Assessment of BER Research in Low-Dose Radiation (LDR)

Gemma Reguera, Subcommittee Chair

BERAC report – Update

April 12, 2024

U.S. DEPARTMENT OF ENERGY | Office of Science

2023 Spring BERAC meeting – New Charge

"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.*"

Charge items:

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, computation)?
2. 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?
3. 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?

https://science.osti.gov/-/media/ber/berac/pdf/202304/2023-183_BERAC_Low_Dose_Charge_Letter_AA-Berhe-Signed.pdf

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Historical background:

- DOE (and its predecessor entities) has a long history of supporting basic research to understand the effects of radiation on living systems.
- 1998-2016: Recent BER program on Low Dose Radiation Research (LDRR)
    - 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.
    - Program ended as BER shifted its portfolio more towards DOE's bioenergy and environmental science needs.

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Resources:

- 2016 report by BERAC Subcommittee on Low Dose Radiation

"The report clearly states that further research into this area is **unlikely to yield 'conclusive' results**. Furthermore, this type of research **does not align with current BER priorities**. Therefore, the BERAC feels strongly that further research on low dose radiation within BER is not warranted."

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The report clearly states that further research into this area is **unlikely to yield 'conclusive' results**. Furthermore, this type of research **does not align with current BER priorities**. Therefore, the BERAC feels strongly that further research on low dose radiation within BER is not warranted.

"However, the report does indicate some **opportunity to reduce uncertainty** in this area. It is our understanding that DOE is already supporting **computational resources** [*to a cross-agency effort toward such a goal*]."

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Resources:

- 2016 report by BERAC Subcommittee on Low Dose Radiation
- 2022 NASEM report: *Leveraging Advances in Modern Science to Revitalize Low-Dose Radiation Research in the United States*
  - Widespread (and increasing) occupational exposure
    - Medical, industrial, military and commercial settings

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  - Widespread (and increasing) occupational exposure
  - Involuntary environmental exposures to vulnerable communities
    - Indigenous communities; atomic veterans; nuclear workers; uranium miners, millers, transporters, and their families; radioactive contamination (nuclear weapons testing/production/waste cleanup)

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  - Widespread (and increasing) occupational exposure
  - Involuntary environmental exposures – environmental injustice
  - Narrow focus of research – epidemiological studies, cancer outcomes
    - Expand biological systems
    - Consider non-cancer health outcomes (cardiovascular disease, neurological disorders, immune dysfunction, and cataracts).

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- 2022 Physical Sciences Subcommittee (PSSC), National Science and Technology Council (NSTC) report – *Radiation Biology: A Response to the American Innovation and Competitiveness Act*

Risk estimates for adverse health outcomes from low-doses and low-dose rates of radiation are uncertain => **uncertainty in regulations** for protection from radiation

BERAC subcommittee formation

Gemma Reguera, Chair, Michigan State University

Michael Bellamy, Memorial Sloan Kettering Cancer Center

Terry Brock, U.S. National Regulatory Commission

Robert F. Fischetti, Argonne National Laboratory

Heather Henry, National Institutes of Health

Evagelia C. Laiakis, Georgetown University

Alexandra Miller, U.S. Department of Defense

R. Julian Preston, U.S Environmental Protection Agency

Lindsay Morton, National Institutes of Health

Antoine Snijders, Lawrence Berkeley National Laboratory

Jeremy Schmutz, HudsonAlpha Institute for Biotechnology

Mariann Sowa, National Aeronautics and Space Administration

Rick Stevens, Argonne National Laboratory

Georgia Tourassi, Oak Ridge National Laboratory

Kerstin Kleese van Dam, Brookhaven National Laboratory

Tristram West
Designated Federal Officer (U.S. DOE-BER)

Goals:

To **discuss** potential research opportunities for BER in low-dose radiation (LDR)

To produce a **report** with sufficient information for BER.

BERAC subcommittee process

1) **Subcommittee meetings:**
   - **Meeting #1** – Introductory meeting [Deliver the charge]
   - **Meeting #2** – Charge item #1 [BER capabilities]
   - **Meeting #3** – Charge item #2 [Program scope]
   - **Meeting #4** – Charge item #3 [Effort complementarity]

2) **BERAC briefing:** By subcommittee chair in the Fall 2023.

2) **Draft Report:** Initiated by subcommittee chair and incorporating feedback from BERAC and all subcommittee members.

4) **Final report:** A short report documenting the final response to the charge.

BERAC subcommittee process

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- **Meeting #2** – Charge item #1 [BER capabilities]
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- **Meeting #4** – Charge item #3 [Effort complementarity]

1. Rationale

2. BER capabilities

3. Program scope

4. Effort complementarity

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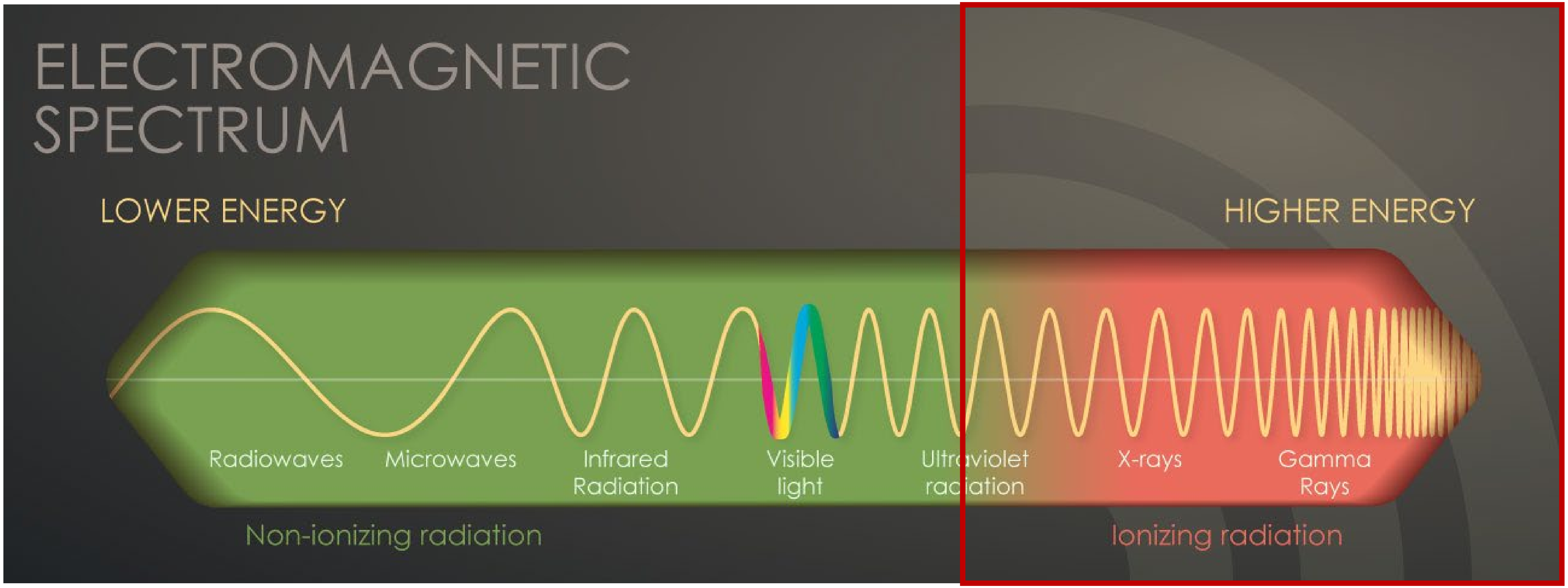
1. Rationale for a BER-Managed LDR Research Program

