Medical Device Sterilization:

Broadening the Possibilities

September 24-25, 2024

Team Nablo – An International Collaboration's Progress the First Five Years

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Pacific Northwest NATIONAL LABORATORY

NNSA National Nuclear Security Administration

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AGENDA

- Team Nablo background
- Testing for influence of Beam Type and Dose Level
- Testing for influence of Dose Rate and Temperature
- Testing for Influence of Oxidative Atmosphere during irradiation
- Testing for Influence of E-beam Energy
- Dose Mapping of products using E-beam, repackaging for optimal DUR
- Latest version of PUFFIn Dose Distribution software tool
- Ongoing and new projects

Origin and Goals of Team Nablo

- This project began in 2018 with funding from the U.S. Department of Energy's National Nuclear Security Administration (NNSA).
- PNNL teamed with major players in the medical and biopharma sterilization industries in order to identify and fill the **data, education and tool gaps** for those companies desiring to transition from cobalt-60 gamma and ethylene oxide to X-ray and electron beam (E-beam) for sterilization.
- **Overall aim is to help industry diversify available irradiation technologies.**
- Brought together a consortium of stakeholders in the US and Europe that includes the medical and biopharma device community, E-beam and X-ray equipment manufacturers, national laboratories, academia, and industrial R&D organizations.

Origin and Goals of Team Nablo

- So far, this project has partnered with 16 separate organizations involved in the sterility assurance community, involving over 15 products and more than 30 different types of polymers.
- Main tasks so far involve **irradiation of numerous medical products (and polymer test samples)to gamma, E-beam and X-ray, then performing coloration, functional and mechanical testing**.
- **Eventually populate a large online library** with data results for numerous polymers, which could allow product manufacturers to make educated decisions about mitigating negative effects and potential transition to alternative sterilization modalities.

Team Nablo – Members 2018-2024

- Pacific Northwest National Laboratory
- Becton-Dickinson
- Stryker
- Sartorius
- Texas A&M University
- Aix Marseille University
- Steri-Tek
- IBA
- Aerial CRT
- AAMI
- Boston Scientific
- Pall
- Bayer
- Millipore Sigma
- Terumo BCT
- E-Beam Services

Some Examples of the Polymers Investigated

- **ABS** - Acrylonitrile butadiene styrene
- **Buna-N** rubber
- **CIIR** - Chlorobutyl rubber
- **EPDM** - Ethylene propylene diene
- **EVA** - Ethyl vinyl acetate
- **HDPE** - High density polyethylene
- **HIPS** - High impact polystyrene
- **LDPE** - Low density polyethylene
- **PA** - Polyamide
- **PE** – Polyester
- **PP** – Polypropylene
- **PTB** - Polybutylene terephthalate
- **PC** - Polycarbonate
- **PET** - Polyethylene terephthalate
- **PETG** - Polyethylene terephthalate glycol
- **PPH** - Polypropylene homopolymer
- **PEO** - Polyolefin elastomer
- **PVC** - Polyvinyl chloride
- **SiR** - Silicone rubber
- **SAN** - Styrene acrylonitrile
- **SBC** - Styrene-butadiene copolymer

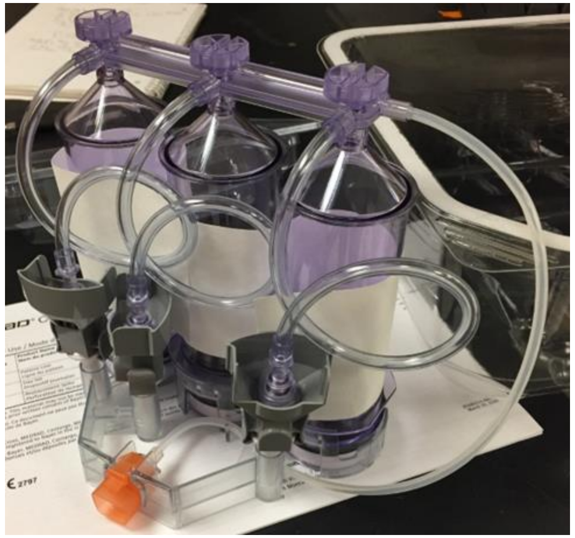
Testing Influence of Dose Level and Radiation Source (Gamma, EB, XR)

Examples of Products Tested to Determine Influence of Dose Level and Radiation Source










Conclusions From Comparison Testing

- Testing of **Dose Levels** in range of 0 to 80 kGy revealed that many properties fall off with doses much greater than sterilization dose.

- Testing for influence of **Radiation Source** (gamma, e-beam and X-ray) revealed the differences in properties of irradiated materials are generally small or non-existent at sterilization doses.

Testing the Influence of Dose Rate and Temperature

DOSE RATE Effects Study Using Polymer Samples from Becton-Dickinson Products

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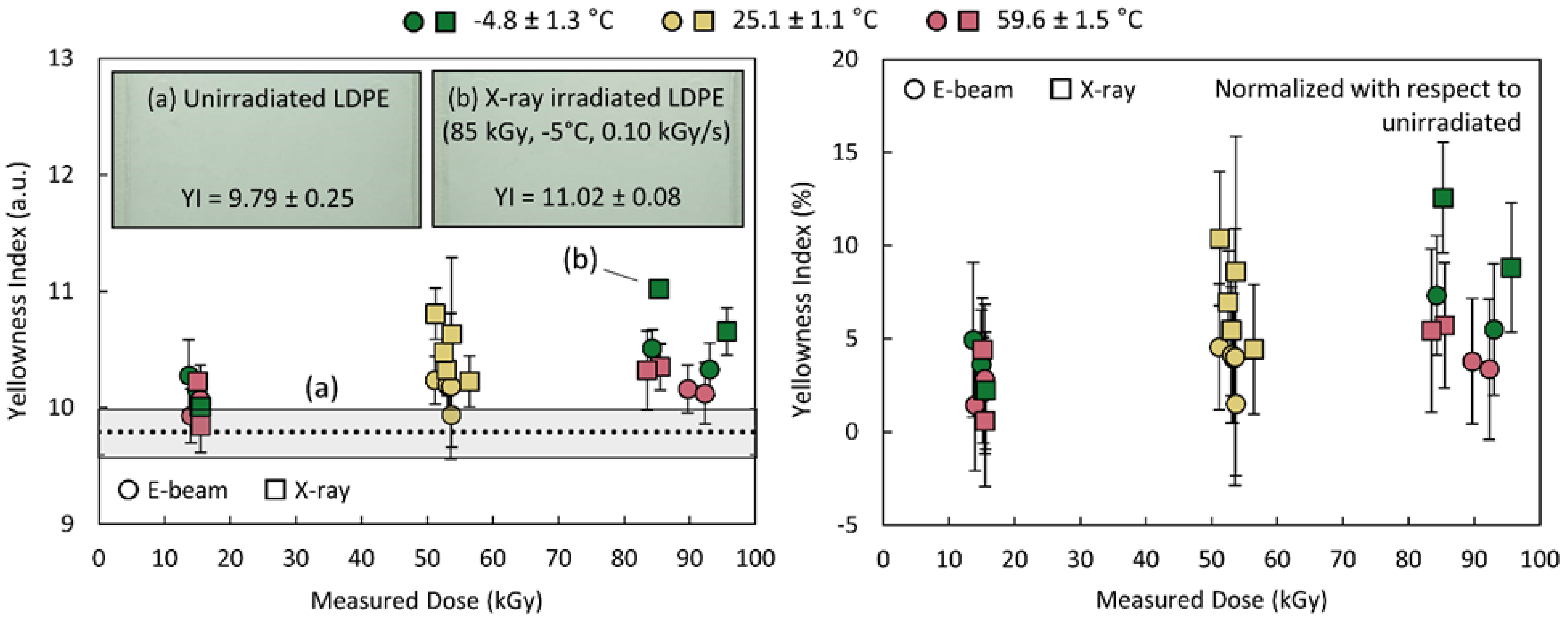
- The experimental design of a dose rate study should consider the environmental conditions (e.g., the temperature range typically encountered in an industrial irradiator, cold temperatures, normal and oxygen-free environment).

