

^{67}Cu radioisotope production with using $^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$ Nuclear Reaction on Cyclone-30 High Current cyclotron

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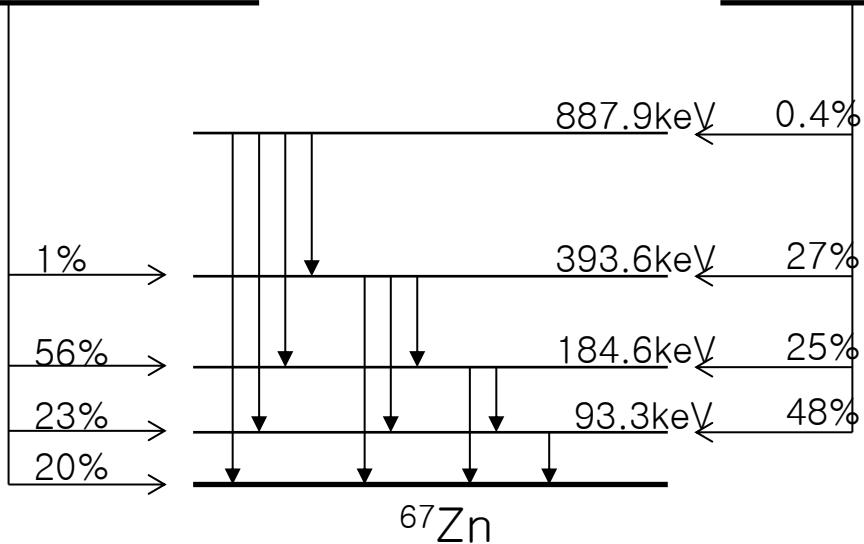
• Physical properties of Cu radionuclides

Radio-nuclide	Half-life	Decay mode(%)	Major γ (keV)	Major β^-/β^+ (keV, %)	Application
^{60}Cu	23.7m	$\beta^+(93), \text{EC}(7)$	826(22), 1332(88)	872(49)	
^{61}Cu	3.32h	$\beta^+(61), \text{EC}(39)$	282(12), 656(10)	523(51)	
^{62}Cu ($^{62}\text{Zn}/^{62}\text{Cu}$)	9.74m	$\beta^+(97), \text{EC}(3)$	1173(0.34)	1316(97)	PET
^{64}Cu	12.7h	EC(43.9), $\beta^-(38.5) \beta^+(17.6)$	1345(0.5)	$\beta^+: 278,$ $\beta^-: 190$	Therapy PET
^{66}Cu	5.4m	$\beta^-(100)$	1039(9)	1112(91)	Therapy
^{67}Cu	61.83h	$\beta^-(100)$	184(48.7), 93(16), 91(7)	$\beta^-: 121(57)$	Therapy