1.1) Background



https://www.cdc.gov/nceh/radiation/ionizing_radiation.html

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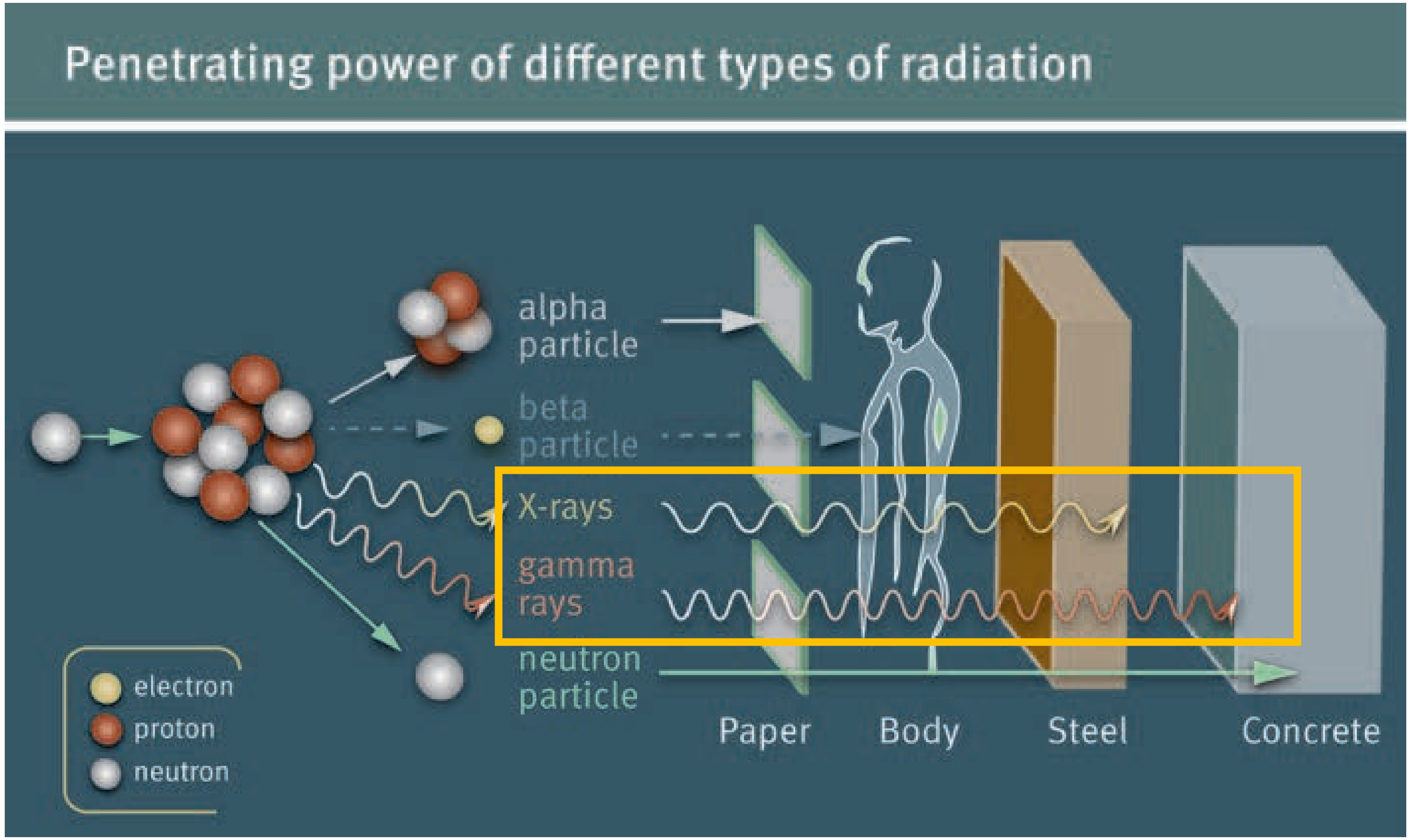
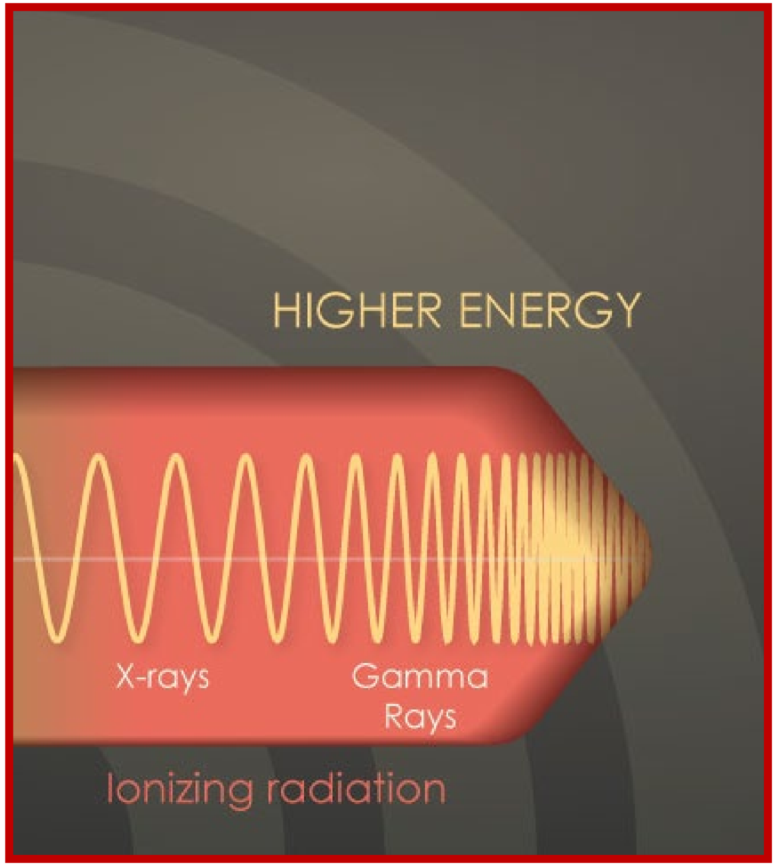


