

Cu-67 DOE Isotope Program User Group Meeting

David A. Rotsch, Argonne National Laboratory

Cu-67 AGENDA

AUGUST 24, 2021, 1 PM EDT

1:00 – 1:10 PM **Dave Rotsch,**
Argonne National
Laboratory (Moderator)
Introduction

1:10 – 1:25 PM **Jack Shively,** City of Hope

1:25 – 1:40 PM **Alan Packard,**
Boston Children's Hospital

1:40 – 1:55 PM **Brian Zeglis,**
Hunter College

1:55 – 2:10 PM **Jennifer Bartels,**
University of Alabama
at Birmingham

2:10– 2:25 PM **Sheamus Gleason,**
Clarity Pharmaceuticals

2:25 – 3:00 PM Moderated Q&A Segment

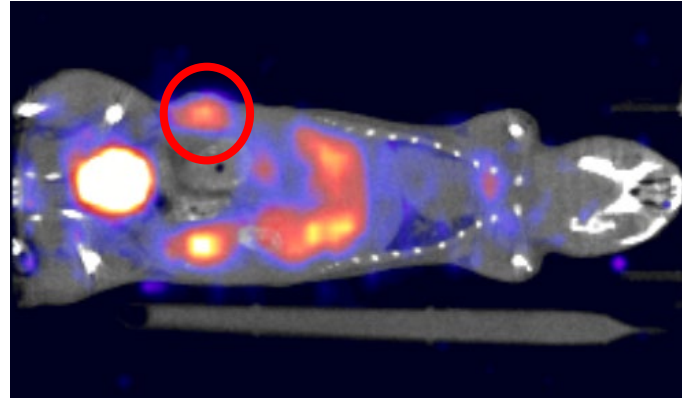
Theranostic approach

Personalized medicine through diagnostic and therapeutic



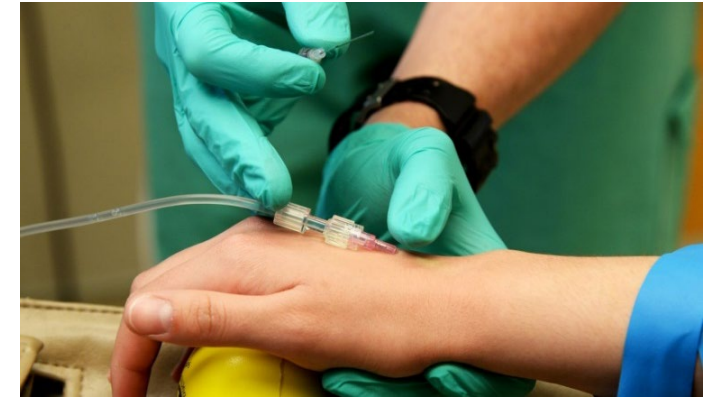
Diagnostic

- SPECT and PET
- $^{43,44}\text{Sc}$, ^{64}Cu , ^{68}Ga , ^{82}Rb , $^{99\text{m}}\text{Tc}$, ^{132}Ce



Therapeutic

- Alpha, Beta, Auger electrons
- ^{90}Y , $^{117\text{m}}\text{Sn}$, $^{188,191,193,195\text{m}}\text{Pt}$, ^{211}At , ^{212}Pb , $^{212/213}\text{Bi}$, ^{223}Ra , ^{225}Ac , ^{177}Lu



Both (Theranostic)

- Real-time monitoring of treatment
- ^{47}Sc , ^{67}Cu , $^{186,188,189}\text{Re}$

Copper-67

- **Theranostic**

- $t_{1/2} = \sim 2.58$ days
- Average β^- : 141 keV
- γ : 184.6 keV (49%)
- Decays to stable Zn

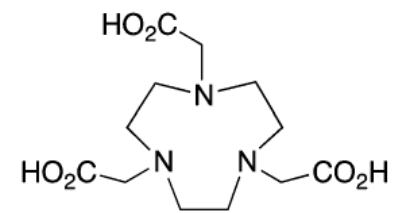
- Match pair with ^{64}Cu

- PET

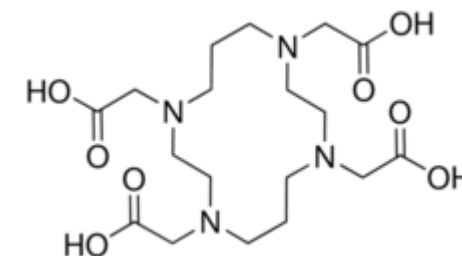
- Uses: treatment of non-Hodgkins lymphoma, neuroblastomas, and other cancers