- The following test materials and irradiation conditions were used in the study:
  - **4 materials** (LPDE, PPH, CIIR and POE)
  - **2 irradiation modalities** (E-beam and X-Ray)
  - **3 dose rates for each irradiation modality**
    - 0.12, 6, 12 kGy/s for E-beam
    - 0.003, 0.12, ≥ 0.23 kGy/s for X-ray
  - **3 dose levels** (in range of 15-85 kGy)
  - **3 irradiation temperatures**

Dose Rate Study Test Results

- **Primary Factors**
  - For E-beam and X-ray irradiated products, the primary factors affecting polymer properties were total dose, followed by temperature.
- **Visual**
  - Yellowness index of Polypropylene homopolymer (PPH) was sensitive to dose, dose rate and temperature.
- **Mechanical**
  - Only polyolefin elastomer (POE) showed a dose rate dependence when observing elongation at break and tensile strength.

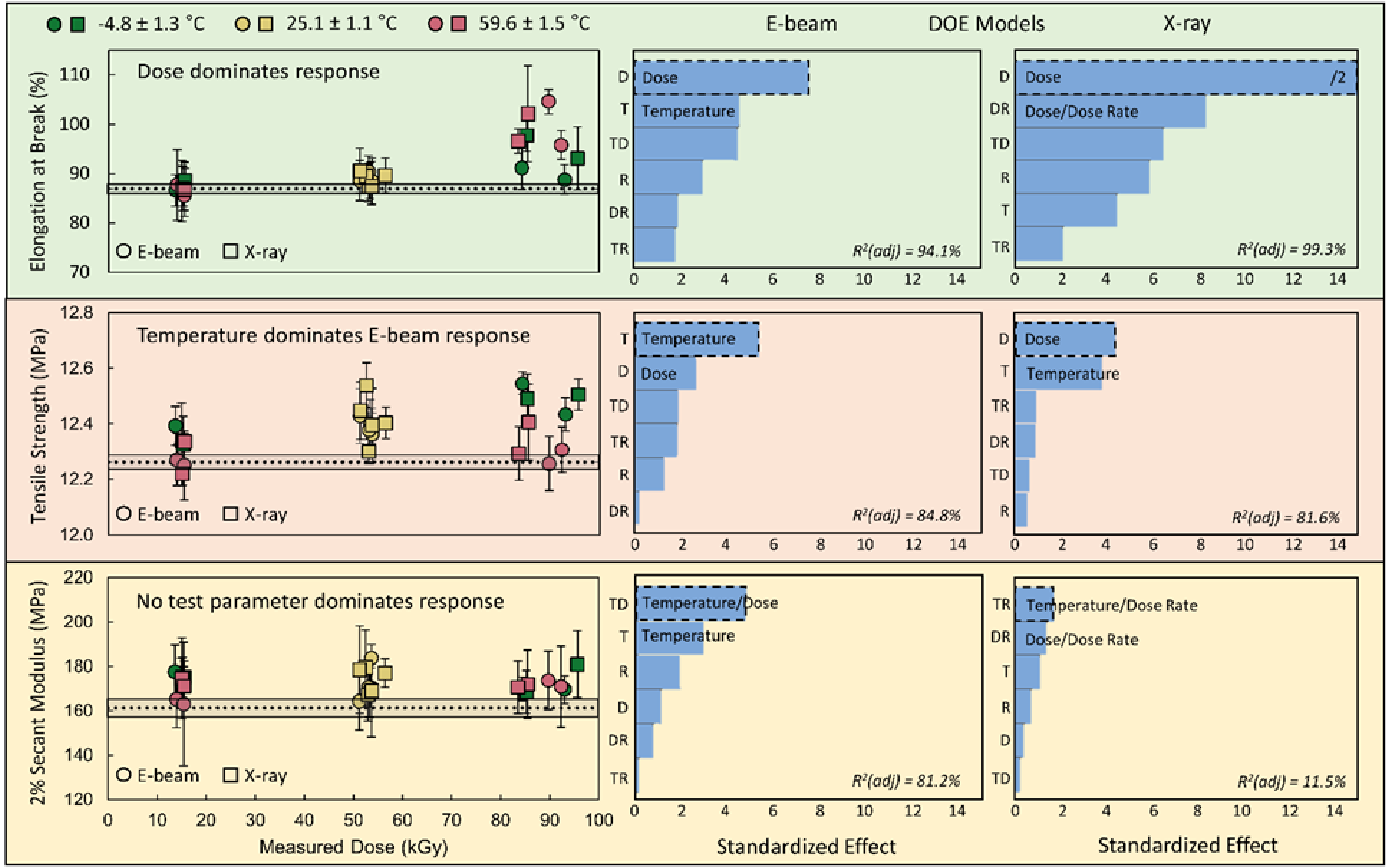
Influence of Dose and Temperature on Yellowness Index of LDPE



- At higher doses, LDPE showed greater increases in Yellowness for X-ray irradiated specimens as compared to E-beam irradiated specimens.

Influence of Dose, Dose Rate and Temperature on Properties of LDPE

- For *Elongation at Break*, dose level dominates response.
- For *Tensile Strength*, temperature dominates response.
- No dominate influences on *Secant Modulus*.
- We may conclude that LDPE undergoes small, but measurable changes that are influenced by dose level and temperature level.



Influence of Dose, Dose Rate and Temperature on Properties of LDPE

Metric	Design of Experiment Factors		
	Temperature (*T*)	Dose (*D*)	Dose Rate (*R*)
YI	Mild variations at low *T*: X-ray	Mild variations at high *D*: X-ray	No variations
EAB	Mild variations at high *T*: Both	Significant variations at high *D*: Both	No variations
TS	Mild variations at low *T*: E-beam	No variations	No variations
SM	No variations	No variations	No variations
CI	Mild variations at high *T*: E-beam	Mild variations at high *D*: E-beam	No variations
Tm	No variations	Significant variations at high *D*: Both	No variations
GF	Mild variations at high *T*: Both	Significant variations at high *D*: Both	No variations

YI = yellowness index; EAB = elongation at break; TS = tensile strength; SM = secant modulus at 2% strain; CI = carbonyl index; Tm = onset melting temperature; GF = gel fraction.

