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The Jackson Laboratory

Mount Sinai Hospital

# Design of 3-D Printed, Highly Tissue-Equivalent Rodent Phantoms, and Use for Validation Comparison of Cs-137 and X-ray Irradiators

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NNSA
National Nuclear Security Administration

CIRMS
Council on Ionizing Radiation Measurements & Standards

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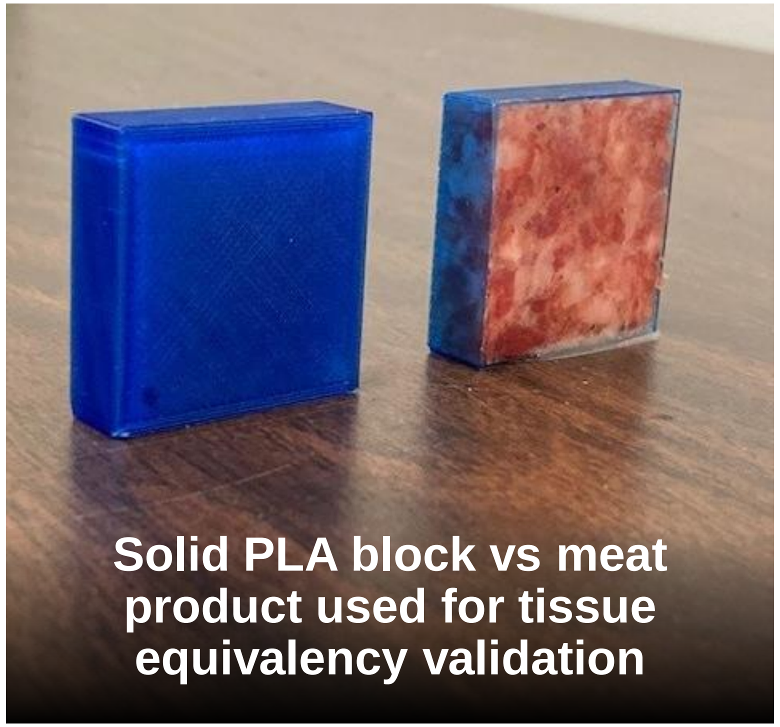
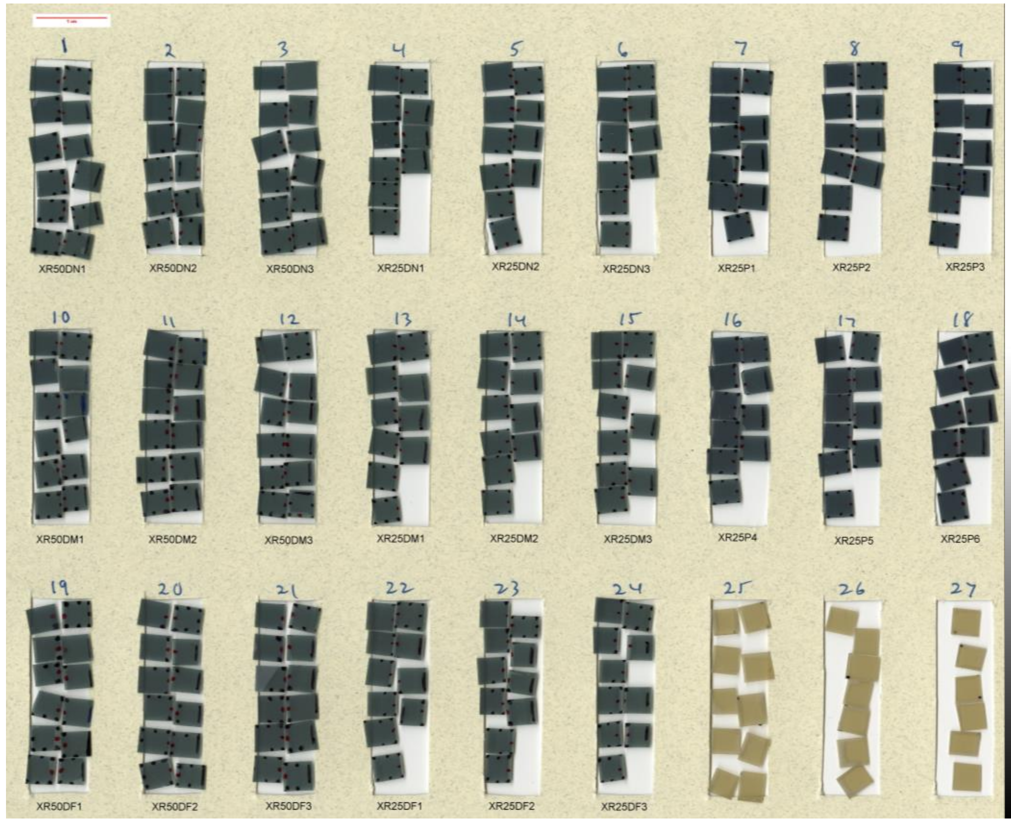
# Overview

- Background & Significance
- Phase 1

  Material Validation & Printing Parameters
- Phase 2
  - Design of Rodent Phantom
- Phase 3
  - Comparison of Depth-Dose Data


Shepard 68-A Cs-137 irradiator at
The Jackson Laboratory
Bar Harbor, ME


Solid PLA block vs meat product used for tissue equivalency validation



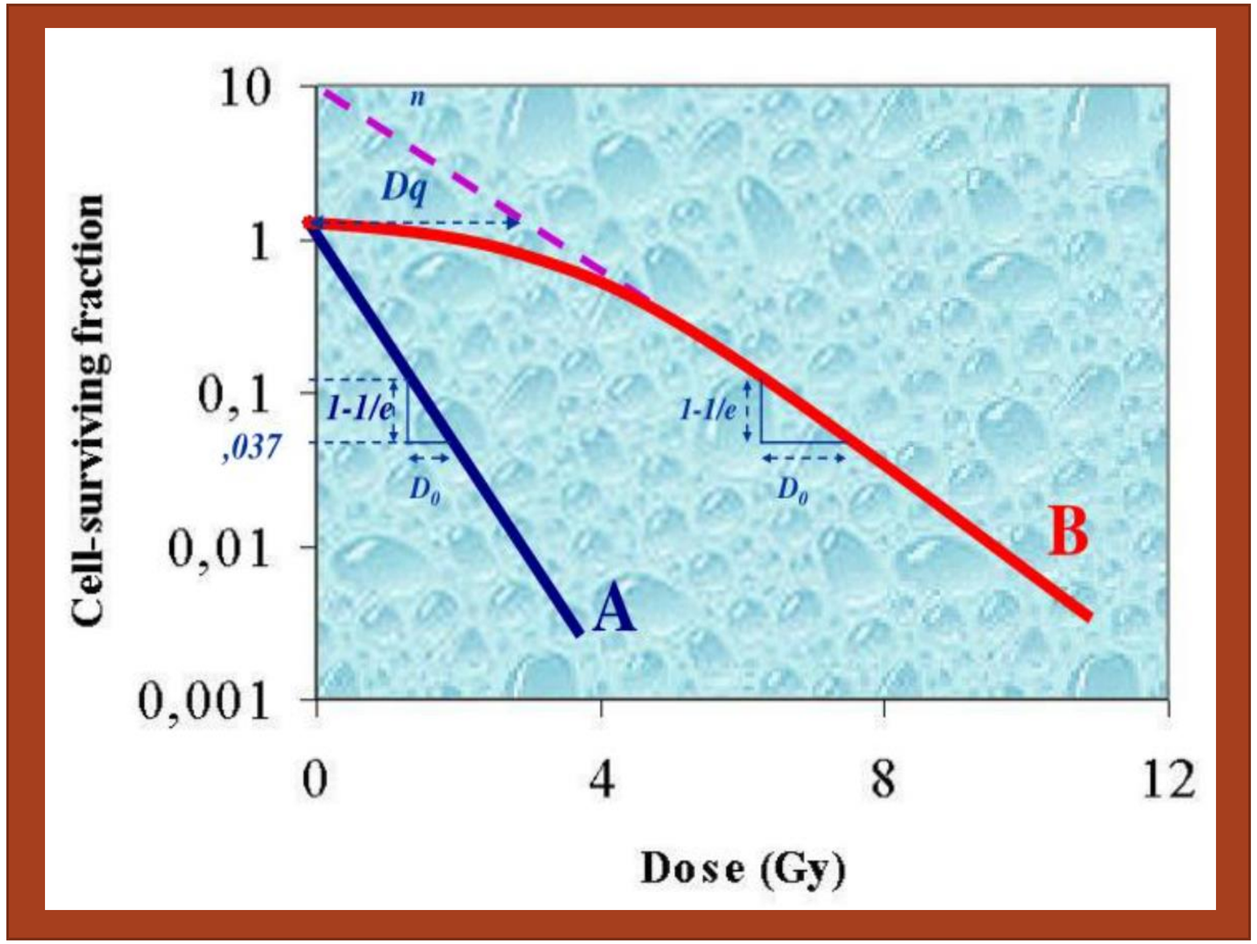
Radiochromic film cut to 5x5mm for use in phantoms

# Background and Significance

# A Need for Tools that Increase Accuracy and Precision of Radiation Dose

- Overall, there is a need for dosimetry tools that provide increased accuracy and precision of delivered radiation dose at depths in specimens.
- One of the applications for use of rodent phantoms is in comparing the dose delivery between different types of radiation fields for specimens of significant mass.
- Such accurate and precise measurements allow biologists to better determine dose response curves (e.g., survival curves), as well as how much a perceived RBE effect is due to difference in dose.
- RBE (Relative Biological Effectiveness) is a relative measure of the negative impact by a given type of radiation per unit of energy deposited in biological tissues.

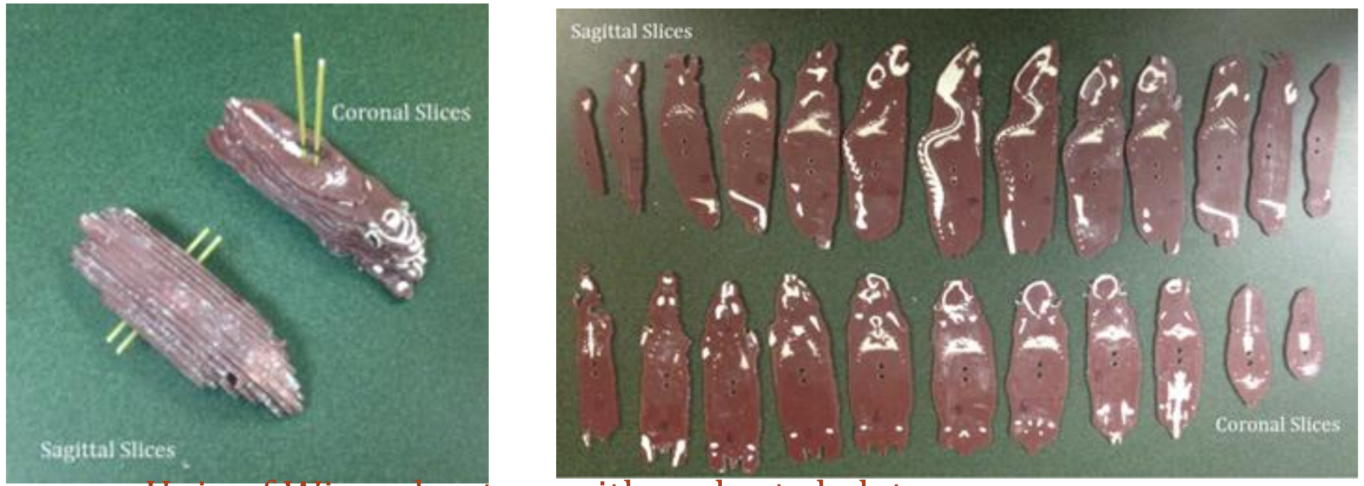
Cell Survival curves



# Available Phantoms

- Over the years there have been numerous polymer-based phantoms that have become commercially-available for both lab animal and human.
- This includes several rodent phantom designs – some all “tissue” and some with simulated bone as well.
- In recent years there has been an increase in 3D-printed phantoms.
- These phantoms purport to be “tissue equivalent”, but there appears to be a lack of published data involving <u>measurements</u> that show that the photon *radiation cross-section* for these phantoms is the same as real tissue (and real bone) across a wide range of photon energies.**

Existing polymer phantoms commercially available



Univ of Wisc. phantom with real rat skeleton and TLD cavities

Human phantom models

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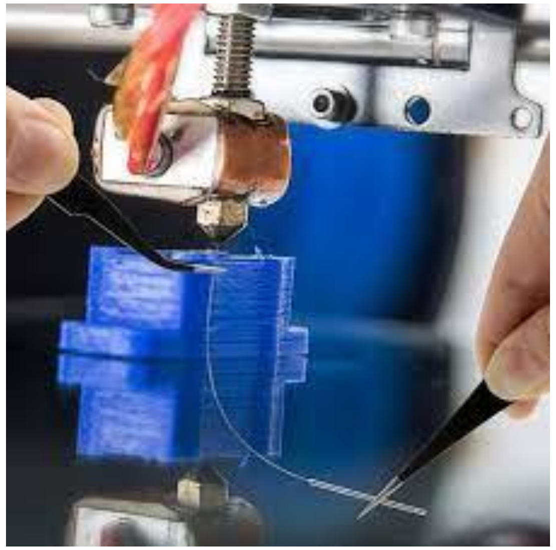
**Filippou, V. and Tsoumpas, C. (2018), *Recent advances on the development of phantoms using 3D printing for imaging with CT, MRI, PET, SPECT, and ultrasound.* Med. Phys., 45: e740-e760.