- Chelation chemistry well-known due to ^{64}Cu PET-analogue

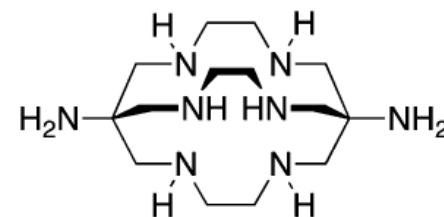
Multi-dentate Bifunctional Chelators



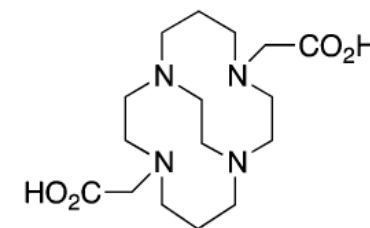
NOTA
1,4,7-triazacyclononane-
1,4,7-triacetic acid



TETA
1,4,8,11-
tetraazacyclotetradecane-
,1,4,8-tetraacetic acid



Diamsar
3,6,10,13,16,19-
hexaazabicyclo[6.6.]eicosane-1,8-
diamine



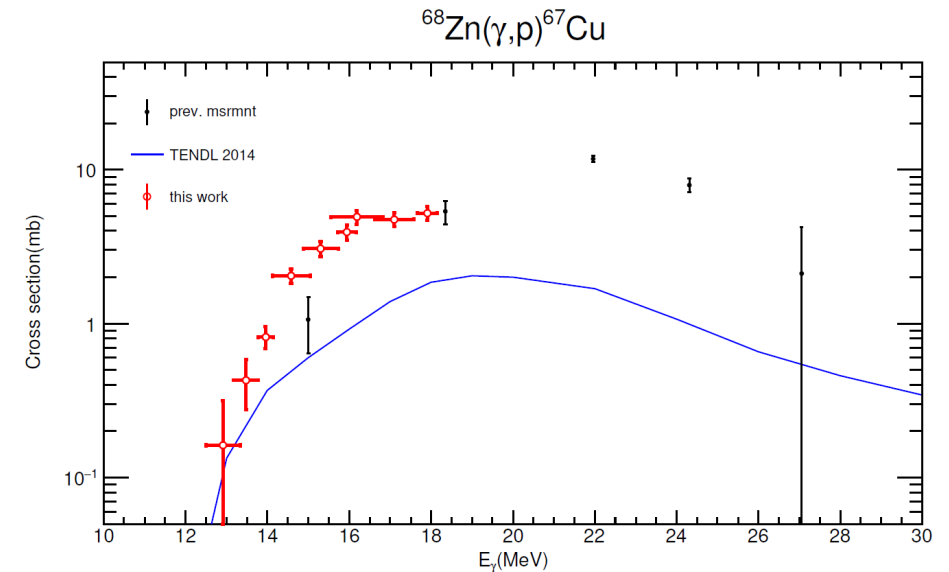
CB-TE2A
4,11-bis-(carboxymethyl)-
1,4,8,11-tetraazabicyclo[6.6.2]-
hexadecane

Copper-67 Production using p and n

- Production methods
 - $^{68}\text{Zn}(p,2p)^{67}\text{Cu}$, $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$, $^{67}\text{Zn}(n,p)^{67}\text{Cu}$, and heavy-ion fragmentation (FRIB Harvesting)
- Reported specific activities
 - 2-20 Ci/mg (74-740 GBq/mg)
 - <20 Ci/mg has demonstrated radiolabeling challenges
- ^{64}Cu is readily available, so why has ^{67}Cu been so difficult?
 - Production rates are relatively low compared to ^{64}Cu
 - Targetry is challenging
 - Zn melting point is low, $\sim 420\text{ }^{\circ}\text{C}$ ($\text{Ni}_{(m)} = 1,455\text{ }^{\circ}\text{C}$)
 - Zn wets and alloys with most metals (targetry considerations are difficult)
 - Cu is ubiquitous building/construction material

