Low Dose Radiation Subcommittee

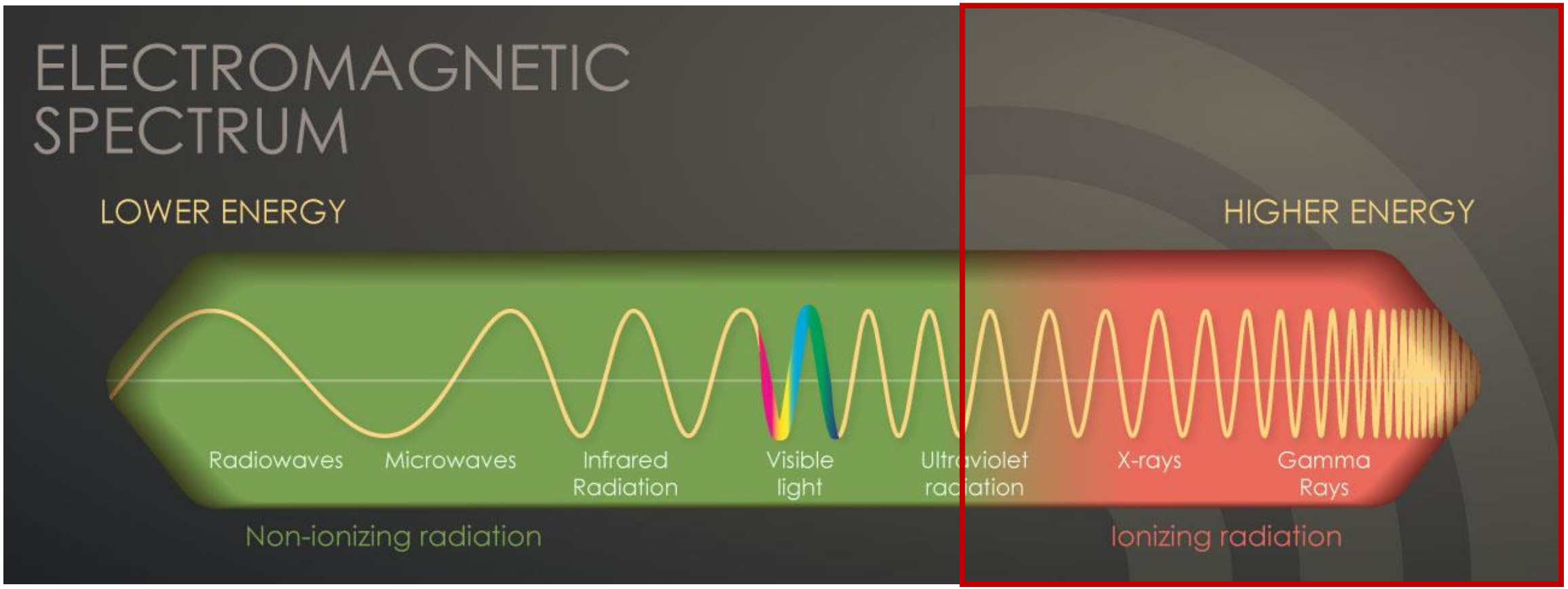
Gemma Reguera, Subcommittee Chair

BERAC briefing

October 20, 2023

U.S. DEPARTMENT OF ENERGY | Office of Science

Background – Low dose radiation

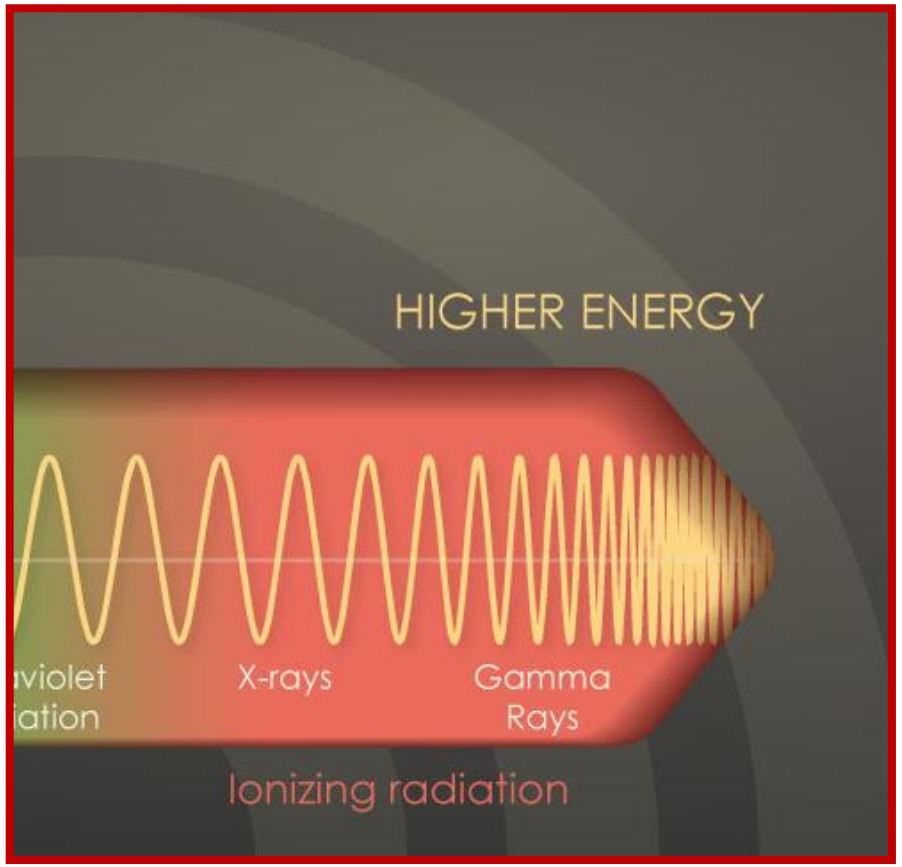


https://www.cdc.gov/nceh/radiation/ionizing_radiation.html

Background – Low dose radiation

Sources:

- **Natural**
  - Space (cosmic, solar) – Air travel
  - Terrestrial (radon)
  - Building materials
- **Man-made**
  - Medical (X-rays, CT/CAT/PET scans, fluoroscopy)
  - Nuclear power generation/accidents
  - Nuclear weapons testing, accidents
  - Consumer products (smoke detectors, luminous paints, clock dials, etc.)