	$\beta^+?$	$\beta^- 3.10$	$\beta^+?$	β^-	$128...$	$\beta^- 1.28...$	$109; 2/3...$	$\gamma 167; 147...$	$\sigma 1.0$	$\gamma 82/133b...$	$\sigma 3.0$	$\gamma \gamma$	$\sigma 0.5$	$\sigma 1.5$	$\sigma 0.14/\sigma 0.20$	$\gamma 1480...$	$\gamma 99...$	$\sigma 0.09/\sigma 0.16$	$\gamma 160...$	$\gamma 155...$	$\gamma 141/142/144$
^{62}Zn		Ga 60 $\beta^+ 8.3; 12.2...$ $\gamma 1004; 3848...$ β^-	Ga 61 168 ms $\beta^+ 8.2...$ $\gamma 88; 418; 124;$ $756...$ β^-	Ga 62 115.99 ms $\beta^+ 8.1...$ $\gamma 954...$	Ga 63 31.4 s $\beta^+ 4.5...$ $\gamma 637; 627;$ $193; 650...$	Ga 64 2.62 m $\beta^+ 2.9; 6.1...$ $\gamma 992; 808...$ $\gamma 1039; 2752;$ $3366; 1387;$ $2195...$	Ga 65 15 m $\beta^+ 2.1; 2.2...$ $\gamma 115; 61; 153;$ $752...$	Ga 66 9.4 h $\beta^+ 4.2...$ $\gamma 1040; 176...$ $\gamma 4296...$	Ga 67 78.3 h ϵ $\beta^+ no \beta^+$ $\gamma 95; 185; 300...$	Ga 68 67.63 m $\beta^+ 1.9...$ ϵ $\gamma 1077; 1533...$	Ga 69 60.108 $\beta^+ 1.7...$ ϵ $\gamma 1040; 176...$	Ga 70 21.15 m $\beta^+ 1.9...$ ϵ $\gamma 1077; 1533...$	Ga 71 39.892 $\beta^+ 1.0; 3.2...$ $\gamma 834; 2202;$ $630; 2508...$	Ga 72 14.1 h $\beta^+ 1.2; 1.5...$ $\gamma 297; 53; 326...$	Ga 73 4.86 h $\beta^+ 1.2...$ $\gamma 534; 2202;$ $630; 2508...$	Ga 74 9.5 s $\beta^+ 2.1; 2.5...$ $\gamma 499; 596...$	Ga 75 2.1 m $\beta^+ 3.3...$ $\gamma 253; 575...$	Ga 76 32.6 s $\beta^+ 5.9...$ $\gamma 563; 546;$ $1108...$	Ga 77 13 s $\beta^+ 5.2...$ $\gamma 469; 459...$		
57 ms	Zn 58 84 ms $\beta^+ 2.53;$ $\gamma 491; 914$	Zn 59 182 ms $\beta^+ 2.5; 3.1...$ $\gamma 670; 61; 273;$ $334...$	Zn 60 2.4 m $\beta^+ 4.4...$ $\gamma 475; 1660;$ $970...$	Zn 61 1.5 m $\beta^+ 0.7...$ $\gamma 41; 597; 548;$ $508...$	Zn 62 9.13 h ϵ $\beta^+ 2.3...$ $\gamma 670; 662;$ $1412...$	Zn 63 38.1 m ϵ $\beta^+ 0.7...$ $\gamma 115...$ $\alpha 1.1-5...$ $\eta_{\alpha} < 1.2E-5$	Zn 64 48.268 ϵ $\beta^+ 0.7...$ $\gamma 1074;$ $\alpha 0.9...$ $\eta_{\alpha} < 2E-5$	Zn 65 244.3 d ϵ $\beta^+ 0.3...$ $\gamma 115...$ $\alpha 6.9...$ $\eta_{\alpha} 0.0004$	Zn 66 27.975 ϵ $\beta^+ 0.3...$ $\gamma 115...$ $\alpha 6.9...$ $\eta_{\alpha} 0.0004$	Zn 67 4.102 ϵ $\beta^+ 0.9...$ $\gamma 1072; 0.9...$ $\alpha 0.9...$ $\eta_{\alpha} < 2E-5$	Zn 68 19.024 ϵ $\beta^+ 0.9...$ $\gamma 1074;$ $\alpha 0.9...$ $\eta_{\alpha} 0.0004$	Zn 69 13.8 h ϵ $\beta^+ 0.9...$ $\gamma 1074;$ $\alpha 0.9...$ $\eta_{\alpha} 0.0004$	Zn 70 56 m ϵ $\beta^+ 0.9...$ $\gamma 1074;$ $\alpha 0.9...$ $\eta_{\alpha} 0.0004$	Zn 71 0.631 ϵ $\beta^+ 0.9...$ $\gamma 1074;$ $\alpha 0.9...$ $\eta_{\alpha} 0.0004$	Zn 72 3.9 h ϵ $\beta^+ 2.5...$ $\gamma 386;$ $\alpha 620...$	Zn 73 2.4 m ϵ $\beta^+ 2.8...$ $\gamma 512;$ $\alpha 487;$ $\eta_{\alpha} 0.0004$	Zn 74 3.9 s ϵ $\beta^+ 4.3...$ $\gamma 499; 596...$	Zn 75 96 s ϵ $\beta^+ 2.1; 2.3...$ $\gamma 49; 144;$ $193...$	Zn 76 10.2 s ϵ $\beta^+ 5.5; 5.9...$ $\gamma 229; 432;$ $156; 606...$	Zn 77 5.6 s ϵ $\beta^+ 4.0...$ $\gamma 199; 76...$ $366; 172...$	