https://energyeducation.ca/encyclopedia/Dosage

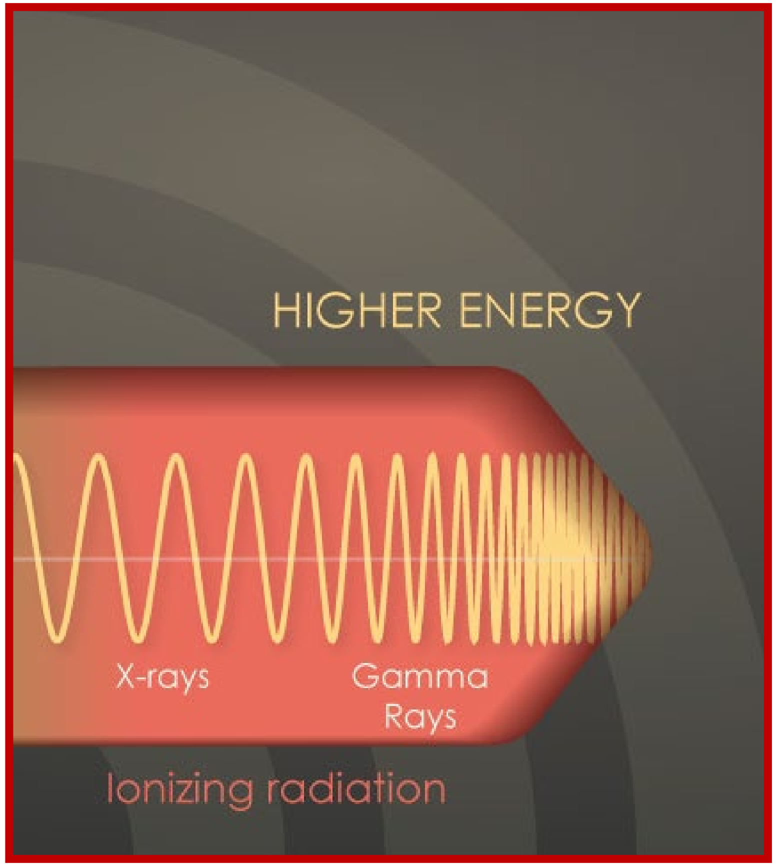


1. Rationale for a BER-Managed LDR Research Program

1.1) Background

SI units:

- <u>Adsorbed dose unit</u> – **Gray (Gy)**
  Absorption of 1 Joule of energy by 1 kg of matter
- <u>Effective dose unit</u> – **Sievert (Sv)**
  Equivalent of 1 Gy of high-penetration X-rays adsorbed by living matter (estimated health risk).



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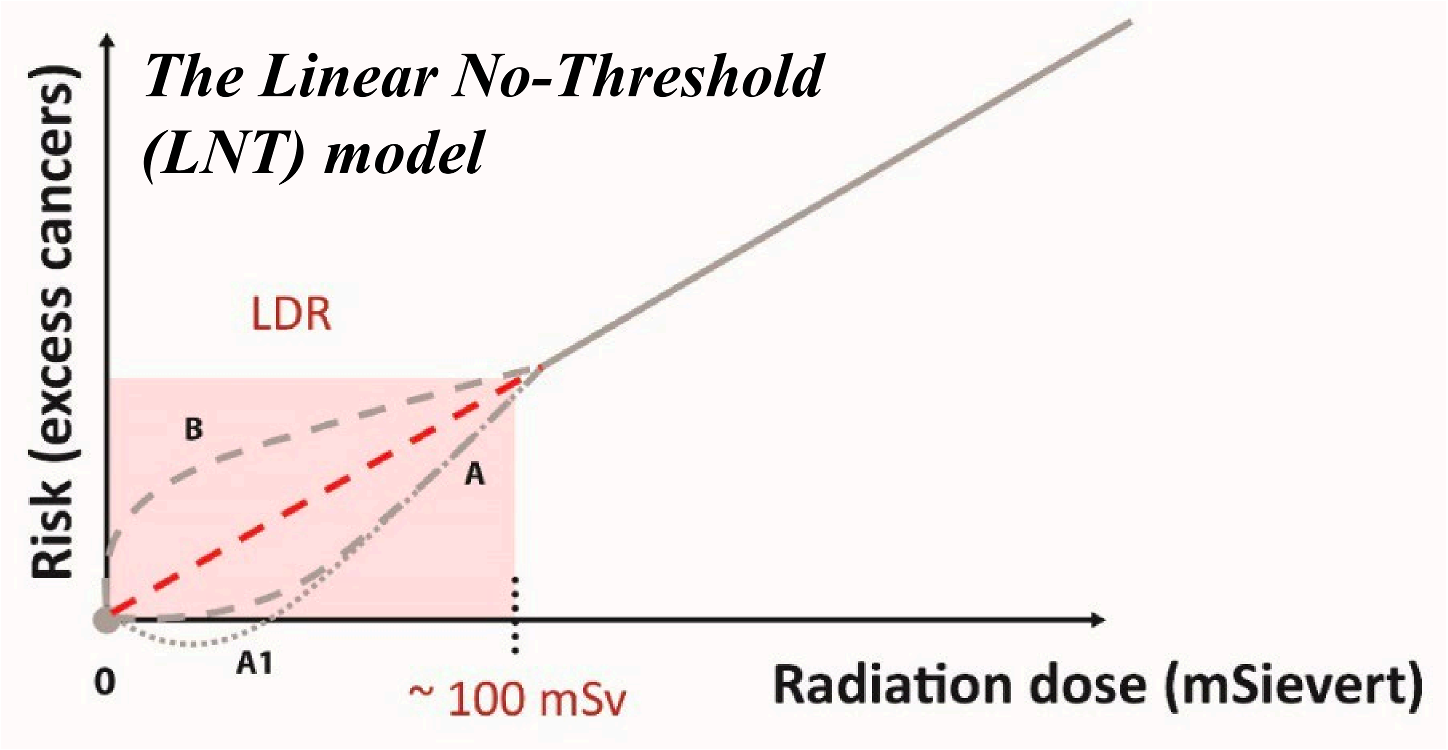
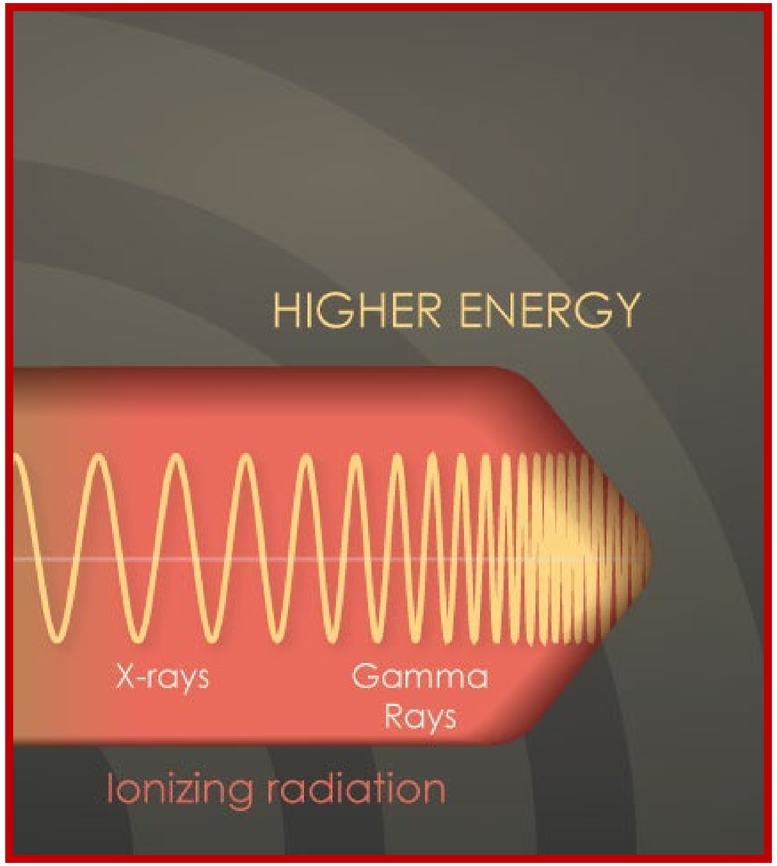