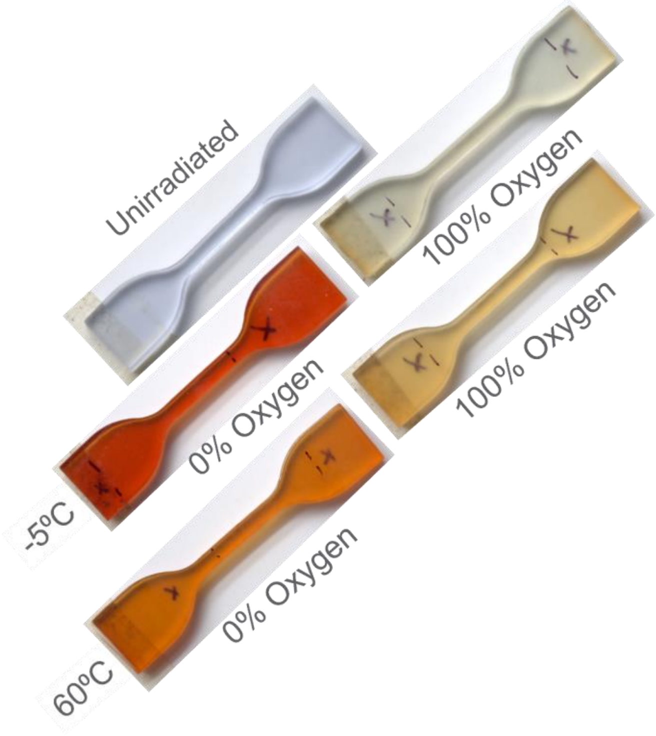
- Based on the results of this study, we may conclude that LDPE undergoes small, but measurable changes, in macroscopic and microscopic properties upon exposure to E-beam and X-ray radiation.

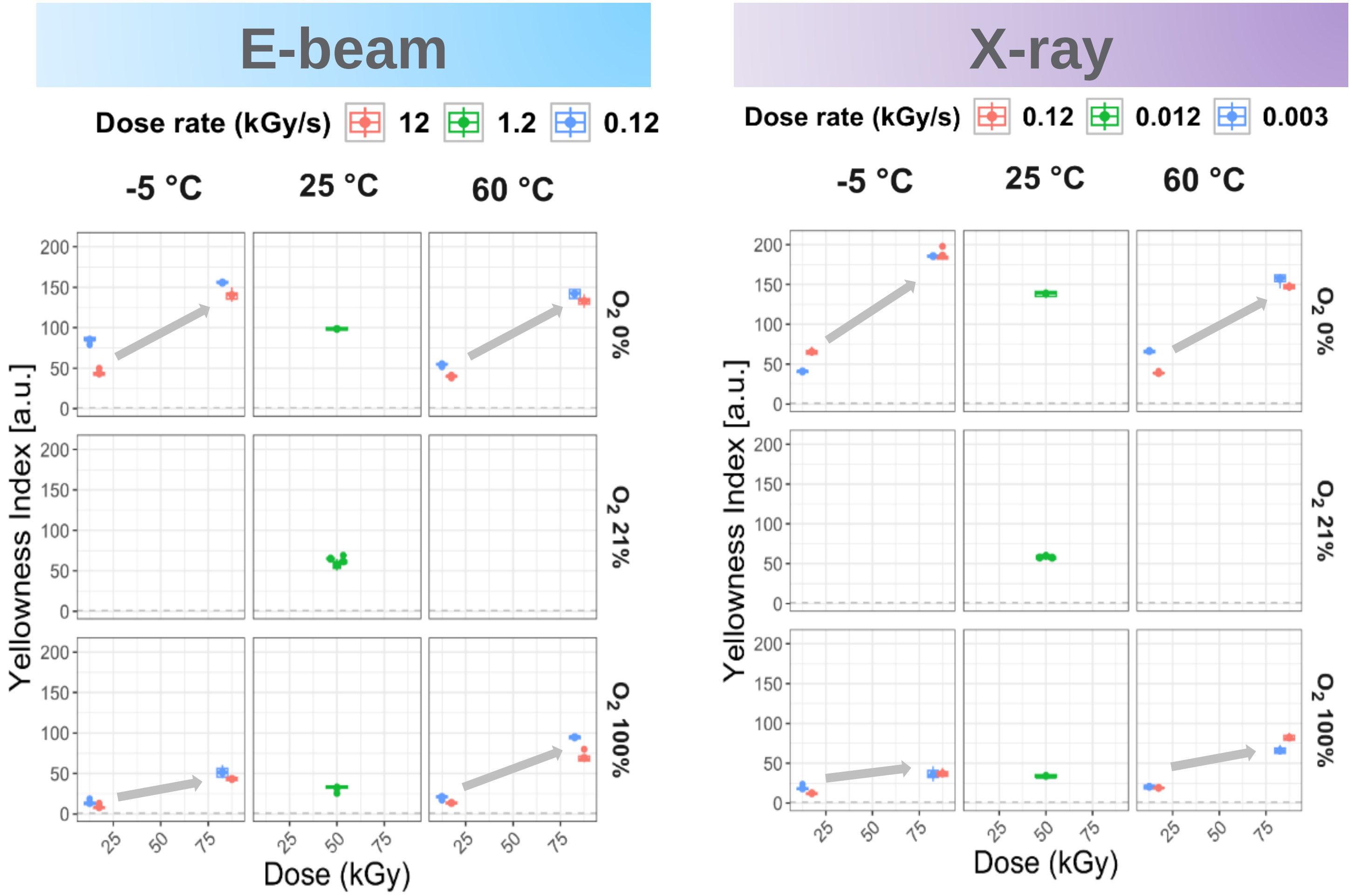
Testing Influence of Oxidative Atmospheres

Dose Rate Study Test Results

- **For both E-beam and X-ray**: 21 irradiation conditions at 3 dose rate levels, 3 dose levels, 3 gas environments, and 3 irradiation temperatures.
- Performed on 8 common polymers (**EVA**, **EVOH**, **CIIR**, **LDPE**, **PE**, **POE**, **PVC**, **PP**)
- The following Post-Irradiation Testing accomplished:
  - ***Visual***
    - Yellowness Index and/or Total Color Change
  - ***Chemical***
    - Electron paramagnetic resonance (EPR)
    - Fourier Transform Infrared Spectroscopy (FTIR)
    - Thermogravimetric Analysis- Mass Spectrometry (TGA-MS
  - ***Mechanical***
    - Tensile and/or Hardness Testing

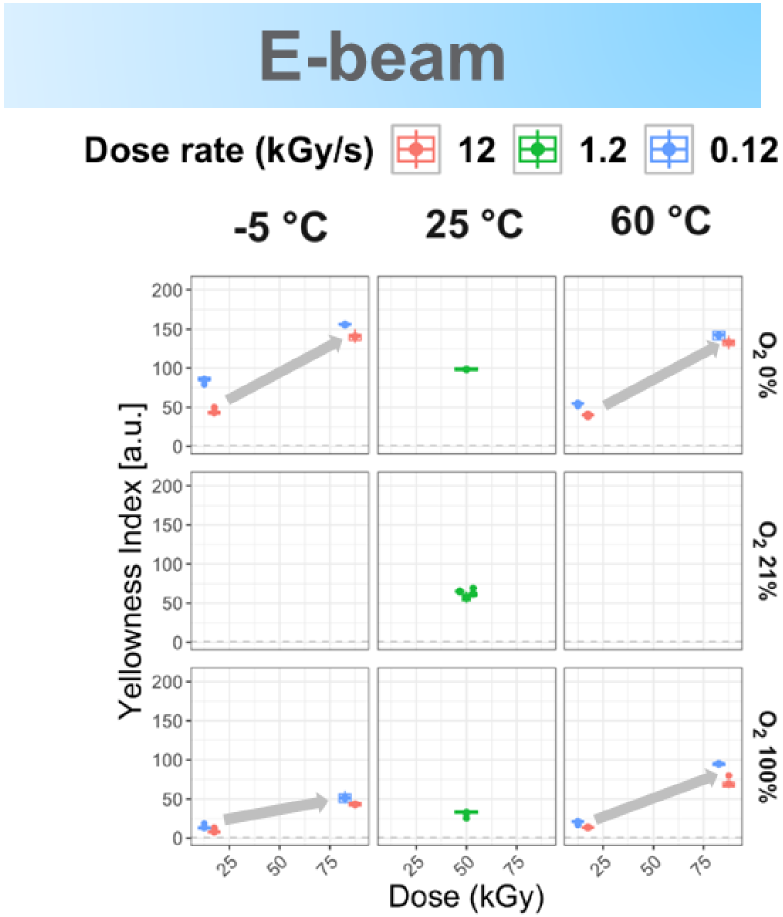
Oxidative Atmospheres – Yellowness Index for PVC