56 ms	Cu 57 199 ms $\beta^+ 1225;$ $\gamma 1112$	Cu 58 3.20 s $\beta^+ 7.5...$ $\gamma 1454; 1448;$ $40...$	Cu 59 82 s $\beta^+ 3.8...$ $\gamma 1302; 878;$ $539; 485...$	Cu 60 23 m $\beta^+ 2.0; 3.9...$ $\gamma 1332; 1792;$ $826...$	Cu 61 3.4 h $\beta^+ 2.9...$ $\gamma 1173...$	Cu 62 9.74 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 63 69.15 ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 64 30.85 ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 65 5.1 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 66 3.0 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 67 61.27 ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 68 3.0 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 69 3.0 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 70 3.0 m ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 71 19.5 s ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 72 6.6 s ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 73 3.9 s ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 74 1.59 s ϵ $\beta^+ 0.6...$ $\gamma 1146...$	Cu 75 1.22 s ϵ $\beta^+ 0.6...$ $\gamma 185; 421;$ $724...$		
55 ms	Ni 56 6.075 d $\epsilon 2976;$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 57 36.0 h $\epsilon 4.6...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 58 68.0769 $\epsilon 1.08...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 59 7.5 - 10 ^a a $\epsilon 1.077...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 60 26.2231 $\epsilon 0.07...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 61 1.1399 $\epsilon 0.07...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 62 3.6345 $\epsilon 0.07...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 63 100 a $\epsilon 0.07...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 64 0.9256 $\epsilon 0.07...$ $\beta^+ 0.8...$ $\gamma 1378; 1920;$ $322...$	Ni 65 2.52 h $\epsilon 0.21...$ $\beta^+ 0.8...$ $\gamma 1482; 1115;$ $366...$	Ni 66 54.6 h $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 1937; 1115;$ $822...$	Ni 67 21 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 1787; 880;$ $1213; 1463$	Ni 68 29 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 1871; 880;$ $1213; 1463$	Ni 69 11.4 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 1036; 78;$ $1213; 1463$	Ni 70 6.0 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 1871; 880;$ $1213; 1463$	Ni 71 2.56 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 534; 2016;$ $876; 94$	Ni 72 1.57 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 166; 1010;$ $876; 94$	Ni 73 0.84 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 166; 694;$ $876; 94$	Ni 74 0.9 s $\epsilon 0.2...$ $\beta^+ 0.8...$ $\gamma 166; 694;$ $876; 94$		

