Warfighter relevant radiation exposure models in the AFRRI TRIGA reactor

Gregory P. Holmes-Hampton, Ph.D.
Principal Investigator
Research Biologist
Armed Forces Radiobiology Research Institute
Uniformed Services University of the Health Sciences

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Presented at:
MHSRS 2026
Ops in a Nuclear Environment: Ensuring Medical Readiness & Preparing for Complex Injuries

Disclaimer: The opinions and assertions expressed herein are those of the presenter and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of War.

Declaration: Neither I nor my family members have a financial interest in any commercial product, service, or organization providing financial support for this research.

This research protocol was reviewed and approved by the USUHS Institutional Animal Care and Use Committee (IACUC) in accordance with all applicable Federal regulations governing the protection of animals in research.

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Acknowledgements

AFRRI Leadership
CAPT Burke
Col Whiteway
CDR King
MAJ Patel

RSD
Andrew Cook
Andy Smolinski
Kyrone Riley
Ben Knibbe
Alena Tsioplaya
Justin Payer
Alia Weaver
Kwasi Sampong
Dave Schauer

HPD
Tim Tylka

DLAR and IACUC
RSG

Funding
NIAID IAA / U01
Carmen Rios
DTRA
Lee Alleman
AFRRI Intramural
USUHS Discovery Award

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Radiation Exposure Scenarios

Accidents

- Nuclear power generators
- Medical radiation therapy
- Industrial radiator
- Lost/stolen medical or industrial radioactive sources

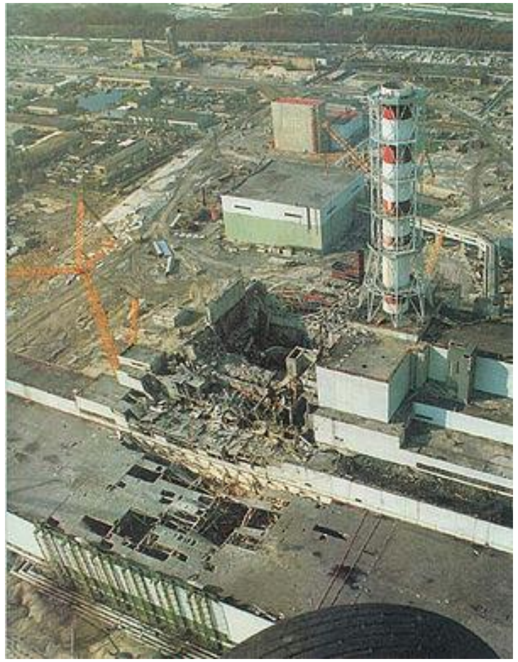
Attacks

- Radiological dispersal device (dirty bomb)
- Attack or sabotage of a nuclear facility
- Use of nuclear weapon

War Fighters Specific Scenarios

- Increased likelihood of being in proximity to a weapon or attack
- May receive orders to enter a contaminated arena for search and rescue or asset recovery

Fukushima 2011



Chernobyl 1986

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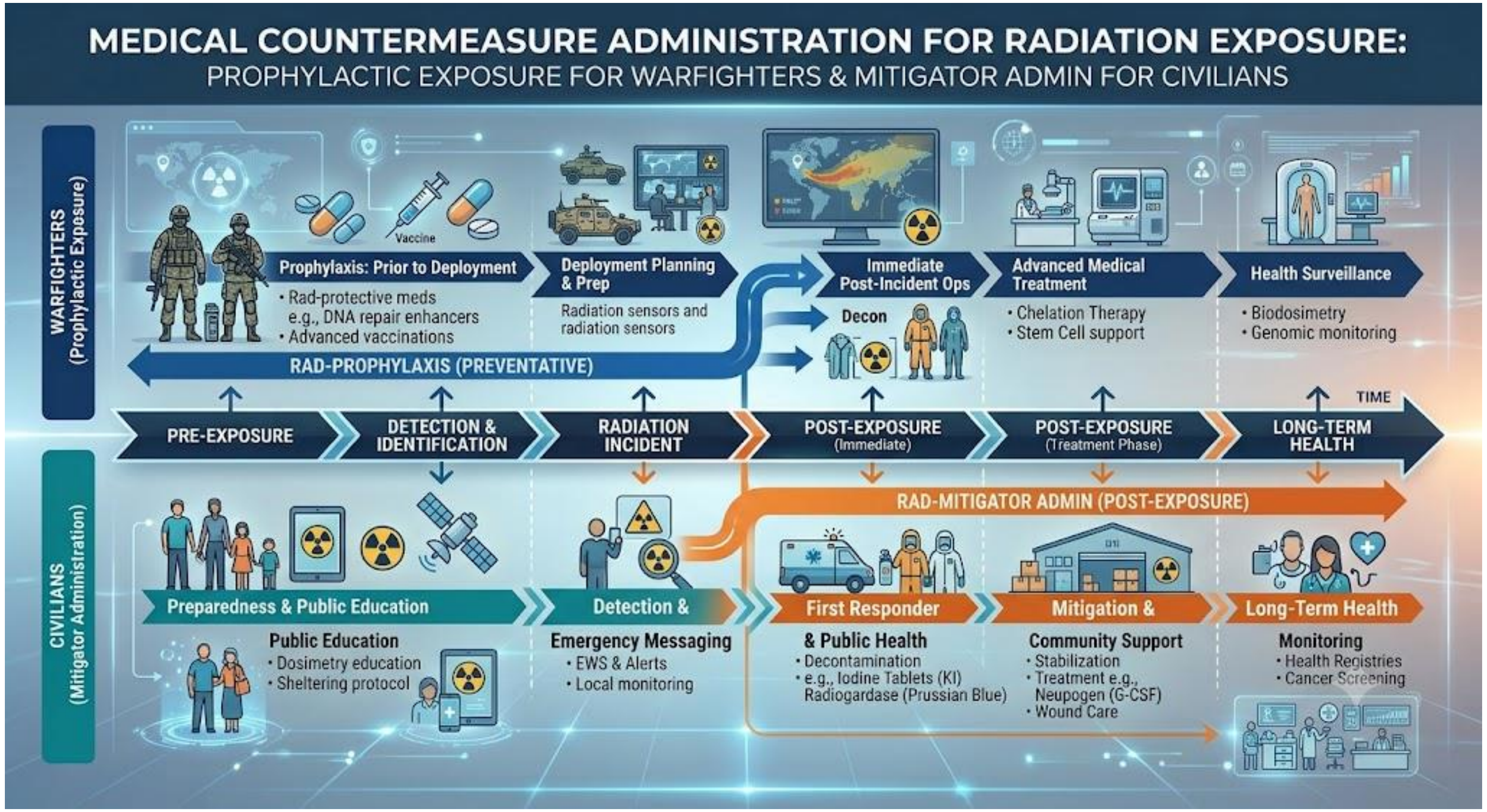
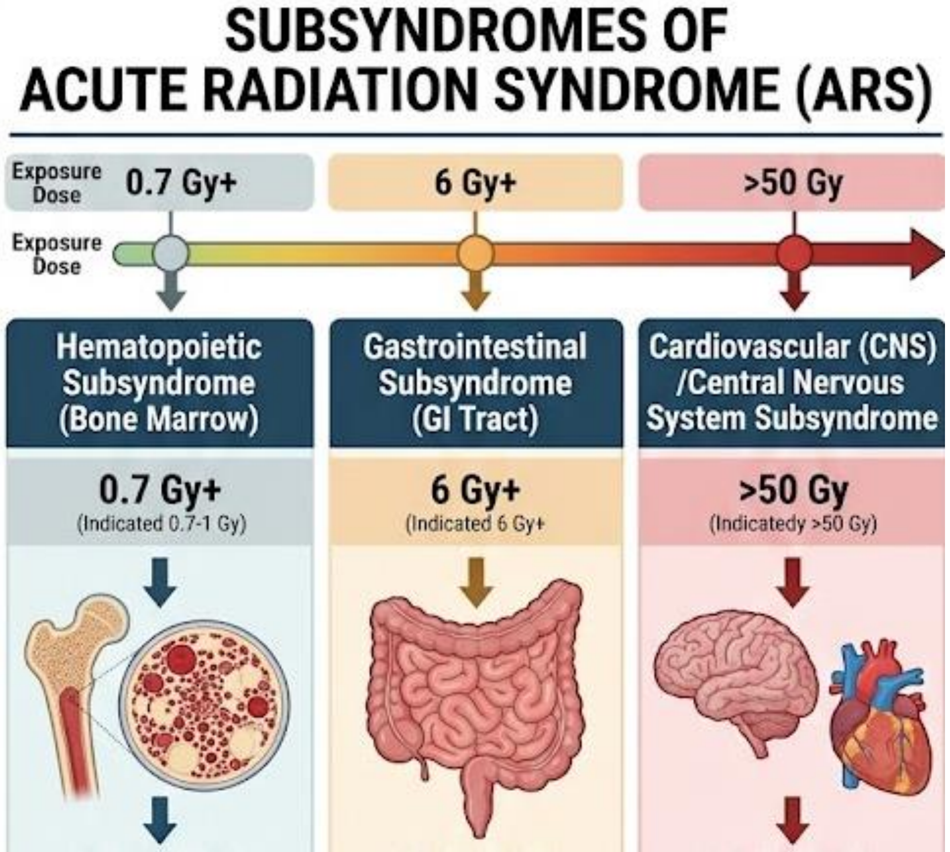
Radiation Subsyndromes and Treatment