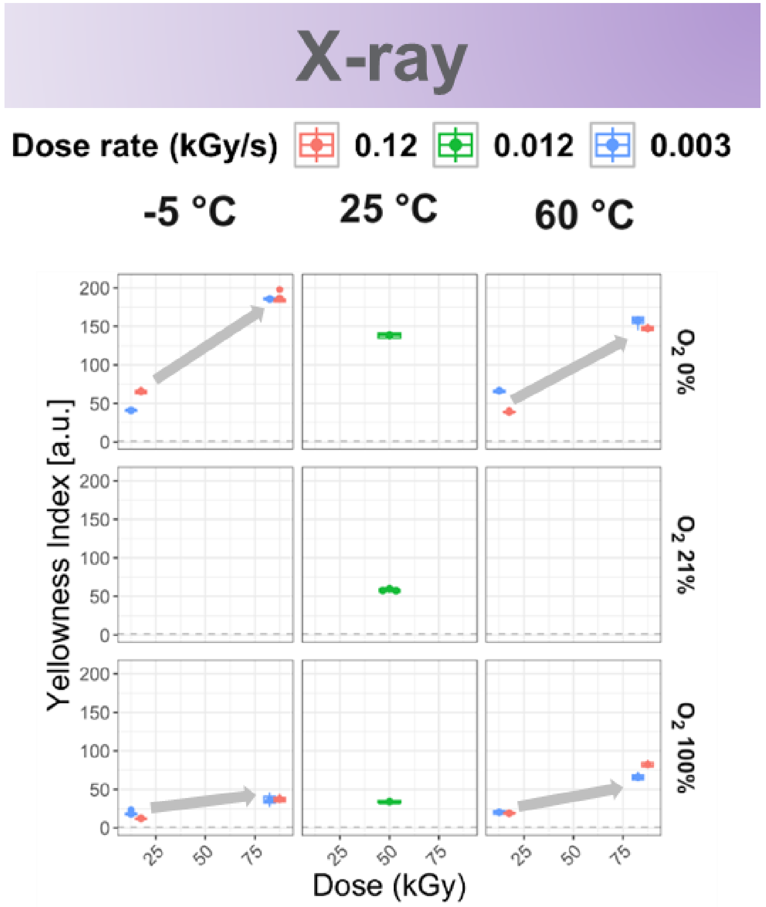




- Reduced yellowing found with increasing O2 for both sources.
- Reduced yellowing also found for E-beam with increasing dose
- Increased yellowing was observed with increasing dose.

Oxidative Atmospheres – Yellowness Index for PVC





- The yellowness index appears to slightly decrease with temperature for both.

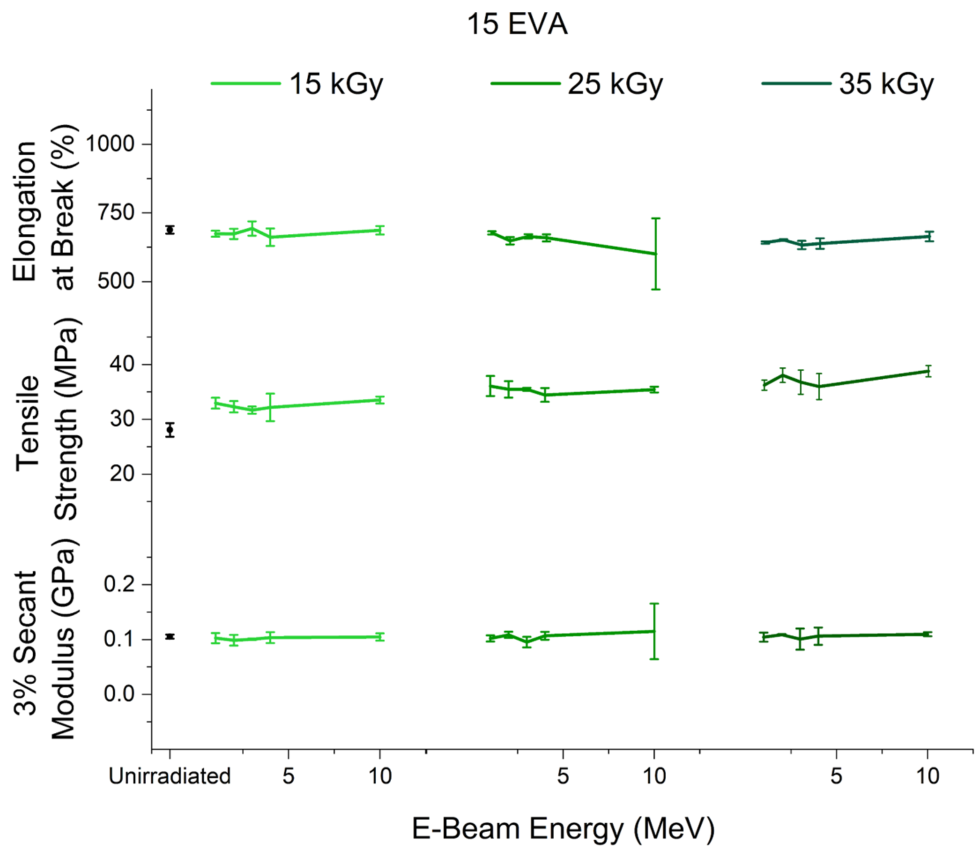
Oxidative Atmospheres – Results Summary

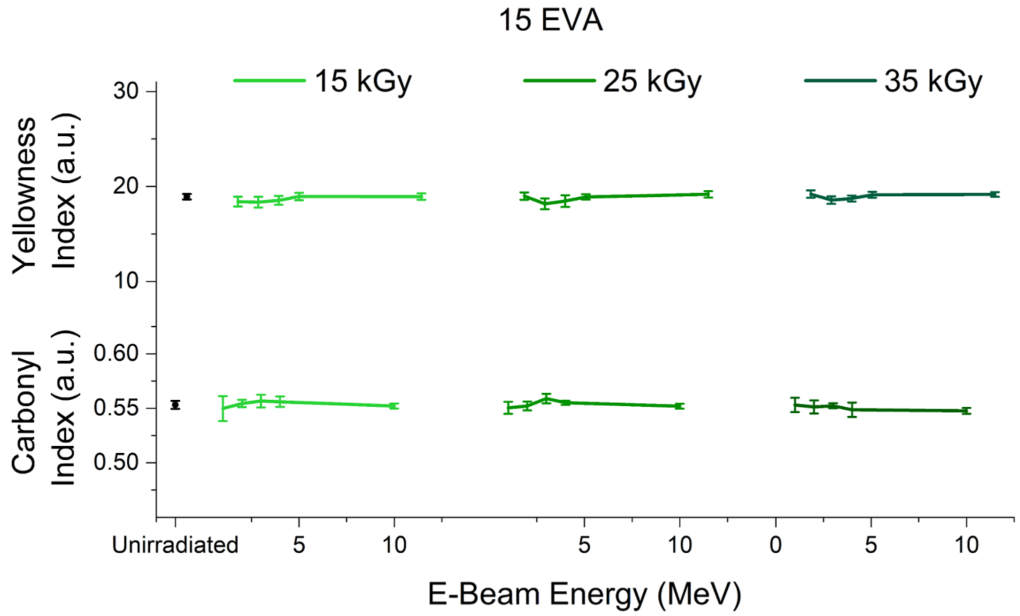
		Observed Effect of Increasing			
Material	**Source**	**Oxygen**	**Temperature**	**Dose**	**Dose Rate**
PP	E-beam	No	No	Reduced Tm & EAB	No
	X-ray	No	No	Reduced Tm & EAB Increased YI	No
PVC	E-beam	Reduced YI	Reduced YI	Increased YI	Reduced YI
	X-ray	Reduced YI	Reduced YI	Increased YI	No
EVA/EVOH	E-beam	No	No	Increased TS	No
	X-ray	No	Decreased YI	Increased TS	No