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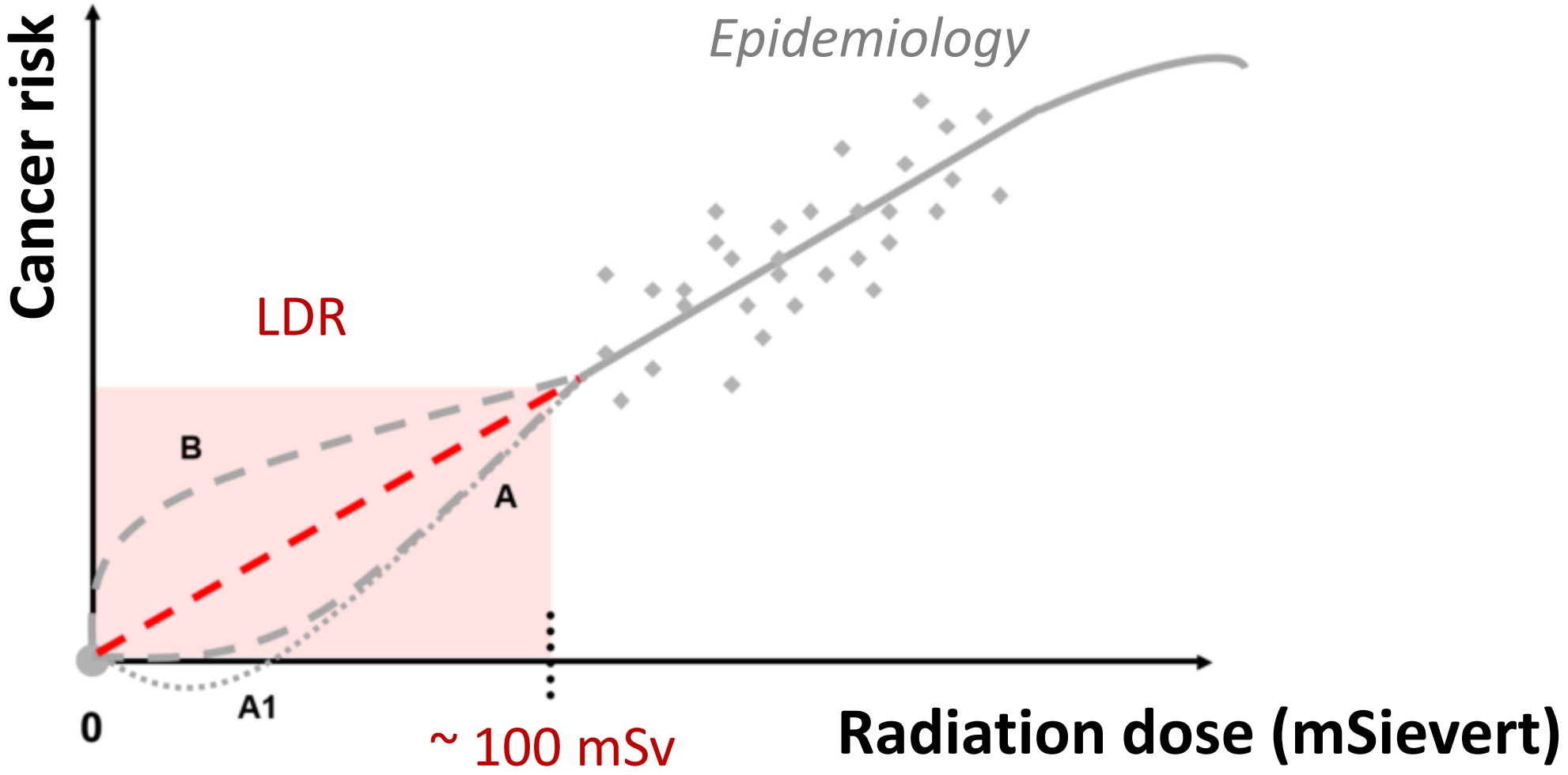
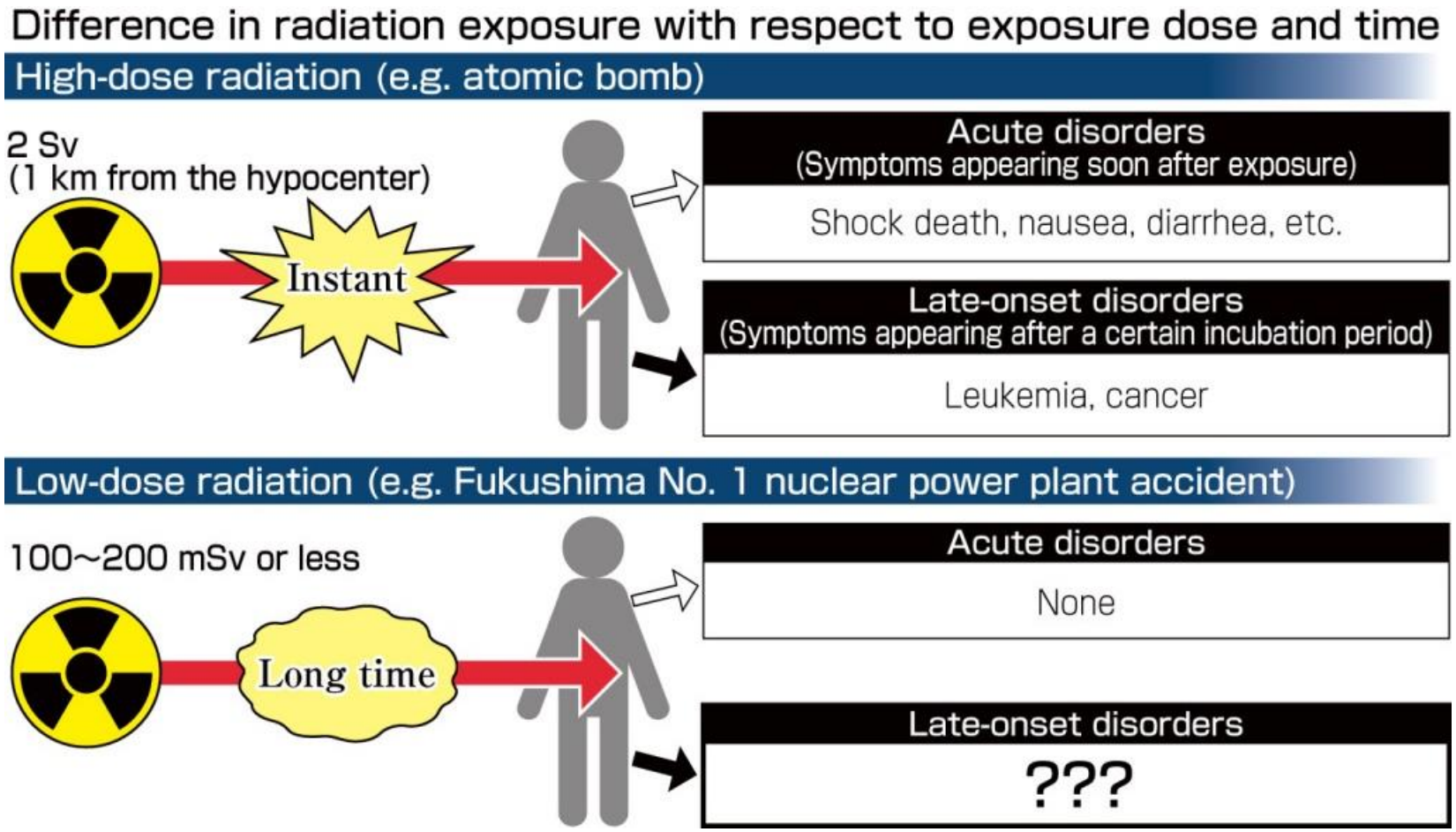