**D Welch *et al* 2015 *Phys. Med. Biol.* **60** 3589

# Advantages of 3D printing phantoms

- Inexpensive and fast for relatively small components
- Easy to revise designs
- Easy to manipulate density
- Increased accuracy in dose measurements
- Ability to produce multi-component phantoms that can be disassembled and reassembled
- Ability to produce single components with heterogeneous subcomponents
- Reduced need for real laboratory animals



Lungman anthropomorphic chest phantom by Kyoto Kagaku co., Japan and lung structures contained within the Lungman phantom.

# Application –
# Mount Sinai Hospital and The Jackson Laboratory

- Facilities like Mount Sinai Hospital system and The Jackson Laboratory are working with the Office of Radiological Security (ORS) within the National Nuclear Security Administration (NNSA).
- These facilities are determining which of their radiation biology studies that historically have used gamma-rays (Cs-137 and/or Co-60) could instead use orthovoltage X-ray beams of maximum energy on the order of 160-320 keV.
- Pacific Northwest National Laboratory (PNNL) has been tasked to assist these facilities with the needed dosimetric measurements comparing the gamma-ray and X-ray irradiators.
- In order to provide measurements of high accuracy and precision so valid comparisons can be made, PNNL utilizes ionization chambers as well as rodent phantoms of high tissue-equivalency (with inserted dosimetry film).

# Irradiators That Were Compared for Dose Delivery

**Cs-137 (JL Shepherd 68-A)**
- 662 keV
- Line source geometry

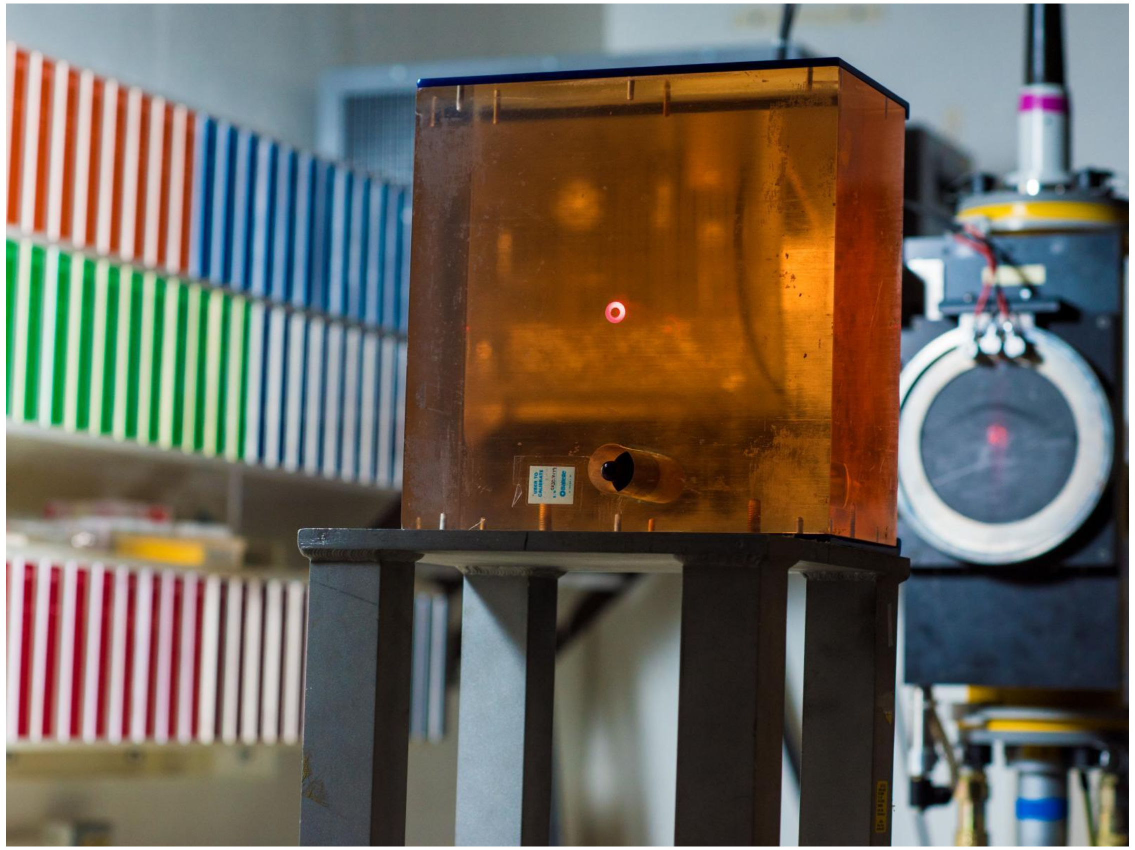
**X-ray (RadSource 2000)**
- 160 keV max
- Point source geometry

**X-Ray (Precision X-RAD320)**
- 320 keV max
- Point source geometry

# PNNL Irradiators Used to Verify Tissue-Equivalency of Rodent Phantoms

## X-ray Irradiator

- 30 – 320 keV
- Point source



## Cs-137

- 662 keV
- Point source

## Co-60

- 1250 keV
- Point source

*krad/hr x 10 = Gy/hr
Dose rate values valid for March 2018
30-degree collimated beam traverses 7-meter room
Dose rate at edge of primary beam is ~9% lower than beam center

# Phase 1:

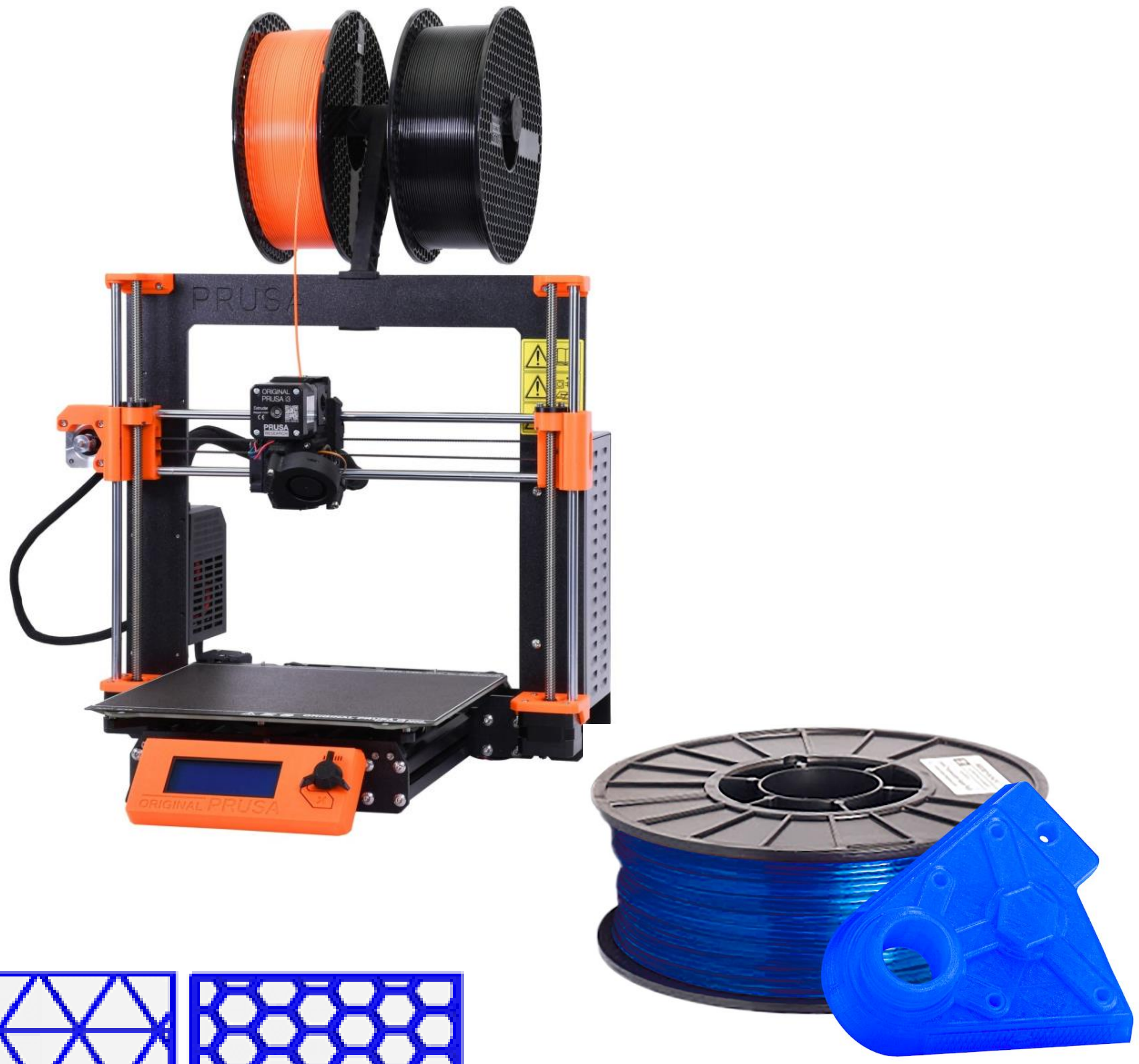
# Material Validation and Printing Parameters

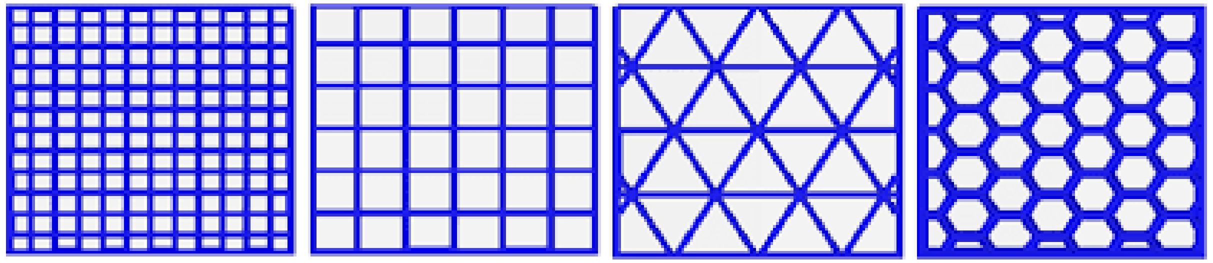
# Material Selection

- Why use plastic as a tissue substitute or surrogate?
- Why PLA as a soft tissue substitute?  Why not ABS for example?
- What parameters determine whether highly tissue equivalent?
- Should one match *density*, or *photon radiation cross section*?

