Cu-67 DOE Isotope Program User Group Meeting

David A. Rotsch, Argonne National Laboratory
### Cu-67 Agenda

AUGUST 24, 2021, 1 PM EDT

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Affiliation</th>
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<tr>
<td>1:00 – 1:10 PM</td>
<td>Dave Rotsch, Argonne National Laboratory (Moderator)</td>
<td>Introduction</td>
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<td>2:25 – 3:00 PM</td>
<td>Moderated Q&amp;A Segment</td>
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Theranostic approach

Personalized medicine through diagnostic and therapeutic agents

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

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

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

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

- Match pair with $^{64}\text{Cu}$
  - PET

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

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

- $^{64}\text{Cu}$ is readily available, so why has $^{67}\text{Cu}$ been so difficult?
  - Production rates are relatively low compared to $^{64}\text{Cu}$
  - Targetry is challenging
    - Zn melting point is low, ~420 °C ($\text{Ni}_{(m)} = 1,455$ °C)
    - Zn wets and alloys with most metals (targetry considerations are difficult)
  - Cu is ubiquitous building/construction material
Photonuclear Production $^{67}\text{Cu}$

- Bremsstrahlung: $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$ and $^{71}\text{Zn}(\gamma,a)^{67}\text{Cu}$
  - $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$ – 12 MeV threshold, peak at ~20 MeV, $\sigma = 26$ mb (~12 mb TENDL)
  - $^{71}\text{Zn}(\gamma,a)^{67}\text{Cu}$ – 15 MeV threshold, peak at 20 MeV, $\sigma = 0.7$ mb

- $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$
  - Enriched $^{68}\text{Zn}$ ingot
    - Enriched targets eliminates co-produced radioisotopes
      - $^{68}\text{Zn}$ – 18.45% abundant
    - Zn targetry considerations
      - No metal contact
      - Target temperature (melting point ~420 °C)

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

- **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
  - $\geq 50$ Ci/mg ($^{67}\text{Cu}$/total Cu at EOB)

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<th>Batch</th>
<th>SA (Ci/mg @ EOB, $^{67}\text{Cu}$ mass corrected)</th>
<th>TETA (mCi/nmole @ time of labeling)</th>
<th>DOTA (mCi/nmole @ time of labeling)</th>
<th>MeCOSAR (mCi/nmole @ time of labeling)</th>
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<td>Average</td>
<td>101.9</td>
<td>1.38</td>
<td>1.18</td>
<td>2.32</td>
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Radiolabeling

Apparent Molar Activity (AMA)

- Radiolabeling occurs ~1 half-life after EOB.

Conditions
- 0.5 M NH$_4$COOH (pH = 5.5)
- 40-90 °C
- 30 minutes
- EDTA added for MeCOSar after labeling

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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-hexazaa-bicyclo[6.6.6]icosan-1-ylamino)-5-oxopentanoic acid
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

• 67Cu-DOTATATE

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<tr>
<th>Temperature</th>
<th>Target SA (µCi/µg)</th>
<th>DOTATATE (µg)</th>
<th>67Cu (µCi)</th>
<th>Labeling efficiency (%)</th>
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<tbody>
<tr>
<td>37°C</td>
<td>100</td>
<td>5</td>
<td>544</td>
<td>19</td>
</tr>
<tr>
<td>65°C</td>
<td>100</td>
<td>5</td>
<td>545</td>
<td>72</td>
</tr>
<tr>
<td>90°C</td>
<td>100</td>
<td>5</td>
<td>550</td>
<td>94</td>
</tr>
<tr>
<td>90°C</td>
<td>10</td>
<td>5</td>
<td>54</td>
<td>97.3</td>
</tr>
<tr>
<td>90°C</td>
<td>50</td>
<td>5</td>
<td>260</td>
<td>97.5</td>
</tr>
<tr>
<td>90°C</td>
<td>100</td>
<td>5</td>
<td>549</td>
<td>98.4</td>
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Work performed by:
Ed Sarduy
Christopher Kutyreff
Jonathan Engle

Work performed by:
Dr. Jen Bartels
Dr. Suzy Lapi

Argonne National Laboratory
NIDC National Isotope Development Center
Isotope Program
U.S. Department of Energy
**67Cu as a Theranostic**

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

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


Work performed by: S. Graves
M. Merrick
Thank You!

For more information: [https://isotopes.gov/](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

• ~200 Ci/mg $^{64}$Cu = ~40 Ci/mg $^{67}$Cu = ~18 Ci/mg $^{177}$Lu

Cold atoms/Hot atoms vs Specific Activity (Ci/mg)
Cu-67
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