• Cu-67 핵적 특성

$^{67}\text{Cu}(\beta^-, 61.8\text{h})$



$^{67}\text{Ga}(\text{E.C.}, 78.3\text{h})$

	^{67}Cu	^{67}Ga
Decay mode	β (100%)	E.C. (100%)
Half-life	61.83 h	78.3 h
γ -rays(keV)	(intensity, %)	(intensity, %)
91.266	7.00	3.11
93.311	16.10	38.81
184.577	48.70	21.41
208.951	0.12	2.46
300.219	0.80	16.64
393.529	0.22	4.56
494.166		0.07
887.688		0.15

- Suitable β^- emission are ideal for use with MAbs and other tumor targeting compounds
- half-life : 61.8hr
- decay mode: 100% β^- decay to ^{67}Zn
- mean β -ray energy: 141keV
- total β -ray intensity: 100%
- mean β -dose: 0.141MeV/Bq s

• Nuclear Reactions for ^{67}Cu production

Reaction	E-Range (MeV)	$E(\sigma_{\max})$ (MeV)	σ_{\max} (mb)	Yield(mCi/ μAh , @ EOB)
$^{68}\text{Zn}(\text{p},2\text{p})^{67}\text{Cu}$	30 ~ 430	>430	24.9	2.0(<100MeV)
$^{71}\text{Ga}(\text{p},3\text{p}2\text{n})^{67}\text{Cu}$	19.2 ~ 55.3	>55.3	2	
$^{67}\text{Zn}(\text{d},2\text{p})^{67}\text{Cu}$	8.1 ~ 15.4	>15.4	5.2	
$^{64}\text{Ni}(\alpha,\text{p})^{67}\text{Cu}$	12.4 ~ 20.8	15.5	15.9	0.022(<23MeV)
nat. $\text{Zn}(\text{p},2\text{p})^{67}\text{Cu}$	52.8 ~ 67.7		4.1	
$^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$	7.7 ~ 35.1	16.7	14.8	0.21(<40MeV), 0.165(<30MeV)
$^{67}\text{Zn}(\text{n},\text{p})^{67}\text{Cu}$	Neutron	22	1.07	
$^{68}\text{Zn}(\gamma,\text{p})^{67}\text{Cu}$	Bremsstrahlung		11	