# Printing Parameters

- **3D Printer:** Prusa i3 MK3S+
- **Filament:** Translucent Blue PRO Series PLA Filament - 1.75mm
- **Printing Parameters:** Adjusted until resulting blocks were within 2% of real tissue:
  - Extruder Temp
  - Bed Temp
  - Infill Percentage
  - Fill Pattern





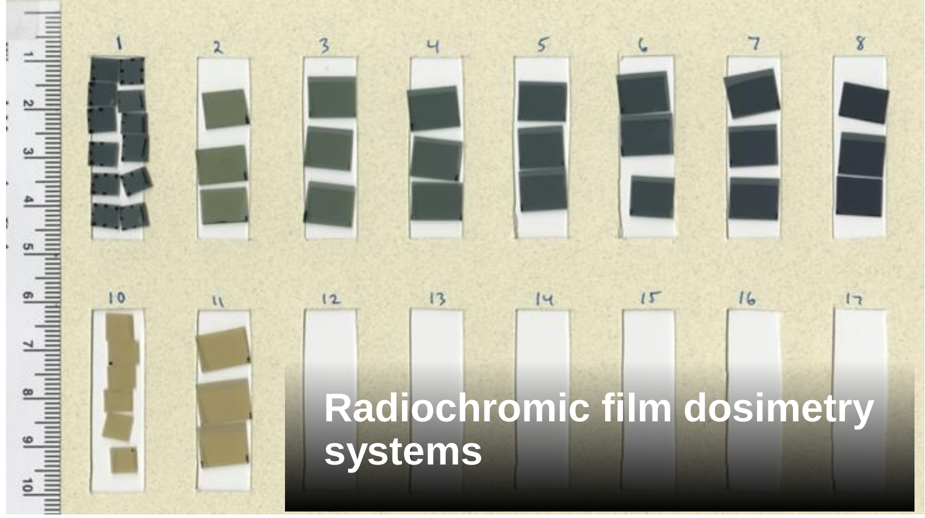
(a) Rectilinear (b) Grid (c) Triangle (d) Honeycomb

# Leveraging some of PNNL’s unique capabilities

- Wide range of radiation types and energies
- NIST-Traceable fields and detectors
- NVLAP-accredited calibrations (Lab Code 105020-0)


High Exposure Facility – 60Co and 137Cs


Precision ionization Chambers



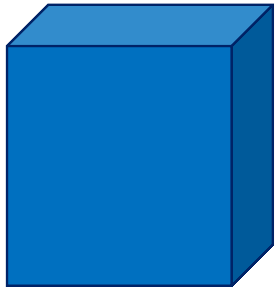
Radiochromic film dosimetry systems


Over 70 ISO and NIST-certified X-ray beam techniques

# Material Validation

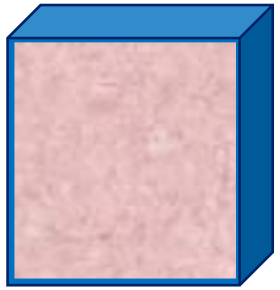
- Utilized meat product that was ~80% muscle tissue and ~20% adipose tissue.
- PLA block and meat block exact same dimensions
- Placed meat product and PLA cube in radiation fields.
- Measured mean signal with ion chamber for each and compared.

Solid 3D printed block



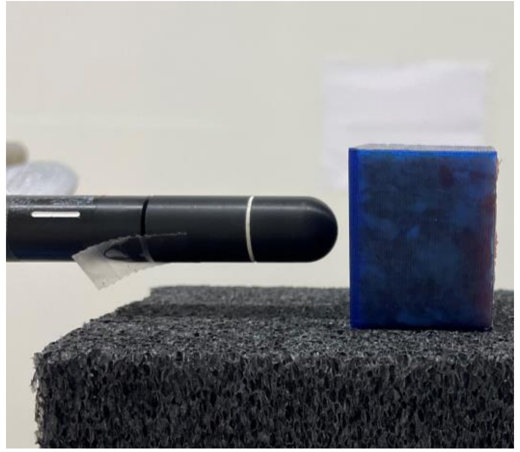
| Mass | Volume | Density |
|---|---|---|
| 29.6 g | 26.1 cc | 1.1 g/cc |

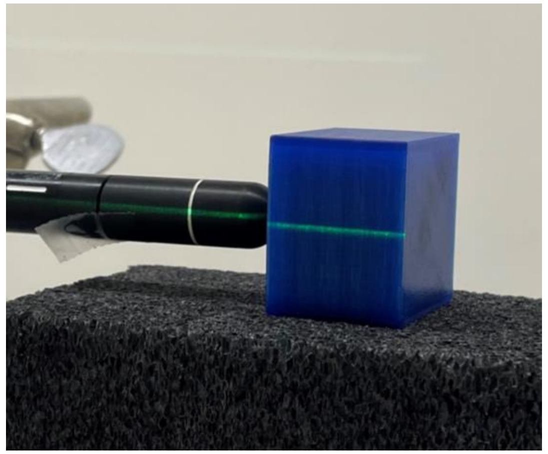
3D printed shell filled with simulated tissue

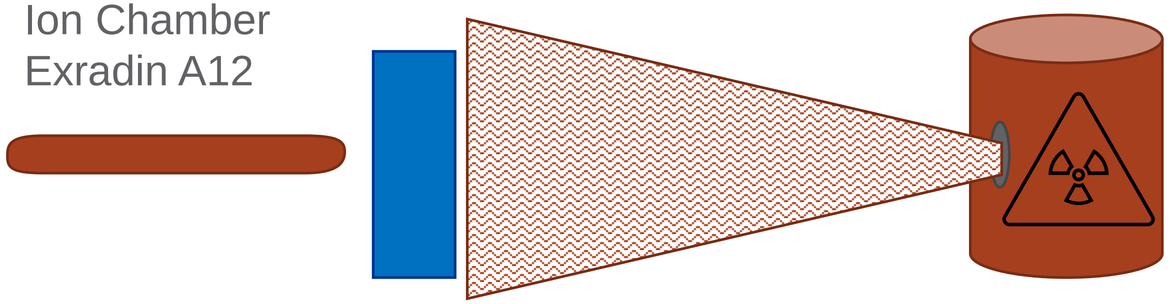


| Mass | Volume | Density |
|---|---|---|
| 22.8 g | 23.0 cc | 0.99 g/cc |

average of 5 measurements







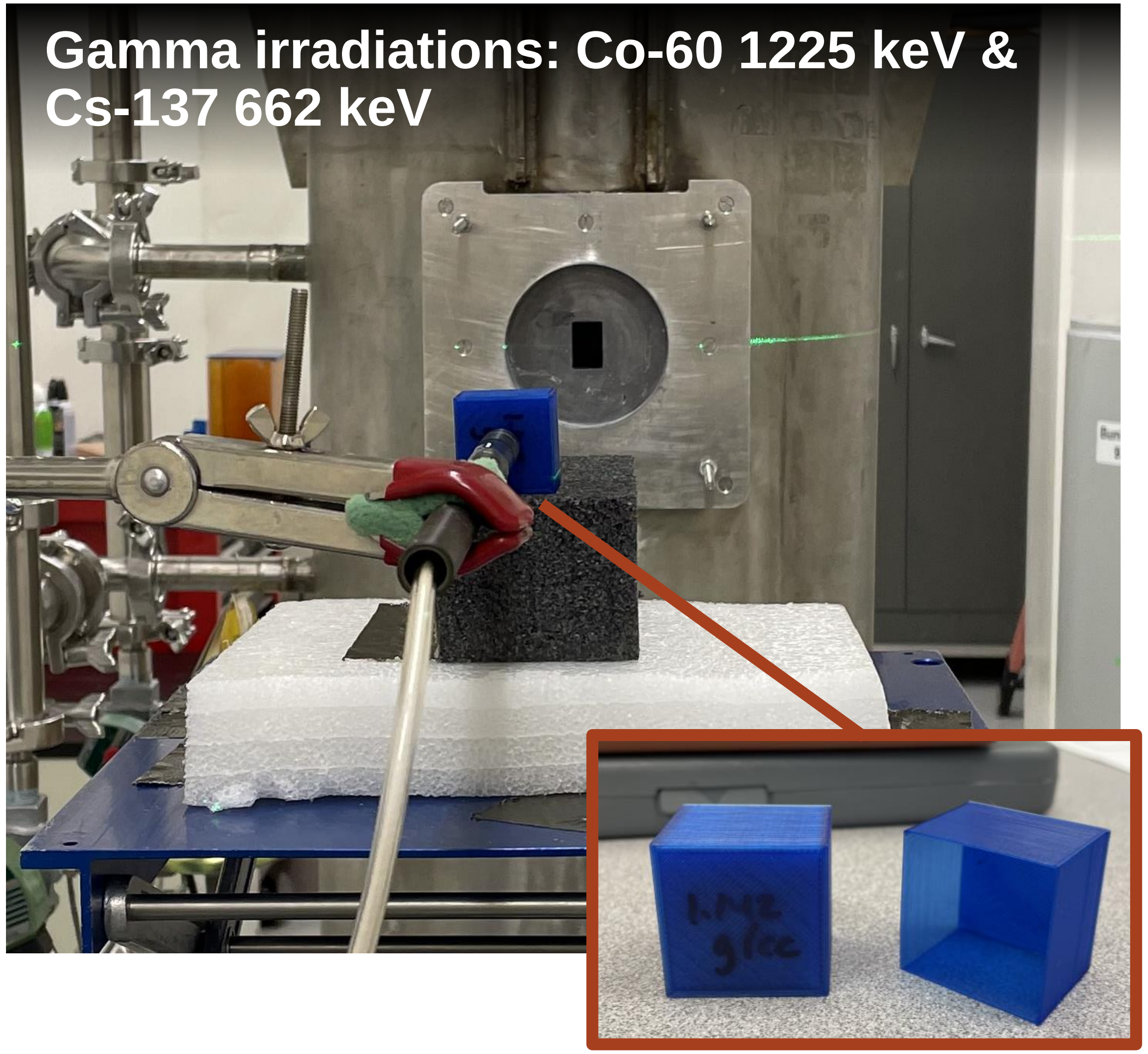
Ion Chamber
Exradin A12

PLA or Tissue

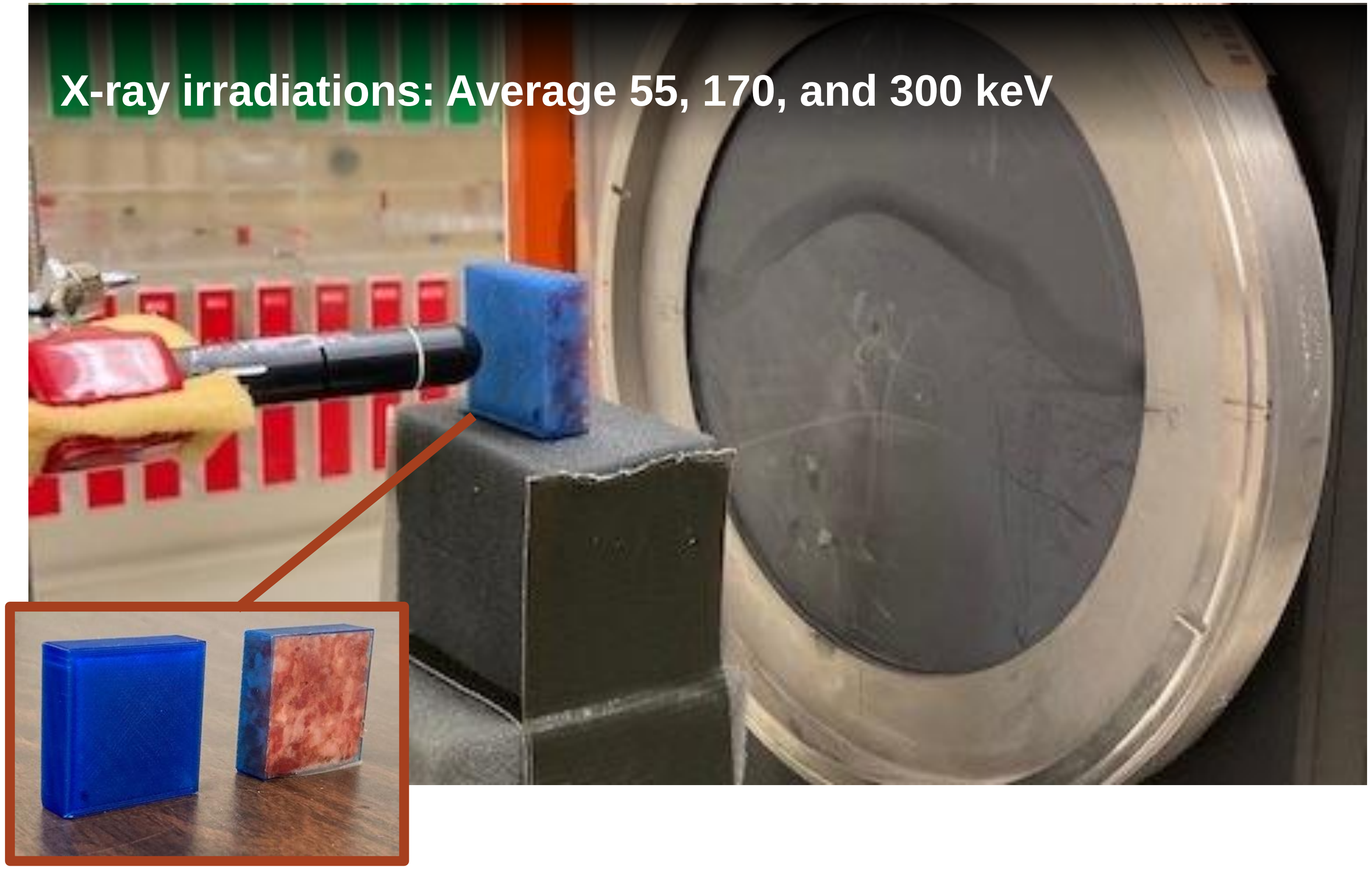
Radiation
Source

# Methods

- Range of photon energies from 50 keV to 1250 keV
- Minimize influence of air and surface scatter
- Recorded ionization chamber signal with both blocks to determine attenuation performance



