A Risk Assessment of the Biocompatibility of Vitamin E Blended UHMWPE

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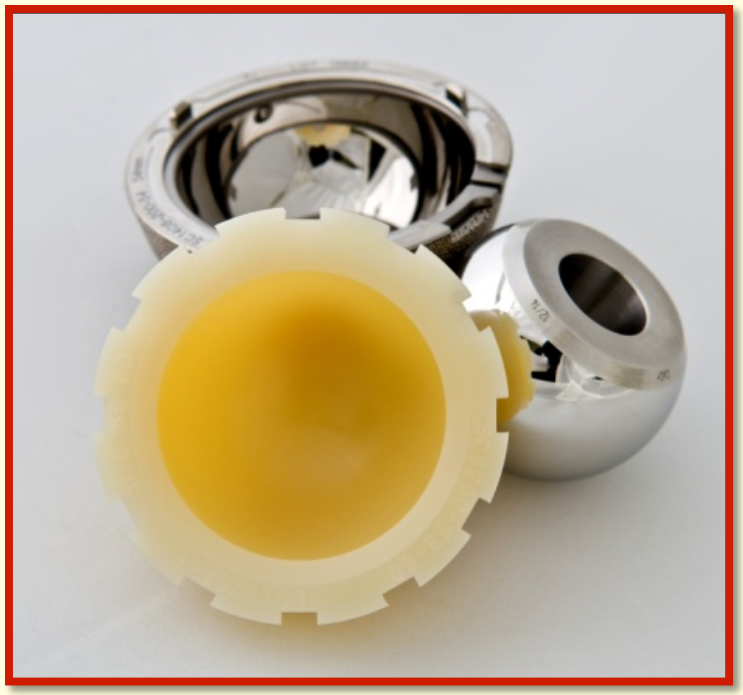
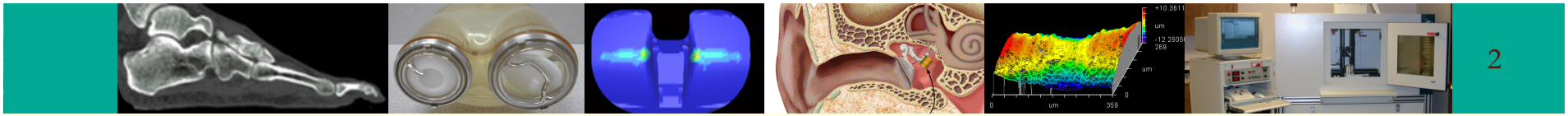
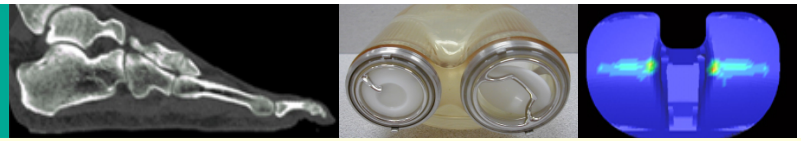
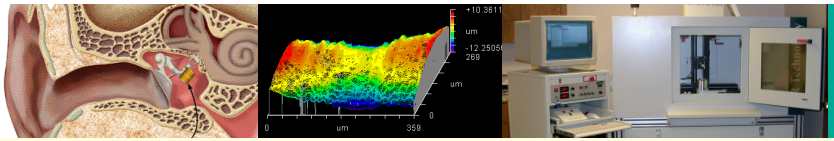
September 22, 2011





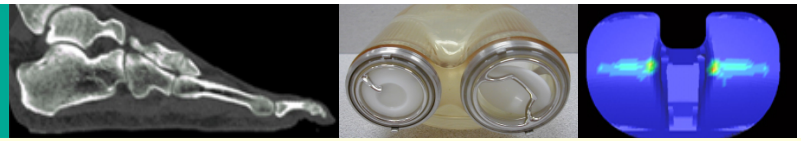
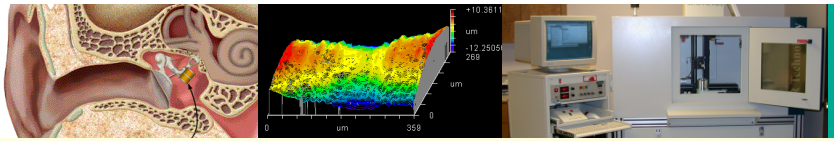
Vitamin E (α-T) Blended Ultra High Molecular Weight Polyethylene (UHMWPE)

- ***In vivo*** **oxidation of UHMWPE results in degradation of molecular weight and reduction of mechanical properties**
- **α-T, a naturally occurring anti-oxidant, proposed ~30 years ago to improve performance/longevity of implant medical devices**
  - Less toxic than synthetic anti-oxidants
    - Important human nutrient
    - 720 mg/d safe dose for most adults (Hathcock et.al, 2007)

EXp Polyethylene (75 kGy 1020-E)