- PP, PVC, and EVA/EVOH responses to E-beam vs. X-ray similar for most properties.
- It is up to the manufacturer to determine if differences in properties caused by atmosphere and related factors are acceptable for their product specs.

Testing Influence of Various E-beam Energies (1, 2, 3, 4 and 10 MeV)

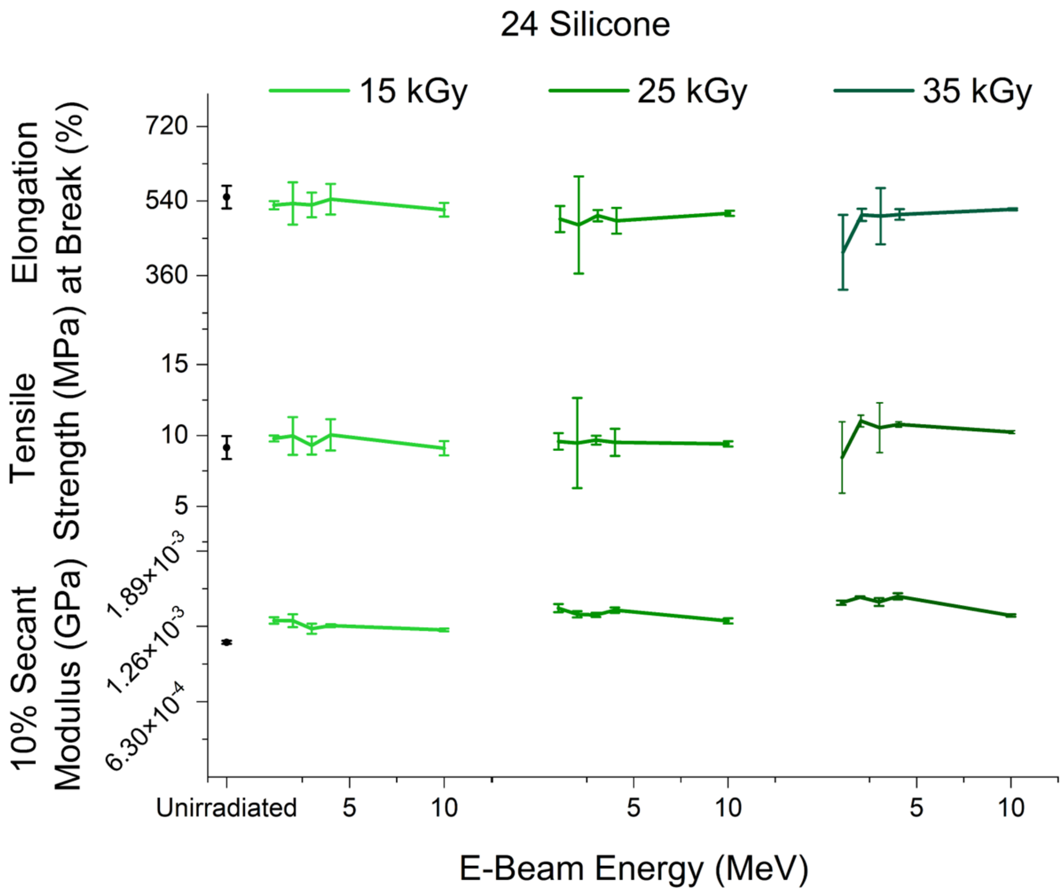
Terumo Materials – Ethylene Vinyl Acetate (EVA) Polymer

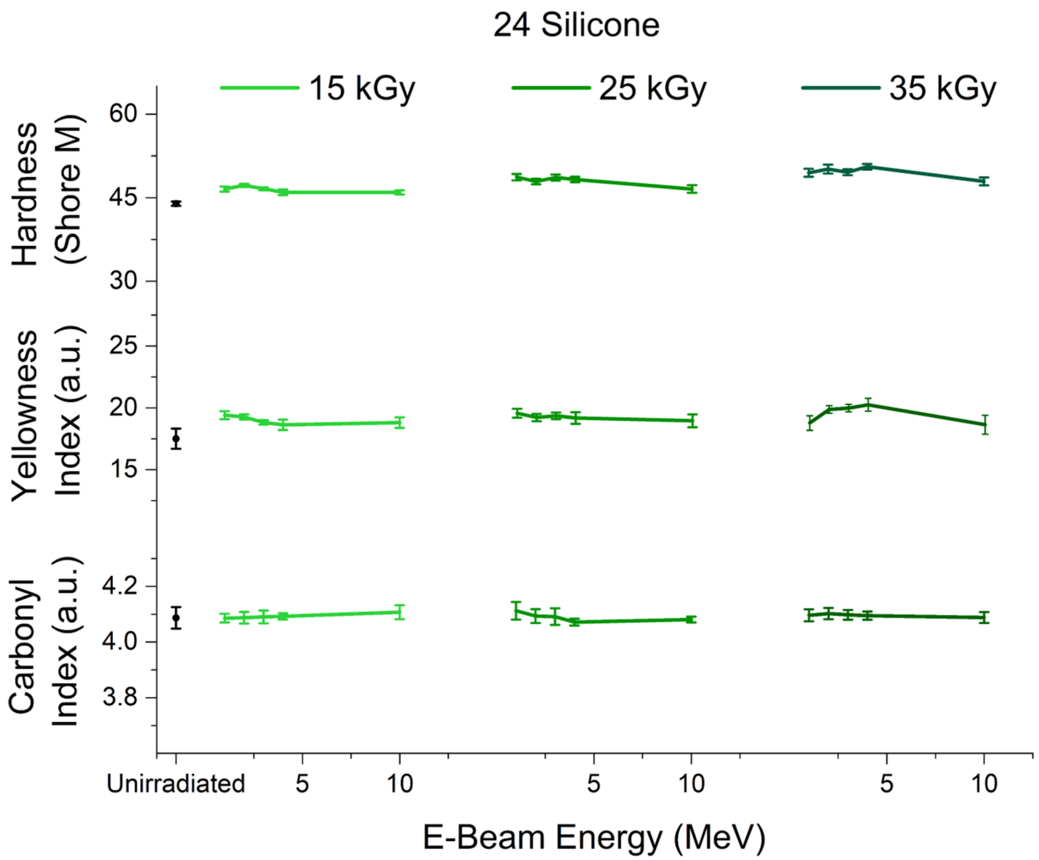




- Tensile strength increased with dose by over 20% at 35 kGy, while maximum strain was found to decrease with increasing dose at low energy (1 to 4 MeV) (p = 0.01).
- Yellowness index slightly increased with E-beam energy for all dose levels