**Gamma irradiations: Co-60 1225 keV & Cs-137 662 keV**

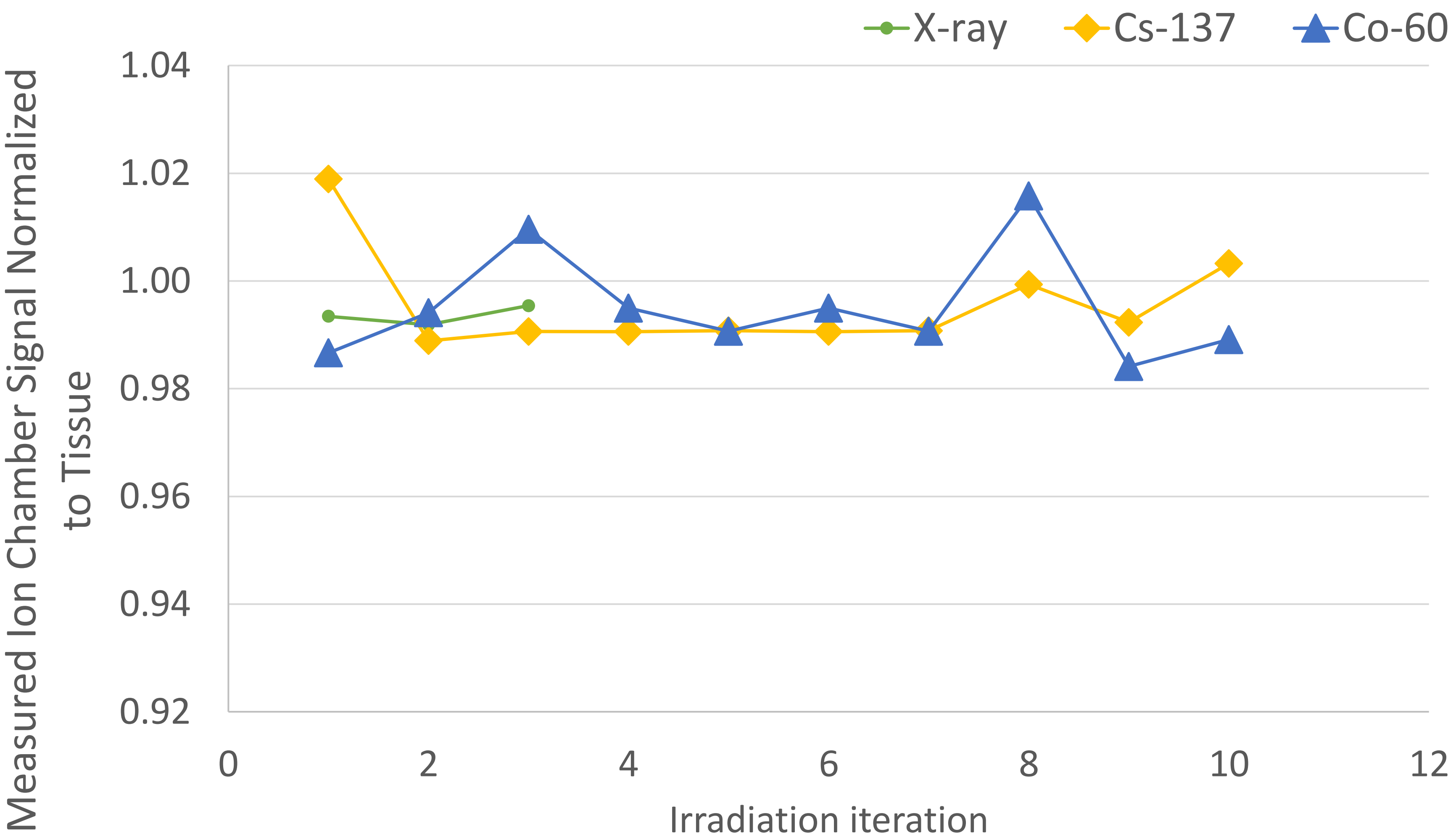


**X-ray irradiations: Average 55, 170, and 300 keV**

# Tissue equivalency of solid 3D printed PLA cubes and 3D-printed shells filled with meat product exposed to X-ray, Cs-137and Co-60

- Over several irradiations, the PLA attenuated the signal measured by the ion chamber within 2% of the same field measured when attenuated with the meat product.
- These test were performed with varying dose rates, the values here are the normalized signal to tissue.
- (PLA /Tissue) under the same irradiation conditions

Error bars are size of symbols

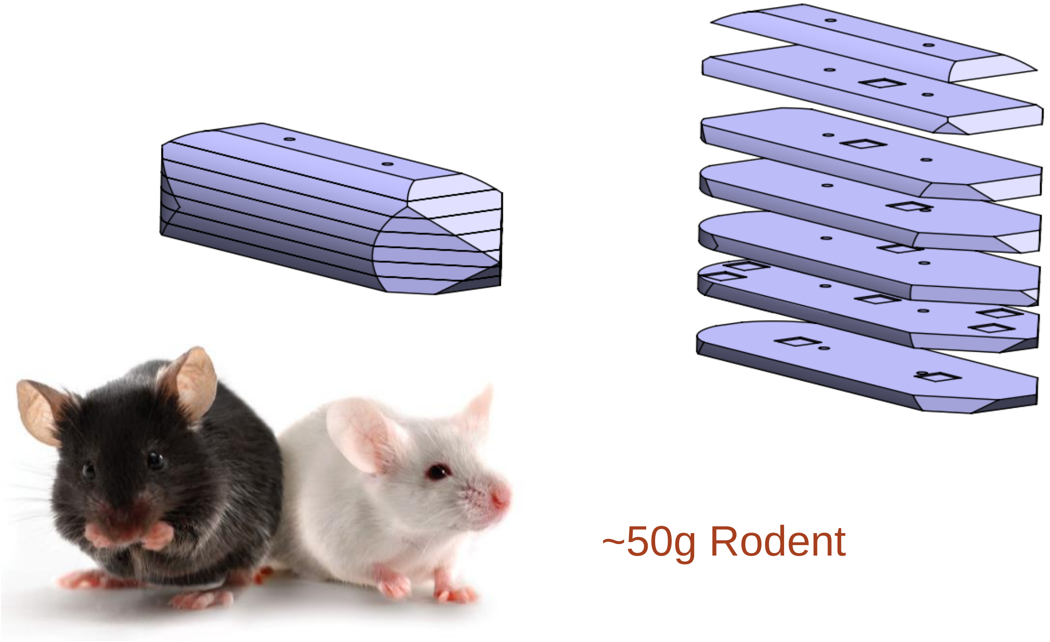


# Phase 2:

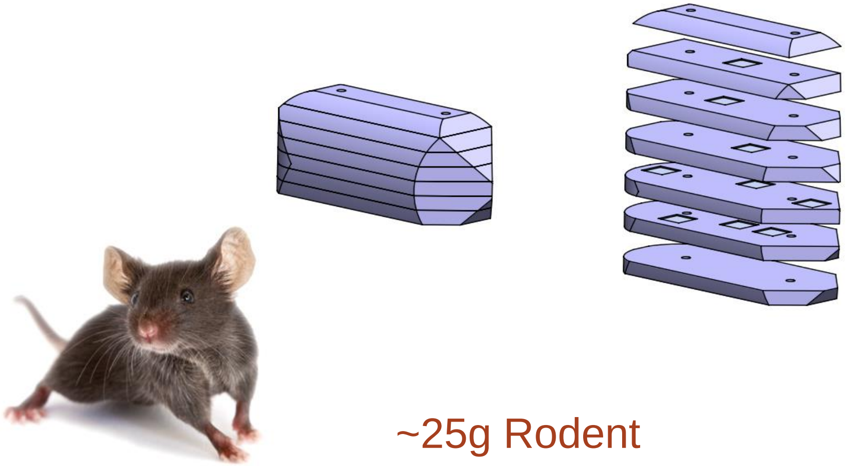
# Design of Rodent Phantoms for the Comparison of Depth-Dose of Gamma and X-ray Irradiators

# Phantom Design

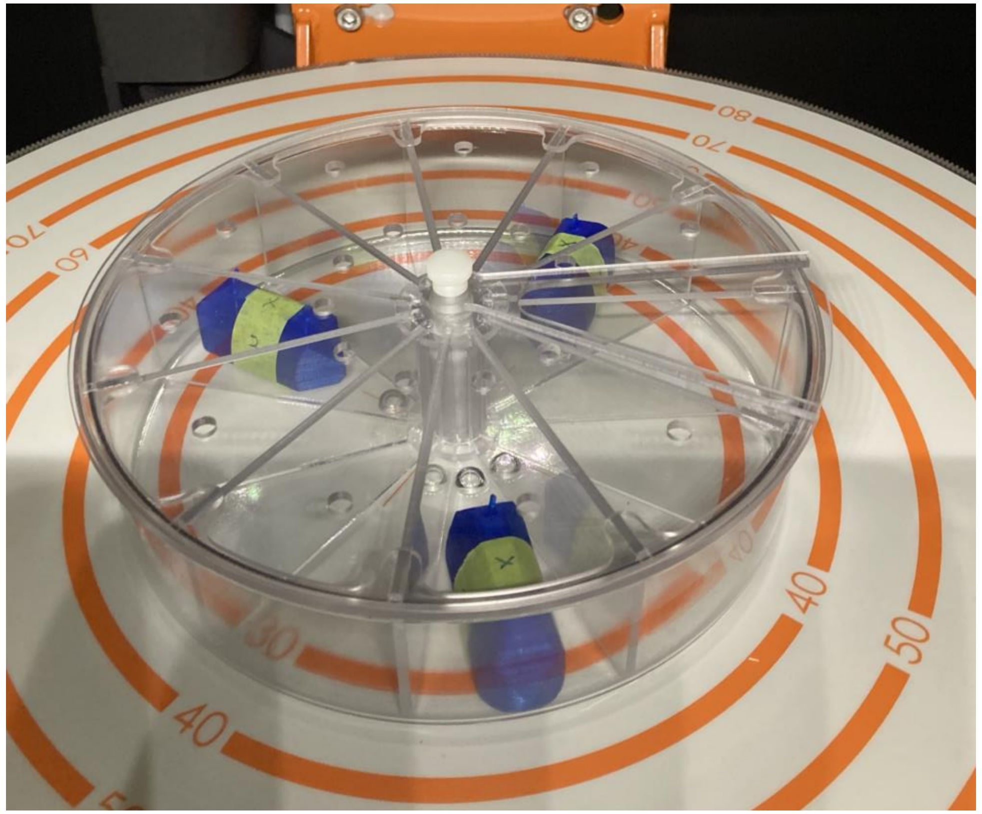
- The **large mouse** phantom is 8.1 cm long and 2.9 cm diameter, and totals 47 grams.
- The **small mouse** phantom is 5.5 cm long and 2.9 cm diameter, and totals 26 grams.
- Additional considerations:
  - Location of cavities
  - Size of cavities
  - Printing limitations