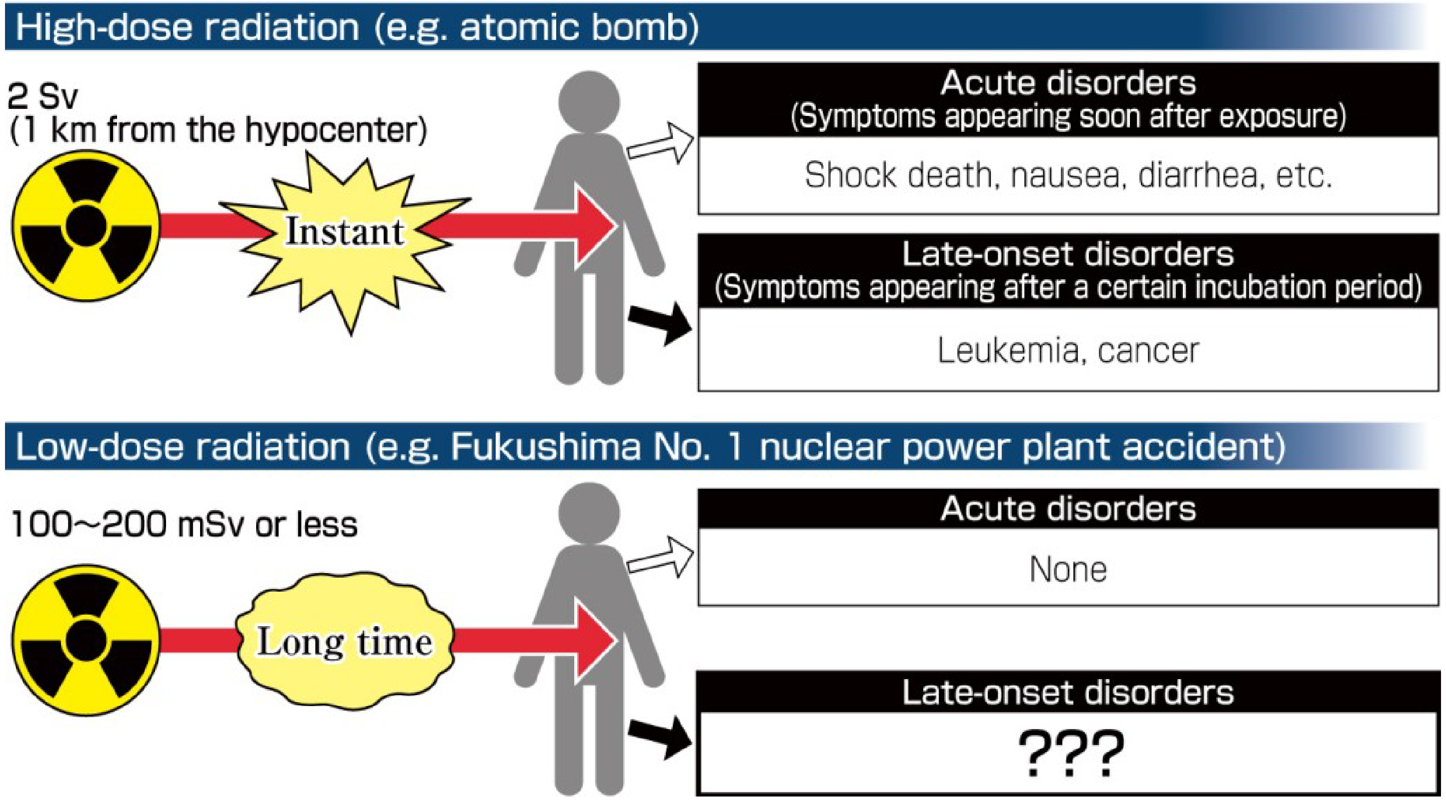


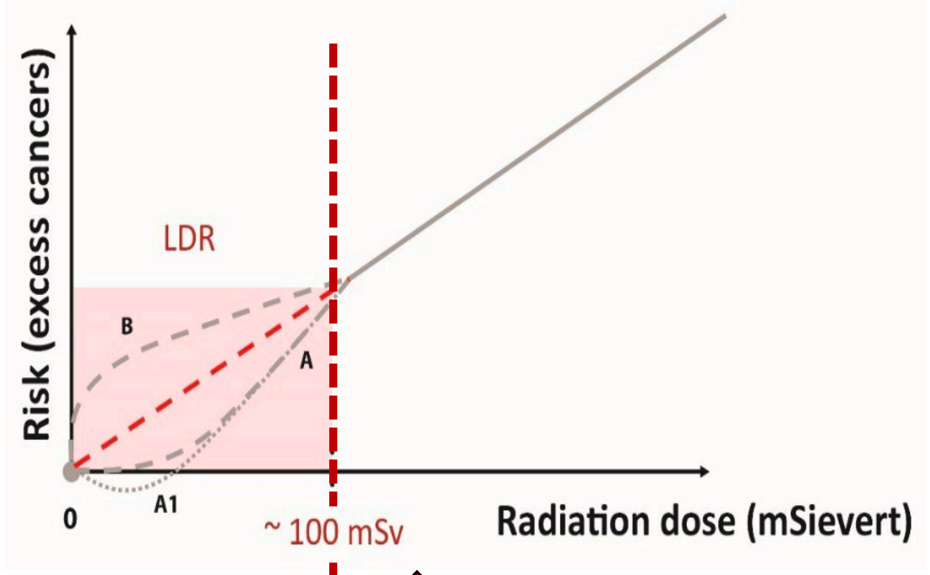
Modified with permission from the Swiss Federal Nuclear Safety Inspectorate ENSI, www.ensi.ch/en/2022/02/10/radiation-biology-3-5-low-doses-and-their-damage-potential/

1. Rationale for a BER-Managed LDR Research Program

1.1) Background

Type of radiation exposure matters (dose and dose rate)





Health risk?