• Yield calculation

$$A(dps) = 6.24 \times 10^{18} \times i \times \frac{N_a \times \rho \times Y_i}{M} (1 - e^{-\lambda t}) \int_{E_1}^{E_2} \frac{\sigma(E)}{S(E)} dE$$

A : activity(dps)

N_a : Avogadro's number

Y_i : isotopic abundance

λ : decay constant

$\sigma(E)$: cross section

E_2 : initial energy

$1 - e^{-\lambda t}$: saturation factor

i : beam current(μA)

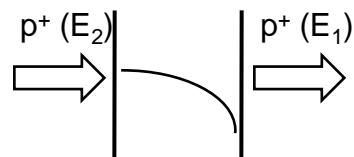
ρ : target material density

M : target material MW

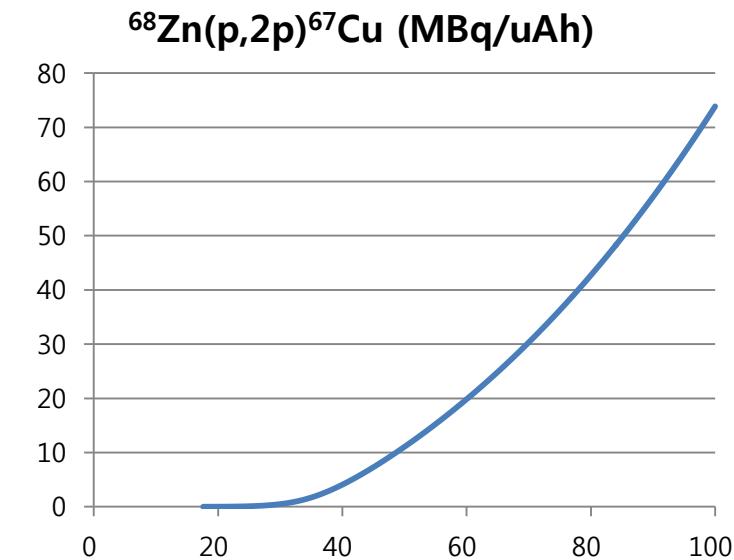
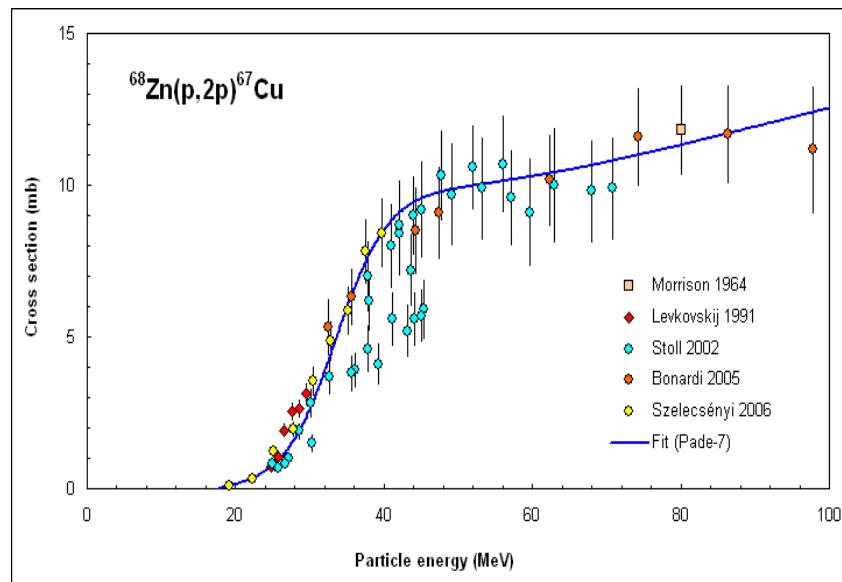
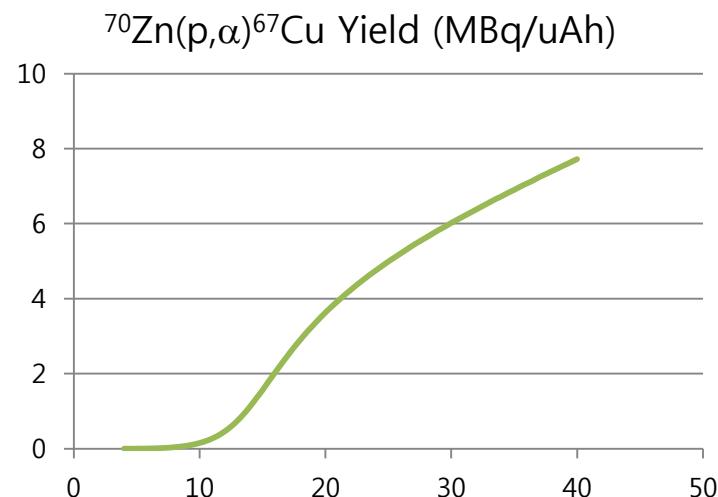
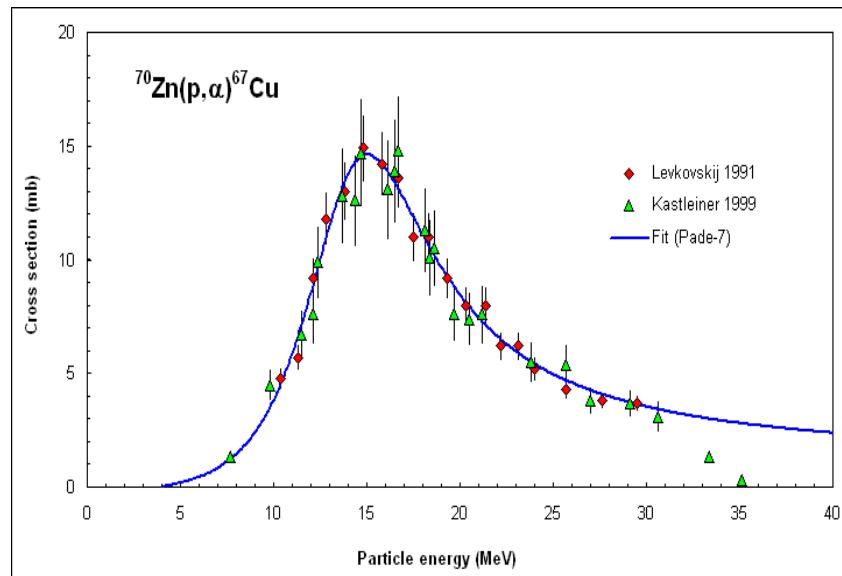
t : irradiation time