Background – Low dose radiation

Dose versus length of exposure



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

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 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.
  - 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 – environmental injustice
    - 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
    - Non-cancer health outcomes (cardiovascular disease, neurological disorders, immune dysfunction, and cataracts).

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"Recent advances in epidemiology, biological understanding of disease occurrence, and computational and analytical technologies can be **leveraged** by a revitalized low-dose radiation research program to improve assessment and understanding of the risks of adverse health effects that result from the radiation exposures received by the U.S. population."

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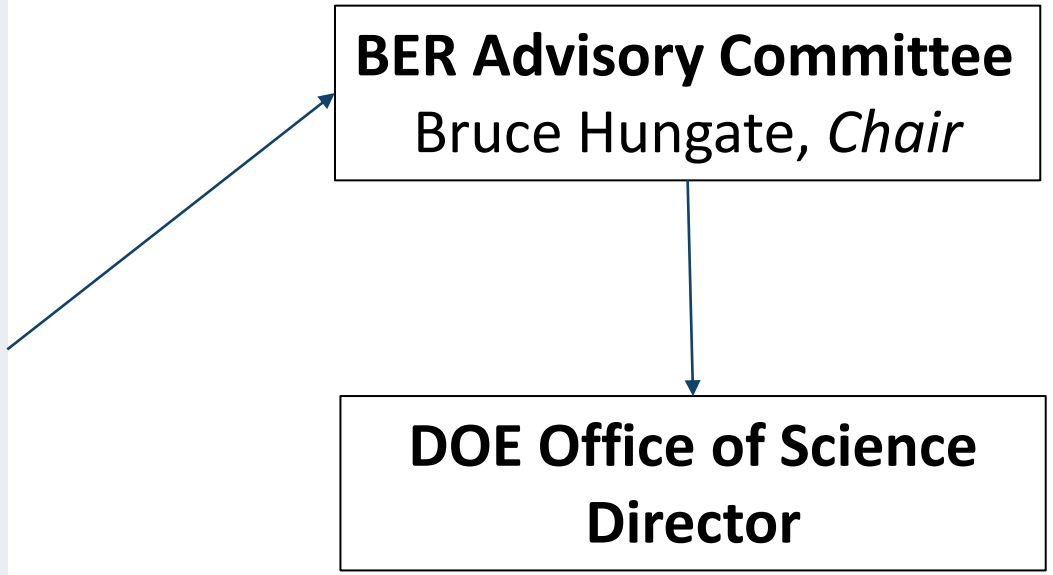
- 2022 Physical Sciences Subcommittee (PSSC), National Science and Technology Council (NSTC) report – *Radiation Biology: A Response to the American Innovation and Competitiveness Act*

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 on Low Dose Radiation

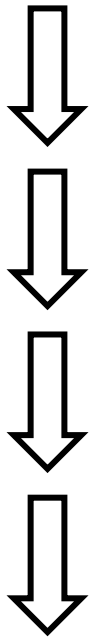
- **Gemma Reguera**, Michigan State - *Chair*
- Jeremy Schmutz, HudsonAlpha
- Kerstin Kleese van Dam, BNL
- Robert Fischetti, ANL
- Lindsay Morton, NHI-NCI
- Heather Henry, NIH-NIEHS
- R. Julian Preston, EPA
- Mariann Sowa, NASA
- Alexandra Miller, AFRRI
- Terry Brock, NRC
- Evagelia Laiakis, Georgetown University
- Rick Stevens, ANL
- Georgia Tourassi, ORNL
- Antoine Snijders, LBNL
- Michael Bellamy, Memorial Sloan Kettering
- **Tris West** – *Designated Federal Officer*



https://science.osti.gov/ber/berac

Subcommittee Process

- **Meetings:** Four meetings to deliver the charge (#1) and to address one of the three charge items, in order (#2-4)