Excess cancer risk

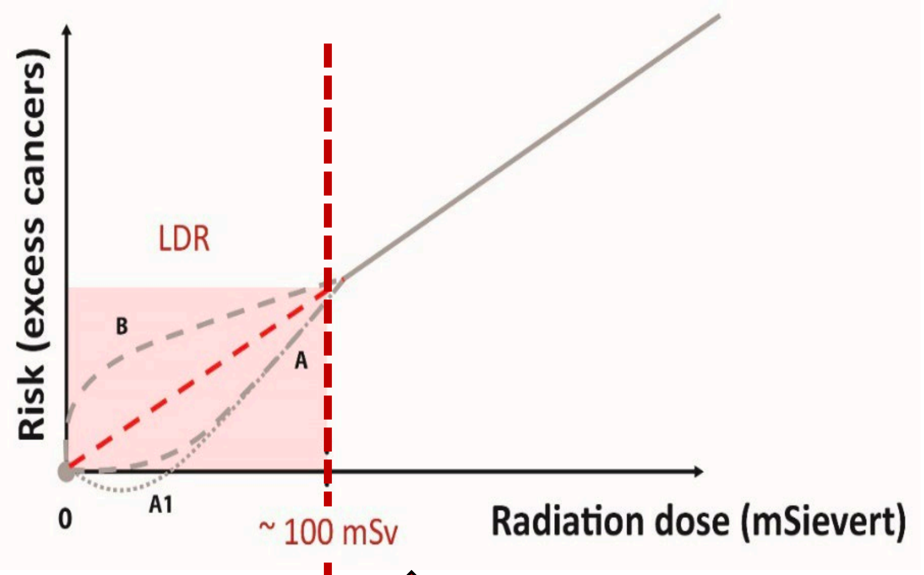
https://www.hiroshimapeacemedia.jp/?p=84674

1. Rationale for a BER-Managed LDR Research Program

1.1) Background

Sources of LDR:

- **Natural**
  - Space (cosmic, solar) – Air travel
  - Terrestrial (e.g., radon gas)
- **Man-made**
  - Medical diagnostics (X-rays, CT/CAT/PET scans, fluoroscopy)
  - Nuclear power sources
  - Nuclear accidents, weapon testing
  - Consumer products (smoke detectors, luminous paints, clock dials)



Health risk?

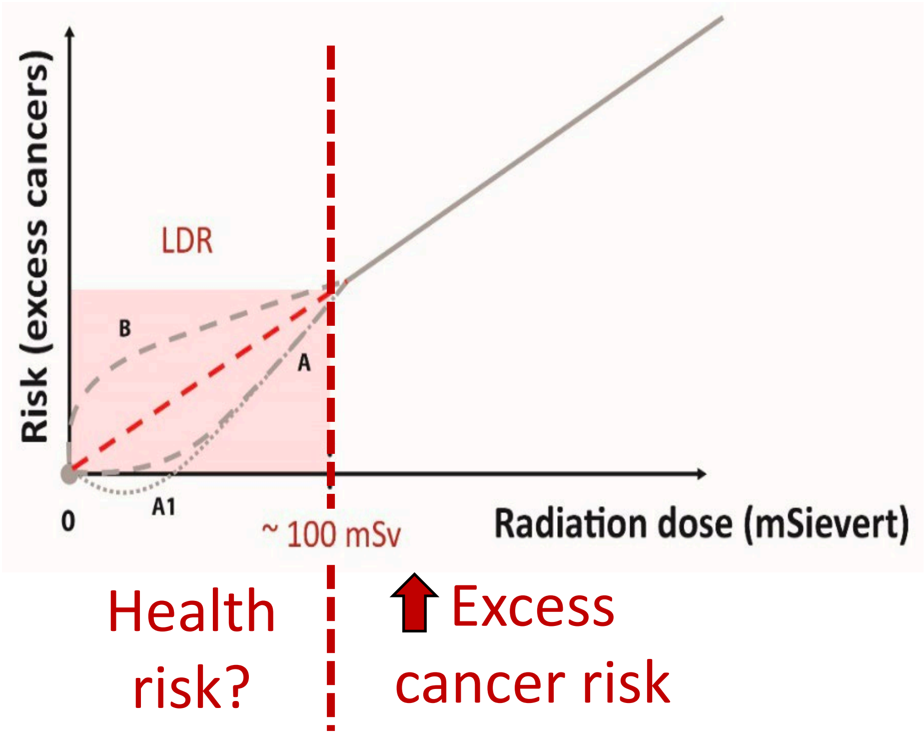
Excess cancer risk

1. Rationale for a BER-Managed LDR Research Program

1.2) Scientific need

The **LNT model** is appropriate for the field of radiation protection. Yet…

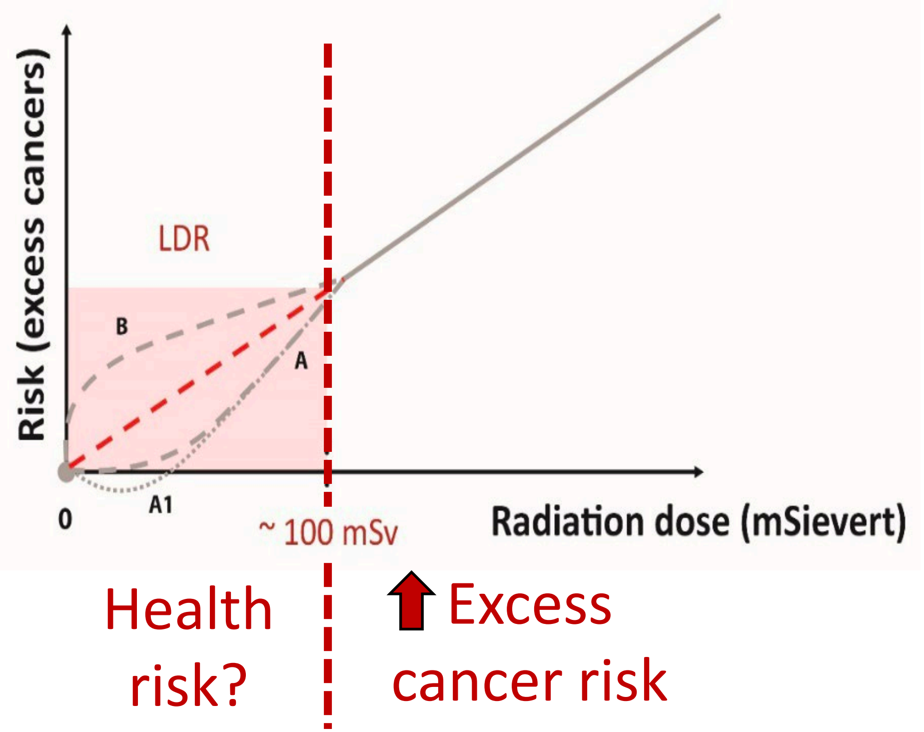
- An incomplete understanding of the **underlying science** limits its interpretation.
  - *Non-cancer outcomes*
- Neither radiobiology nor epidemiology provides evidence of this **model's accuracy at low doses**.
  - *Health risks in the LDR?*



