriate biological experimental system is essential to produce data that accurately identify the effects of LDR exposure on living organisms and predict potential effects in humans. These experimental systems should allow scientists to study the biological and health consequences of LDR in a controlled and systematic manner. Various experimental biological systems used in radiation research need to be considered in LDR studies in the context of each study's specific research goals and scale. Specific experimental systems selected for study will generally be those most likely to predict the required outcome, namely the effects (qualitative and/or quantitative) of LDR in humans. These experimental systems include, but are not limited to, cell cultures systems, human stem cells, tissue on a chip, *in vitro* 3D organoid systems, and animal systems.

Key Findings

- **Experimental Cell Culture Systems —** *In vitro*–grown bacterial or yeast cells enable researchers to study the immediate effects of radiation exposure on individual cells and observe changes in cell behavior, such as DNA damage, cell cycle alterations, and cellular responses to radiation.

Such cultures can also be examined over relatively short time intervals after exposure. These systems may be less predictive of *in vivo* outcomes but can be very informative in identifying genes and processes that can be used as biomarkers for LDR-induced cancer and noncancer endpoints.

- **Human Stem Cells** — Human stem cells, including induced pluripotent stem cells (iPSCs), are used to create human-derived cell systems for studying radiation effects on specific cell types. These experimental systems can help elucidate, for example, the mechanisms underlying radiation-induced damage and potential repair.
- **Tissue on a Chip** — Advances in this technology now enable researchers to combine multiple systems on one chip that can interact with each other, therefore providing better representations of LDR effects on cellular responses than cell cultures or organoid models.
- ***In Vitro* 3D Organoid Experimental Systems —** Organoid cultures are three-dimensional structures established from cells that mimic the structure and function of specific organs or tissues. These experimental systems can be used to study the effects of LDR on organ-specific responses and offer a bridge between cell culture and experimental animal systems.
- **Experimental Animal Systems —** Researchers have traditionally used animals such as mice and rats to study the effects of LDR on whole organisms. This approach provides insights into systemic responses to radiation exposure, including effects on tissues, organs, and overall health. These animal systems are often used for long-term studies to investigate chronic health effects. Population-based experimental models for determining inter-individual genetic differences, including sex differences in LDR risk assessment, are recommended. Modified genetic mouse strains, humanized mice, and other predictive models of human outcomes may also be used. In addition, recent advances in genome editing of zebrafish may be leveraged for LDR research. The transparency, rapid development, and genetic similarities to humans make the zebrafish model system particularly valuable for studying developmental traits that may be associated with LDR responses.

Researchers can and have used a fairly extensive list of additional cellular and whole-animal experimental systems to successfully identify LDR effects. However, extrapolating from such data to predict human effects at low doses and dose rates is more subjective than for human- or laboratory mammalian animal-based experimental systems. In the end, the choice of experimental biological system is dictated by a study's specific research question and scale, ranging from molecular and cellular responses to systemic health effects. Integrating data from various biological models can provide a comprehensive understanding of LDR effects and help inform radiation protection standards and guidelines. However, as noted, model selection should reflect the current need of predicting adverse effects in humans at low doses and dose rates of radiation.

3.3 Radiation Biology and Epidemiology Data Integration

Accurately assessing the cancer and noncancer risks following exposure to low doses and/or low dose rates of radiation is unlikely from epidemiology studies alone. Thus, any approach to assess LDR risk will require some form of extrapolation from available epidemiological data to the levels of interest (<100 mSv). Integrating radiation biology data obtained at doses close to or at 1 mSv could greatly enhance the risk projection process.

Key Findings

- This integration could be achieved by applying Biologically-Based Dose-Response (BBDR) models. The parameters for such models would be values from radiation epidemiology studies and bioindicators from radiation biology studies. The basis for such an approach is to apply Adverse Outcome Pathway assessments, whereby steps along a pathway from an initial event to the adverse outcome (cancer or noncancer) are characterized by Key Events (KEs). Such KEs can serve as parameters for a BBDR model. Reliance on extrapolation will be minimized, thereby reducing uncertainty in LDR risk projections.
- This type of approach could be considered for inclusion in a LDR research program; it has been applied in several published research studies.

3.4 Technology Integration

Efforts to generate predictive, AI-ready data that capture biological–LDR responses will benefit from integrating both established multiomic capabilities and emerging technologies. This integration—which includes technologies such as advanced imaging (e.g., hyperspectral and cryo-electron microscopy), genomics and other omic capabilities, and computational modeling—could lead to a more comprehensive understanding of LDR effects and potential risks for organisms and ecosystems.