Images prepared with Google Gemini

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Radiation Medical Countermeasure Development

Product Development Under the Animal Rule

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Non Binding Recommendations:

1. Well understood model of injury
2. *Effect demonstrated in more than 1 species OR in 1 species that is sufficient to demonstrate efficacy*
3. Endpoint in animals is linked to endpoint in humans
4. PK/PD available to predict human dose

*likely referring to compounds not active in species other than human (or NHP)

Approved mitigators for Acute Radiation Syndrome

- Neupogen (filgrastim) – approved March 2015
  - Nypozi (filgrastim-txid) - approved June 2024
  - Zarxio (filgrastim-sndz) - approved October 2024
  - Releuko (filgrastim-ayow) - approved April 2025
  - Ennumo (pegfilgrastim-pccg) – approved May 2026
- Neulasta (pegfilgrastim) – approved November 2015
  - Udenyca (pegfilgrastim-cbqv) – approved November 2022; single-dose prefilled auto-injector approved March 2023
  - Stimufend (pegfilgrastim-fpgk) - approved September 2023
  - Ziextenzo (pegfilgrastim-bmez) – approved February 2024
  - Fylnetra (pegfilgrastim-pbbk) – approved April 2025
  - Armlupeg (pegfilgrastim-unne) – approved November 2025
- Leukine (sargramostim) – approved March 2018
- NPLATE (romiplostim) – approved January 2021

- **All approvals will be conducted in Animal models**
- **No drugs are currently approved as prophylactics**

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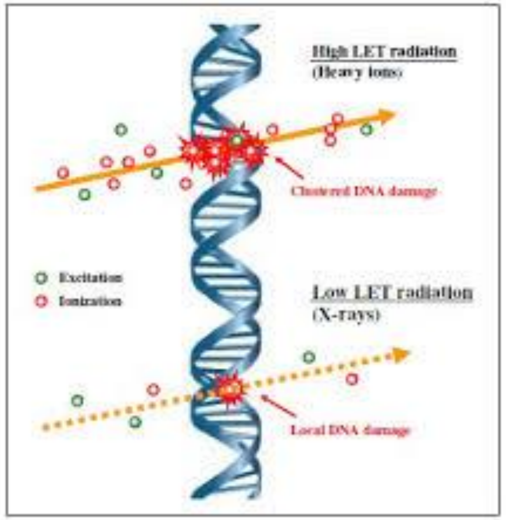
Neutron to Gamma Ratios and RBE

- Neutron/ mixed Field = Detonation
- Gamma = Fall Out

- Neutrons = High LET = More Damage
- Gamma = Low LET = less damage



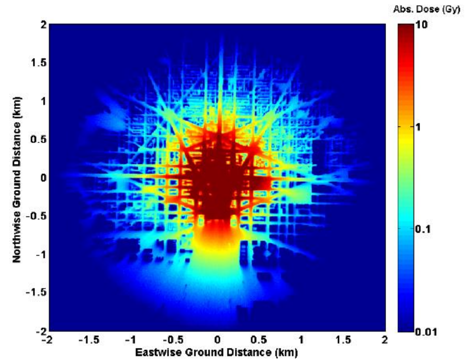


Figure 5-4. Urban photon absorbed dose from both leakage photons and secondary photons from neutron interactions.

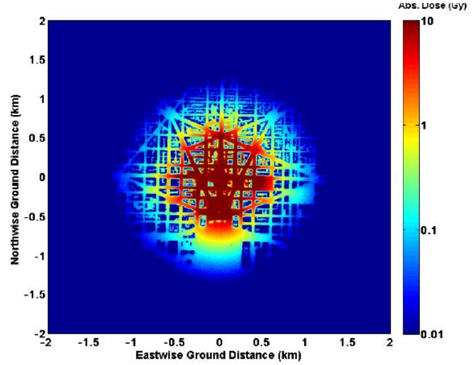


Figure 5-3. Urban neutron absorbed dose.