Meeting #1 – Introductory meeting [Deliver the charge]

Meeting #2 – Charge item #1 [BER capabilities]

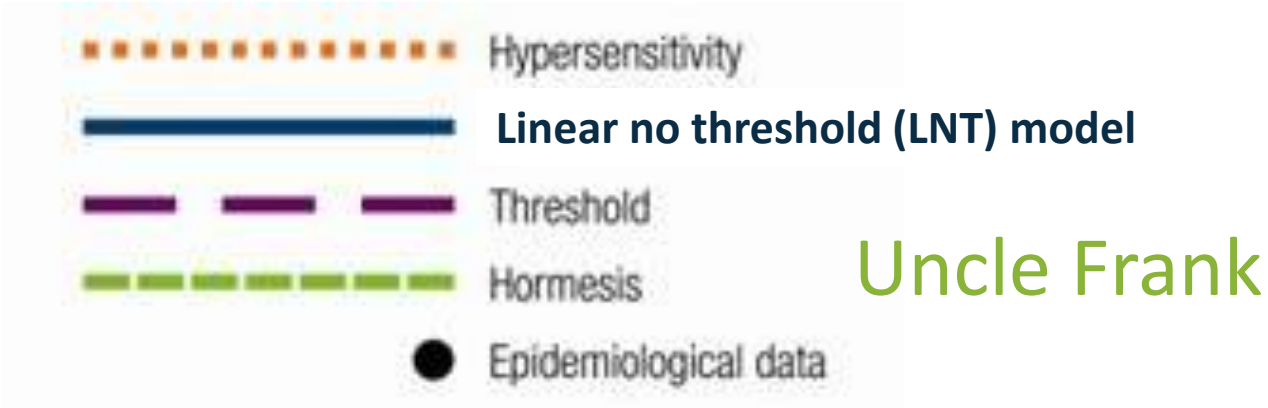
Meeting #3 – Charge item #2 [Program scope]

Meeting #4 – Charge item #3 [Effort complementarity]

- **Report:** A final response to the charge needs to be documented in a short report. This can be in a brief memo format or longer if desired.

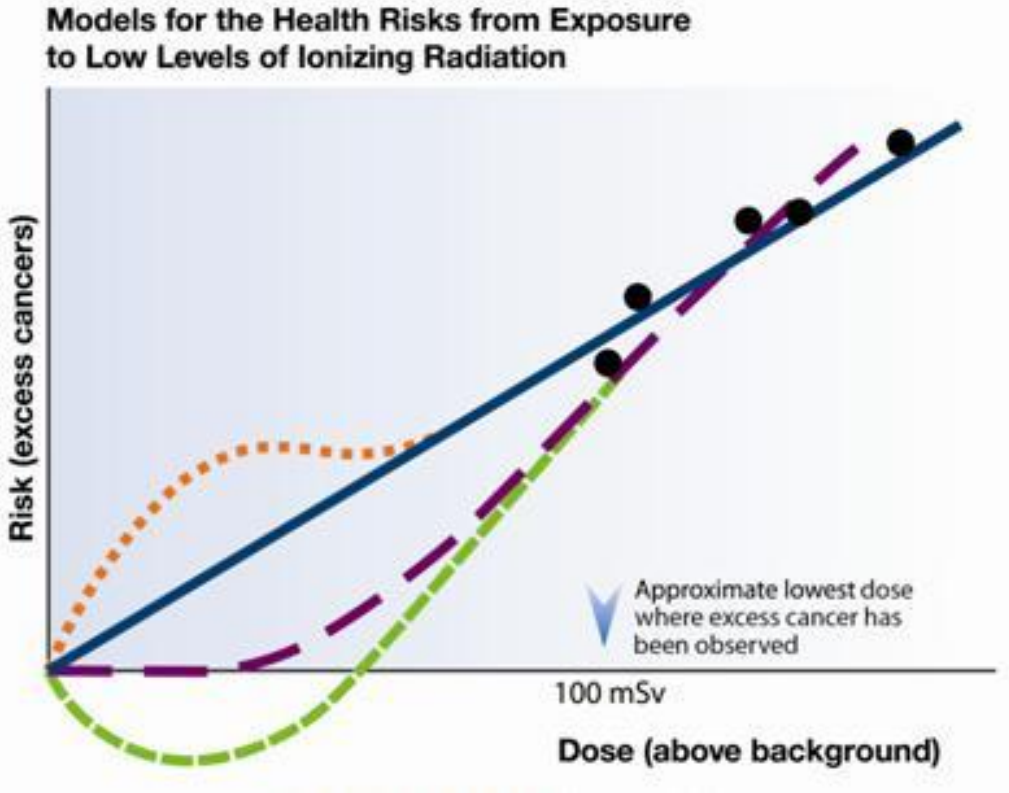
Charge item #1 – DOE-BER capabilities

Meeting #2: [*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)?



Uncle Frank

http://nuclearsafety.gc.ca/eng/resources/health/linear-non-threshold-model/index.cfm