Key Findings

- BER is involved in genomic, transcriptomic, proteomic, and metabolomic research efforts, including integrated multiomic studies of microbial communities in environmental systems, and the development of advanced sequencing and analytical techniques. All could be components of an LDR research program.
- DOE-enhanced investments in both single-cell omics and, more recently, in spatial omics could revolutionize the field and would benefit other programs in an LDR research program. Single-cell omics capabilities and the much-lower cost of high-throughput sequencing could enable researchers to identify and characterize LDR-induced scare mutations and quantify protein expression levels in cells within complex tissues. The latter is particularly important to investigate differential responses of cells and tissues to LDR.
- Molecular markers for noncancer outcomes of LDR exposure need to be considered when establishing biological systems for experimentation; the landscape of health and disease states modulated by LDR remains largely opaque.
- Fourier-transform infrared spectroscopy and other spectroscopy-based approaches are highly sensitive and can be used to detect changes in vibrational modes of molecules due to LDR exposures.
- Scanned ion beam mass spectrometry for protein and transcription levels enables imaging assessment of specific low dose–induced changes at multiple times after exposure across tissue cell types and regions.
- Establishing precise dose-response relationships for LDR exposure is crucial. This involves defining how the incidence of various adverse health effects changes with radiation exposure. Dose-response curves are needed for multiple outcomes for organisms and ecosystems.
- BER currently supports research in the areas of systems biology, synthetic biology, and microbiome science. This research includes studying complex biological systems and their

interactions. This area of research remains largely unexplored but might be considered as a component of an LDR research program if more supporting information can be provided.

3.5 Computational Integration

BER provides access to high-performance computing resources, including supercomputers, for modeling and simulations in areas such as climate science, systems biology, and environmental research. It also invests in (1) predictive numerical model development (multiscale); (2) data assimilation and integration for computational models; and (3) data science and analytics capabilities to process, analyze, and model large datasets generated by biological and environmental research projects. BER also leverages emerging technologies, such as exascale computing, quantum computing, and large language and foundation models, to advance science. All these capabilities could benefit LDR research.

Key Findings

- Such computational methods and resources can be used to design new experiments; increase the sensitivity of existing methods; and analyze results fast and efficiently to test, validate, and improve existing LDR theories.
- New computational methods can leverage the wealth of existing LDR knowledge in the literature, in data collections, and models to build and improve knowledge models and create digital twins for *in silico* testing of new ideas where experiments would be challenging.
- Such computational resources could increase the sensitivity of epidemiological and experimental studies to resolve uncertainties in the Linear No-Threshold (LNT) model within the LDR region.
- Computational integration is also essential to analyze complex biological responses to LDR and identify molecular and cellular markers for acute versus late-onset LDR health outcomes.
- Collaborative computational environments funded by BER can provide a focal point for the LDR community to share datasets, models, software, and insights and foster new collaborations and ideas.

3.6 Exposure Environments

Expanding the range of exposure environments, experimental model systems, and biological variables influencing health outcomes could greatly advance LDR science.

Key Findings

- BER has a long tradition in environmental remediation research, including the development of technologies for cleaning up contaminated sites and addressing issues related to nuclear waste. The latter could be sources of LDR relevant to the proposed research program.
- The DOE national laboratory complex provides access to a wide array of well-characterized exposure environments including alpha, beta, gamma, and X-rays at different energy levels. The importance of mixed-field neutron exposure at low doses to military personnel or first responders should not be excluded.
- Animal and human studies need to address the differential impacts of external exposure versus internal exposure (e.g., inhalation and ingestion) and correlations with health outcomes.
- Other factors such as age, gender, sex, and genetics also need to be considered.

3.7 Noncancer Adverse LDR Health Effects

LDR research to date has generally focused on potential cancer risks (excess cancer risk in exposed individuals). However, it is essential to recognize that with more concentrated exposure, LDR has the potential to induce a range of noncancer responses.