From DTRA-TR-13-045 (R1) - Monte-Carlo Modeling of the Prompt Radiation Emitted by a Nuclear Device in the National Capital Region, Revision 1

*Table 2-III. Typical Neutron-to-Gamma and Neutron Dose-to-Total Dose Ratios**

Yield (Kt)	n/g	n/n + g	Range
0.1	4.6	0.82	360 meters
1.0	3.0	0.75	650 meters
10.0	1.6	0.62	1040 meters
100.0	0.47	0.32	1500 meters
1000.0	0.042	0.04	2280 meters

* Assumptions: HOB = $60W^{1/3}$ meters, where W = yield in kilotons; air density is equal to 0.9, relative to sea level; fission only device; total dose is equal to 2600 cGy.

NATO Handbook 1996, UNCLASSIFIED

- **Depending on numerous factors, Neutron to Gamma Ratios are highly variable**
- **Neutrons Produce more damage than Gammas for the same dose**
- **In an urban environment shielding may lead to non-homogeneous exposure**

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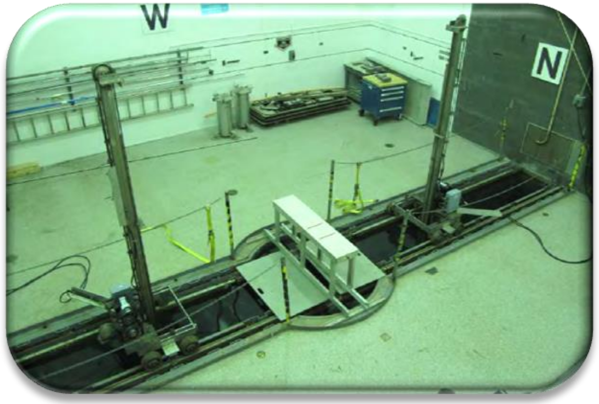
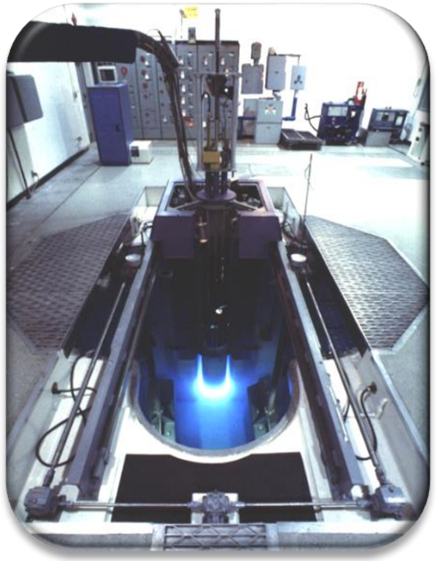
Animal Models for Radiation Exposure at AFRRI

High Level Cobalt-60



- Gamma irradiation, Akin to nuclear fallout
- Total Body Irradiation in mice (and other species)
- Represents a worst-case scenario in terms of damage to the organism
- Produces H-ARS

TRIGA Reactor



- Variable Neutron Gamma Ratios, akin to nuclear detonation
- Total Body and Partial body Irradiation in mice (and other species)
- Produces H-ARS, and GI-ARS

Linear Accelerator

- X-Ray irradiation, akin to nuclear fallout
- Partial body Irradiation in mice (and other species)
- Produces GI-ARS

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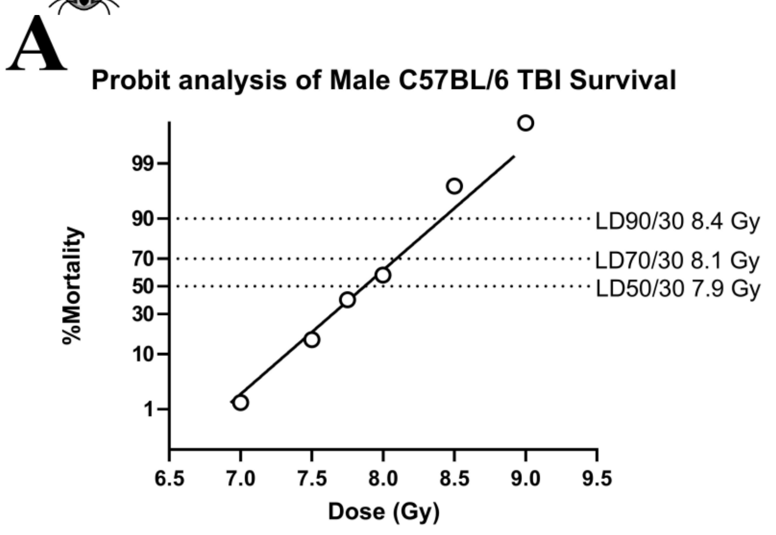
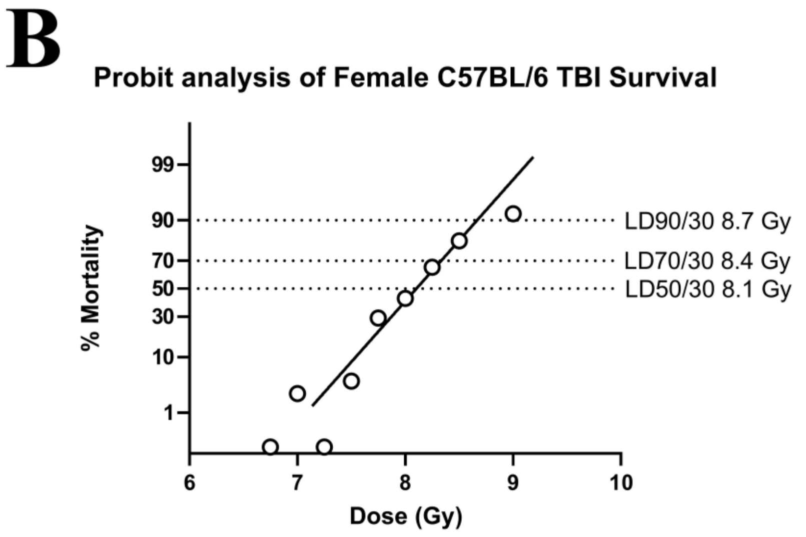
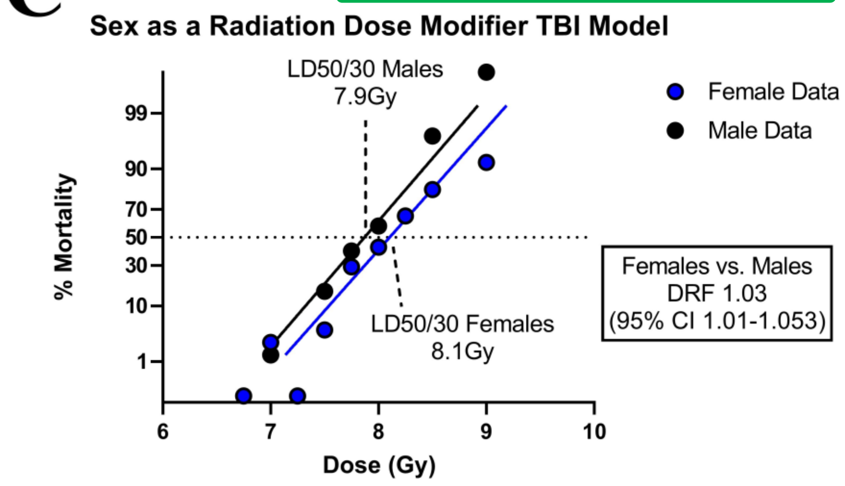
Lethality in the Co60 source (TBI)