1. Rationale for a BER-Managed LDR Research Program

1.3) Grand challenges

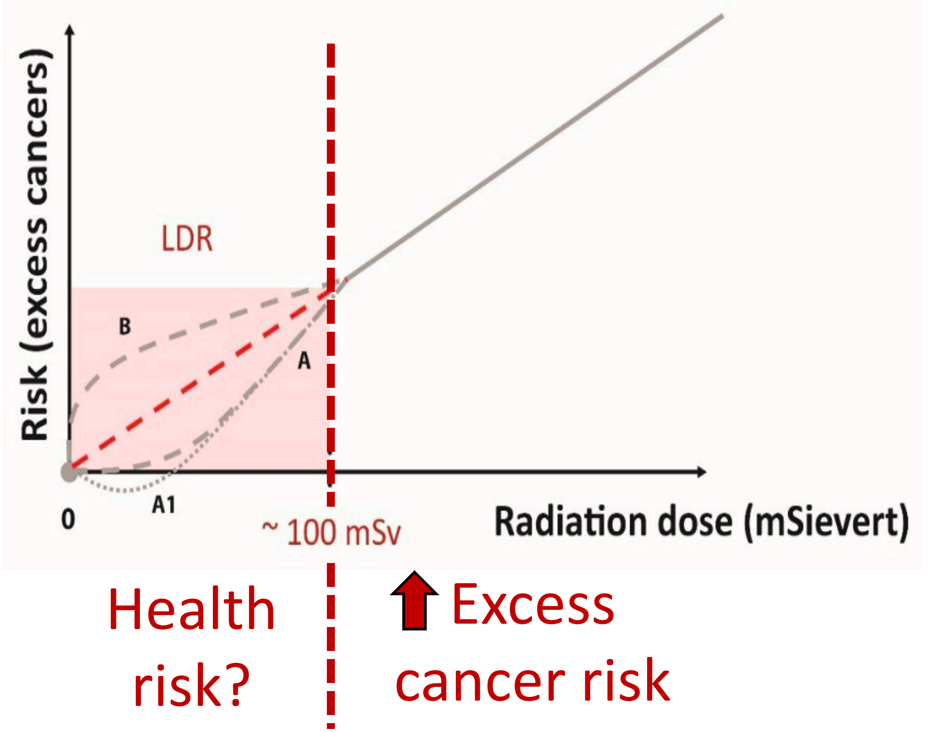
- Controlled LDR emission and calibration standards
- Biological systems for studies
- Integration of large datasets/variables and predictive modeling



1. Rationale for a BER-Managed LDR Research Program

1.3) Grand challenges

- ❖ Controlled LDR emission and calibration standards
  - ○ ***BER capabilities in this area***
- ❖ Biological systems for studies
  - ○ ***BER success in the study of complex biological systems at various scales***
- ❖ Integration of large datasets/variables and predictive modeling
  - ○ ***BER omics and computational capabilities***



1. Rationale for a BER-Managed LDR Research Program

1.4) Scientific opportunities for BER

- **Mission:** Transformative science and scientific user facilities to achieve a predictive understanding of *complex biological systems* for energy and infrastructure security, independence, and *prosperity*.
- **Programming:** BER success in programs to *advance understanding of biological processes* at *various scales* (from molecular and genomics-controlled scales to much larger scales).
- **History:** Long history in supporting basic research to understand the *effects of radiation on living systems*.

1. Rationale for a BER-Managed LDR Research Program

1.5) Report conclusions

- 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.

2. BER capabilities for LDR research

Charge Question #1: [*What are the capabilities*?]
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)?

2. BER capabilities for LDR research

2.1) Controlled LDR Emission and Calibration Standards

Key for data reproducibility and cross-comparisons of LDR studies but require specialized equipment, instrumentation, and expertise.

Key Findings

- DOE is the only federal agency with *capabilities and instrumentation for LDR dose control and calibration* in experiments at all scales.

2. BER capabilities for LDR research

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Key for data reproducibility and cross-comparisons of LDR studies but require specialized equipment, instrumentation, and expertise.

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.

2. BER capabilities for LDR research

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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.
- Dosimetry and calibration standards (provided by national laboratories) will enable physics–biology correlations and <u>*accurate description of the radiation dose and rate in biological systems*</u>.

2. BER capabilities for LDR research

2.2) Biological Capabilities

Translating broader biological research to LDR research ultimately depends on generating reproducible data from biological model systems.

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 as well as epidemiological studies.

2. BER capabilities for LDR research

2.2) Biological Capabilities

Translating broader biological research to LDR research ultimately depends on generating reproducible data from biological model systems.

Key Findings

- BER capabilities in genome biology, population-based model systems, and computation.
- *Molecular and cellular studies could fill knowledge gaps* that epidemiological studies cannot address.
  - Experimentally refine the LNT model from right (macroscale) to left (molecular/microscale) to link radiation dose to cancer and noncancer outcomes.

2. BER capabilities for LDR research

2.2) Biological Capabilities

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Key Findings

- BER capabilities in genome biology, population-based model systems, and computation.
- Molecular and cellular studies could fill knowledge gaps that epidemiological studies cannot address.
- Deepening the understanding of biological responses to LDR stressors could lead to *biological and medical breakthroughs in other fields*.
    - Importance of archiving biological research data in public databases

2. BER capabilities for LDR research

2.2) Biological Capabilities

Translating broader biological research to LDR research ultimately depends on generating reproducible data from biological model systems.

Key Findings (continued)

- *Internal exposure* to LDR (e.g., inhalation) is a critical and unaddressed knowledge gap.

2. BER capabilities for LDR research

2.2) Biological Capabilities

Translating broader biological research to LDR research ultimately depends on generating reproducible data from biological model systems.

Key Findings (continued)

- 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. BER capabilities for LDR research

2.3) Computational Capabilities

BER's advanced computational capabilities (improved LDR data analysis, classical statistical modeling, machine learning (ML), and the deployment of state-of-the-art artificial intelligence (AI) technologies) could generate:

- *predictive models* of LDR dose responses *for experimental validation*
- *novel hypotheses* and previously unknown biological processes from data-driven modeling efforts.

2. BER capabilities for LDR research

2.3) Computational Capabilities

Key Findings

- BER computational capabilities can help transform LDR research.
  - Synergistic interagency efforts could be transformational.
  - ✓ Example: CANcer Distributed Learning Environment (CANDLE), an interagency collaborative project between BER and the National Cancer Institute that applies deep-learning methods on high-performance and leadership-class computing platforms to support *cancer research* and enable *precision medicine*.

2. BER capabilities for LDR research

2.3) Computational Capabilities

Key Findings

- BER computational capabilities can help transform LDR research.
- Efforts could be expanded to advance LDR research ***beyond cancer*** topics (e.g., noncancer endpoints such as cardiovascular and neurological outcomes).
  - Opportunity to fill an existing research gap in BER's current portfolio:
    - ✓ interagency collaborations on computational cancer research that is NOT low dose and
    - ✓ computational LDR research that is NOT interagency.