Key Findings

- **Strokes** — Epidemiological studies show direct correlations between low-dose irradiation and the risk of stroke, although the dose response is not linear (Little et al. 2021). Animal studies further suggest that a threshold dose may be needed to increase the risk of stroke but only during acute exposure (around 0.1 Gy in irradiated rats; Takahashi et al. 2020).
- **Cataracts** — Prolonged exposure to low doses of ionizing radiation, particularly to the eyes, has been linked to an excess cataract risk in some cohorts; other ocular endpoints such as glaucoma and macular degeneration have also been proposed for LDR (Little et al. 2021).
- **Cardiovascular Effects** — Occupational and environmental dose levels (<0.5 Gy) may increase the risk of cardiovascular diseases, including atherosclerosis (i.e., hardening of the arteries) and coronary artery disease (Little 2016; Little et al. 2021). As with stroke, the excess risk may depend on whether exposure is acute or chronic (Little et al. 2023).
- **Reproductive and Developmental Effects** — The association between LDR during pregnancy and low birth weight, miscarriage, and stillbirth outcomes suggests that this type of radiation exposure can pose risks to both the developing fetus and the pregnant mother (Frangione et al. 2023).
- **Thyroid Dysfunction —** The thyroid gland is sensitive to radiation exposure, and even low doses of radiation can disrupt its function (Cioffi et al. 2020). This may result in thyroid disorders, including hypothyroidism or hyperthyroidism.
- **Cognitive Effects** — Some studies suggest that LDR exposure may have cognitive effects, particularly in children (Pasqual et al. 2021). LDR has also been positively associated with Parkinson's disease in several cohorts of exposed adults among radiation workers and veterans (Dauer et al. 2023). However, more research is needed to describe these effects and understand the mechanisms of cognitive-related radiation-induced deficit.
- **Immunological Effects** — LDR may permanently alter the immune system, potentially accelerating immune senescence and weakening the body's ability to fight infections (Lumniczky et al. 2021). However, confounding factors such as overall health condition, genetic background, age, and lifestyle can sometimes influence immunological functions in opposing ways. Hence, LDR may be better regarded as an immunomodulatory agent (Lumniczky et al. 2021).
- **Chronic Inflammation** — LDR exposure may trigger chronic inflammation, which is linked to various health conditions. However, anti-inflammatory effects are also possible due to the spectrum of immune modulatory effects associated with LDR (Rödel et al. 2012).
- **Lifespan Shortening —** Some animal studies indicate that prolonged LDR exposure may reduce lifespan under some conditions (e.g., caloric restriction; Yamauchi et al. 2019), although these findings may not directly translate to humans. Beneficial effects such as delays in cellular senescence and increases in lifespan have also been reported (Xu et al. 2022), which may reflect the wide range of immunomodulatory effects associated with LDR exposure.

As with cancer, the relationship between LDR and noncancer outcomes can be complex and may vary depending on several factors such as the type of radiation; the dose; duration of exposure; and an individual's age, genetics, and health status.

3.8 Dose-Response and Dose Rate-Response Relationships

Correlating LDR dose and rate to biological response is key for health risk projections. Radiation dose rate is particularly important: A 12 Gy radiation dose can be considered a High Dose Radiation (HDR) level by the International Commission on Radiologic Units and Measurements when delivered at a rate of 1 h (> 12 Gy/h).

Key Findings

- The LNT model assumes a linear relationship between dose and cancer risk in the low-dose region and cannot predict noncancer outcomes. Furthermore, the model does not consider the effect of low-dose rate on health outcomes.
- BER capabilities in physics and biology research may be leveraged to establish dose-response correlations for LDR exposure and define the magnitude of any dose-effectiveness reduction factors for low-dose rate. This involves defining how the risk of various health effects changes with different levels of radiation exposure.

3.9 Impacts of Advancing LDR Grand Challenge Research

Addressing these grand challenges promises to reduce uncertainties associated with risk projections for low dose and low-dose rate exposures. These improvements, in turn, enhance the development of radiation protection standards and treatments to mitigate any harmful effects of LDR (e.g., radioprotectors and radiation injury treatments). Progress in this area may also inform interventions (e.g., drugs and other treatments) for protecting individuals in cases of accidental exposure or in certain occupational settings with heightened acute and/or chronic LDR exposure risk. BER's research agenda could also advance LDR research in less understood areas, including:

- **Bystander Effect —** Irradiated cells can influence the physiology of neighboring cells, a bystander effect that can lead to unexpected health outcomes, including acute and late-onset disorders.
- **Genomic and Epigenetic Effects** — Investigating how LDR exposure impacts the human genome and epigenome is another key, yet largely unexplored, area of research. Understanding how LDR induces changes to DNA and gene expression and the potential long-term consequences is essential.