~50g Rodent



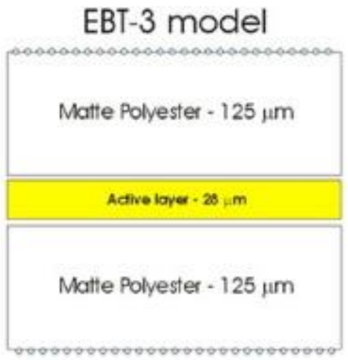
~25g Rodent

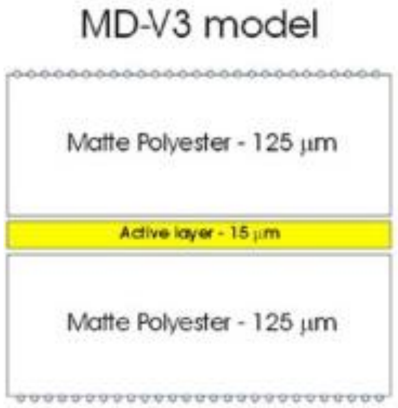


JAX XRAD320 pie cage scenario with the 25g rodent

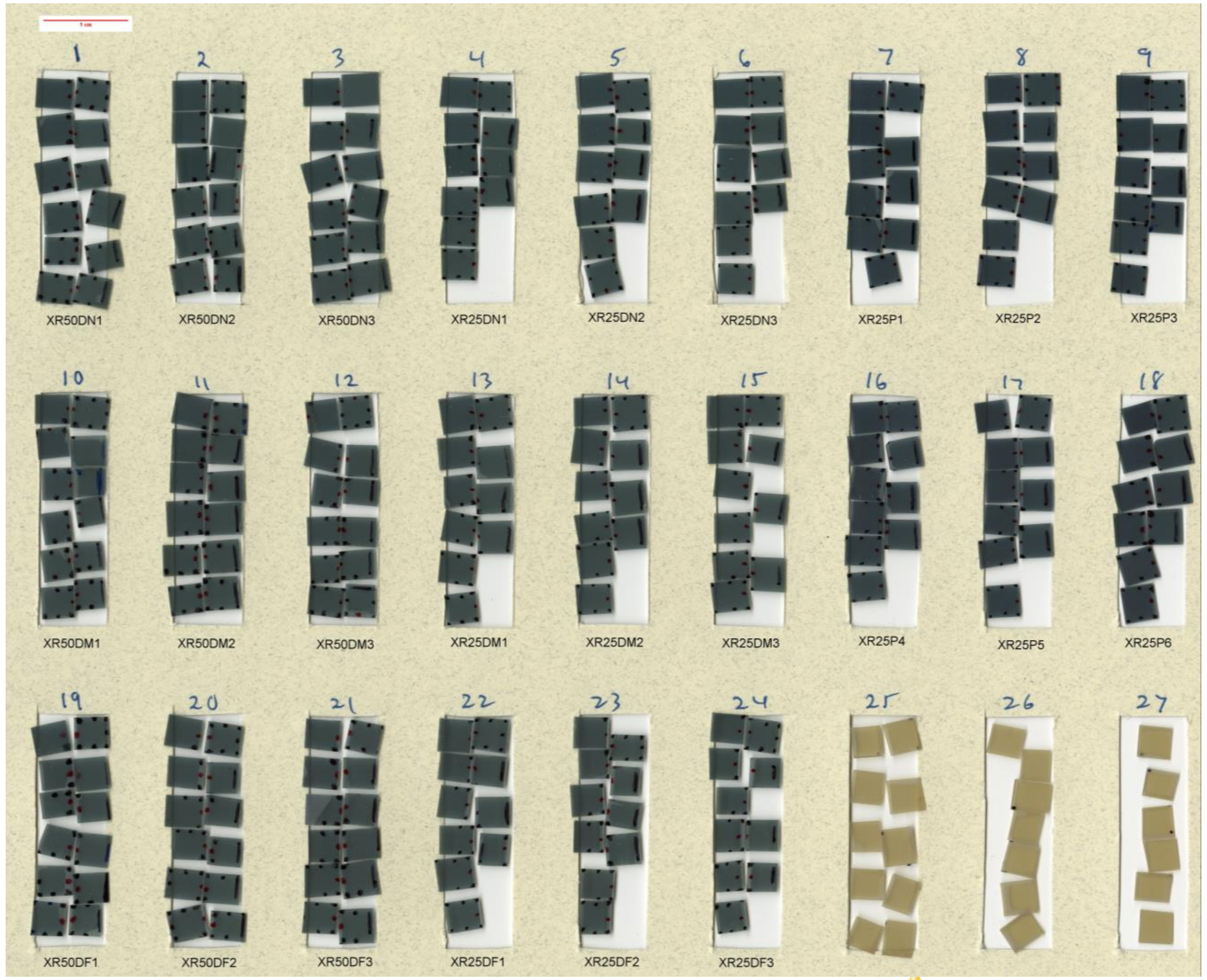
# Dosimetry: *Radiochromic Film*

- **Equipment** – EPSON Scanner 10000xl





- **Material** – Ashland radiotherapy films
  - Gafchromic™ EBT3
    - ✓ Dynamic dose range:  0.2 – 10 Gy
  - Gafchromic™ MDV3
    - ✓ Dynamic dose range: 1 – 100 Gy



ImageJ

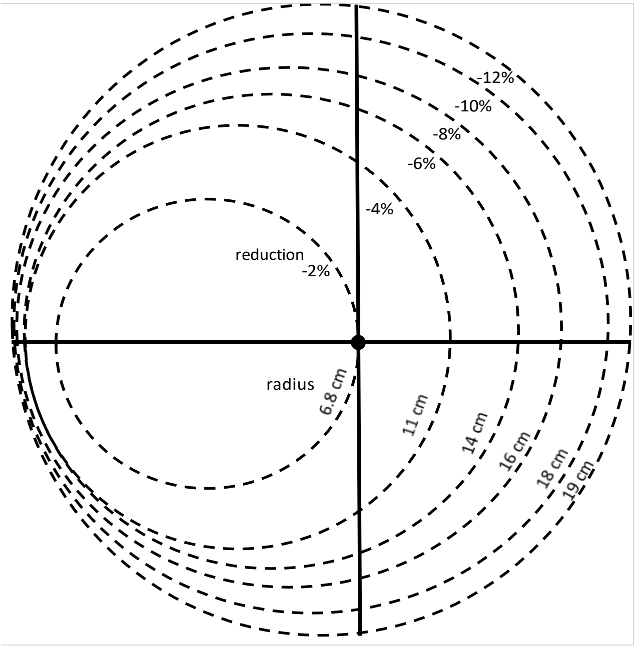
Ashland (2017) *tools for radiology and radiotherapy applications*. Available at: https://www.ashland.com/industries/medical/radiotherapy-films.

# Phase 3:

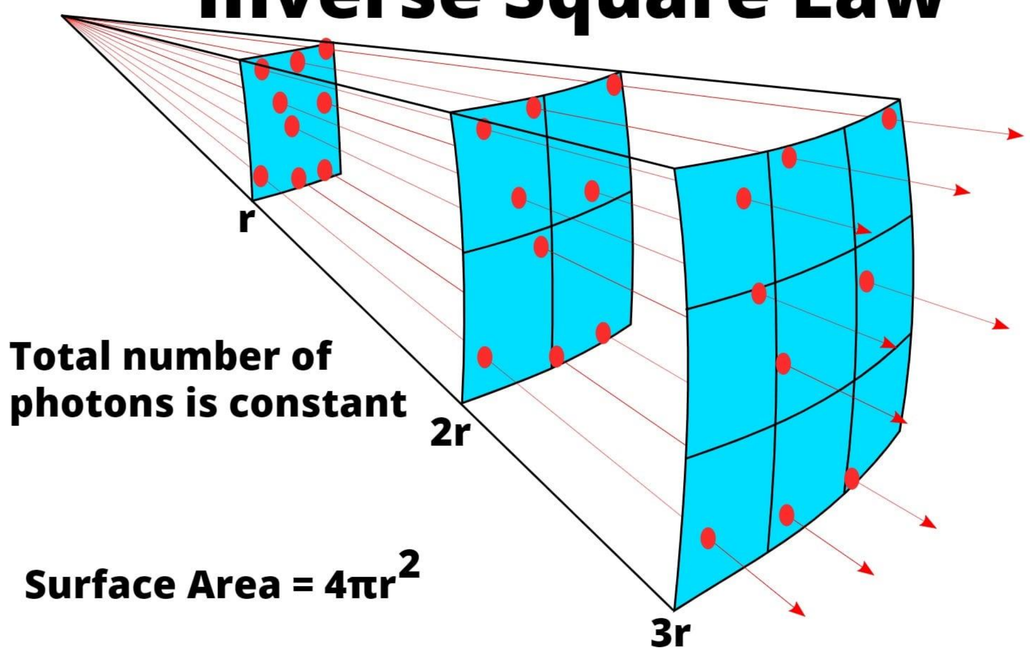
# Real Application - Comparison of Depth-Dose for Cs-137 and X-ray Irradiators

# Irradiator Physical Characteristics
# Impact Dose

- Self-shielded irradiators typically do not have uniform fields, and the relatively close source distances exacerbate this non-uniformity.
- The combination of the ***radiation field geometry*** and ***where the specimen is placed within this field*** can have a major influence on the dose distribution within specimens of significant mass.
- The geometry of the radiation field is influenced by ***source geometry*** *(point source or line source?)*, the ***type of collimation***, the ***size of the irradiation chamber***, and the ***percentage of scatter*** from the chamber walls.



**Angled X-ray target creates the "heel effect"**


**Inverse Square Law**

# Warning: Sources of error can easily add up to 20-30%!

| Main Sources of Error in Delivered Dose to Specimen | Potential Magnitude of Uncertainty at ~95% Confidence Level | Uncertainty Values Can Be Obtained From… |
|---|---|---|
| Calibration of detector used for measurements | 3-10% | Calibration certificate. 3% value typical for high precision ionization chamber, and 10% for low precision passive dosimeter (TLD or film) |
| Detector wall thickness much greater than needed for CPE | 2% for gamma-ray and 5% for X-ray | Published data. |
| Detector calibrated with field with significantly different effective energy. | 5% if ion chamber, and 15% for TLD or OSLD | Published energy dependence curves for these various detectors. |
| Using Exposure or Air-Kerma instead of absorbed dose to tissue or water (or visa-versa) | 5-12% | Published conversion factors. |
| Min/max dose ratio within specimen | For one-sided irradiation, 10% for gamma-ray and 15- 20% for X-ray (for typical lab mouse) | Published depth dose or depth dose distribution values for ~25 gram mouse. |
| Specimen positioned outside of uniform field in x-y plane, as well as z-plane | 20% for both gamma-ray and X-ray | Published field uniformity data for associated irradiator. |
| Beam attenuation due to specimen container and/or multiple specimens | 5% for gamma-ray and 10% or more for X-ray | Published data or own calculations using beam effective energy and mass energy absorption coefficients. |
| Potential Combined Uncertainty or Error in Dose to Specimen (at the 95% confidence level): **25-35%** (using RSS) | | |

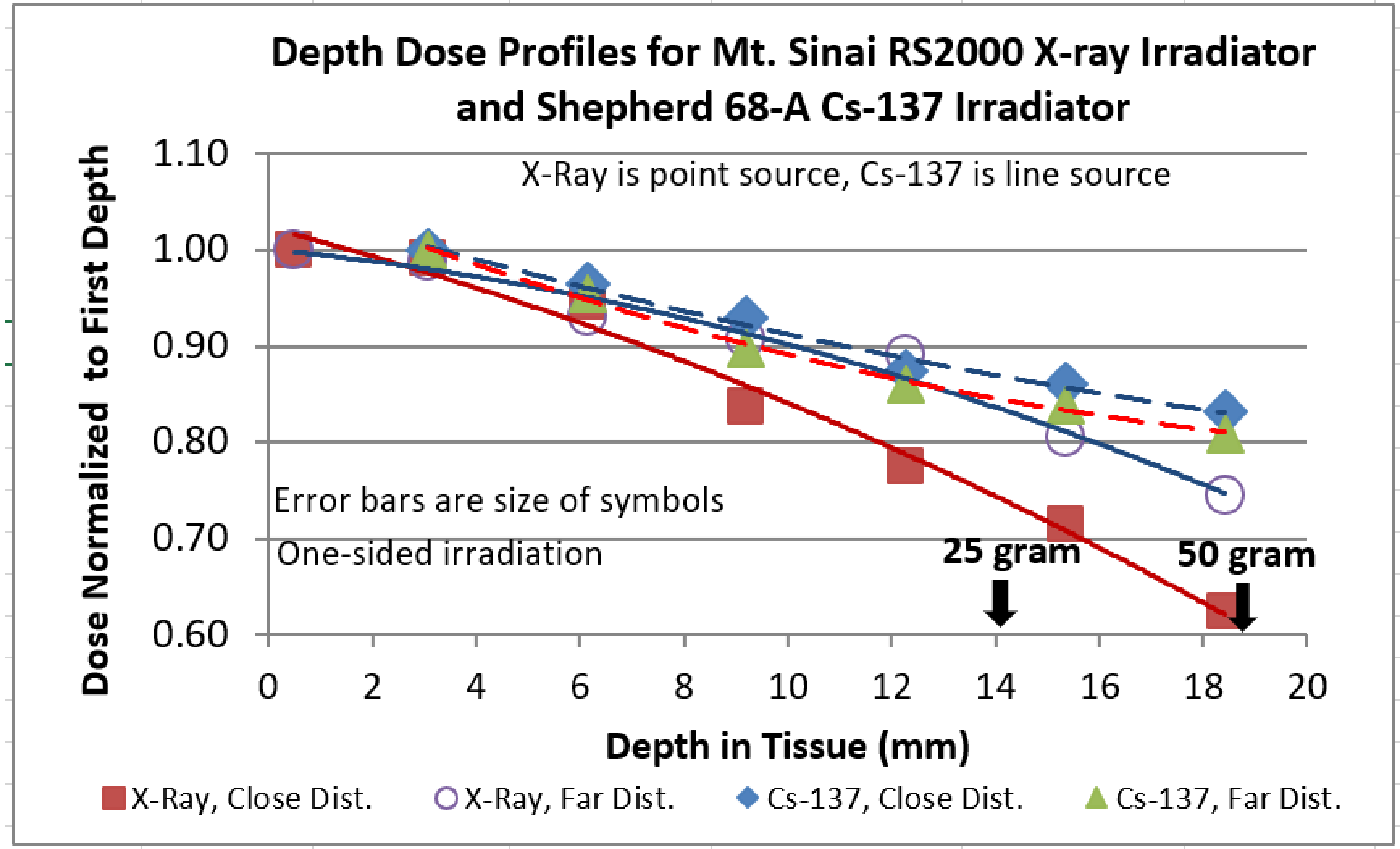
Researchers can make all these errors and may still claim the dose is "Traceable" to a primary standard!