2. BER capabilities for LDR research

2.3) Computational Capabilities

Key Findings

- BER computational capabilities can help transform LDR research.
- Efforts could be expanded to advance LDR research *beyond cancer* topics (e.g., noncancer endpoints such as cardiovascular and neurological outcomes).
  - Opportunity to fill an existing research gap in BER's current portfolio:
  - Leverage existing collaborations between DOE and the U.S. Department of Veterans Affairs to integrate this important demographic group in future LDR research.
    - ✓ Prior joint work focused on prostate cancer among Million Veterans program members.

2. BER capabilities for LDR research

2.3) Computational Capabilities

Key Findings

- BER computational capabilities can help transform LDR research.
- Efforts could be expanded to advance LDR research beyond cancer topics (e.g., noncancer endpoints such as cardiovascular and neurological outcomes).
- Computational tools (e.g., deep-learning methods) could improve the predictive value of biological responses to LDR at all scales (molecular, cellular, microbiological, epidemiological).
    - Biological systems (microbes, plants, humans) used as biosensors to detect radiation threats, thereby improving health and safety and providing insights into how ecosystems respond to LDR.

2. BER capabilities for LDR research

2.4) Interdisciplinary Research

Key to advance LDR research.

Key Findings

- An LDR program would follow the BER tradition of encouraging *interdisciplinary research and collaboration* across various scientific disciplines.
  - ✓ Record of fostering partnerships between biologists, environmental scientists, chemists, physicists, and computational scientists both within DOE and with other federal and nonfederal organizations.

2. BER capabilities for LDR research

2.4) Interdisciplinary Research

Key to advance LDR research.

Key Findings

- An LDR program would follow the BER tradition of encouraging interdisciplinary research and collaboration across various scientific disciplines.
- <u>*DOE's unique capabilities*</u> for LDR science addresses 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*).

2. BER capabilities for LDR research

2.4) Interdisciplinary Research

Key to advance LDR research.

Key Findings

- An LDR program would follow the BER tradition of encouraging interdisciplinary research and collaboration across various scientific disciplines.
- DOE's unique capabilities for LDR science addresses 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. BER capabilities for LDR research

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

Charge question #2: [*What does the program include*?]
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?

YES!
Broad LDR research program managed (or coordinated) by BER to address *grand challenges*.

1. Dosimetry
2. Experimental biological systems,
3. Integration of science areas, technology, computation
4. Exposure environments
5. Noncancer adverse LDR health effects, and
6. Dose-response correlations.

3. LDR Program Scope and Grand Challenges

3.1) Dosimetry

BER capabilities for studying physical phenomena and correlations with biological outcomes.

Key Findings

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

3. LDR Program Scope and Grand Challenges

3.2) Experimental Biological Systems

Several experimental biological systems should be considered to address specific questions in LDR research, provided they allow for:

1) controlled, systematic experimentation and
2) extrapolation of LDR effects to humans.

3. LDR Program Scope and Grand Challenges

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2) extrapolation of LDR effects to humans.

Individual cells → Organisms

Bacteria, yeast
Short time, molecular work
Less predictive, useful for biomarkers

Human-derived cell lines
Specific cell types
LDR damage and repair

Tissue-on-a-chip
Specific tissues built on chips
Organ-specific cellular responses to LDR

Organoids
3D organ mimics
Organ-specific responses, development

Whole animals
Mice and rats (systemic, chronic, population outcomes)
Zebrafish (genome editing, developmental traits)

3. LDR Program Scope and Grand Challenges

3.3) Radiation Biology and Epidemiology Data Integration

Epidemiological studies alone cannot predict noncancer outcomes nor health risks from LDR. Some form of extrapolation is needed.

Key Findings

- Radiation biology data (doses as low as 1 mSv) can be used to extrapolate epidemiological data.

3. LDR Program Scope and Grand Challenges

3.3) Radiation Biology and Epidemiology Data Integration

Epidemiological studies alone cannot predict noncancer outcomes nor health risks from LDR. Some form of extrapolation is needed.

Key Findings

- Radiation biology data (doses as low as 1 mSv) can be used to extrapolate epidemiological data.
- Integration via Biologically-Based Dose-Response (BBDR) models.
  - Radiation epidemiology data (cancer or noncancer outcomes) + bioindicators from radiation biology studies.
  - Applies Adverse Outcome Pathway assessments to identify “Key Events” from an initial event to the adverse outcome.
  - Reduces uncertainty in LDR risk projections.

3. LDR Program Scope and Grand Challenges

3.4) Technology integration

Integrating both established multiomics and emerging technologies (advanced imaging, single-cell omics, computational modeling) is needed to generate predictive, AI-ready data that capture biological LDR responses.

Key Findings

- BER is involved in integrated *multiomic studies* of microbial communities in environmental systems, and in the development of *advanced sequencing and analytical techniques*. Similar approaches could be applied to LDR.

3. LDR Program Scope and Grand Challenges

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Key Findings

- BER is involved in integrated *multiomic studies* of microbial communities in environmental systems, and in the development of *advanced sequencing and analytical techniques*. Similar approaches could be applied to LDR.
- DOE-enhanced investments in both *single-cell omics* and, more recently, in *spatial omics* could revolutionize the field and would benefit other programs beyond the LDR research program.

3. LDR Program Scope and Grand Challenges

3.4) Technology integration

Integrating both established multiomic and emerging technologies (advanced imaging, single-cell omics, computational modeling) is needed to generate predictive, AI-ready data that capture biological LDR responses.

Key Findings (continued)

- Establishing *precise dose-response relationships* for LDR exposure for multiple LDR outcomes and from organisms and ecosystems.
    - *Spectroscopy-based approaches* (e.g., Fourier-transform infrared spectroscopy) 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.

3. LDR Program Scope and Grand Challenges

3.4) Technology integration

Integrating both established multiomic and emerging technologies (advanced imaging, single-cell omics, computational modeling) is needed to generate predictive, AI-ready data that capture biological LDR responses.

Key Findings (continued)

- BER's research in *systems biology, synthetic biology, and microbiome science* could be expanded to LDR (if more supporting information can be provided).

3. LDR Program Scope and Grand Challenges

3.5) Computational Integration

Importance of integrating BER's high-performance computing resources, as well as data science and analytics capabilities for modeling and simulations. Also leveraging emerging technologies, such as exascale computing, quantum computing, and large language and foundation models, to advance LDR science.

Key Findings:

- Help design new experiments; increase the sensitivity of existing methods; and analyze results fast and efficiently to test, validate, and improve existing LDR theories.

3. LDR Program Scope and Grand Challenges

3.5) Computational Integration

Importance of integrating BER's high-performance computing resources, as well as data science and analytics capabilities for modeling and simulations. Also leveraging emerging technologies, such as exascale computing, quantum computing, and large language and foundation models, to advance LDR science.

Key Findings (continued)

- Mine the LDR literature, 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.
- Increase the sensitivity of epidemiological and experimental studies to resolve uncertainties in the LNT model within the LDR region.

3. LDR Program Scope and Grand Challenges

3.5) Computational Integration

Importance of integrating BER's high-performance computing resources, as well as data science and analytics capabilities for modeling and simulations. Also leveraging emerging technologies, such as exascale computing, quantum computing, and large language and foundation models, to advance LDR science.