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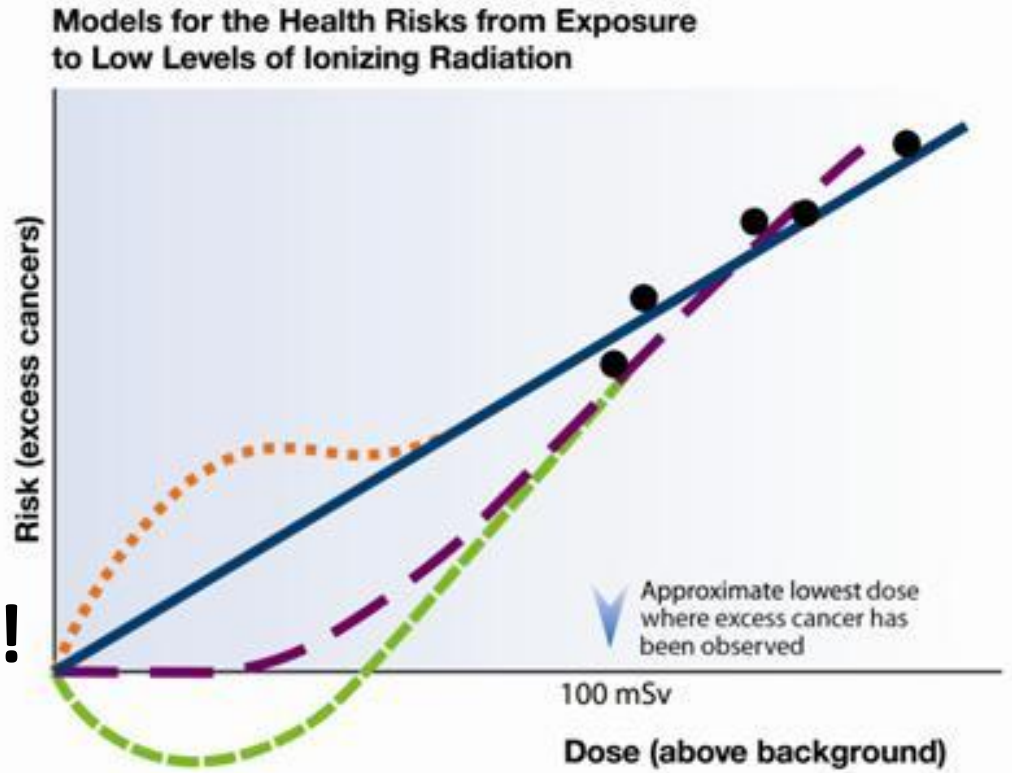

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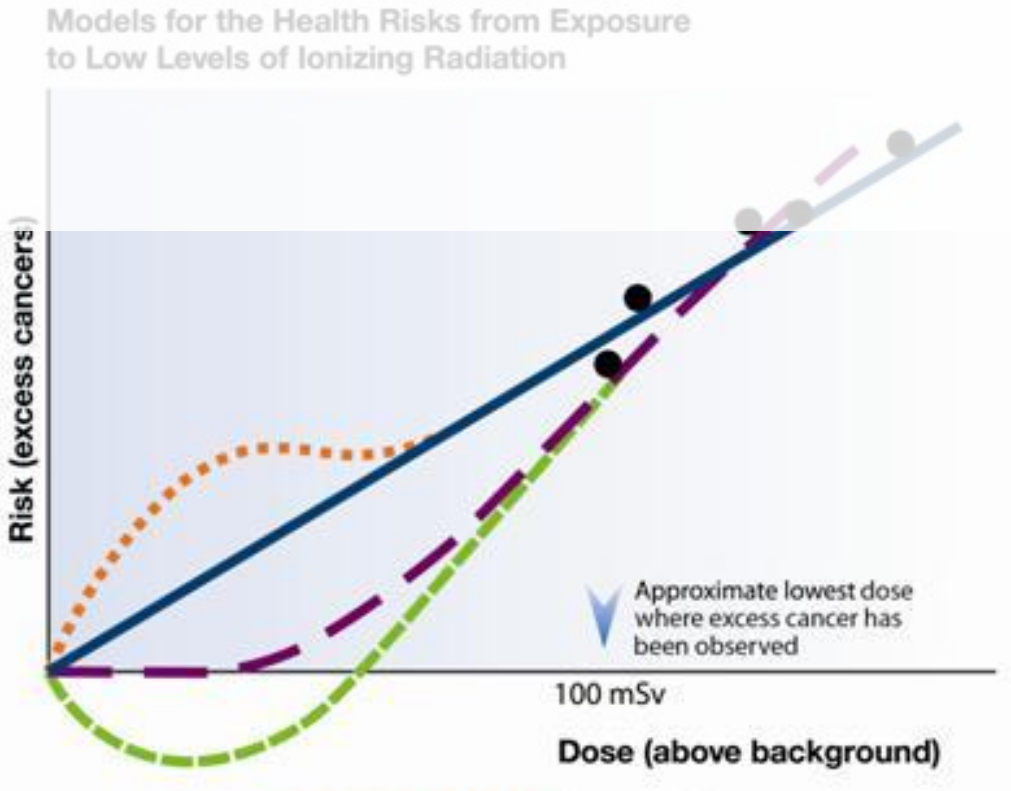
Are there existing technical capabilities and areas of foundational science expertise within BER that could be employed in low dose radiation research (e.g., genomics, instrumentation, computation)?

Summary of Meeting #1 discussions

1. **Low dose radiation**
   - Controlled emission – Instrumentation



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Meeting #2: [*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)?

Summary of Meeting #1 discussions

1. Low dose radiation
2. **Biological system** (*clean data*)
    - Type, response – Instrumentation, genome biology (*2022 NAS report*)

2022 NAS report– Chapter 2: Low-Dose Radiation Exposures and Health Effects

- Defining health and safety issues that need to be guided by an improved understanding of low-dose and low-dose-rate radiation health effects (*non-cancer health outcomes*)
- Involuntary exposure to vulnerable populations (*health disparities*)

Charge item #1 – DOE-BER capabilities

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Summary of Meeting #1 discussions

1. **Low dose radiation**
2. **Biological system** (*clean data*)
3. **Computational**
   - Data analysis, correlations, models, machine learning

2022 NAS report– Chapter 4: Status of Low-Dose Radiation Research
"DOE-National Cancer Institute (NCI) collaborative project CANDLE (CANcer Distributed Learning Environment), which aims to develop deep learning methods on computing platforms to support cancer research and enable precision medicine (Peterson and Cooke, 2019)."

Interagency collaboration on computational research regarding cancer (not low dose).
1.Computational research on low-dose (which is NOT interagency).

Charge item #1 – DOE-BER capabilities

Meeting #2: [*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)?

Summary of Meeting #1 discussions

1. **Low dose radiation**
2. **Biological system** (*clean data*)
3. **Computational**
   - Data analysis, correlations, models, machine learning
   - Opportunities for inter-agency collaborations on LDR

Currently:
- Interagency collaboration on computational research regarding cancer (not low dose).
- Computational research on low-dose (which is NOT interagency).