Terumo Materials – Silicone Polymer





- Tensile strength increases with dose at 10 MeV energy.
- Modulus and hardness increase with dose but *decrease with energy*

Oxidative Atmospheres – Results Summary

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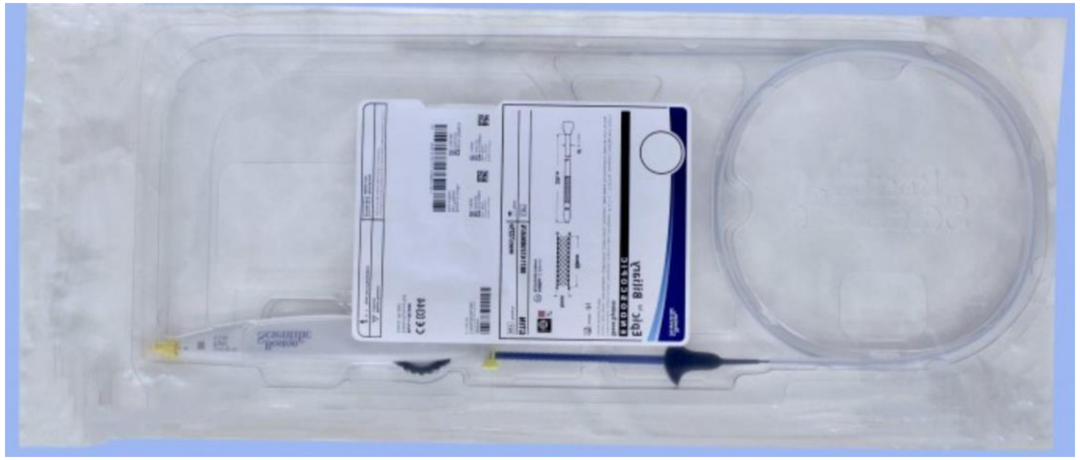
Material	Observed Dose Effect	Observed E-beam Energy Effect
PVC (Hard)	Increase in YI with dose	Strain appears lower at 10 MeV
PC	Increase in YI with dose	Decrease in YI with energy
Polyester	Increase in strength at 10 MeV	Strain and strength appear higher at 10 MeV
EVA	Increase in strength and YI with dose	Increase in YI with energy
Silicone	Increase in modulus and hardness with dose	Decrease in modulus and hardness with energy

PVC = polyvinyl chloride; PC = polycarbonate; EVA = ethylene-vinyl acetate; Strain = elongation at break; TS = tensile strength; YI = yellowness index; CI = carbonyl index; Stiffness = secant modulus; H = hardness.

Dose Mapping of E-beam Irradiated Products and Repackaging until Desired DUR Achieved

Products Submitted for E-Beam Dose Mapping and Repackaging Study



Example of Product Packaging Arrangements

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Millipore Steritest 2 passes, @4.5 fpm/pass, double-sided

X Y

A
B
C
D
E

Beam directions

Detailed E-beam Dose Mapping and Repackaging

1. **Dose map,**
2. **Rearrange/repackage,**
3. **Repeat until desired DUR achieved.**

Figure 6: Top view; Photo of dosimeters placed in original dose-map sample

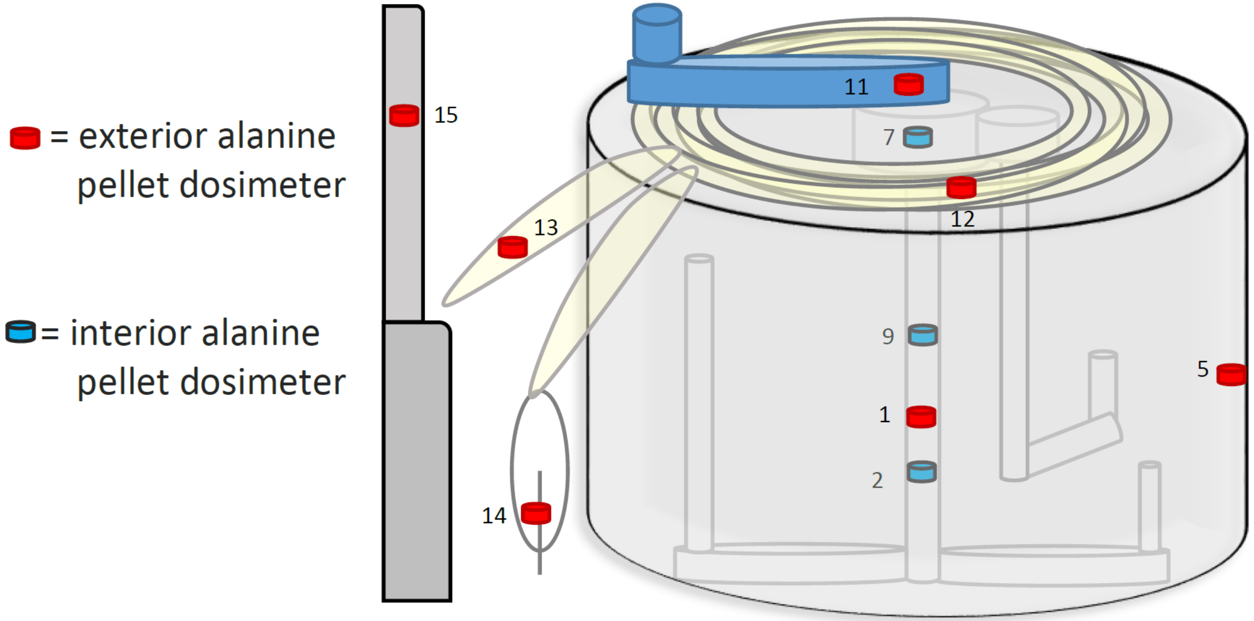

Figure 2: Diagram of top view of MixEvac 3 Bone Cement Mixer

DUR Results for Initial Packaging & Repackaging

- Results are for products in their shipper cases.
- Publication in progress

Device and Packaging	10 MeV E-beam DUR Two-sided Irradiation
Millipore Steritest (as-is packaging)	1.64
Bayer Stellant (as-is packaging)	1.71
Bayer Stellant (reduced by 1 layer)	1.40
Bayer Spectris Solaris (as-is packaging)	1.46
Bayer Spectris Solaris (reduced by 1 layer)	1.40
Bayer Centargo (as-is packaging)	2.04
Bayer Centargo (reconfigured)	1.65
Boston Scientific Wallstent (7 layers)	1.66
Pall Kleenpak (as-is packaging)	1.53
Sartorius Pro Mixer 50 L (as-is packaging)	2.16
Sartorius Pro Mixer 100 L (as-is packaging)	2.14
Sartorius Levi Mixer 100 L (as-is packaging)	1.86
Sartorius Cubical Pro Mixer 100 l (as-is packaging)	2.05

Simplified Dose Distribution Software Tool

PENELOPE Monte Carlo-Based Software Tool

- A software package has been developed that provides 2D & 3D visualization of dose distribution in static products – PUFFIn (**P**ENELOPE **U**ser **F**riendly **F**ast **I**nterface),
- Developed for use as a teaching/learning tool for novices to be able to visualize the dose distribution in single and multiple (boxed) products of relatively simple geometries and using a regular/common computer.
- A special application focus is the comparison of dose distribution (Dose Uniformity Ratios) for cobalt-60 versus e-beam and X-ray.
- Utilizes the PENELOPE* Monte Carlo code, which is more amenable than other transport codes for the application.
- This graphical user interface allows for the calculation of dose distribution from almost any input file – 2D images, CAD files, and DICOM files from a CT scan.