# Background on Mount Sinai

- The Mount Sinai Health System is an integrated health care system founded in 1852, consists the Icahn School of Medicine at Mount Sinai and eight hospital campuses in the New York metropolitan area, as well as a large, regional ambulatory footprint.
- Mount Sinai is internationally acclaimed for its excellence in research, patient care, and education across a range of specialties.
- As a part of the ORS program for disposal of Cesium Irradiators (CIRPS), my co-author Mark Murphy performed the comparison studies to migrate research and blood product irradiation from Cs-137 irradiator to the RS2000 X-ray irradiator in 2017.

# Depth-Dose in Vertical Axis within Specimens – RS2000 & 68-A Irradiators

- Figure provides Depth-Dose curves in direction of primary beam, for a RadSource RS2000 160 kVp X-Ray, and a Shepherd & Associates Model 68-A Cs-137 irradiator, both located at Mount Sinai.
- Obtained using a 50-gram tissue-equivalent rodent phantom.
- Tissue depths associated with the typical rodent sizes (25 grams and 50 grams) are labeled.
- Shows that differences in field geometry can overwhelm differences in energy spectra!



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# Comparison Of Cs-137 & X-ray Irradiators in Terms of Depth-Dose

Mount Sinai
Hospital

- The dose fall-off in rodents for the160 kV X-ray is greater than Cs-137 irradiators by 2-11% depending on irradiator
- For most all applications at Mt. Sinai, this difference in depth-dose for their new X-ray was acceptable.

| Irradiator Comparison | Rodent Size | Max Dose Fall-off and % Difference* | Min/Max Dose Ratio and % Difference* |
|---|---|---|---|
| $^{137}$Cs Model 68-A versus RS2000 X-ray at 160 kV | 25 g | A=0.85, B=0.83, **2%** | --- |
| | 50 g | A=0.81, B=0.75, **6%** | A=0.81, B=0.75, **6%** |
| $^{137}$Cs Custom versus XRAD X-ray at 160 kV | 25 g | C=0.88, D= 0.78, **10%** | --- |
| | 50 g | C=0.83, D=0.72, **11%** | C=0.81, D=0.71, **10%** |
| $^{137}$Cs Custom versus XRAD X-ray at 300 kV | 25 g | C=0.88, E=0.90, **2%** | --- |
| | 50 g | C=0.83, E=0.84, **1%** | C=0.80, E=0.86, **6%** |

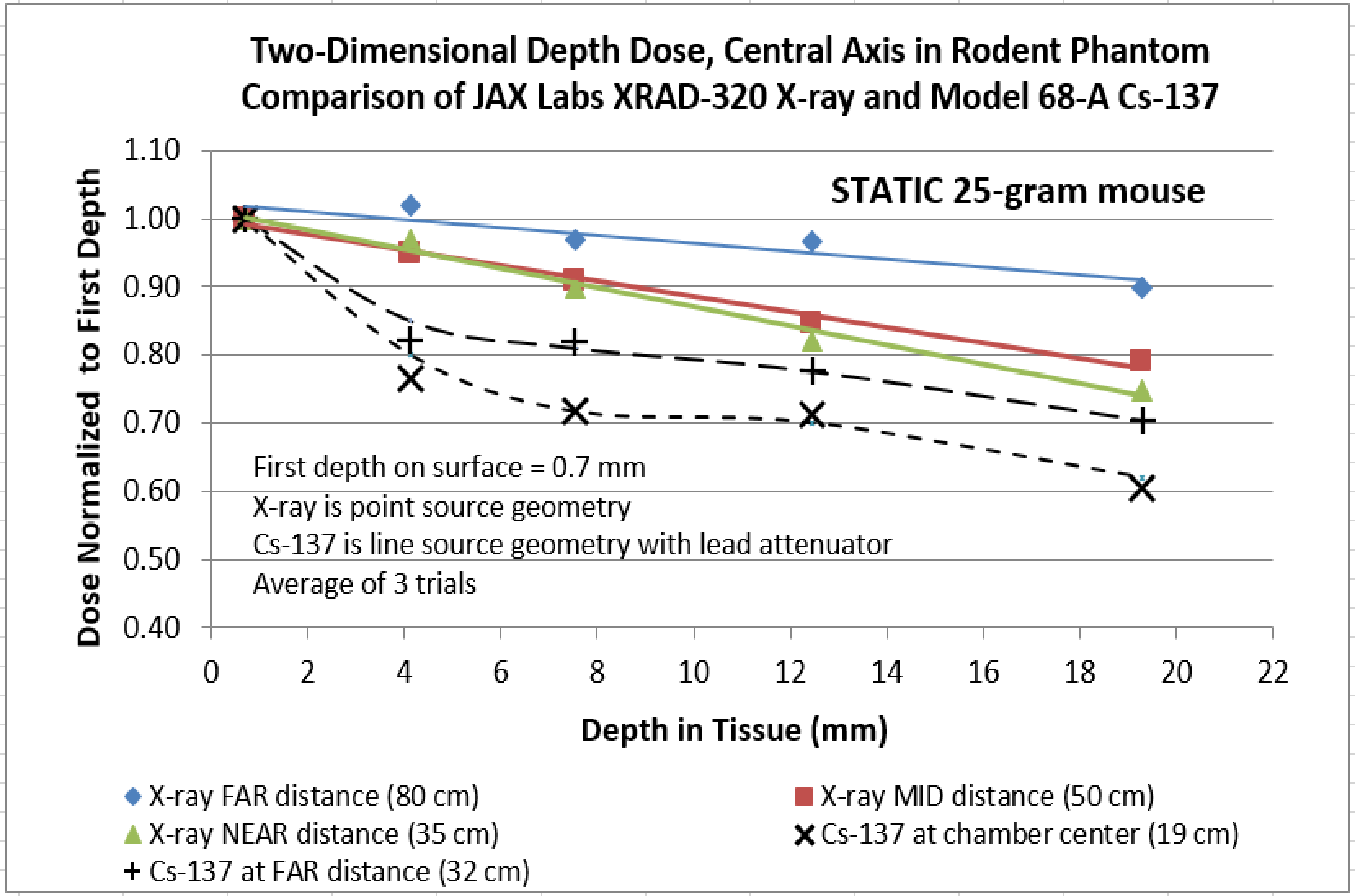
* A= Mount Sinai Shepherd $^{137}$Cs Model 68-A
B= Mount Sinai RS2000 160 kVp X-ray
C= PNNL $^{137}$Cs Custom box irradiator
D= PNNL Precision XRAD 320 kVp at 160 kV
E= PNNL Precision XRAD 320 kVp at 300 kV

# Background on JAX

- The Jackson Laboratory (JAX) is a world leader in mammalian genetics and human genomics research. Founded in 1929 to uncover the genetic basis of cancer, JAX pioneered the use of laboratory mice as models for human disease and provided the basis for many modern medical treatments.
- JAX® Mice are the industry standard for animal model research. Rigorous Animal Health Programs and stringent genetic quality standards ensure the reproducibility and validity of experimental data.
- Researchers at JAX use ionizing radiation in research utilizing genetically modified mouse models, inbred mice from different genetic backgrounds and genetically diverse mice. Research includes radiation gonadotoxicity, immune response, cancer and aging.
- Migration from gamma irradiators to X-ray devices requires development of new standardized methods for specific mouse models to ensure continuity and reproducibility of research at JAX.
- Goals for this project: Comparing the effects of X-ray vs Cs radiation on oocyte radiosensitivity  and survival in different mouse models.

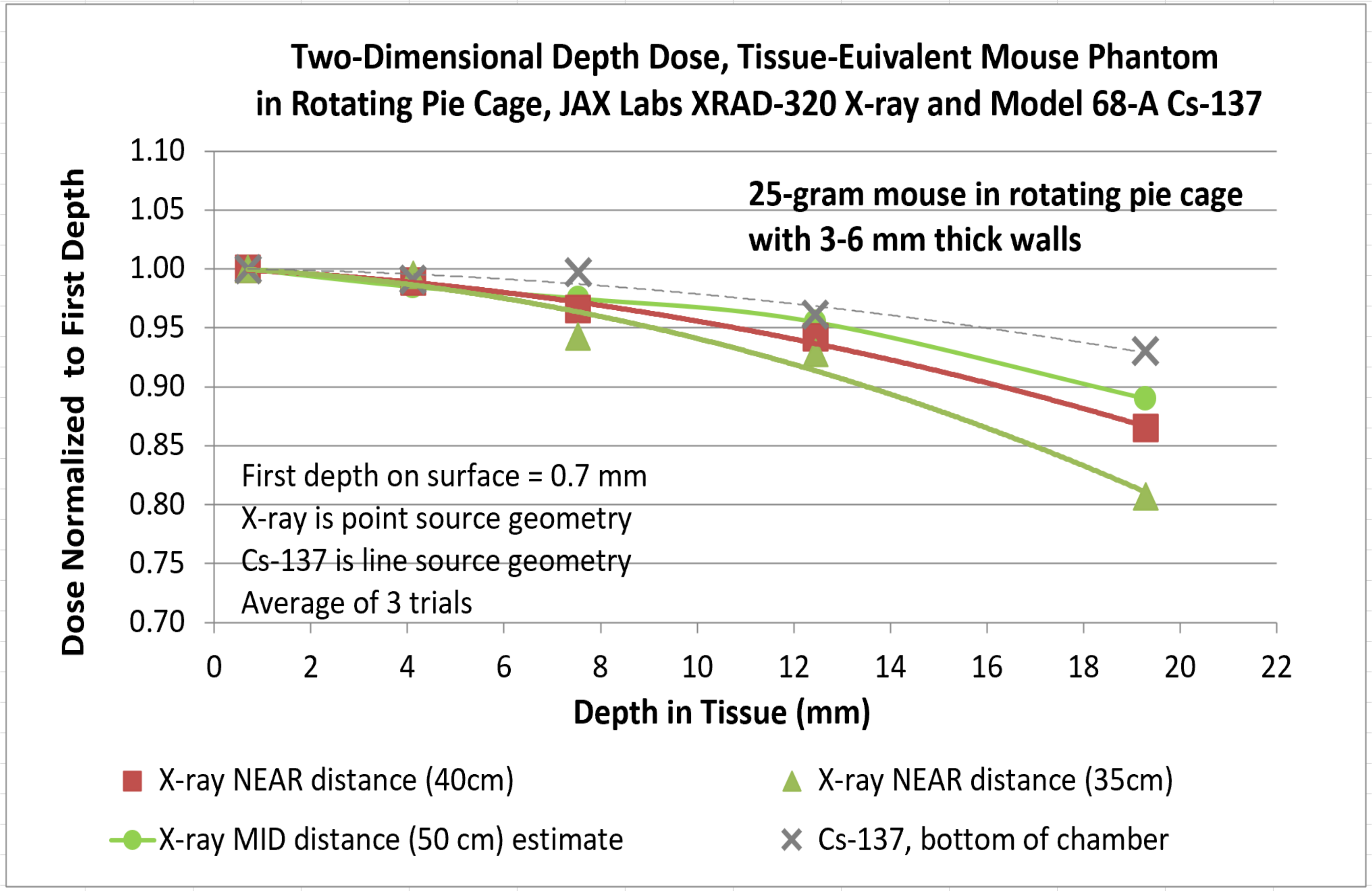
# Depth-Dose in Vertical Axis within Specimens JAX Labs X-ray & Cs-137 Irradiators

- Shows large fall-offs for the **X-ray irradiator** at the NEAR source distance due to the poor irradiation geometry.
- **For the Cs-137 irradiator**, shows largest dose fall-off is due to the dosimetry film on the surface of the phantom over-responding to Compton electrons and ~80 keV characteristic X-rays produced at the surface of the lead attenuator, which do not penetrate much past 2-mm depth.
- Fortunately, the walls of rodent containment easily block these unwanted radiations



# Depth-Dose in Specimens in Rotating Pie Cage JAX Labs X-ray & Cs-137 Irradiators

- When compared to the STATIC mouse depth-dose curves, shows that use of a rotating turntable can improve the dose distribution.
- Also shows how the plastic wall of pie cage **drastically improves the dose fall-off** by blocking the Compton electrons and 80-keV characteristic X-rays created at surface of lead attenuator in the Cs-137 irradiator.
- Shows that the depth dose for X-ray is approximately 4-12% greater than for Cs-137, depending on distance.