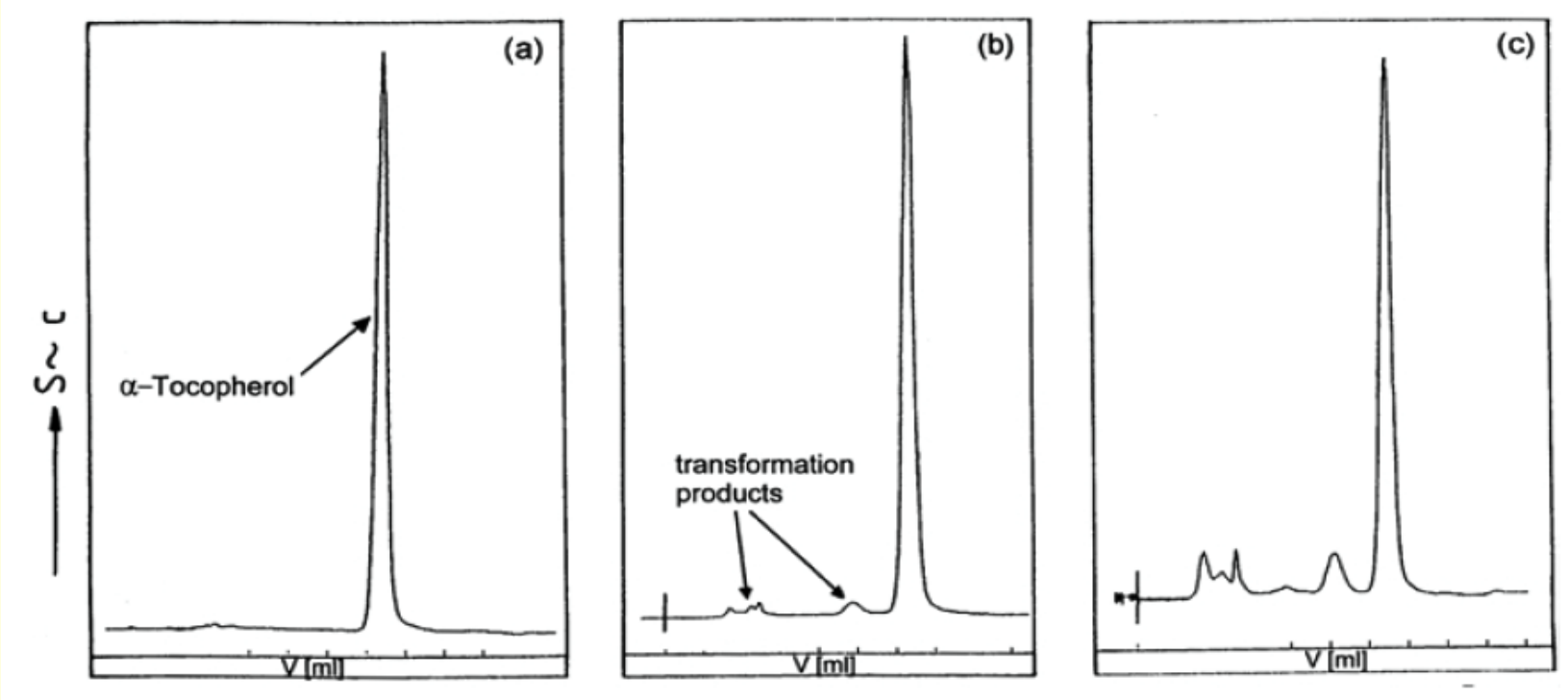
- **EXp Polyethylene (StelKast) is a blend of UHMWPE and α-T**
  - GUR 1020-E (Ticona), 1000 ppm (0.1%) α-T
    - Provides oxidative stability
  - γ-irradiation crosslinked with 75kGy
    - Highly crosslinked per ASTM F2565
  - Sterilized by EO
  - Hereafter, “75 kGy 1020-E”

At Issue, α-T Degradation During Acetabular Liner Manufacturing

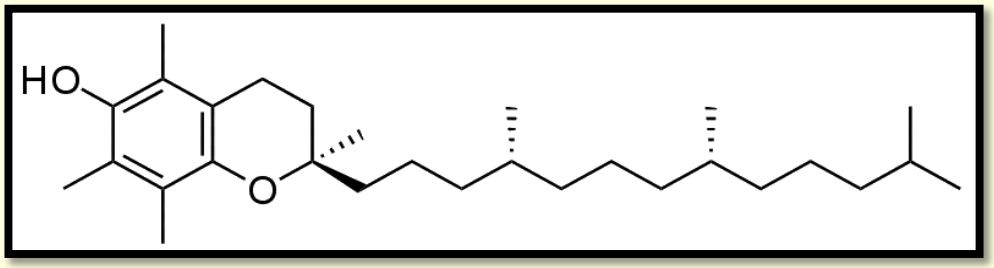
- **Acetabular liners are manufactured by consolidating GUR 1020-E resin powder that has been pre-blended with α-T and then γ-irradiating**
  - Vitamin E may be occluded in the UHMWPE crosslinked polymer matrix or chemically bonded
- **Wolf et.al, (2002): irradiation can be a source of potential α-T degradation**
  - Observed α-T degradation products not identified