Photonuclear Production ^{67}Cu

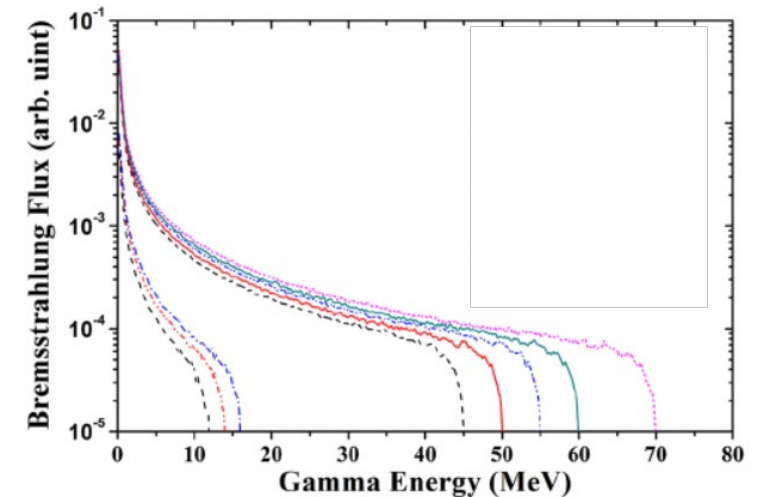
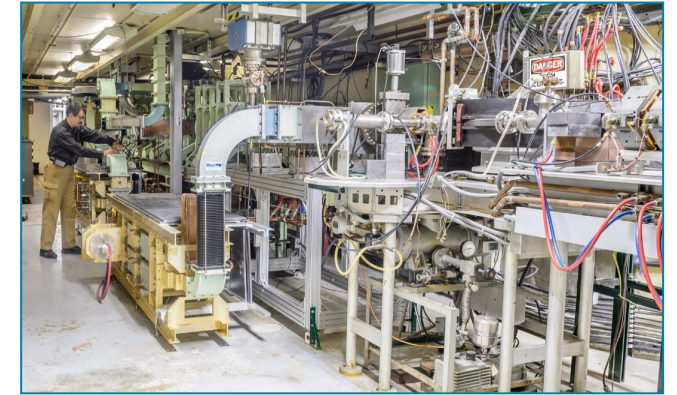
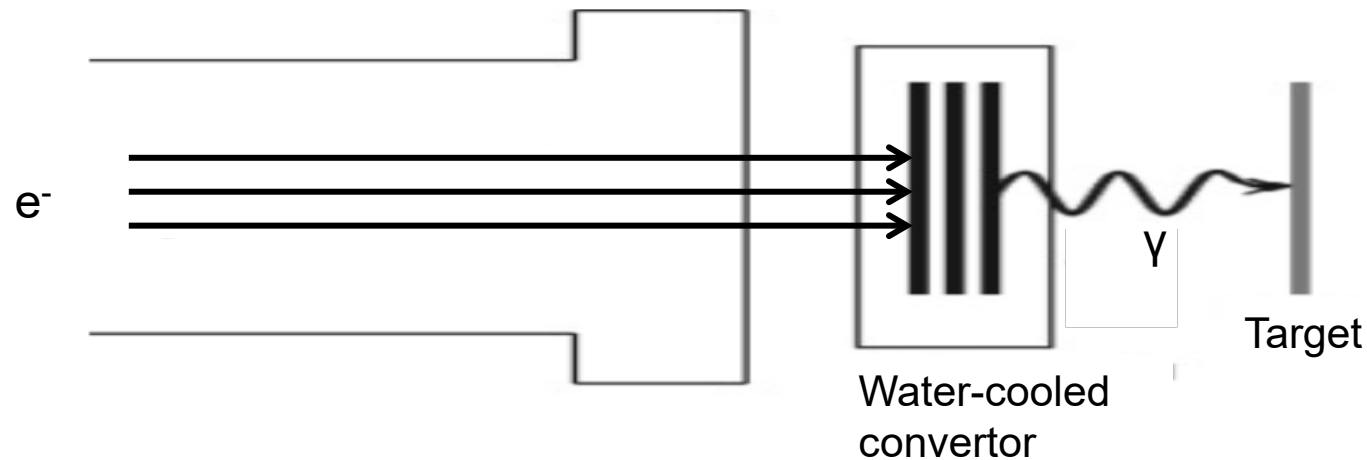
- Bremsstrahlung: $^{68}\text{Zn}(\gamma, p)^{67}\text{Cu}$ and $^{71}\text{Zn}(\gamma, \alpha)^{67}\text{Cu}$
 - $^{68}\text{Zn}(\gamma, p)^{67}\text{Cu}$ – 12 MeV threshold, peak at ~20 MeV, $\sigma = 26$ mb (~12 mb TENDL)
 - $^{71}\text{Zn}(\gamma, \alpha)^{67}\text{Cu}$ – 15 MeV threshold, peak at 20 MeV, $\sigma = 0.7$ mb
- $^{68}\text{Zn}(\gamma, p)^{67}\text{Cu}$
 - Enriched ^{68}Zn ingot
 - Enriched targets eliminates co-produced radioisotopes
 - ^{68}Zn – 18.45% abundant
 - Zn targetry considerations
 - No metal contact
 - Target temperature (melting point ~420 °C)