4. BER Research Program Complementarity

Research funding for LDR studies has traditionally come from various sources, including government agencies, private foundations, research institutions, and industry. The subcommittee identified BER as uniquely positioned for (1) supporting calibration exercises that will define dosimetry for LDR research and (2) integrating advanced biological and computational technologies into LDR research that leverage BER capabilities in these areas. When assessing biological systems for LDR research, the subcommittee identified complementary, but not duplicative, efforts by other federal programs that could lead to synergistic interagency collaborations. The sections below describe several such programs.

4.1 IARPA TEI-REX Program — Biomarker Discovery

The Intelligence Advanced Research Projects Activity (IARPA) established the Targeted Evaluation of Ionizing Radiation EXposure (TEI-REX) program[4] to address the intelligence community's need for methods to evaluate individuals and organisms exposed to low doses of ionizing radiation (potentially as low as 5cGy). These levels are in the LDR range and scope of a BER program. The methods developed in the TEI-REX program thus could help advance and complement DOE initiatives.

For example, TEI-REX anticipates discovering biomarkers and developing models for radiation exposure using samples that can be collected noninvasively (e.g., through hair, skin, and sweat). The program also studies microbiome responses and adaptations to radiation stimuli. These are biological specimens and population-level model systems that BER could target as well. Additionally, the TEI-REX program is investigating non-transient biomarkers that may reveal acute responses to radiation exposure, an approach that could also be useful to understand LDR effects.

Although the program's initial focus is on developing methods and identifying robust biomarkers at higher radiation exposures, the goal is to move toward the LDR region. Establishing dosimetry standards via calibration exercises is also expected. Thus, there is clear alignment between TEI-REX and BER interests as well as opportunities for collaborations. The TEI-REX program could also be a source of archival samples, data, and models for future characterization leveraging the omics and computational capabilities of BER.

4.2 National Cancer Institute — Archival Tissues and Radio-Epidemiology

Some members of the subcommittee suggested leveraging BER omics capabilities to characterize relevant biospecimens (e.g., archival tissues) using, for example, transcriptomics and single-cell genomics, but other areas of complementarity may exist with federal programs including the National Cancer Institute (NCI) of the National Institutes of Health (NIH). A 2022 LDR report by the National Science and Technology Council (NSTC) provides a comprehensive description of opportunities to advance LDR research in areas of overlap among federal agencies, such as big data epidemiological studies, enhanced animal models, and mechanistic studies toward biomarker identification (NSTC 2022).

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[4] www.iarpa.gov/research-programs/tei-rex

Radio-epidemiology research is particularly important, as it can identify linkages between low-dose irradiation and various noncancer health outcomes to guide the proposed LDR program. Also important is coordinating efforts in this space with other DOE programs, such as the U.S. Transuranium and Uranium Registries,[5] as well as international cooperative programs such as the Radiation Effects Research Foundation,[6] a U.S.-Japan cooperative research institute for the study of health impacts from atomic bomb radiation. Such synergies can greatly facilitate LDR research to address many unresolved questions.

4.3 DoD AFRRI — Animal Models

The U.S. Department of Defense (DoD) at the Armed Forces Radiobiology Research Institute (AFRRI) has a long-running program (more than 63 years) in radiation health research. AFFRI has multiple radiation sources including, a Training, Research, Isotopes, General Atomics (TRIGA) Mark-4 Reactor; high- and low-level cobalt-60 facilities; a linear accelerator; a small animal radiation research platform (SARRP); and a computerized tomography (CT) scanner. AFRRI has several animal models available for LDR research including nonhuman primates, swine, ferrets, and rodents.

Most of AFRRI's research has traditionally centered on high-dose radiation and acute radiation syndrome, but the focus has more recently expanded to include low dose. After a nuclear accident or detonation, military personnel could be exposed to high, low, or a combination of radiation dose and dose-rate exposures.

AFRRI leads countermeasure development efforts to identify novel biomarkers of exposure. Recent emphasis in LDR exposures has focused on nonlethal effects, including cognitive decline, neurobiology, and cardiotoxicity at low mixed-field neutron exposures followed by low-dose-rate gamma exposure. However, DoD's LDR program is not funded to a level to contribute to a change in military operational exposure guidance. LDR studies would greatly benefit military readiness following a nuclear detonation. Moreover, DoD would benefit from a training program to increase lost radiation biology expertise.

4.4 NASA — Memorandum of Understanding with DOE

Understanding the health effects of low-dose cosmic radiation is critical to advancing space exploration. Exposure to low-dose space radiation can lead to immune system dysregulation and metabolic reprogramming (Li et al. 2015; Laiakis et al. 2021) consistent with other noncancer health outcomes observed during occupational or environmental LDR exposure on Earth. This affords many opportunities for synergies between LDR programs at DOE and NASA, potentially through a memorandum of understanding. Additional information about NASA's radiation research can be found in the NSTC LDR report (NSTC 2022).