Charge item #1 – DOE-BER capabilities

Meeting summary:

1. **Low dose radiation control** in experimental systems – DOE is the only agency with capabilities and instrumentation for LDR dose control/calibration in experiments at all scales.
   - DOE strengths in this area could alleviate concerns about the agency having a COI as regulatory agency.
   - Will enable single-cell studies – leveraged by DOE-BER strengths in genome science (single-cell omics technologies are not fully developed but could be the focus of investments to support this and other programs).
   - Training programs may be needed to prepare a workforce for LDR research (loss of critical expertise at DOE in this area could limit these efforts).
   - Dosimetry and calibration standards (provided by National Labs) are needed to enable physics-biology correlations.

Charge item #1 – DOE-BER capabilities

Meeting summary:

1. **Low dose radiation control** in experimental systems
2. **Biological system** for experimentation (types, responses)
    - Need to cover molecular, cellular and epidemiological studies leveraging DOE capabilities in genome biology and computation.
    - Broad RFA (to reduce uncertainties in the LDR region of the LNT model).
    - Epidemiological studies with increased sensitivity to capture LDR phenomena.
        - Beyond cancer – focus on non-cancer health outcomes and vulnerable populations (2022 NAS report).
        - Internal exposure to LDR (e.g., inhalation) is a critical knowledge gap.
    - Molecular and cellular studies could fill the gap of knowledge that epidemiological studies cannot fill in. The idea is to move in both directions of the LNT model, from right (macroscale) to left (molecular/micro scale), until data is collected to reveal an experimentally validated LDR plot.

Charge item #1 – DOE-BER capabilities

Meeting summary:

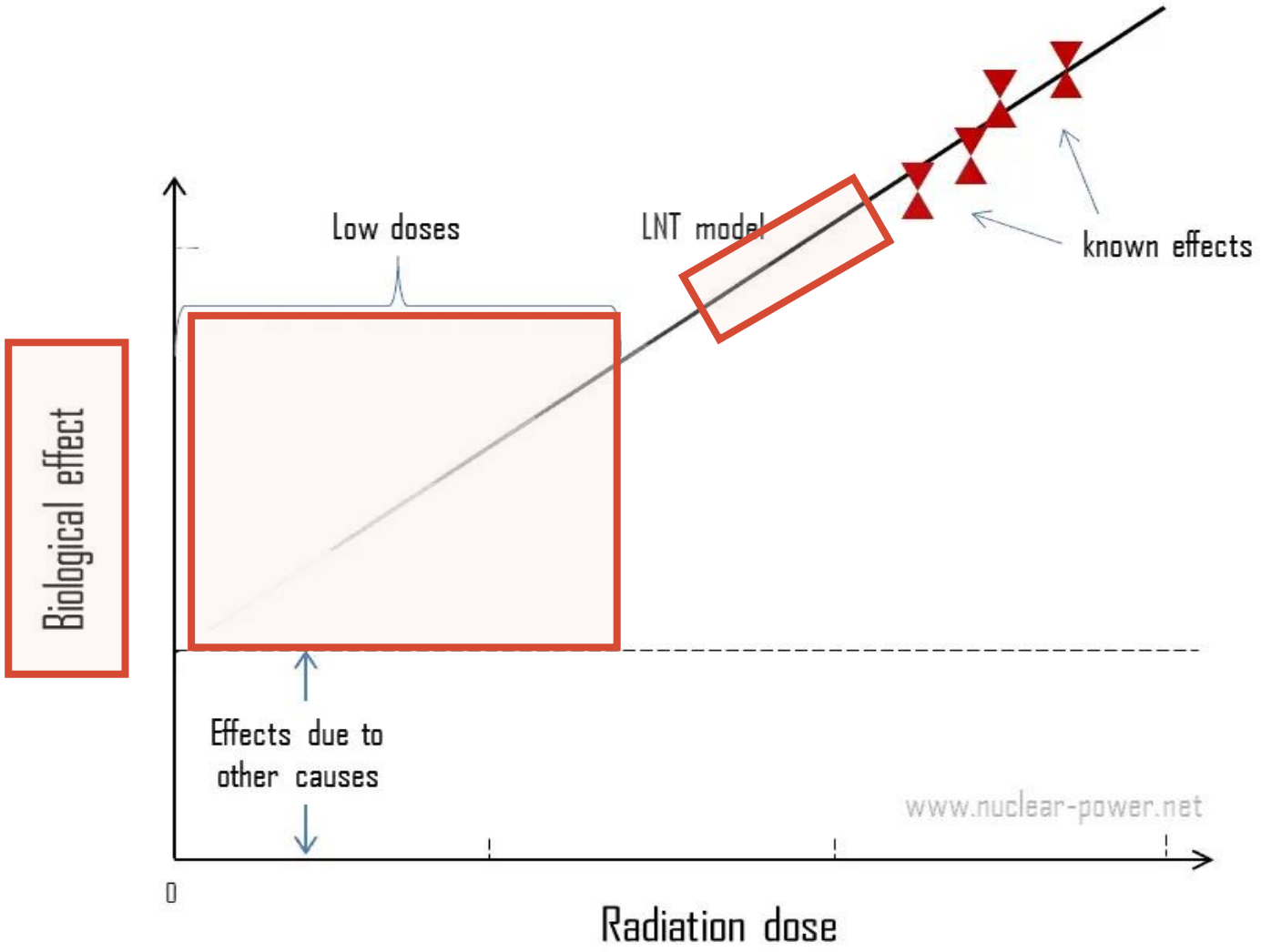
1. **Low dose radiation control** in experimental systems
2. **Biological system** for experimentation (types, responses)
3. **Computational studies** – Data analysis, correlations, models, machine learning.
    - Needed to develop predictive models for epidemiological studies.
    - Applicable to predictively model molecular and cellular responses.