Koning, A.J., et al. *TENDL-2014: TALYS-based evaluated nuclear data library*. 2014, Available from: ftp://ftp.nrg.eu/pub/www/talys/tendl2014/gamma_html/gamma.html

Low Energy Accelerator Facility (LEAF)

- High energy electrons are bombarded on convertor
- Electrons brake on the convertor and produce Bremsstrahlung photons
- Photons interact with the target primarily via (γ, n) , (γ, p) , and (γ, α)



Photonuclear Production of ^{67}Cu , $^{68}\text{Zn}(\gamma, p)^{67}\text{Cu}$

- Certificate of Analysis
 - 2 Ci at end of bombardment (EOB)
 - ~1.2 Ci at time of Shipping (806 available with NIDC 24-hr decay allowance)
 - Shipped as solid CuCl_2
 - Identified by 93 and 184 keV gamma emissions
 - $\geq 99\%$ radionuclide purity
 - ≥ 50 Ci/mg (^{67}Cu /total Cu at EOB)

Batch	SA (Ci/mg @ EOB, ^{67}Cu mass corrected)	TETA (mCi/nmole @ time of labeling)	DOTA (mCi/nmole @ time of labeling)	MeCOSAR (mCi/nmole @ time of labeling)
Average	101.9	1.38	1.18	2.32

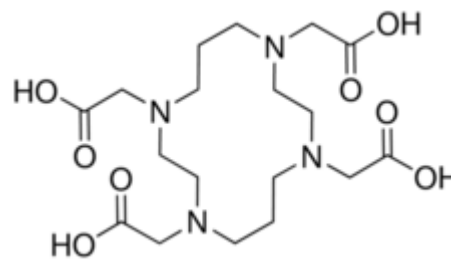
Radiolabeling

Apparent Molar Activity (AMA)

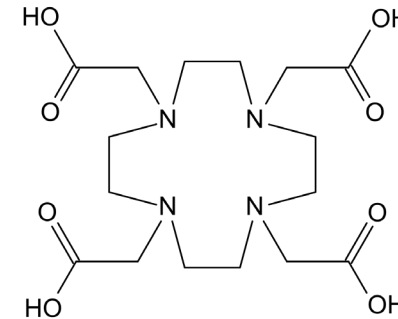
- Radiolabeling occurs ~1 half-life after EOB.

Conditions

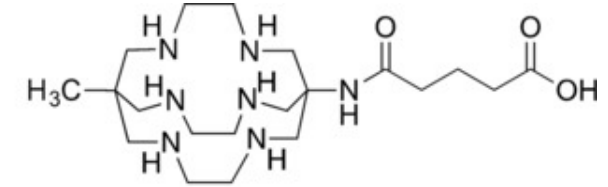
- 0.5 M NH_4COOH (pH = 5.5)
- 40-90 °C
- 30 minutes
- EDTA added for MeCOSar after labeling