- Total Body Irradiation (Co60)- mouse

~0.6Gy/min







- Males are slightly more radiosensitive
- LD50 ~8 Gy
  - Males 7.86 (95% CI 7.76-7.97)
  - Females 8.10 (95% CI 8.00-8.19)
- LD70 ~8.2Gy
  - Males 8.10 (95% CI 7.98-8.22)
  - Females 8.33 (95% CI 8.23-8.45)
- LD90 ~8.5Gy
  - Males 8.43 (95% CI 8.29-8.61)
  - Females 8.68 (95% CI 8.55-8.86)

Very Robust model, 10+ years of data

Cytogenetic and Genome Research
Original Article
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Received: March 31, 2023
Accepted: June 18, 2023
Published online: June 22, 2023

Sex as a Factor in Murine Radiation Research: Implications for Countermeasure Development

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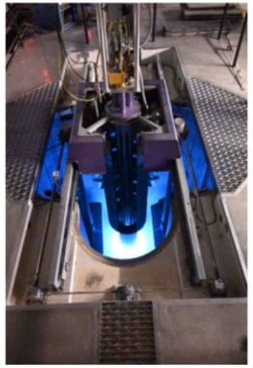
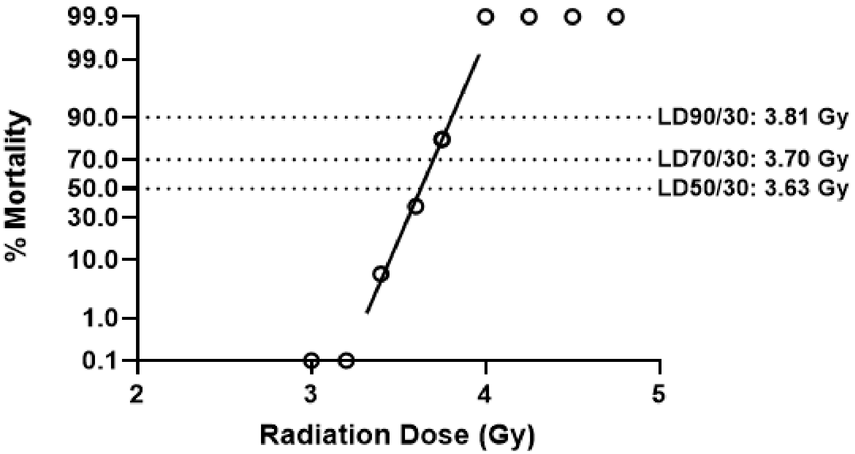
Lethality in the AFRRI TRIGA (TBI)

<u>Ways to Modulate Neutron Gamma Ratios</u>

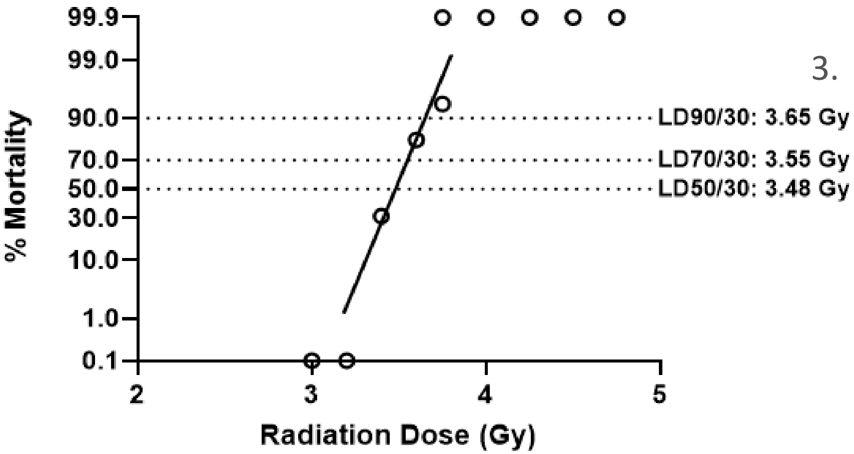
1. Shielding
2. Distance
   1. In exposure room
   2. Core in pool
3. Power



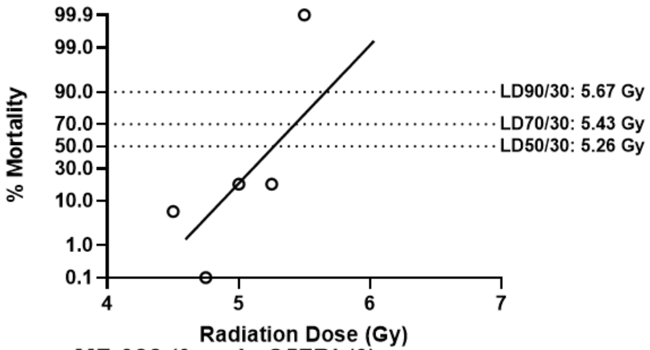
96% Neutron 4% Gamma (male C57BL/6)