* Salvat, F. 2019. PENELOPE, a code system for Monte Carlo simulation of electron and photon transport, NEA/MBDAV/R(2019)1.

PUFFIn 2D – Photo Input

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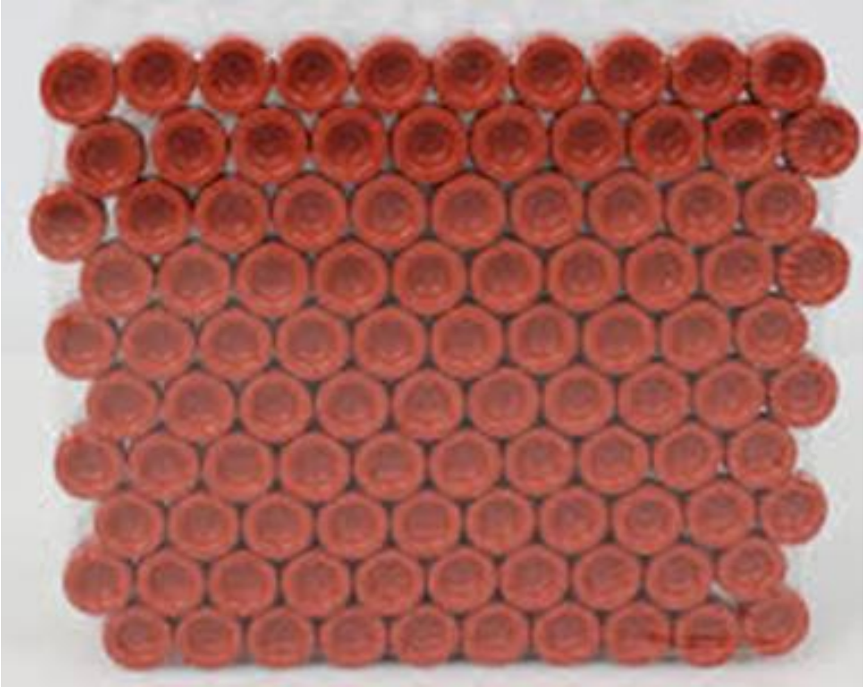
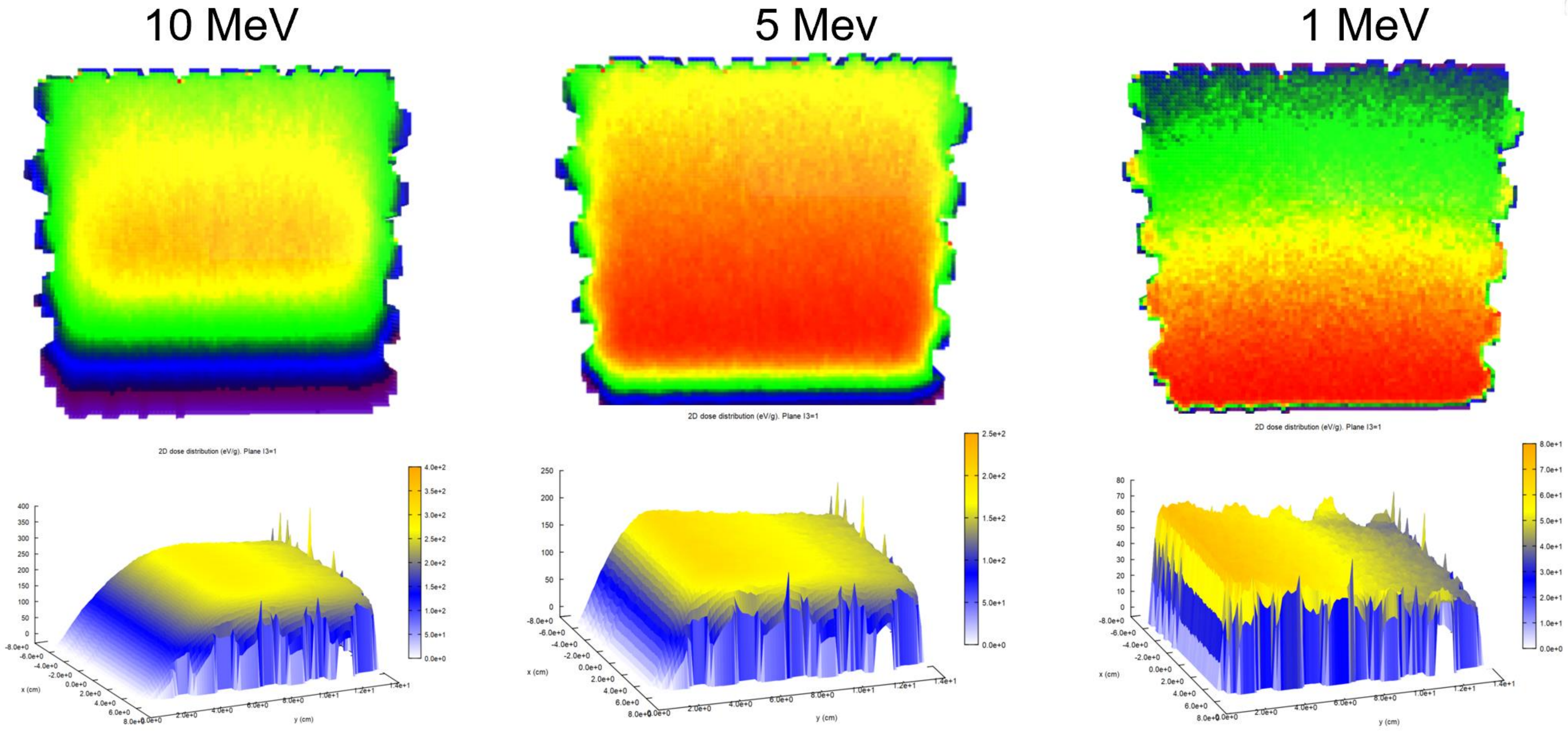
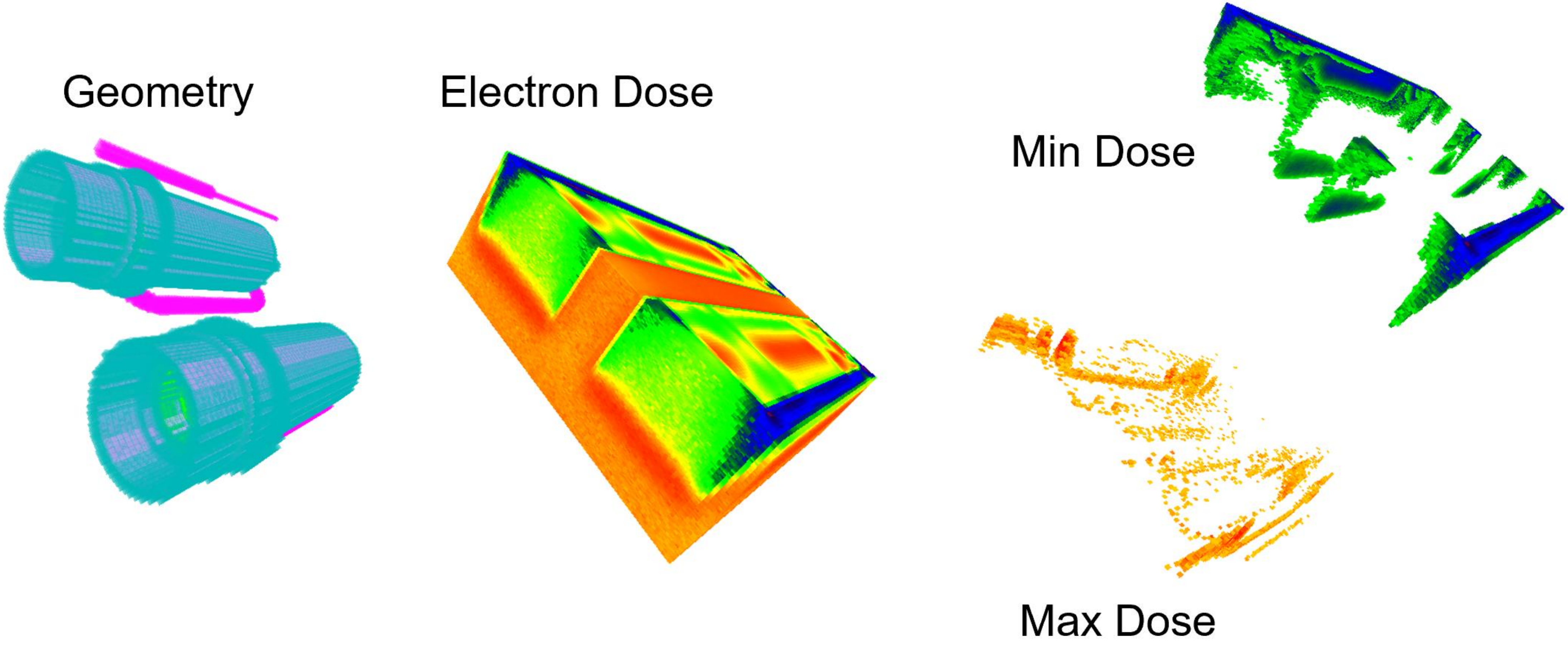