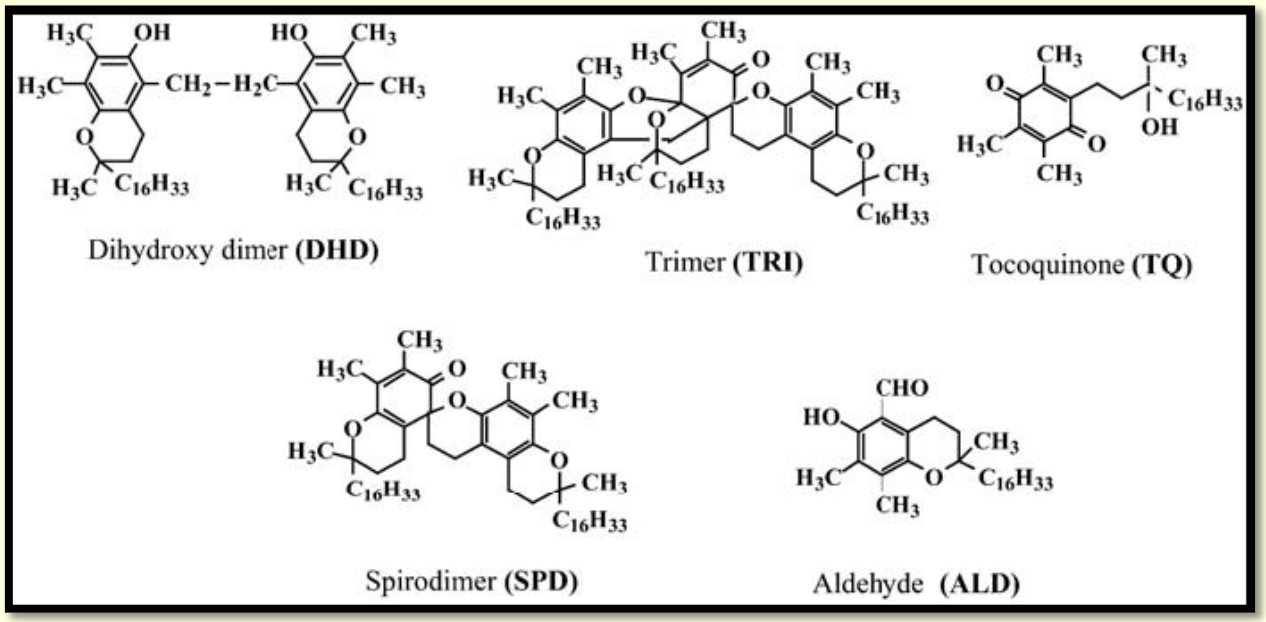
Irradiation and α-T UHMWPE Transformation Products (Wolf, et.al, 2002)

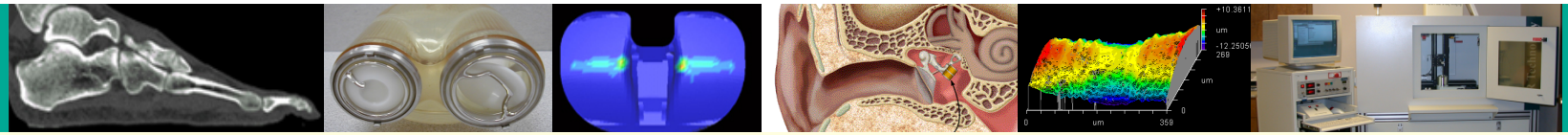


HPLC-data of α-T and its transformation products, extracted from UHMW-PE samples before processing (a), after sintering without special precautions to exclude oxygen (b), and after γ- sterilization

α-T UHMWPE Degradation (Al-Malaika, 2004)

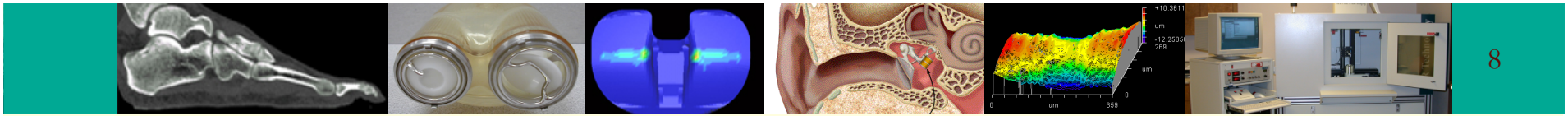






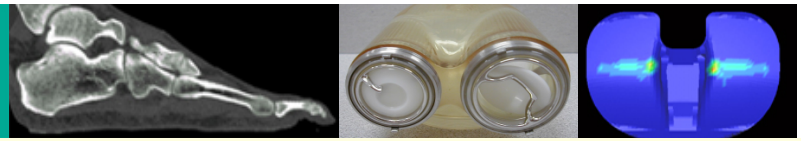
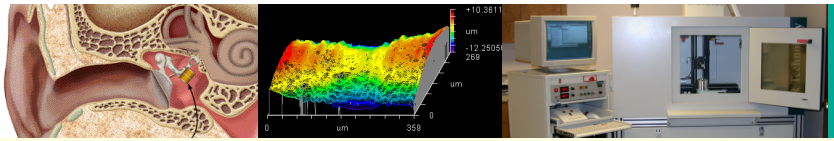
Evaluation of α-T Degradation in 75 kGy 1020-E Acetabular Liners

- **Previous Data**
  - Basic biocompatibility testing available on GUR 1020-E α-T resin powder that was not previously γ-irradiated
  - Wolf, et al, used consolidated material with higher α-T concentration and lower γ-irradiation dose
- **However, these data cannot be bridged to the 75 kGy 1020-E acetabular liners**
  - More α-T
  - Higher γ-irradiation