TETA
1,4,8,11-
tetraazacyclotetradecane-
1,4,8-tetraacetic acid



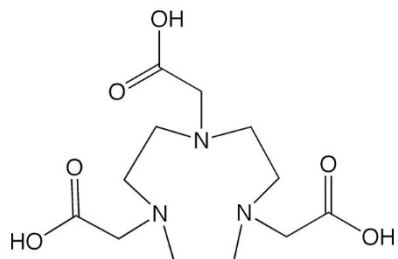
DOTA
1,4,7,10-
Tetraazacyclododecane-
1,4,7,10-tetraacetic acid



MeCOSar
5-(8-methyl-
3,6,10,13,16,19-hexaaza-
bicyclo[6.6.6]icosan-1-ylamino)-5-
oxopentanoic acid

Batch	SA (Ci/mg @ EOB, ^{67}Cu mass corrected)	TETA (mCi/nmole @ time of labeling)	DOTA (mCi/nmole @ time of labeling)	MeCOSAR (mCi/nmole @ time of labeling)
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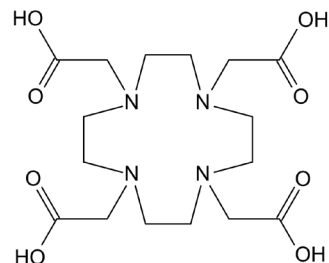
Independent quality evaluation



NOTA

2.3 mCi/nmol

pH 5.5, NaOAc buffer
Reaction time: 30min@25°C



DOTA

3.6 mCi/nmol

pH 5.5, NaOAc buffer
Reaction time: 30min@90°C



Work Performed by:

Ed Sarduy

Christopher Kuttyreff

Jonathan Engle

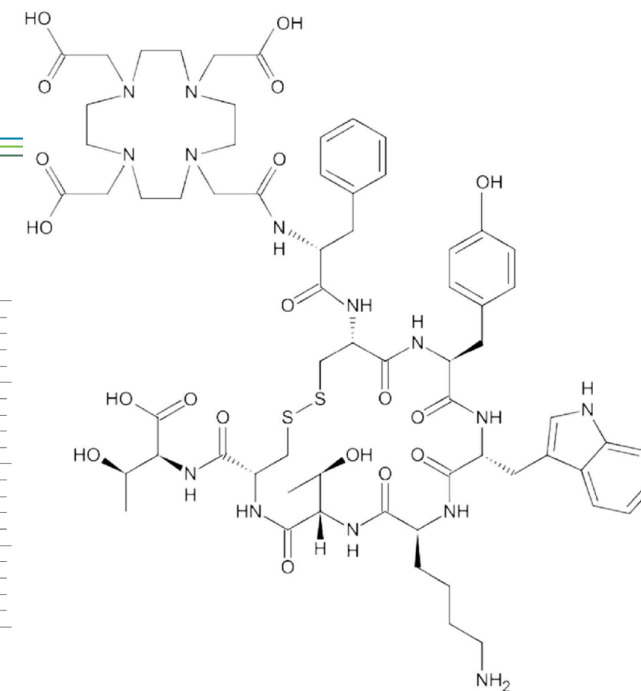
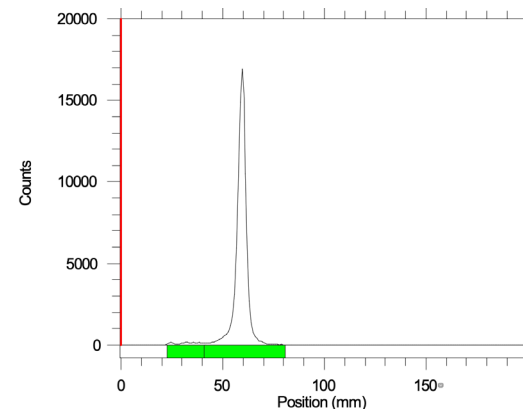


Work performed by:

Dr. Jen Bartels

Dr. Suzy Lapi

• ⁶⁷Cu-DOTATATE

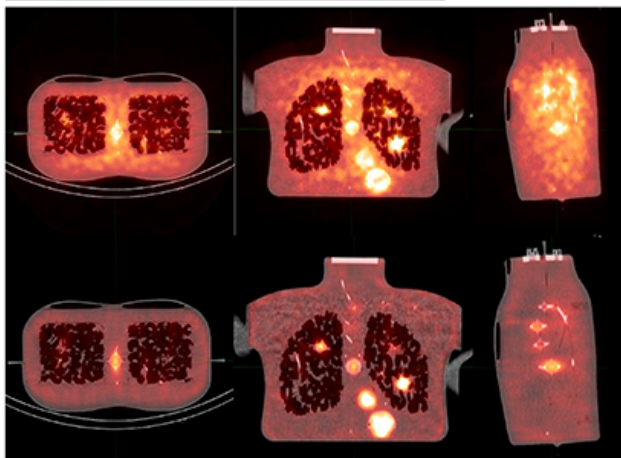


Temperature	Target SA (μCi/μg)	DOTATATE (μg)	⁶⁷ Cu (μCi)	Labeling efficiency (%)
37°C	100	5	544	19
65°C	100	5	545	72
90°C	100	5	550	94
90°C	10	5	54	97.3
90°C	50	5	260	97.5
90°C	100	5	549	98.4

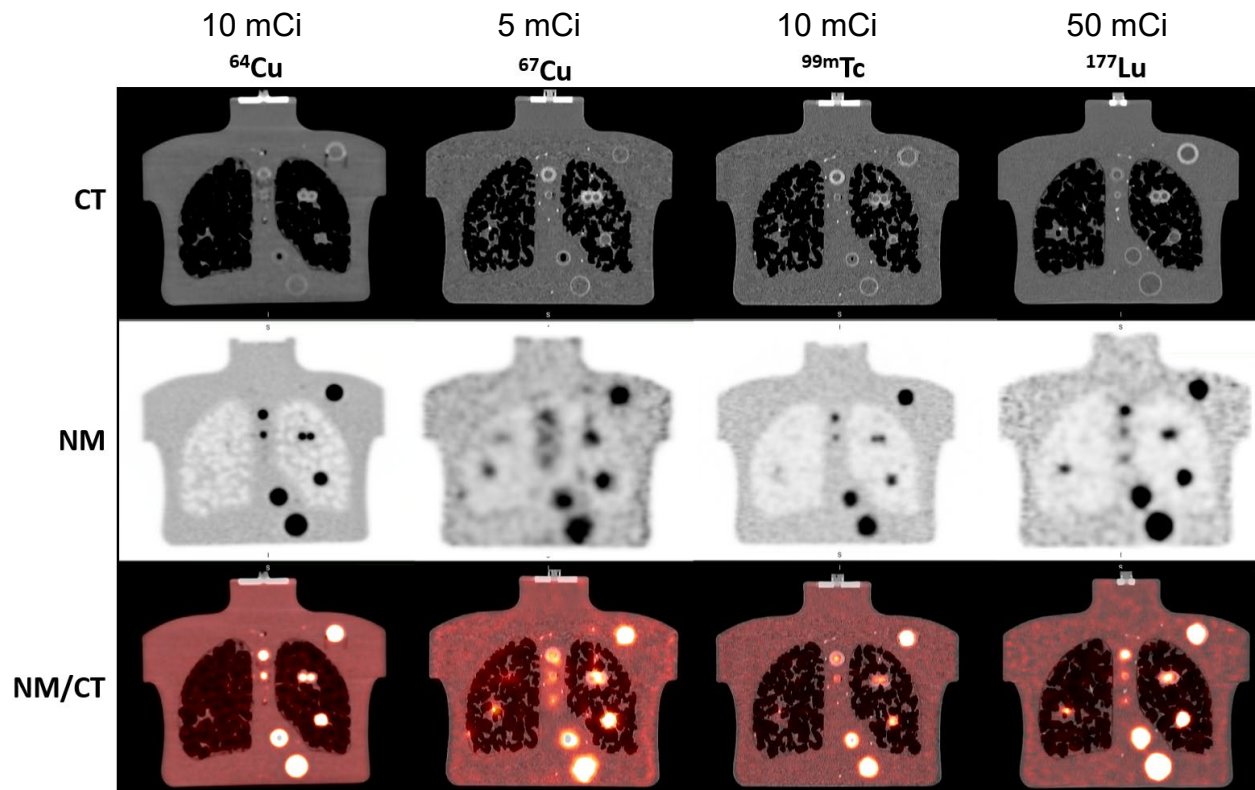
^{67}Cu as a Theranostic



Society for Nuclear Medicine and Molecular Imaging (SNMMI) Clinical Trials Network (CTN) anthropomorphic chest phantom.