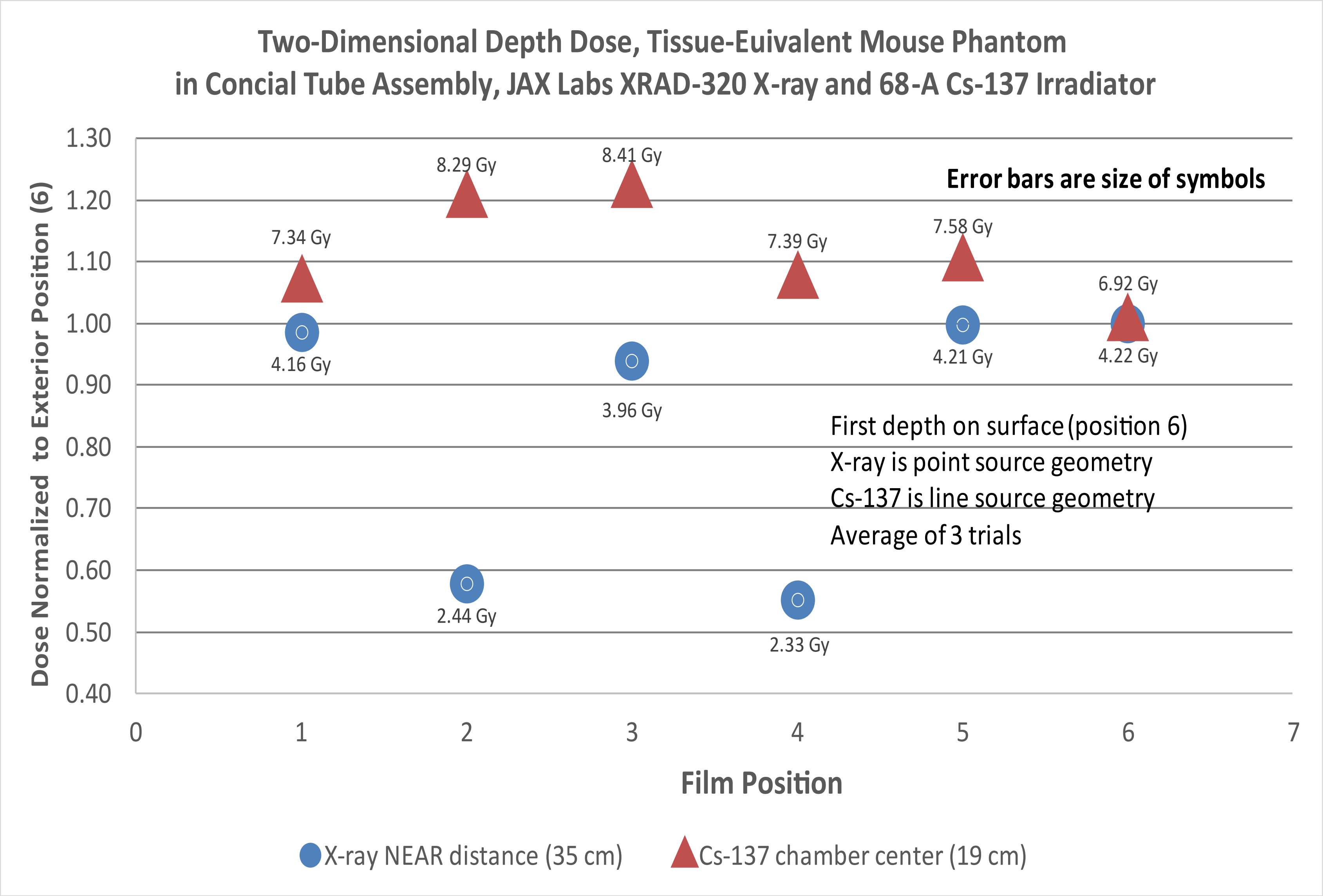


**Two-Dimensional Depth Dose, Tissue-Euivalent Mouse Phantom in Rotating Pie Cage, JAX Labs XRAD-320 X-ray and Model 68-A Cs-137**

25-gram mouse in rotating pie cage with 3-6 mm thick walls

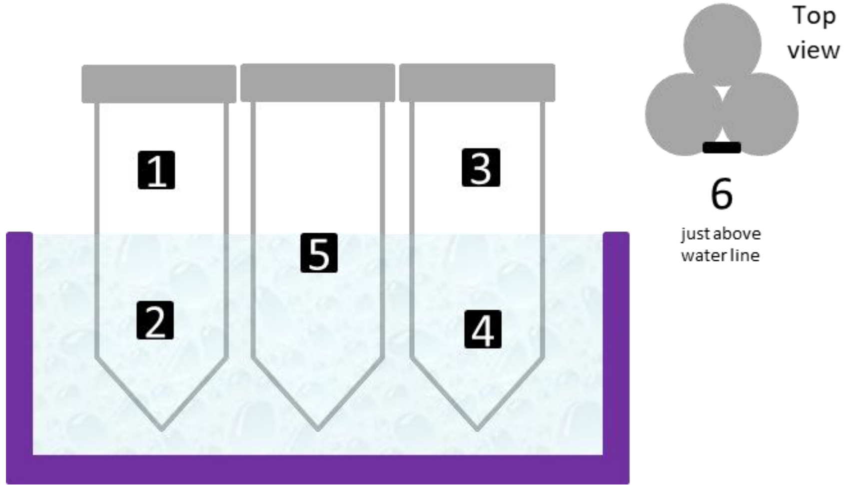
First depth on surface = 0.7 mm
X-ray is point source geometry
Cs-137 is line source geometry
Average of 3 trials

# Dose Distribution within Conical Tube Solution
# JAX Labs X-ray & Cs-137 Irradiators



**Error bars are size of symbols**

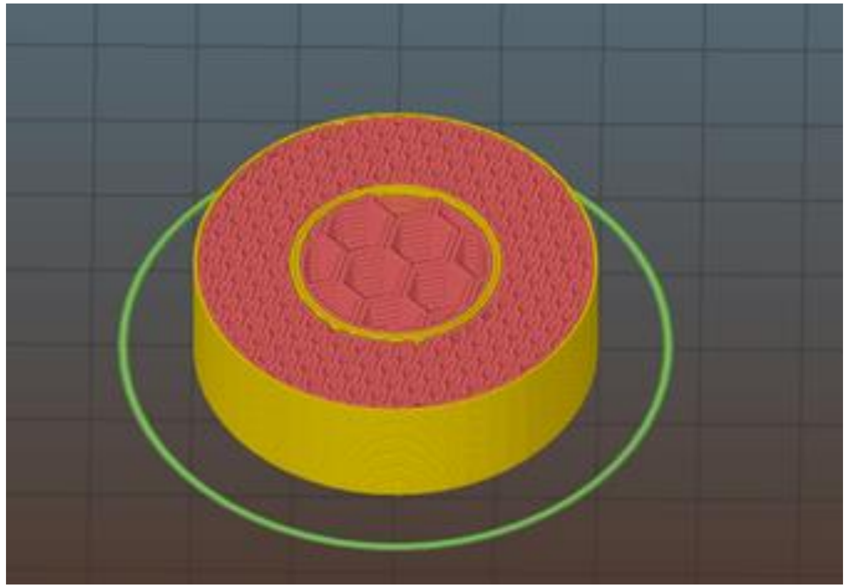
First depth on surface (position 6)
X-ray is point source geometry
Cs-137 is line source geometry
Average of 3 trials

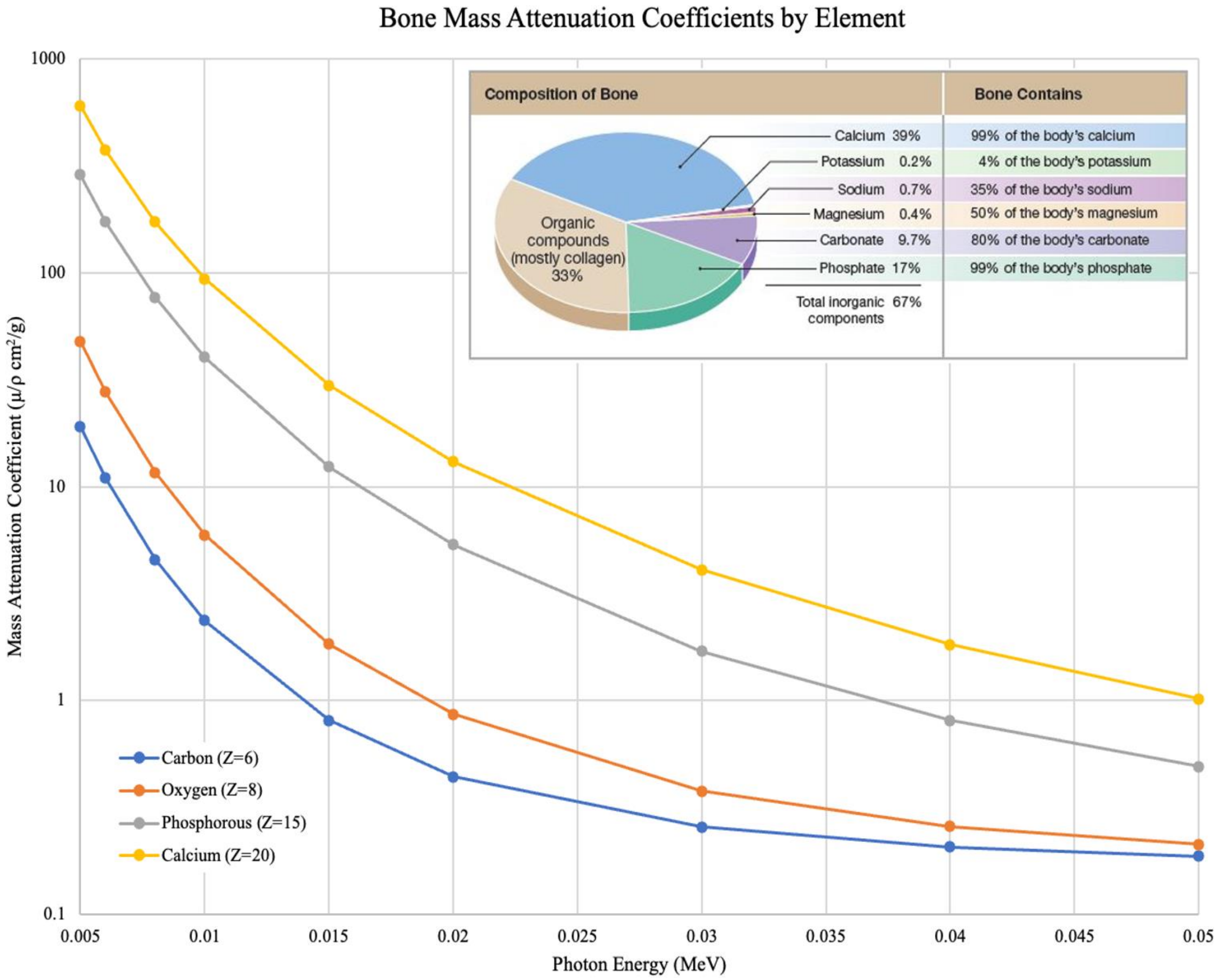


This large variation in dose across the Conical tubes in the X-ray can be improved greatly by simply placing the tubes in a reclining position.