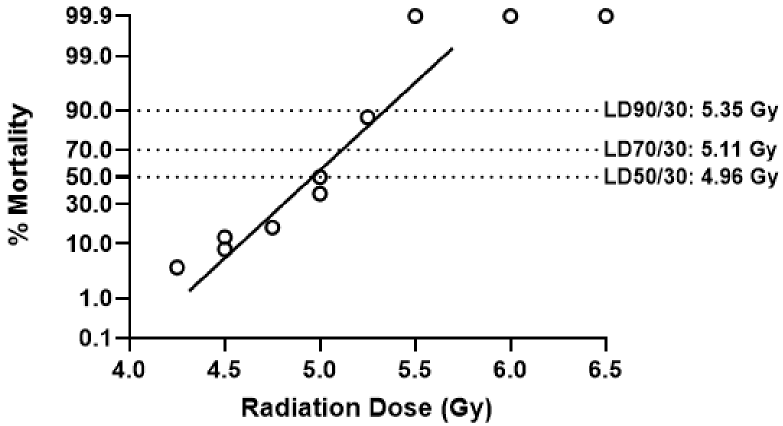
96% Neutron 4% Gamma (female C57BL/6)



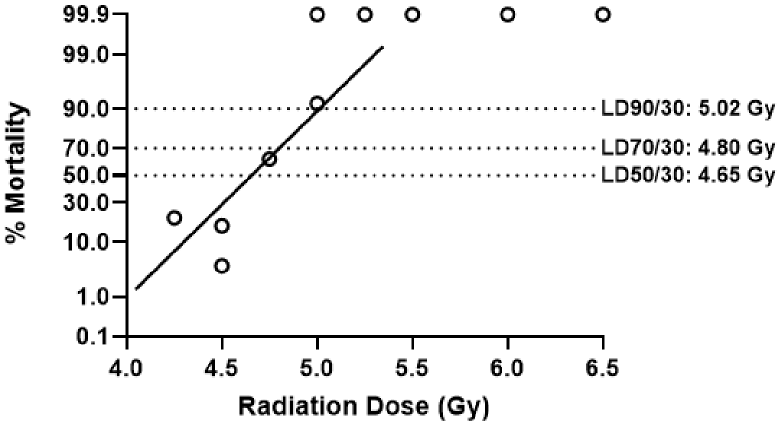
50% Neutron 50% Gamma (male C57BL/6)



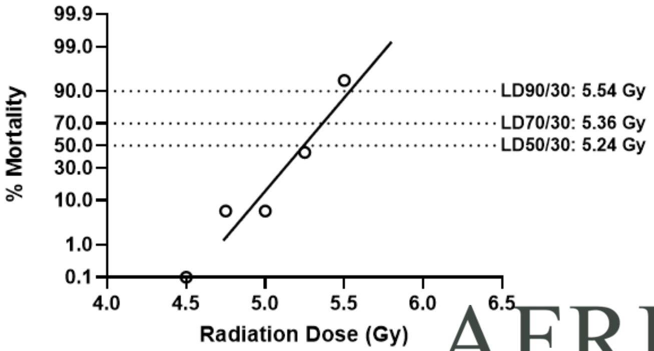
65% Neutron 35% Gamma (male C57BL/6)



65% Neutron 35% Gamma (female C57BL/6)



MF-022 (female C57BL/6)



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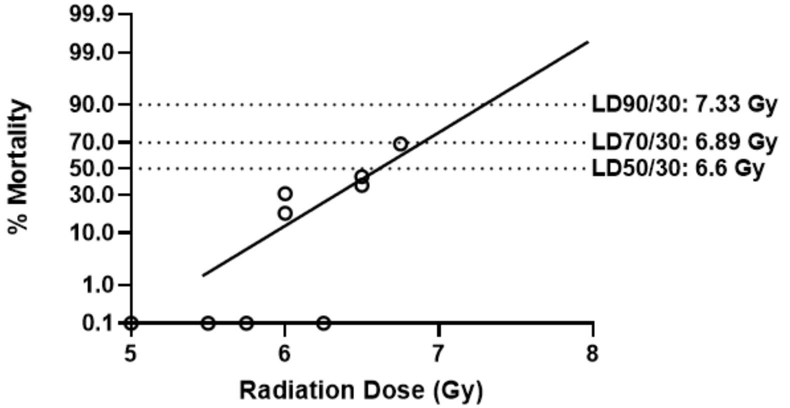
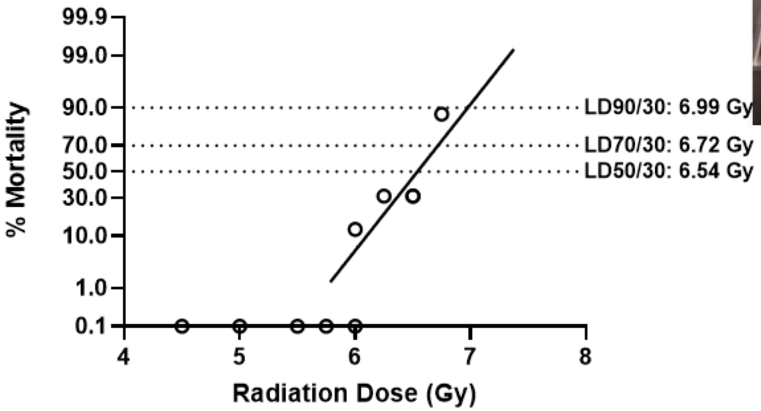
Lethality in the AFRRI TRIGA (TBI)

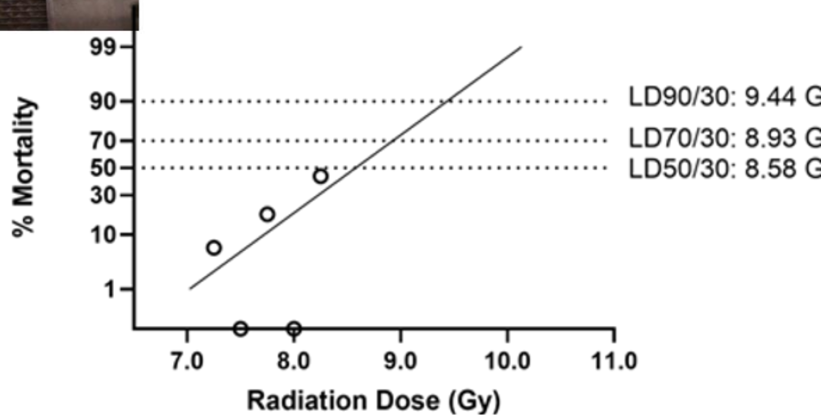
33% Neutron 67& Gamma (male C57BL/6)