- Import a photo to calculate the DUR in 100 BD Tubes.
- 69 X 69 voxels
- Calculation takes about 5 minutes.

PUFFIn 2D – BD Blood Tubes



PUFFIn 3D – Min and Max Dose Locations



Ongoing and New Projects

The Tony Faucette Library for Radiation Effects on Polymers

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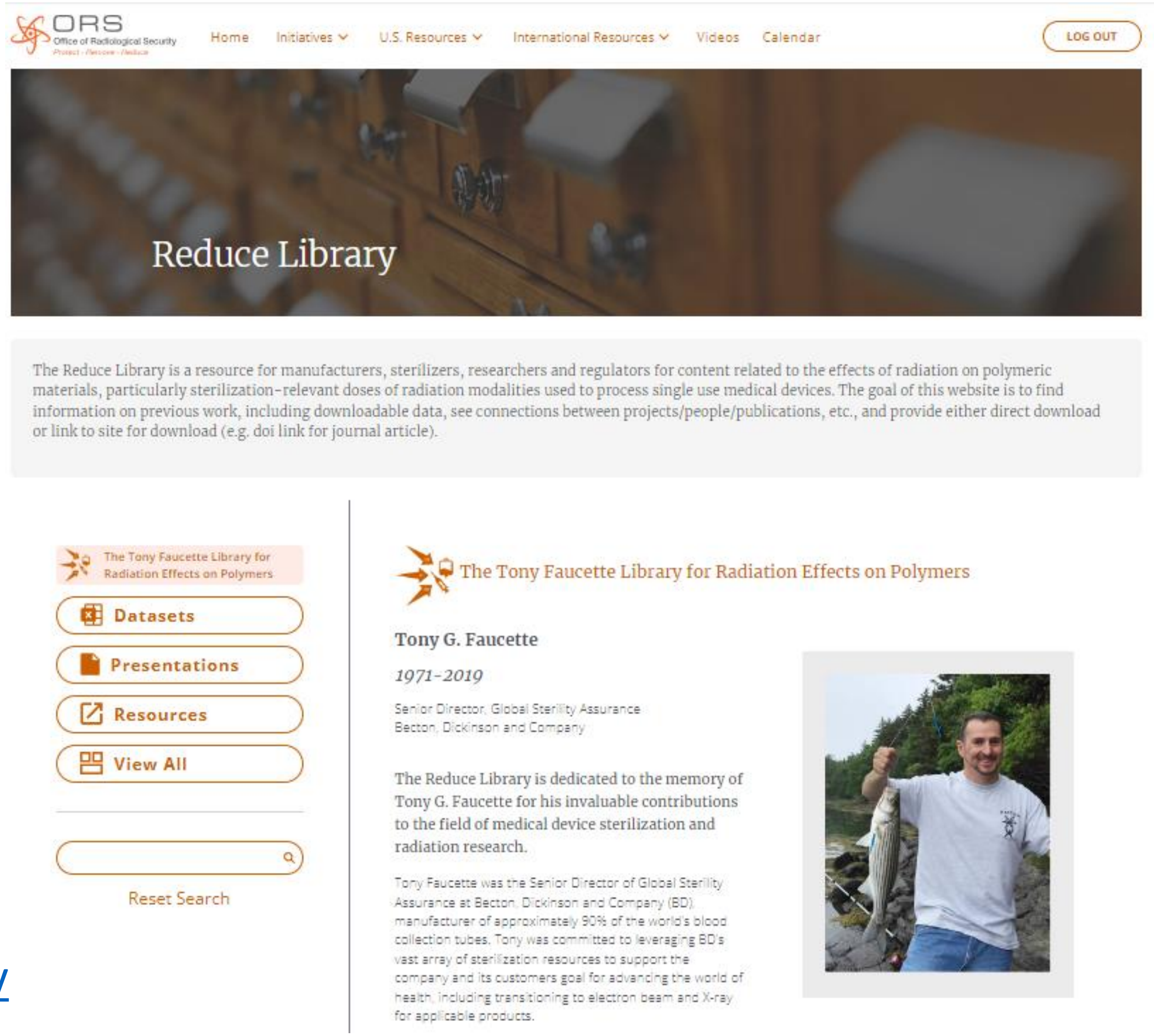
- Growing number of datasets include from BD and Stryker products.
- Presentations and other resources also available.
- Access is free but requires approved registration to the ORS Portal.



The Library may be found here:
https://orsportal.pnnl.gov/en/initiative/reduce-library

New Projects

Influence of Radiation Source on Extractables and Leachables

- Material analysis of PP & PEBAX from FDA Abbreviated Protocol round robin study
- Material and extractables analysis of effects of Gamma, E-beam, X-ray on PP and Polyisoprene from high volume BD product

Identifying and Filling Gaps in Primary, Routine or Process Control Dosimetry

- For E-beam and X-ray facilities, especially for low energies

Influence of Radiation Source on Clinical results of Filled Tubes

- Material and blood analyte analysis of effects of Gamma, E-Beam, X-ray on evacuated blood collection tubes with functional additives (e.g., heparin, EDTA)

New ideas for filling data, education or tool gaps?

- Please contact *mark.murphy@pnnl.gov* or *leo.fifield@pnnl.gov*

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Questions?

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