Charge item #1 – DOE-BER capabilities

Meeting summary:

1. Low dose radiation control
2. Biological system
3. Computational studies

Goal:
Remove or lower uncertainties in the LDR region of the LNT model.



Charge item #1 – DOE-BER capabilities

Grand Challenges

1. **Dosimetry** – Dose needs to be defined so the studies and outcomes can be correlated.
   - Define dosimetry (what needs to be reported and described).
   - Calibration to standard sources

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   - Define dosimetry (what needs to be reported and described).
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2. **Experimental systems** exist to generate ***clean data*** (biological-dose responses) but instrumentation is lacking.
   - DOE investments in single-cell omics – it will benefit other programs in the BER portfolio.
   - Molecular markers for non-cancer outcomes of LDR.

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   - DOE investments in single-cell omics – it will benefit other programs in the BER portfolio.
   - Molecular markers for non-cancer outcomes of LDR.
3. **Computational integration** of experimental data to develop predictive models.
   - This could prove critical to advancing epidemiological studies.
   - Essential to identify biomarkers (molecular, cellular) of adverse LDR outcomes.

Charge item #1 – DOE-BER capabilities

Grand Challenges

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   - Define dosimetry (what needs to be reported and described).
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2. **Experimental systems** exist to generate ***clean data*** (biological-dose responses) but instrumentation is lacking.
   - DOE investments in single-cell omics – it will benefit other programs in the BER portfolio.
   - Molecular markers for non-cancer outcomes of LDR.
3. **Computational integration** of experimental data to develop predictive models.
   - This could prove critical to advancing epidemiological studies.
   - Essential to identify predictive markers (molecular, cellular) for LDR responses.
4. **Exposure environments** need to be defined to advance the science in this field
   - External vs. internal
   - Workforce expertise – Need of training programs

Charge item #2 – LDR program scope

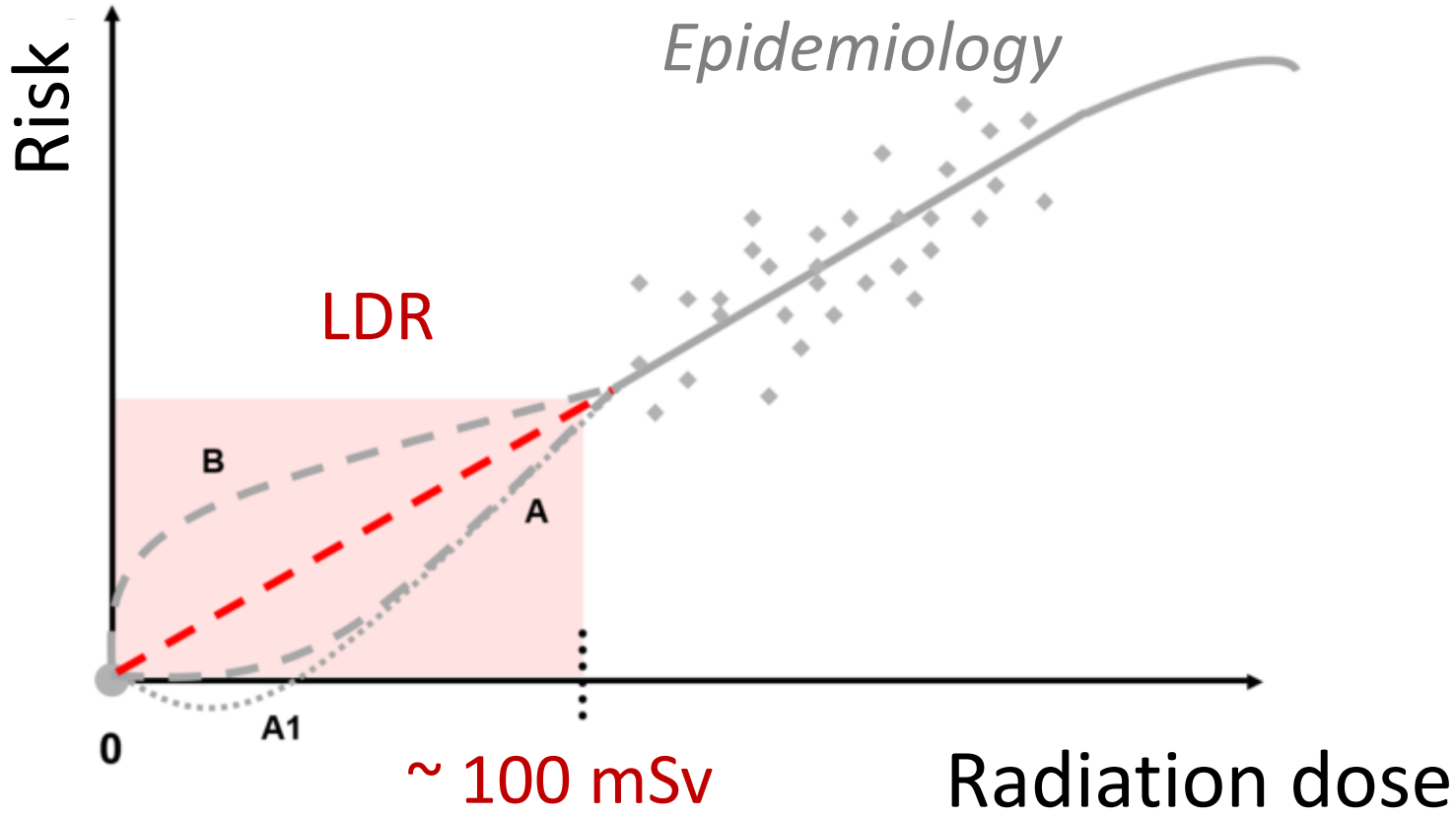
Meeting #3: [*What does the program include*?]
Can a program of **basic research** be identified using DOE capabilities to make specific advances towards understanding the effects of low dose radiation exposure on human biological systems?