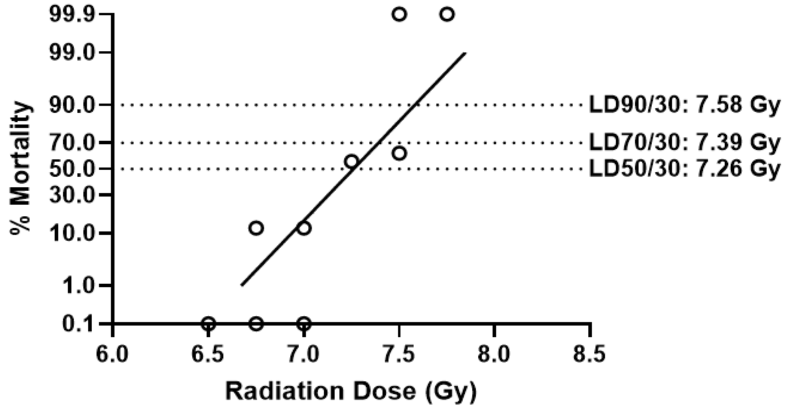
33% Neutron 67% Gamma (female C57BL/6)



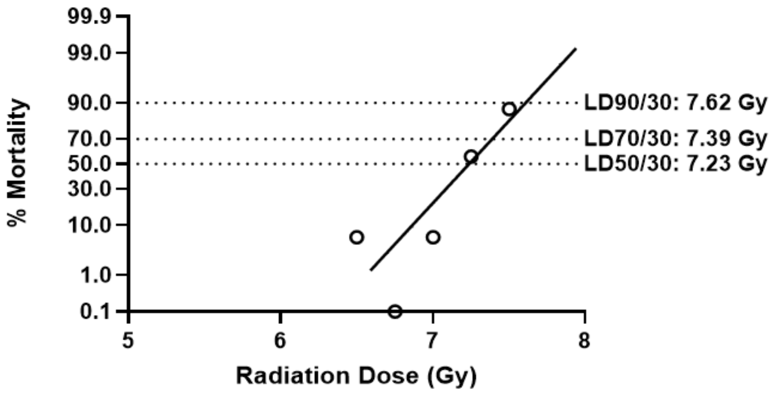
Probit analysis male C57BL/6
5% neutron and 95% gamma



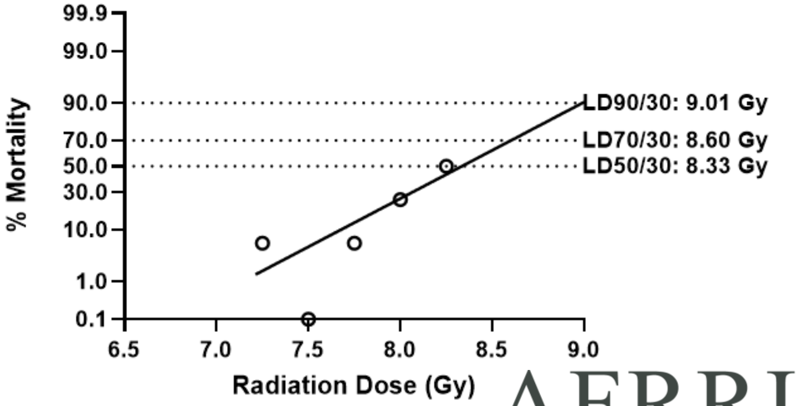
15% Neutron 85% Gamma (male C57BL/6)



15% Neutron 85% Gamma (female C57BL/6)



5% Neutron 95% Gamma (female C57BL/6)



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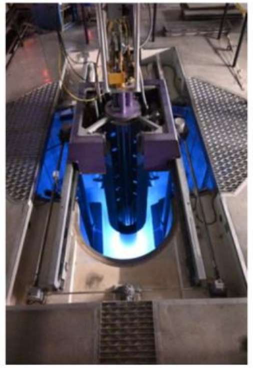