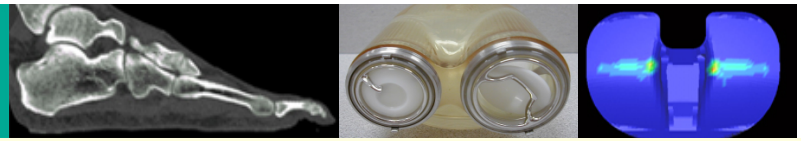
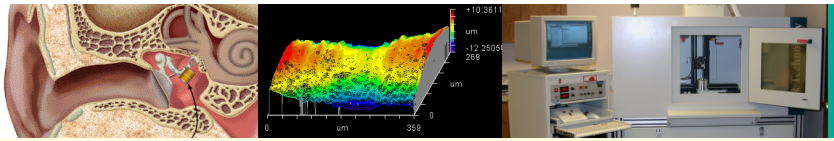
Research and Regulatory Questions

- Is the α-T contained in the 75 kGy 1020-E acetabular liner susceptible to extraction?
- Are potential α-T degradation products extractable?
- Does 75 kGy 1020-E satisfy the biocompatibility requirements of ISO 10993?

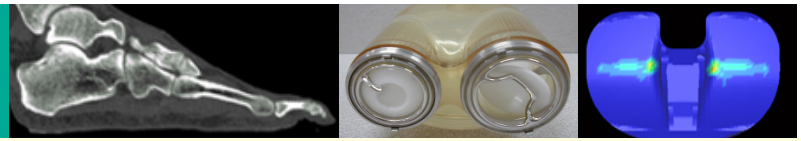
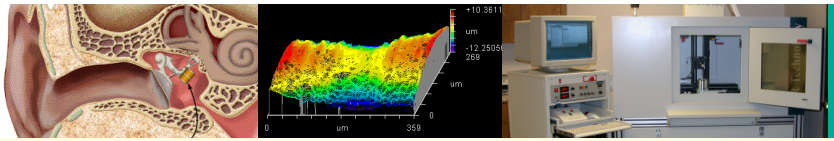
Is α-T in 75 kGy 1020-E Susceptible to Extraction?

- **Experimental methodology**
  - Polar, isopropanol (IPA) and non-polar, hexane extractions
  - IPA extractions occurred at room temperature for 18 hours.
  - Hexane extractions 74 -78°C for 72 hours
  - Evaluate changes in mass and conduct chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectroscopy (LC-MS).
- **Compare results to controls**
  - γ- Irradiated ProForm™ GUR 1050 acetabular liners
  - Raw α-T sample (Ticona, Oberhausen, Germany)

Extracts and Analyses Summary

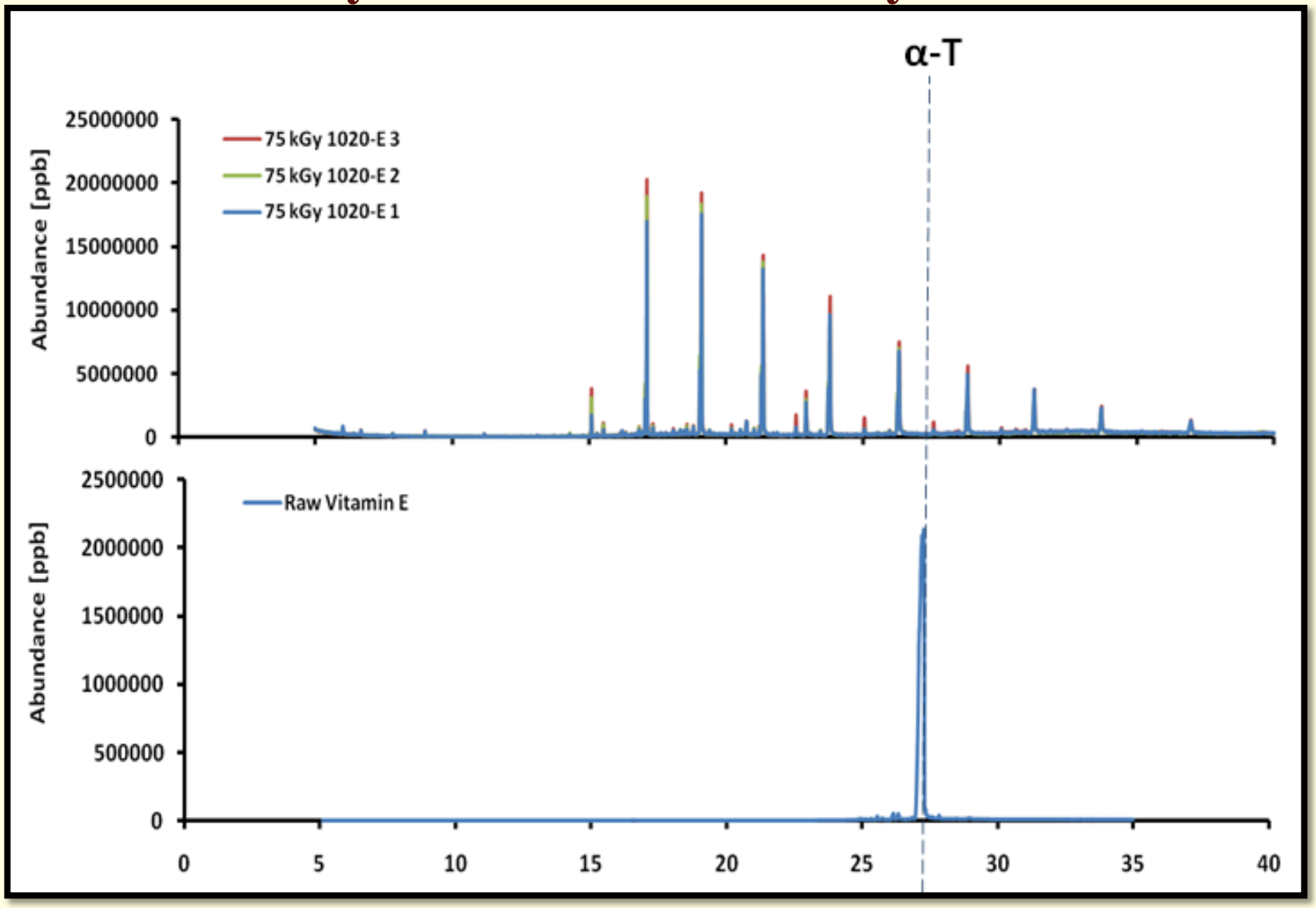
Material	Solvent	Analytical Techniques
75 kGy 1020-E	Hexane	GC-MS, LC-MS
75 kGy 1020-E	IPA	GC-MS, LC-MS
25kGy 1050	Hexane	GC-MS
Raw α-T	Hexane	GC-MS