4.5 Other Potential Collaborations

Additional government agencies and foundations, both national and international, have overlapping interests in radiation research and may be also considered for joint LDR Requests for Applications.

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[5] ustur.wsu.edu

[6] www.rerf.or.jp/en/

Government Agencies

- **U.S. Nuclear Regulatory Commission (NRC) —** NRC funds research related to the regulation and safety of nuclear materials and radiation sources.
- **U.S. Environmental Protection Agency (EPA) —** EPA supports research on environmental radiation and its impact on human health and ecosystems.
- **National Institutes of Health —** NIH provides funding for radiation research. Some of the intramural and extramural programs focused on basic, clinical, and epidemiologic research in radiation-exposed populations also include LDR exposures as a program element. For example, the Radiation Therapeutics and Biology Study Section focuses "on therapeutic interactions of ionizing radiation, radionuclides, electromagnetic radiation, and heat at the molecular, cellular, organ, and patient levels." The type of radiation is one of the exposure variables considered by this NIH program.
- **National Cancer Institute —** NCI is the federal government's principal agency for cancer research and training and the largest funder of cancer research in the world.

International Research Programs

- **Canadian Nuclear Laboratories (CNL) —** CNL's LDR research program is regarded as "the world's most robust, centrally coordinated and long-lived" (Wang et al. 2019). In addition to mechanistic studies, CNL has expanded its research focus to areas highlighted in this report, such as dosimetry, therapeutical use of LDR, and health impacts of space radiation (Wang et al. 2019).
- **International Atomic Energy Agency (IAEA):** IAEA supports research on radiation safety, radiation protection, and related areas worldwide[7].
- **European Commission (EC):** The EC funds research in Europe, including studies on LDR and its effects. Some of the current programs (Cho et al. 2019) fund research on:
    - LDR risk, such as the Multidisciplinary European Low Dose Initiative (MELODI). The MELODI platform[8] interfaces with other international partners such as IAEA.
    - Radioecology, including the European Radioecology Alliance (ALLIANCE).
    - Dosimetry, such as the European Radiation Dosimetry Group (EURADOS).

Private Foundations

- Foundations, such as the American Cancer Society and the Lasker Foundation, may provide research grants and fellowships for radiation research, including LDR studies.

Industry and Private Sector

- Private companies and organizations in the nuclear industry, medical imaging, and radiation therapy may fund research on radiation-related topics, including LDR.

Nonprofit Organizations

- Nonprofit organizations focused on radiation safety and public health, such as the Health Physics Society, may offer research grants and support for relevant studies.

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[7] www.iaea.org/topics/radiation-protection/patients

[8] melodi-online.eu/

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Acronyms and Abbreviations

3D	three dimensional
AFFRI	Armed Forces Radiobiology Research Institute
ALARA	As Low As Reasonably Achievable
ALLIANCE	European Radioecology Alliance
AI	artificial intelligence
ARS	acute radiation syndrome
BBDR	Biologically-Based Dose-Response models
BERAC	Biological and Environmental Research Advisory Committee
BER	DOE Biological and Environmental Research program
CANDLE	CANcer Distributed Learning Environment
CT	computerized tomography
CAT	computed axial tomography
CNL	Canadian Nuclear Laboratories
DoD	U.S. Department of Defense
DOE	U.S. Department of Energy
EC	European Commission
EM	electromagnetic
EPA	U.S. Environmental Protection Agency
EURADOS	European Radiation Dosimetry Group
IAEA	International Atomic Energy Agency
IARPA	Intelligence Advanced Research Projects Activity
ICRP	International Commission on Radiological Protection
iPSCs	induced pluripotent stem cells
KEs	Key Events
LDRR	BER’s former Low Dose Radiation Research program
LDR	low-dose radiation
LNT	Linear No-Threshold
MELODI	Multidisciplinary European Low Dose Initiative
ML	machine learning
NASEM	National Academies of Science, Engineering, and Medicine
NCI	National Cancer Institute
NIH	National Institutes of Health
NSTC	National Science and Technology Council
PET	positron emission tomography
SARRP	small animal radiation research platform
TEI-REX	Targeted Evaluation of Ionizing Radiation Exposure program
TRIGA	Training, Research, Isotopes, General Atomics