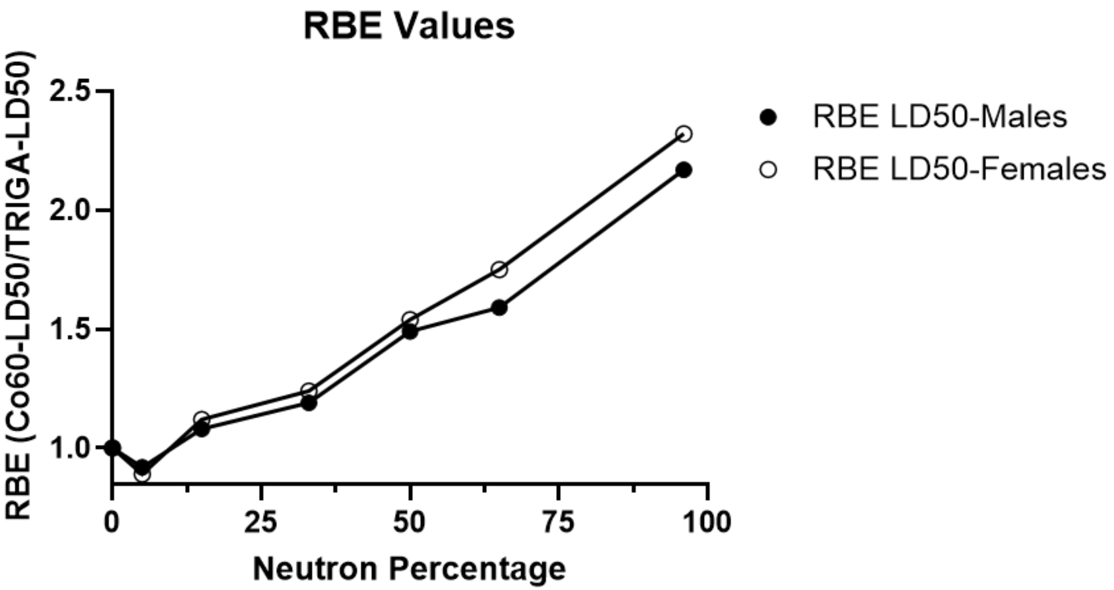

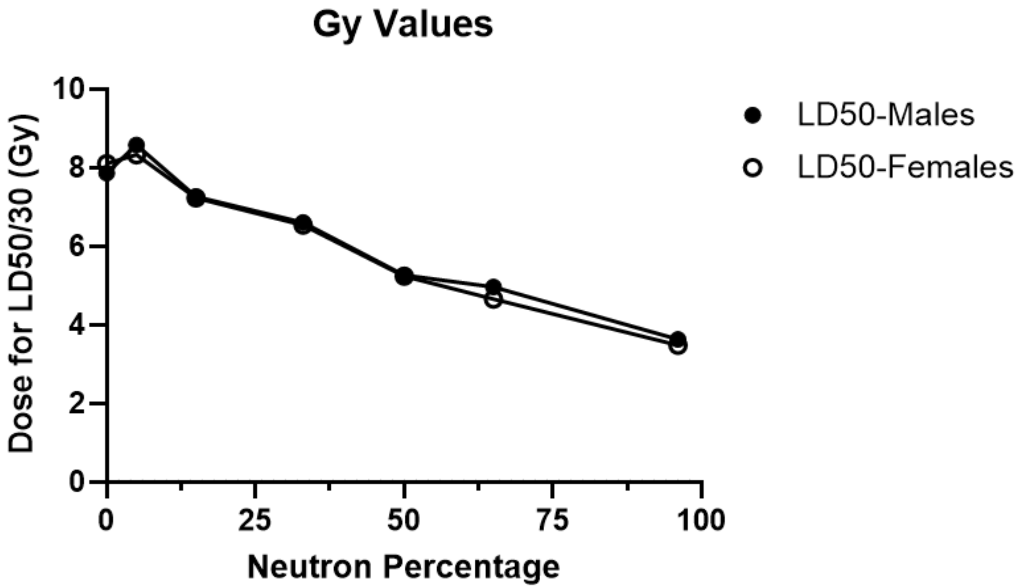

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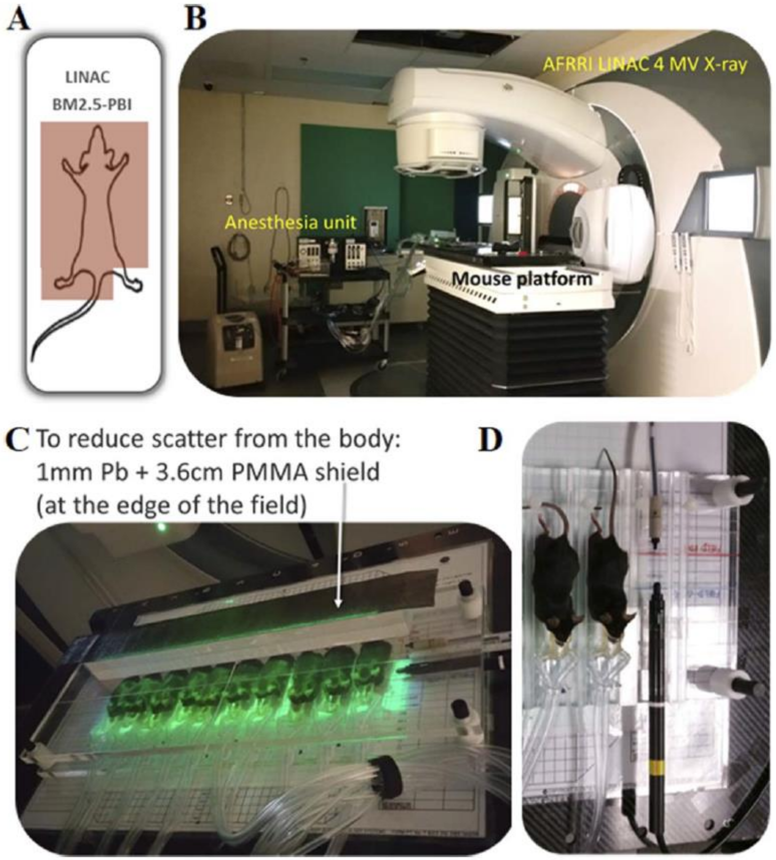
Lethality in the AFRRI LINAC (PBI)



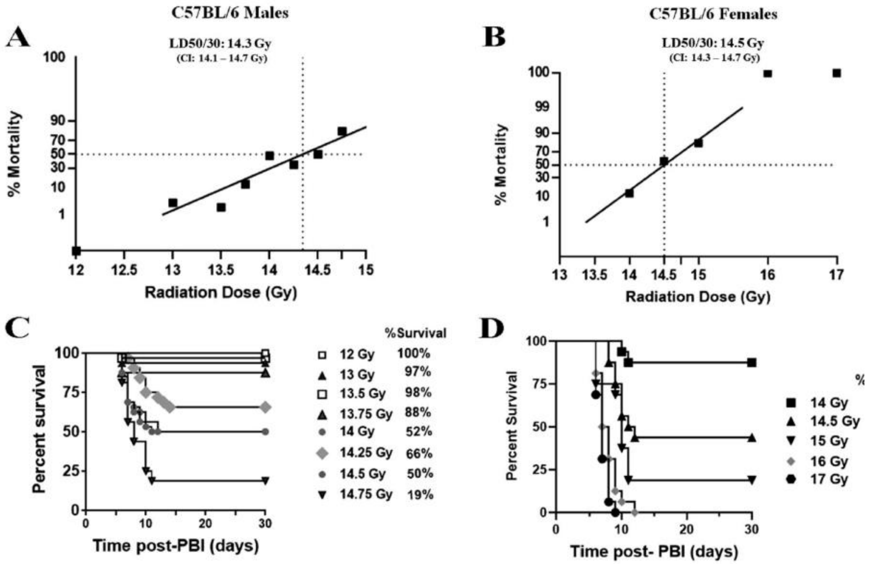
RADIATION RESEARCH 201, 19–34 (2024)
0033-7587/24 $15.00

DOI: 10.1667/RADE-23-00068.1

Development of a Multi-Organ Radiation Injury Model with Precise Dosimetry with Focus on GI-ARS

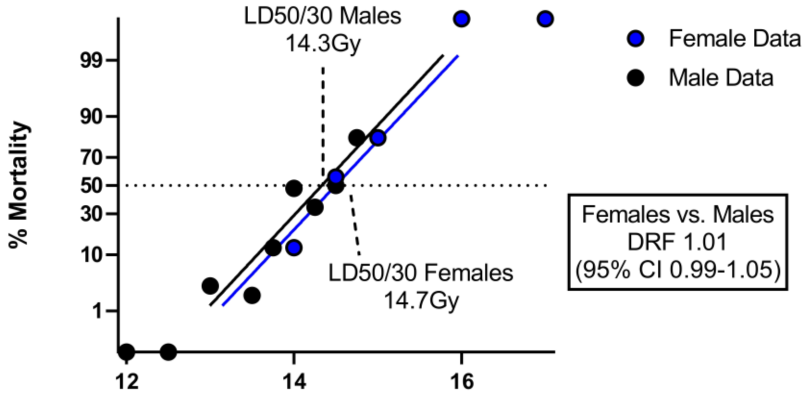
Vidya P. Kumar,[1] Kefale Wuddie, Alena Tsioplaya, Alia Weaver, Gregory P. Holmes-Hampton, Sanchita P. Ghosh