Charge item #2 – LDR program scope

- Address Grand Challenges identified during our 2nd meeting
  - Dosimetry
  - Biological studies (molecular, cellular and epidemiological)
  - Computational integration

Charge item #2 – LDR program scope

- ❑ Address Grand Challenges identified during our 2nd meeting
- ❑ **Goal:** Remove or lower uncertainties in the LDR region of the LNT model.



Charge item #2 – LDR program scope

- ❑ Address Grand Challenges identified during our 2nd meeting
- ❑ **Goal:** Remove or lower uncertainties in the LDR region of the LNT model.
- ❑ Human vs non-human models for biological studies

1. Cell Culture Models
2. Animal Models
3. Human Epidemiological Studies
4. In Vitro 3D Organoid Models
5. Zebrafish Models
6. Human Stem Cells
7. Drosophila (Fruit Fly) Models
8. Yeast Model
9. In Silico Models (computational models and simulations)

ChatGPT

Computer program

Charge item #2 – LDR program scope

- ❑ Address Grand Challenges identified during our 2nd meeting
- ❑ **Goal:** Remove or lower uncertainties in the LDR region of the LNT model.
- ❑ Human vs non-human models for biological studies
- ❑ Leverage DOE capabilities
  - To address dosimetry
  - To harness strengths in systems biology
  - To computationally analyze data

Charge item #2 – LDR program scope

- ❑ Address Grand Challenges identified during our 2nd meeting
- ❑ **Goal:** Remove or lower uncertainties in the LDR region of the LNT model.
- ❑ Human vs non-human models for biological studies
- ❑ Leverage DOE capabilities
- ❑ **Scope:** Links between LDR physics and biology
  - Identify LDR capabilities for **controlled dosimetry** (report available for all agencies)
  - Identify **experimental systems** suitable for testing
  - Identify computational capabilities to **correlate physics-biology**.

Charge item #3 – Program complementarity

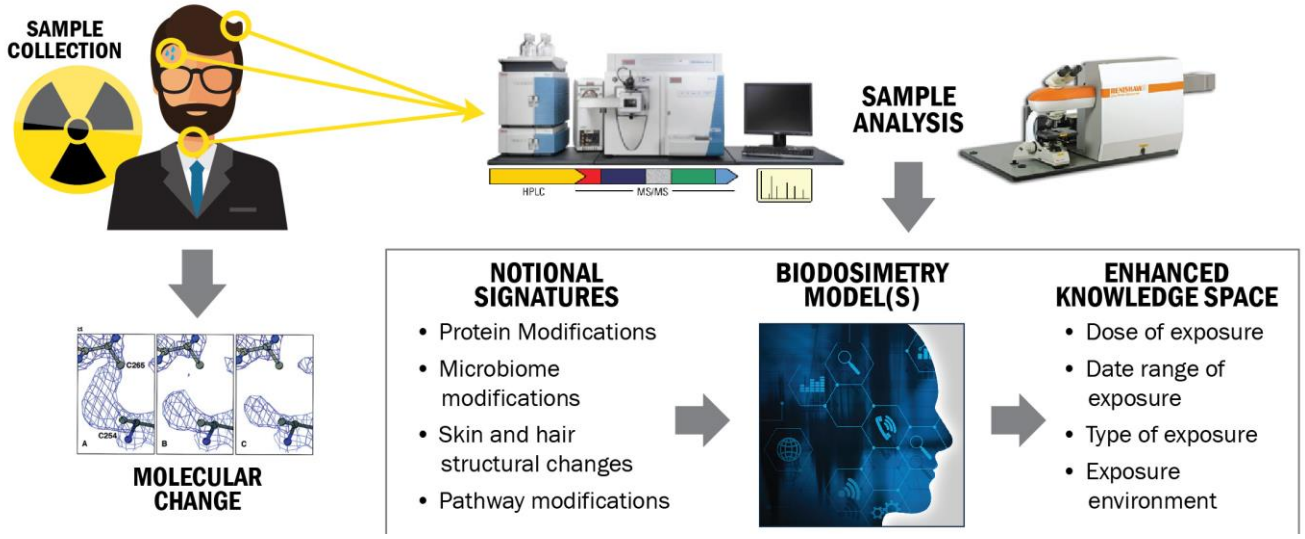
Meeting #4: [*How is it complementary and not duplicative*?]
Is the identified program non-duplicative and complementary to efforts in other agencies (e.g., NIH, DHS, EPA, NASA) and would there be opportunities to leverage such efforts?

1. **Dosimetry** – DOE-BER unique capabilities for dosimetry control
   - Synchrotron source – control the energy range (often missed in LDR studies).

Charge item #3 – 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?

1. **Dosimetry** – DOE-BER unique capabilities for dosimetry control
2. **Biological systems** – Synergy leveraging DOE-BER genomic science capabilities
   - Biomarker discovery – IARPA TEI-REX
     - Doing calibration exercises (dosimetry harmonization)



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   - Biomarker discovery – IARPA TEI-REX
   - Archival tissues – NIH-NCI
     - Omics characterization of archival tissues (transcriptomics, single-cell cell genomics, etc.)
     - Biospecimen collection and characterization

NIH NATIONAL CANCER INSTITUTE

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   - Biomarker discovery – IARPA TEI-REX
   - Archival tissues – NIH-NCI
   - Animal models – DoD AFRRI
     - Non-lethal, non-cancer endpoints
     - LDR and animal behaviors (cognition)
     - Loss of radiobiology expertise (training programs)

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   - Biomarker discovery – IARPA TEI-REX
   - Archival tissues – NIH-NCI
   - Animal models – DoD AFRRI
   - DOE MOU with NASA
     - Many opportunities for collaborations
     - Potential to replicate the NSTGRO graduate training program for dosimetry

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2. **Biological systems** – Synergy leveraging DOE-BER genomic science capabilities
3. **Computational integration** – DOE-BER unique capabilities for dosimetry control

Future Steps

=> Finalize report: Before the end of the Fall

https://www.ans.org/news/article-4144/ans-virtual-event-experts-share-their-expectations-for-lowdose-radiation-research/