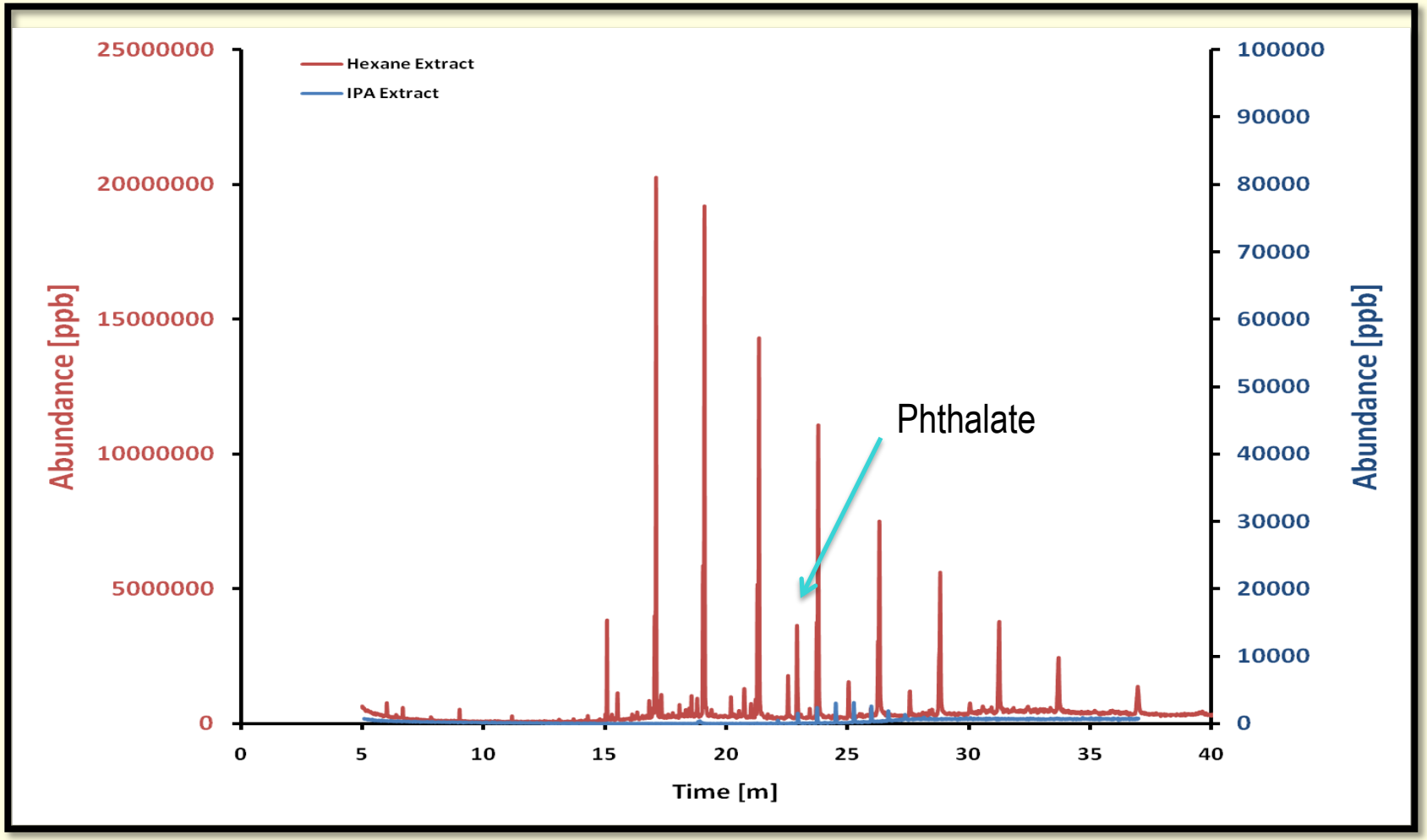
Summary of Results

- **Sample extractions resulted in mass changes of < 0.05%**
- **Hexane and IPA extracts**
  - No α-T and or degradation products detected with either GC-MS or LC-MS
- **Hexane extracts analyzed with GC-MS demonstrated**
  - Hydrocarbons for both the 75kGy 1020-E and 25kGy 1050 materials
  - Phthalates