Key Findings (continued)

- 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. LDR Program Scope and Grand Challenges

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.

3. LDR Program Scope and Grand Challenges

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:

- 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.

3. LDR Program Scope and Grand Challenges

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:

- 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. LDR Program Scope and Grand Challenges

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:

- Strokes
  - Direct but nonlinear correlations between LDR and the risk of stroke in epidemiological studies
  - A threshold dose may be needed to increase the risk of stroke but only during acute exposure (around 0.1 Gy in irradiated rats)

3. LDR Program Scope and Grand Challenges

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:

- Strokes
- Cataracts
  - Prolonged LDR exposure, 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

3. LDR Program Scope and Grand Challenges

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:

- Strokes
- Cataracts
- Cardiovascular effects
    - Occupational and environmental dose levels (<0.5 Gy) may increase the risk of cardiovascular diseases
    - As with stroke, the excess risk may depend on whether exposure is acute or chronic

3. LDR Program Scope and Grand Challenges

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:

- Strokes
- Cataracts
- Cardiovascular effects
- Reproductive and developmental effects
    - Association between LDR during pregnancy and low birth weight, miscarriage, and stillbirth

3. LDR Program Scope and Grand Challenges

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:

- Strokes
- Cataracts
- Cardiovascular effects
- Reproductive and developmental effects
- Thyroid dysfunction
  - Hypo or hyperthyroid

3. LDR Program Scope and Grand Challenges

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:

- <u>Cognitive effects</u>
  - LDR-induced cognitive deficits, particularly in children
  - Positive association with Parkinson's disease in several cohorts of exposed adults among radiation workers and veterans

3. LDR Program Scope and Grand Challenges

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:

- Cognitive effects
- Immunological effects
  - Permanent changes in the immune system that could accelerate immune senescence and weaken the body's ability to fight infections
  - Confounding factors (overall health condition, genetic background, age, and lifestyle) that could influence immunological functions in opposing ways.
  - LDR may be better regarded as an *immunomodulatory agent*

3. LDR Program Scope and Grand Challenges

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:

- Cognitive effects
- Immunological effects
- Chronic Inflammation
  - LDR exposure may trigger chronic inflammation (linked to various health conditions).
  - Anti-inflammatory effects are also possible due to the spectrum of immune modulatory effects associated with LDR

3. LDR Program Scope and Grand Challenges

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:

- Cognitive effects
- Immunological effects
- Chronic Inflammation
- Lifespan shortening
    - Animal studies suggest that prolonged LDR exposure may reduce lifespan under some conditions (e.g., caloric restriction)
    - Beneficial effects have also been reported (reflecting wide range of immunomodulatory effects of LDR)

3. LDR Program Scope and Grand Challenges

3.8) Dose-Response and Dose Rate-Response Relationships

Correlating LDR dose and rate to biological response is key for health risk projections.

Key Findings

- The LNT model does not consider non-cancer outcomes nor 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. LDR Program Scope and Grand Challenges

3.9) Impacts of Advancing LDR Grand Challenge Research

Key Findings:

- Improved risk projections for low dose and low-dose rate exposures

3. LDR Program Scope and Grand Challenges

3.9) Impacts of Advancing LDR Grand Challenge Research

Key Findings:

- Improved risk projections for low dose and low-dose rate exposures
- Enhanced radiation protection standards and treatments to mitigate any harmful effects of LDR (e.g., radioprotectors and radiation injury treatments).
- Informed interventions (e.g., drugs and other treatments) in cases 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
  - Genomic and epigenetic effects

4. BER Research Program Complementarity

Meeting #4: [*How is it complementary and not duplicative*?]
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?

Key Findings:

- 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*.
- 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*.

4. BER Research Program Complementarity

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 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).

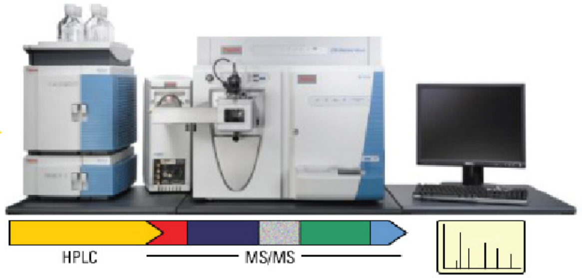
- Although the program's initial focus is on developing methods and identifying robust biomarkers at higher radiation exposures, the goal is to move toward the LDR region.
- The methods developed in the TEI-REX program thus could help advance and complement DOE initiatives.

4. BER Research Program Complementarity

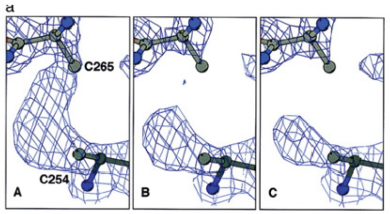
4.1) IARPA TEI-REX Program — Biomarker Discovery

TEI REX
Advancing Biodosimetry

SAMPLE COLLECTION



SAMPLE ANALYSIS



MOLECULAR CHANGE

NOTIONAL SIGNATURES

- Protein Modifications
- Microbiome modifications
- Skin and hair structural changes
- Pathway modifications

BIODOSIMETRY MODEL(S)

ENHANCED KNOWLEDGE SPACE

- Dose of exposure
- Date range of exposure
- Type of exposure
- Exposure environment

4. BER Research Program Complementarity

4.2) National Cancer Institute — Archival Tissues

- 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).

4. BER Research Program Complementarity

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- Other 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* (2022 LDR report by the National Science and Technology Council).

4. BER Research Program Complementarity

4.2) National Cancer Institute — Archival Tissues

Key findings:

- Importance of **coordinating efforts for radio-epidemiology research**:
  - With other DOE programs, such as the U.S. Transuranium and Uranium Registries
  - With international cooperative programs such as the Radiation Effects Research Foundation, 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. BER Research Program Complementarity

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*.
- 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.
- Recent emphasis on nonlethal effects of LDR, including cognitive decline, neurobiology, and cardiotoxicity.

4. BER Research Program Complementarity

4.4) NASA — Memorandum of Understanding with DOE

- Understanding the health effects of cosmic LDR is critical to advancing space exploration.
- Evidence is emerging that low-dose space radiation can lead to noncancer health outcomes (immune system dysregulation and metabolic reprogramming) similar to those observed during occupational or environmental LDR exposure on Earth.
- Opportunities for synergies between LDR programs at DOE and NASA, potentially through a memorandum of understanding.

4.5) Others — National and International

Concluding Remarks

It’s happening!

Integrated Biological and Computational Low-Dose Radiation Research

Announcement Number: DE-FOA-0003281
Fiscal Year: 2024
Post Date: 12/21/2023
Close Date: 4/2/2024 11:59:00 PM

- Pre-applications are Required.
- Pre-applications must be submitted by an authorized institutional representative.
- Pre-applications due February 6, 2024 at 5:00 pm Eastern Time.
- Pre-applications Response Date is February 20, 2024 at 5:00 pm Eastern Time