# Improvements & Future Work

- Improve variation of film response for mini-films
- Test PLA tissue formulation to photons at higher (megavoltage) energies
- Investigate tissue equivalency of commercially available 3D-printed bone substitute
- Design of bone substitute by tuning microstructure, PLA and higher Z filament (Calcium? Ceramic/Metal oxides?)
- Research need for phantom components with vascular structure for clinical applications





Bone Mass Attenuation Coefficients by Element

# Conclusion

- The tissue-equivalency of material can be measured to a high degree of accuracy and precision by using the correct equipment and accredited photon fields across a range of energies.
- Utilizing simple to print 3D-printed phantoms can improve…
  - Accuracy of measurements
  - Allows for consistent protocol to compare in multiple irradiator/energy range
- 3D-printed rodent phantoms used in tandem with well-calibrated radiochromic film can be an effective tool to characterize and compare radiation fields.
- Allows researchers to better determine how much of a perceived RBE effect is due to unknown differences in dose delivery.
- Allows researchers to continue work when transitioning to a new irradiator.

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Hospital

# Thank you

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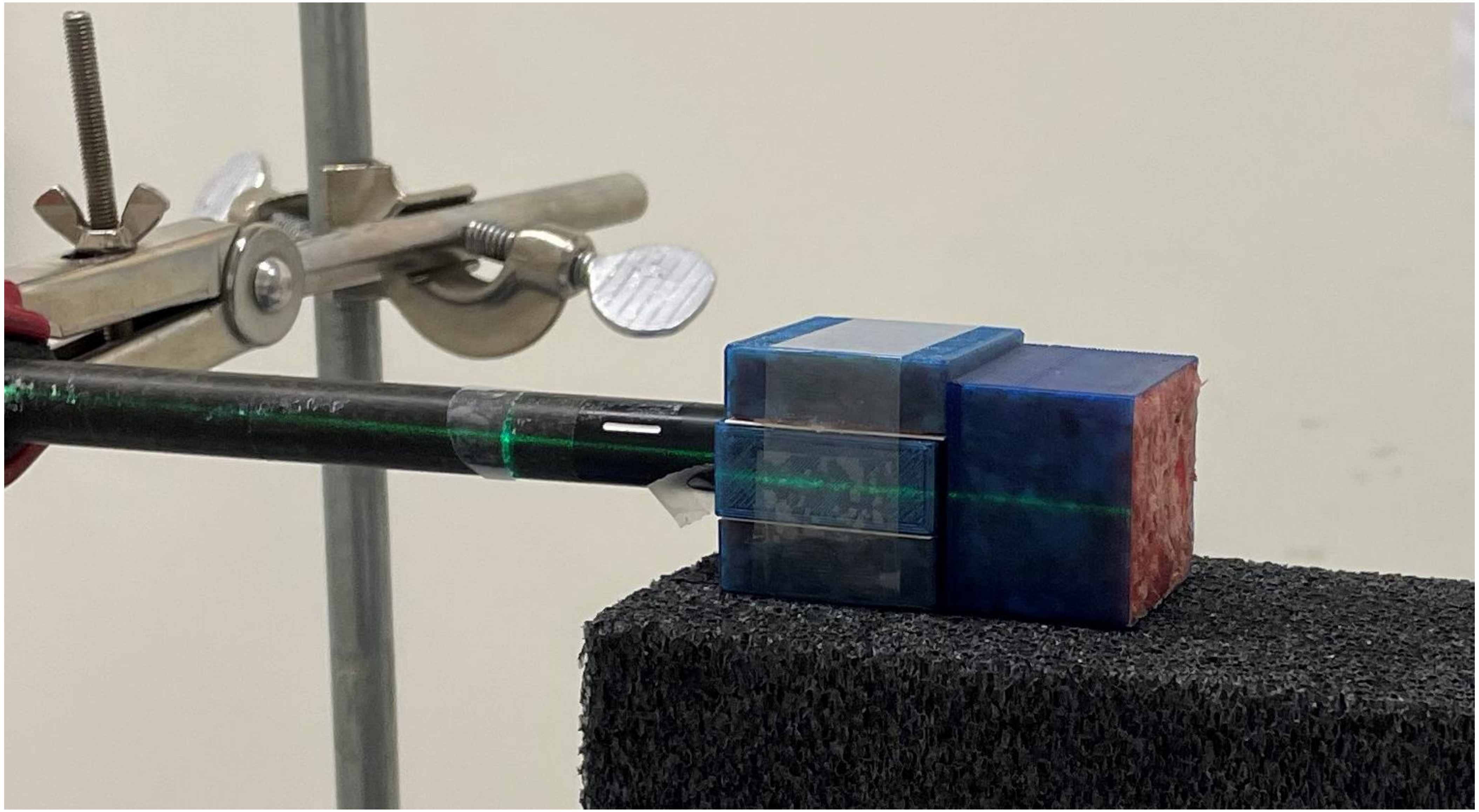
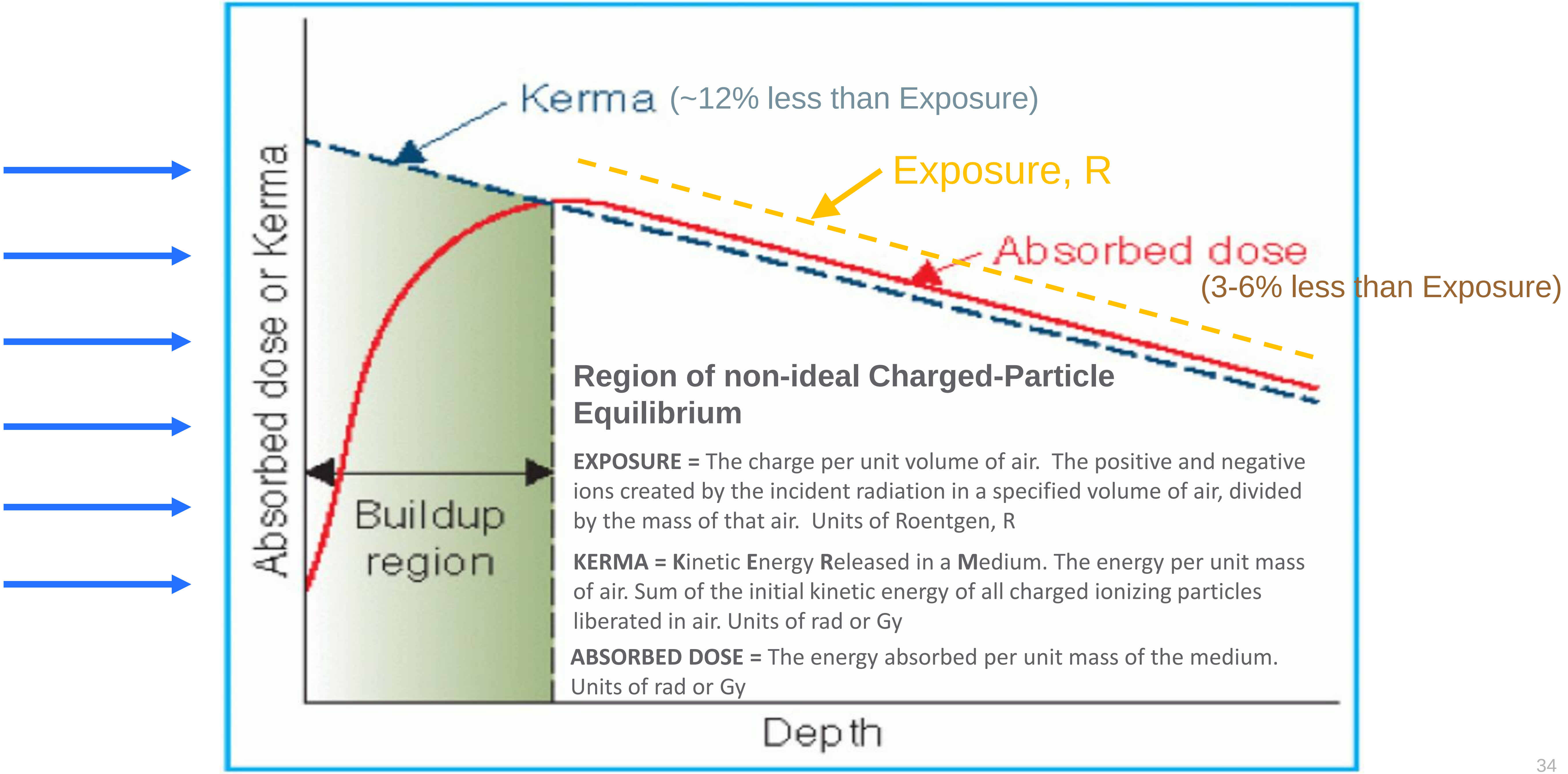
# Simulation of Full Depth in Tissue



# Exposure versus Kerma versus Absorbed Dose



**Region of non-ideal Charged-Particle Equilibrium**

**EXPOSURE =** The charge per unit volume of air. The positive and negative ions created by the incident radiation in a specified volume of air, divided by the mass of that air. Units of Roentgen, R

**KERMA = K**inetic **E**nergy **R**eleased in a **M**edium. The energy per unit mass of air. Sum of the initial kinetic energy of all charged ionizing particles liberated in air. Units of rad or Gy

**ABSORBED DOSE =** The energy absorbed per unit mass of the medium. Units of rad or Gy

# Options for Measurement of "Dose", and Associated Units

| "Dose" Type | Formula and Explanation | SI Units | Non-SI Units |
|---|---|---|---|
| **Exposure, X**<br>(Charge per unit volume) | $X = \Delta Q / \Delta m$, where $\Delta Q$ are the electric charges (positive and negatively charged ions) created by the incident radiation in a specified volume of air, divided by the *mass* $\Delta m$ of that air. The relationship between *Absorbed Dose* and *Exposure* dose is $D = f \cdot X$, where *D* is absorbed dose and *f* is a coefficient of a value that depends on the type of medium being irradiated. *f* is always <1.0 | Couloumb/kilogram or C/kg | Roentgen, R<br>1 R = 2.58E-4 C/kg |
| **Air Kerma, K**<br>(energy per unit mass of air) | **K**inetic **E**nergy **R**eleased in a **M**edium. The sum of the initial kinetic energy of all charged ionizing particles liberated by uncharged ionizing radiation in a given mass of air. In the region of CPE, Kerma and Absorbed Dose are equal. | J/kg = Gray (Gy) | rad<br>1 Gy = 100 rad |
| | | | |
| **Absorbed Dose, D**<br>(energy per unit mass of medium) | $D = \Delta E / \Delta m$, where $\Delta E$ is the *energy* lost from the radiation beam, and $\Delta m$ is the *mass* of the medium into which the energy is absorbed. | J/kg = Gray (Gy) | rad<br>1 Gy = 100 rad |

# Dosimetry Standards/Guides Used in Radiation Biology

- **ICRU 30 “Quantitative Concepts and Dosimetry in Radiobiology**” is more comprehensive than most standards. Like TRS-398, it contains information on measuring accurate absorbed dose using ionization chambers, but it also has a lot of information on survival curves, linear energy transfer (LET) and Lineal Energy, animal and cell culture exposure systems, scatter and charge particle equilibrium, along with recommended minimum dosimetric and irradiation geometry information required.
- **AAPM TG 61 “40-300 kV X-ray Beam Dosimetry in Radiotherapy and Radiobiology**” focuses on how to accurately measure absorbed dose of x-ray beams using ionization chambers in air or in water. Generally, the chambers are calibrated in terms of air kerma split into two major energy divisions (superficial and orthovoltage), centered around 100 keV.
- **AAPM TG 51 and IAEA TRS-398 “Absorbed Dose Determination in External Beam Radiotherapy...”** focuses on how to measure, traceably and accurately, absorbed dose in an external beam, in particular absorbed dose to water, whether for gamma ray, x-ray, Linac, electrons, or protons, whether using an ionization chamber in air or in water phantom. Generally, these two protocols are for megavoltage beams (i.e. energies greater or equal to that of Co-60) and use ionization chambers calibrated to absorbed dose to water. Various corrections that are needed to determine the absorbed dose to water, including differences in beam quality are provided in these protocols.
- Article published as a result of the 2012 Dosimetry Standardization Workshop at NIST:

Journal of Research of the National Institute of Standards & Technology Volume 118 (2013). *The Importance of Dosimetry Standardization in Radiobiology*. Marc Desrosiers, Larry DeWerd, James Deye, Patricia Lindsay, Mark Murphy, Michael Mitch, Francesca Macchiarini, Strahinja Stojadinovic and Helen Stone