GC-MS Analysis of α-T and 75 kGy 1020-E Extracts



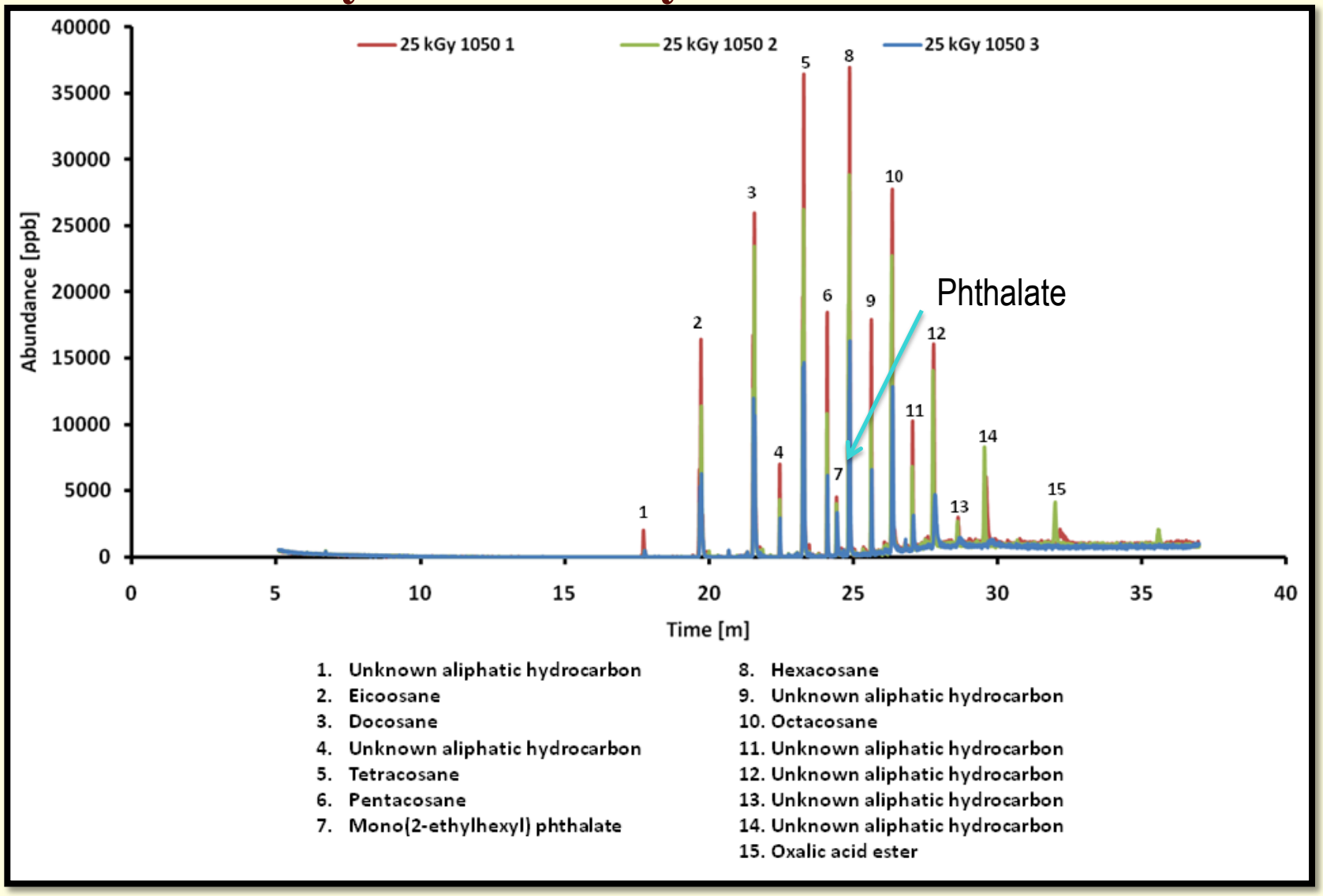
Hexane (Red) and IPA (Blue) GC-MS Analyses

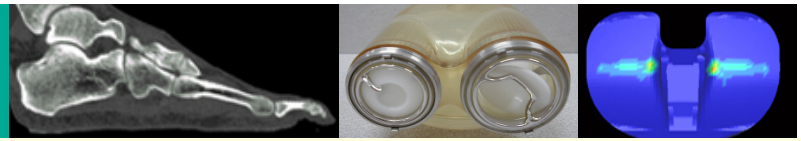
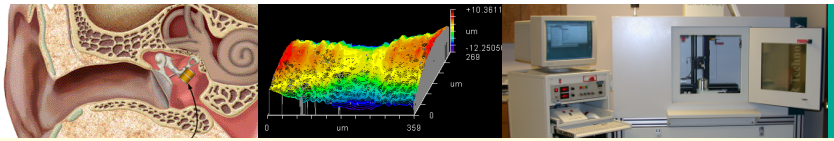