Armed Forces Radiobiology Research Institute, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20889



Model Credit:
Dr. Vidya Kumar

Sex as a Radiation Dose Modifier - PBI Model



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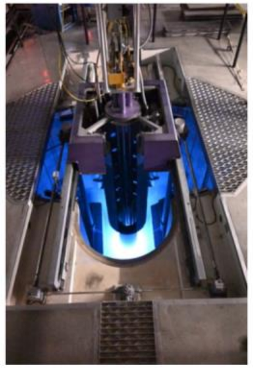
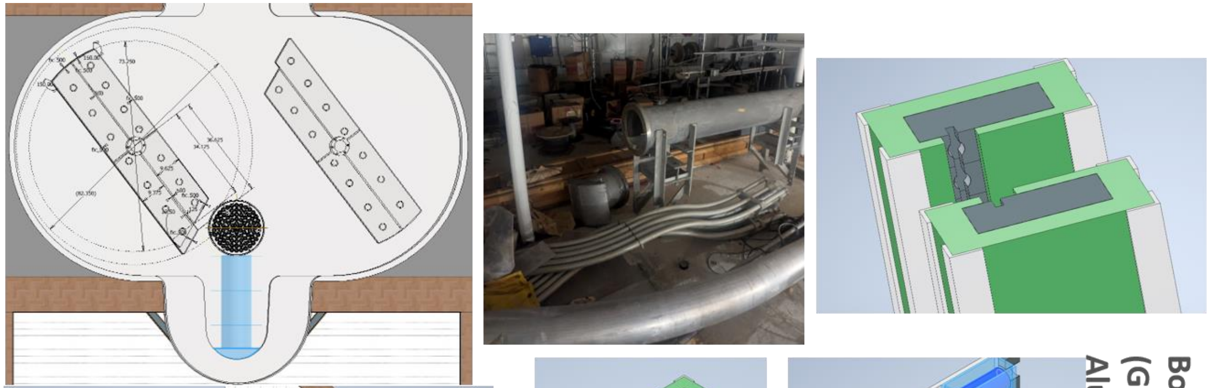
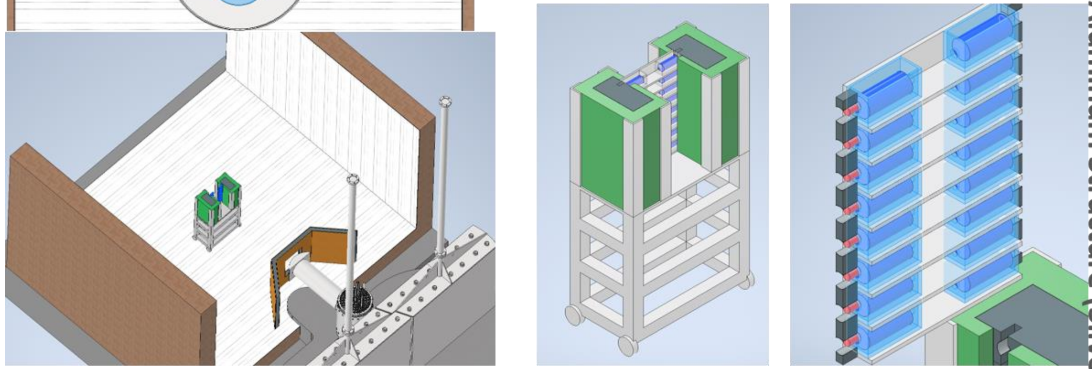
Development of PBI model in the AFRRI TRIGA

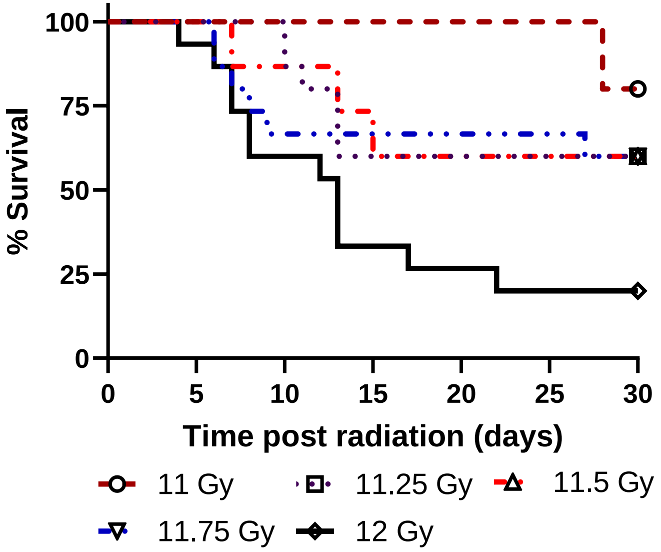




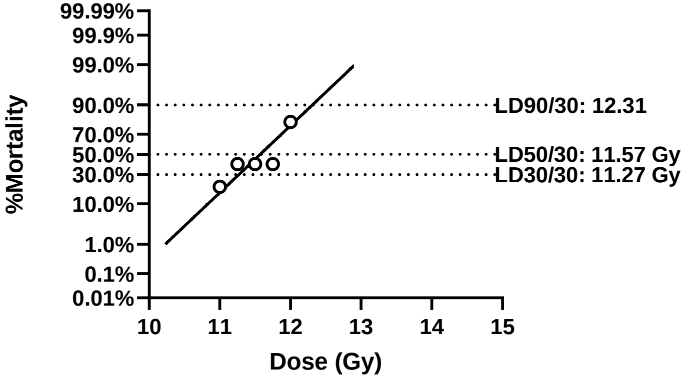


Lead (Black)
Cadmium (Gray)
Borated-polyethylene (Green)
Aluminum Structure (Silver)

MF-PBI-03
30 day survival



MF-PBI Probit curve
Based on MF-PBI-02 and 03



LD50/30 is estimated to be 11.57 Gy compared to 6.9 Gy in the MF TBI model.

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Conclusions

- We have established several models relating to real scenarios
  - TBI Gamma – Fall Out
  - TBI Mixed Field – Detonation
  - PBI X-ray – Fall out with Shielding
  - PBI Mixed field – Detonation with Shielding
- A real exposure is likely to be non homogenous, with sufficient shielding from an urban environment it is possible to induce GI-ARS
- We have established lethality curves in all these models
- We have tested Medical Countermeasures in all of these models to identify candidates to improve survivability

Questions?

Thank you