$S(E)$: stopping power

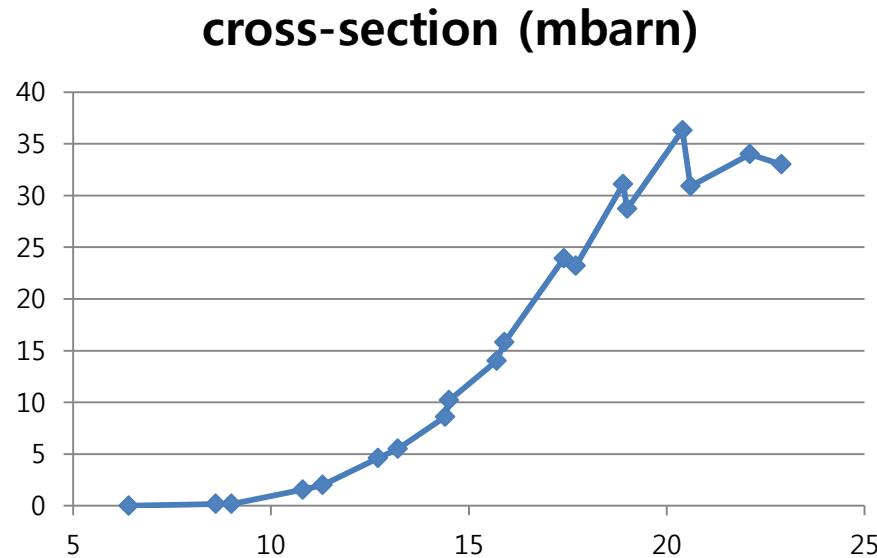
E_1 : final energy



• $^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$, $^{68}\text{Zn}(\text{p},2\text{p})^{67}\text{Cu}$ 여기함수와 누적 수율 평가 :