Peaks 1-4/6-11: hydrocarbons

Peak 5: diethylhexyl phthalate

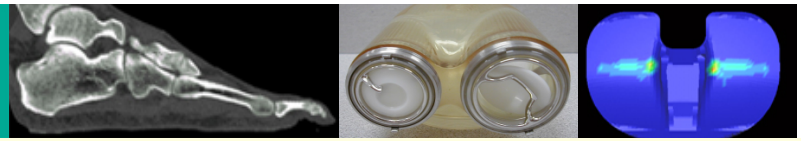
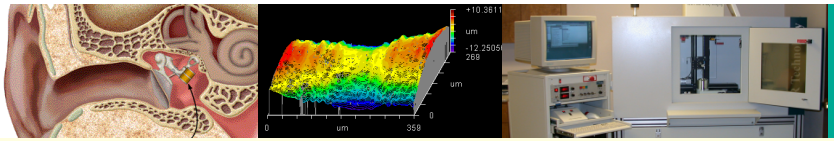
GC-MS Analysis of 25 kGy 1050 Hexane Extract



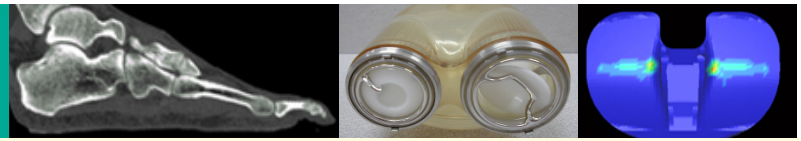
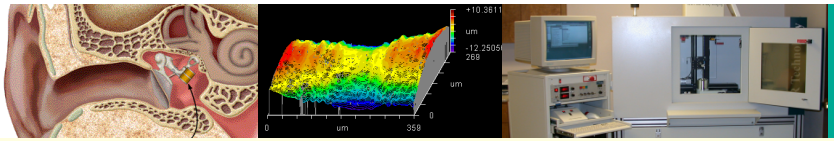
Phthalates are Exogenous Contaminants

- Phthalate esters found in 75 kGy 1020-E and GUR 1050 are not α-T transformation or degradation products
- Present in both 75 kGy1020-E and GUR 1050 samples
- Product packaging for 75 kGy 1020-E and 25kGy 1050 is a potential phthalate source

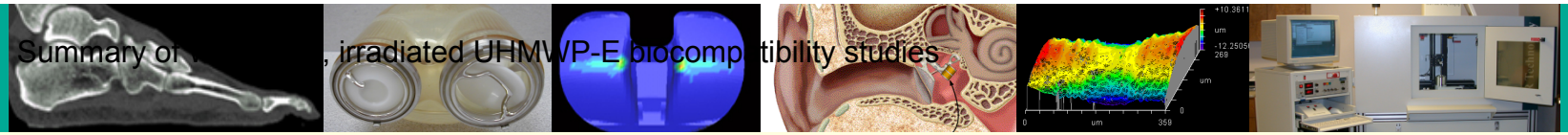
Worse Cast α-T Exposure Scenario Is Below Concern for Adverse Biologic Response

- **If 100% of α-T in 75 kGy GUR 1020-E were to elute out of the implant in a single day:**
  - A typical orthopedic part is ~ 100 g or less
  - GUR 1020 E contains 1,000 ppm of α-T
  - The maximum total amount of α-T in the liner is estimated to be ~ 1 mg or less
  - Similarly, Wolf et.al, maximum exposure is estimated to be 8 mg
  - 1 mg of synthetic alpha tocopherol is the equivalent of 1.1 IU (International Units).
  - In comparison, the daily recommended oral intake of vitamin E is generally 15 – 30 IU.

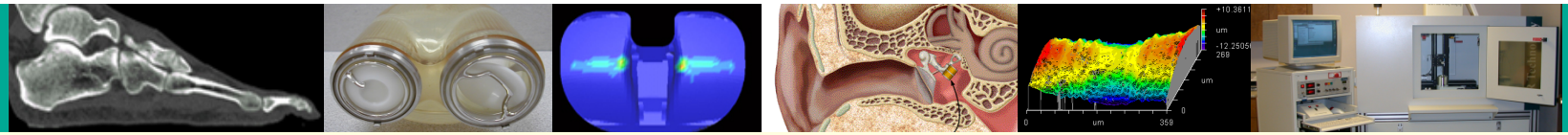
Biocompatibility of 25 kGy UHMWPE with α-T

- **Wolf et. al, (2002, 2006, and 2007) evaluated the biocompatibility of consolidated and irradiated UHMWPE α-T transformation products**
  - Same source of α-T (Ticona, Oberhausen, Germany)
  - No adverse biocompatibility effects
- **Irradiation experiments included 2,000, 4,000, and 8,000 ppm concentrations of α-T pre-blended with GUR 1020 resin.**
  - Biocompatibility testing performed on 8,000 ppm-blended material after gamma sterilization (25 kGy) to simulate a 'worst case'
- **In contrast, 75 kGy 1020-E has 1,000 ppm α-T**



Wolf et al. Biocompatibility Results

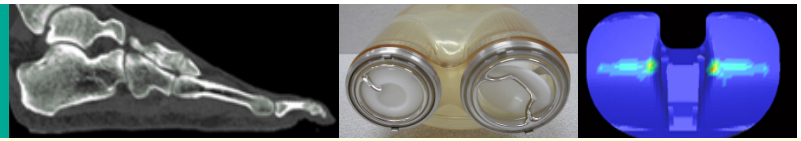
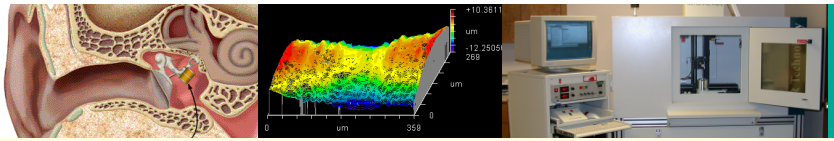
Study	Resin	α-T (PPM) Concentration	Radiation Dose (kGy)	Testing	Results
Wolf et.al, (2002)	GUR 1020	8,000	25	Cytoxicity (Mouse cells)	Negative
Wolf et.al, (2002)	GUR 1020	8,000	25	Genotoxicity (Ames assay)	Negative
Wolf et.al, (2006)	GUR 1020	8,000	25	Subcutaneous Rat	Negative
Wolf et.al, (2007)	GUR 1020	8,000	25	Cytotoxicity (Human cells)	Negative