Comparison of ^{67}Cu SPECT/CT images acquired using the low-energy high-resolution (LEHR) collimator and the medium energy (ME) collimator.



MJ Merrick, et. al, "Imaging and Dosimetric Characteristics of ^{67}Cu " *Phys. Med. Biol.* **2021**, 66 035002, <https://doi.org/10.1088/1361-6560/abca52>



Work performed by:
S. Graves
M. Merrick

Thank You!

For more information: <https://isotopes.gov/>

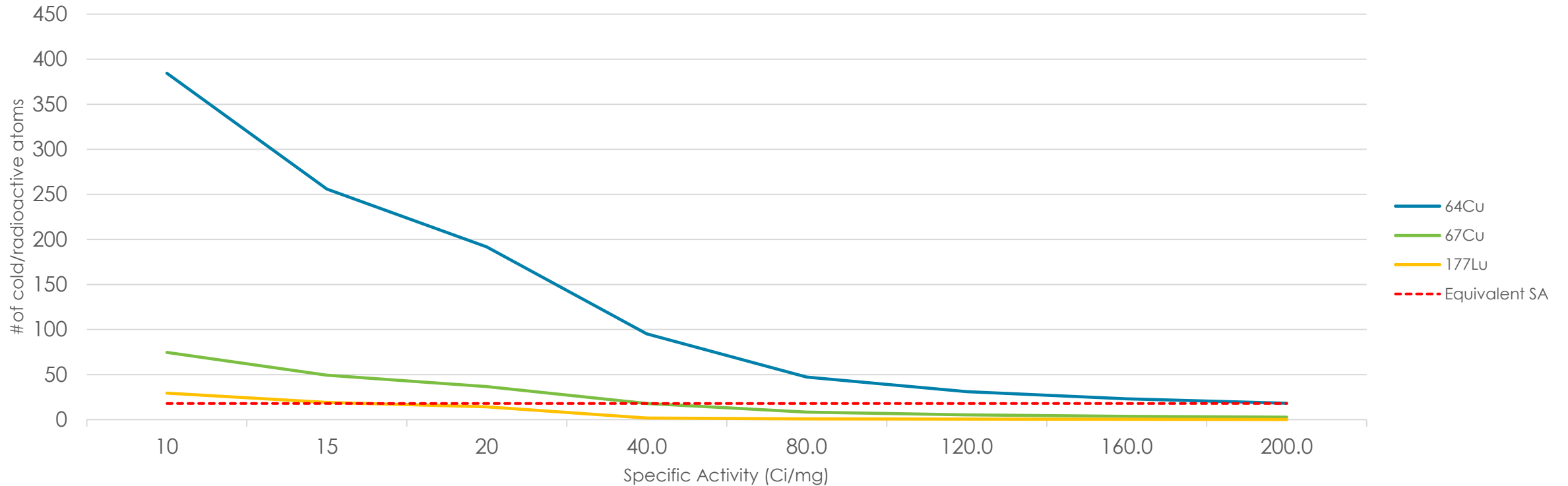
^{67}Cu test batch recipient responses

- 51.23 Ci/mg (^{67}Cu /total Cu, @ EOB)
- *“Very nice product! We’re looking forward to doing more studies with Cu-67. Please keep us posted on the next time you are producing material, and we’ll plan a larger mouse study.”*
- *“In summary, we were very happy with our experience, and are pleased to see that high quality Cu-67 may soon be more widely available...”*
- *“The Cu-67 labeled beautifully... very interested in planning animal experiments with Cu-67.”*

■ ■ Impurity ratio vs specific activity

- $\sim 200 \text{ Ci/mg } ^{64}\text{Cu} = \sim 40 \text{ Ci/mg } ^{67}\text{Cu} = \sim 18 \text{ Ci/mg } ^{177}\text{Lu}$

Cold atoms/Hot atoms vs Specific Activity (Ci/mg)



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