Biocompatibility Testing Matrix— ISO 10993 Requirements for Implant Devices

Device Categories			Biological									
			Initial								Other[4]	
Body Contact		Contact Duration A-Limited (≤ 24 hours) B-Prolonged (> 24 hours to ≤ 30 days) C-Permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation	Systemic Toxicity Subacute (Subchronic		Genotoxicity	Implanation	Hemcompatibility	Chronic Toxicity	Carcinogenicity
Implant Devices	Tissue/Bone	A	■	■	■	○						
		B	■	■	■	■	■	■	■			
		C	■	■	■	■	■	■	■		■	■
	Blood[3]	A	■	■	■	■	■		■	■		
		B	■	■	■	■	■	■	■	■		
		C	■	■	■	■	■	■	■	■	■	■

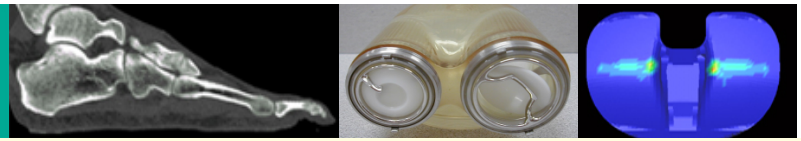
■ ISO Evaluation tests for consideration
○ Additional tests which the FDA considers may be applicable

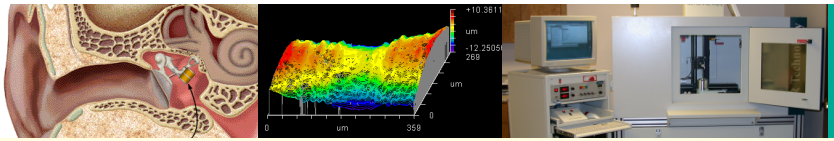



Biocompatibility Testing of 75 kGy 1020-E

Testing	Results
Cytoxicity (Mouse L-929 Fibroblast cells)	Negative
Genotoxicity (Ames assay)	Negative
Mutagenicity (Mouse Micronucleus)	Not Mutagenic
Skin Irritation (Rabbit)	Non-irritant
Sensitization (Guinea Pig)	Negative
Subcutaneous Implantation^{+}, 14 day (Rabbit)	Non-irritant
Subcutaneous Implantation^{+}, 13 week (Rabbit)	In Progress

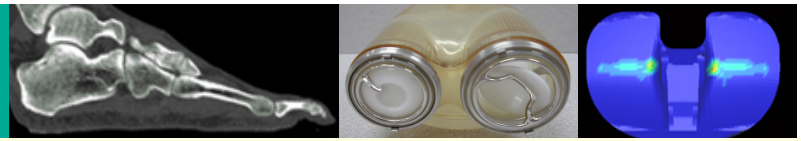
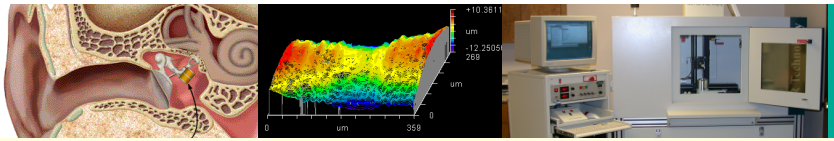
$^{+}$ 75kGy 1020-E plugs and particles used for implantation





Summary

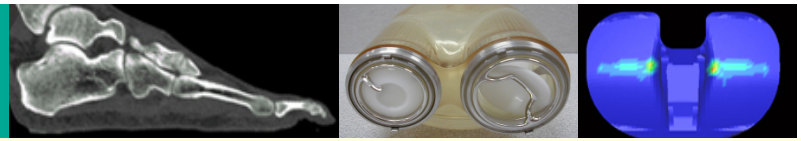
- Extraction experiments and biocompatibility testing confirm that 75 kGy GUR 1020-E acetabular liners are safe for humans
- FDA 510(k) clearance, April 2011
- Market place introduction, July 2011

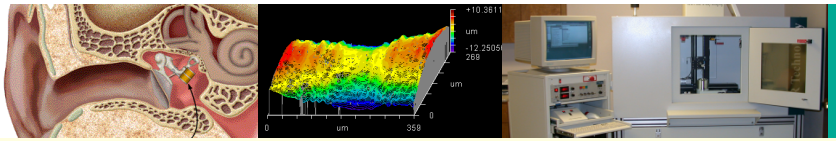



Word of Caution…

- **Results for 75kGy 1020-E (or Wolf's results) may not be applicable to other UHMWPE medical device products derived from GUR 1020-E with a different radiation dose**

- **Evaluate combination of α-T and irradiation doses**
  - Product performance
  - Product safety
    - HPLC/GC analyses
    - Biocompatibility





Thank you