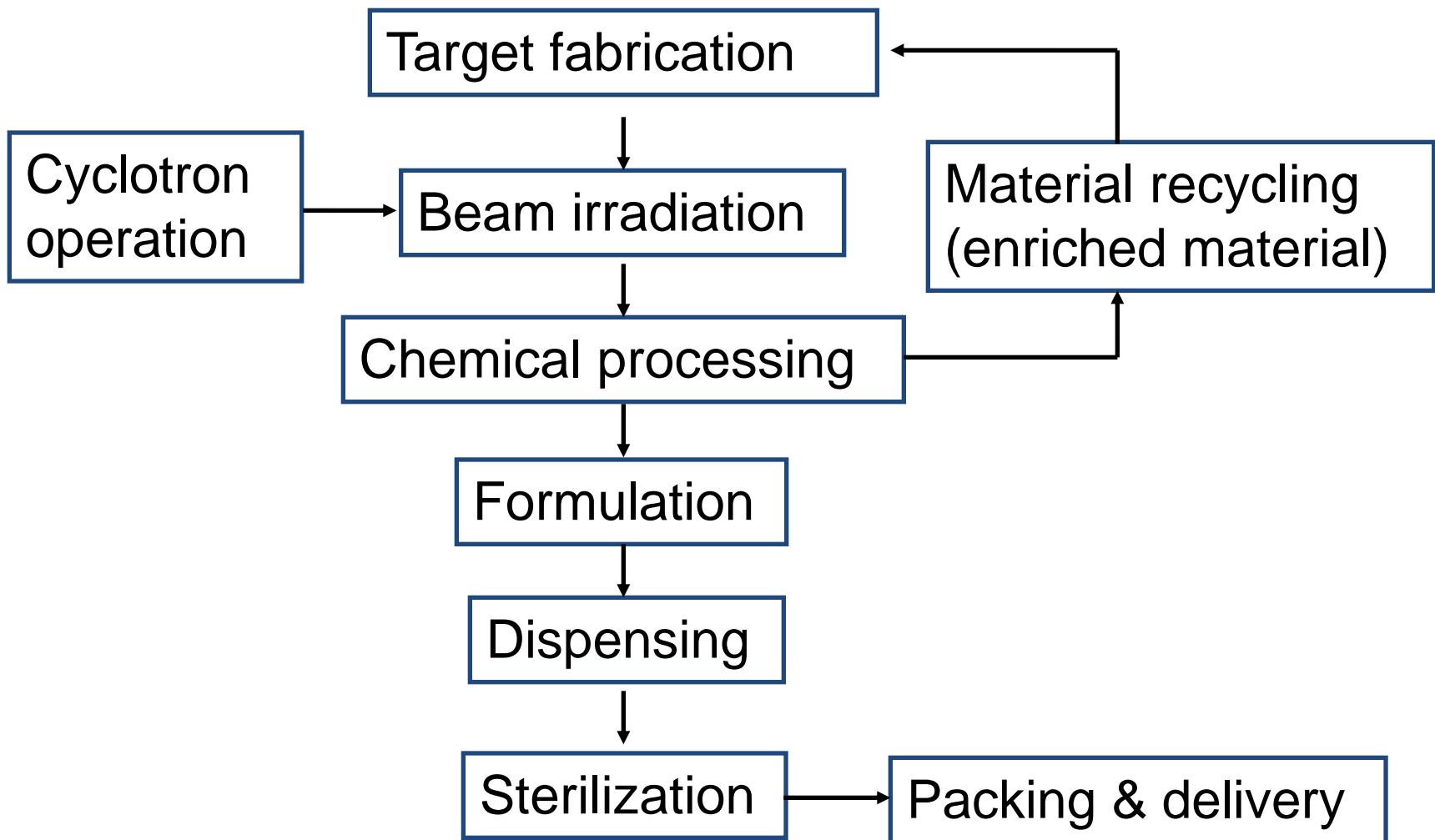


- ${}^{64}\text{Ni}(\alpha, \text{p}) {}^{67}\text{Cu}$ reaction의 cross-section



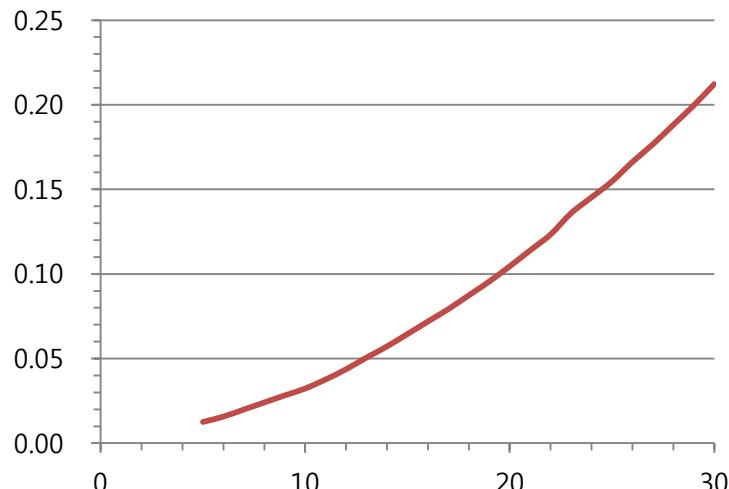
- Cross section data from National Nuclear Data Center (BNL)
- 단점: alpha particle 의 low beam current → low production yield

- Typical processing sequence of RI production



• ^{70}Zn Target System

proton range(mm) in Zn-70



Range of protons in Zn-70 target tilted 6° to the beam direction.

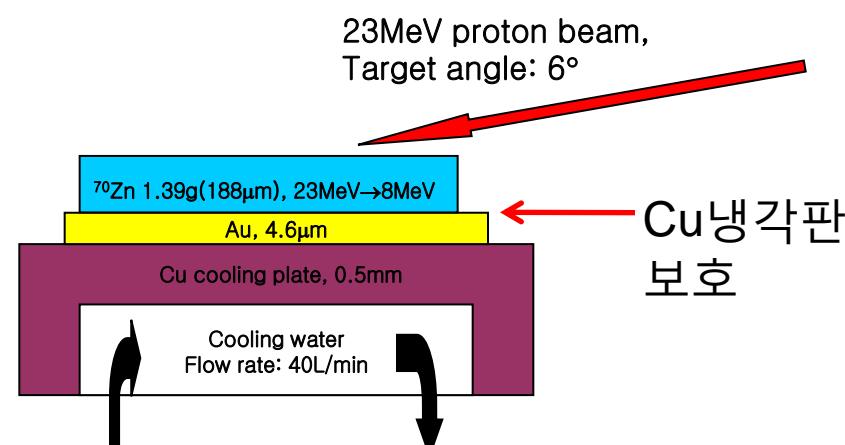
Target에 발생 열량: $\text{Watt} = \Delta E \times I$
 $(23\text{MeV} \times 200\mu\text{A} = 4.6 \text{ kwatt}/10\text{cm}^2)$

^{70}Zn 농축 표적량 계산 ($d=7.39\text{g/cm}^3$):

- Proton beam energy : $23 \rightarrow 8\text{MeV}$,
- Target thickness calculated with e-loss :
 0.114cm

^{70}Zn target weight (target angle : 6°)

$$= 0.012\text{cm} \times 10\text{cm}^2 \times 7.39\text{g/cm}^3 = 0.87\text{g}$$



^{70}Zn target assembly

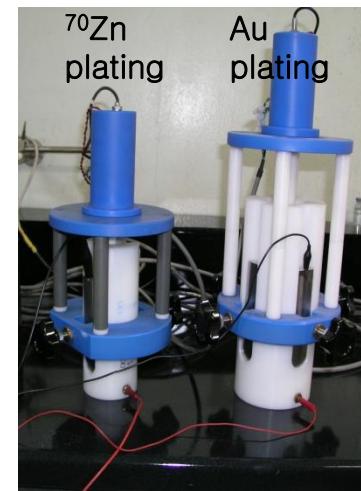
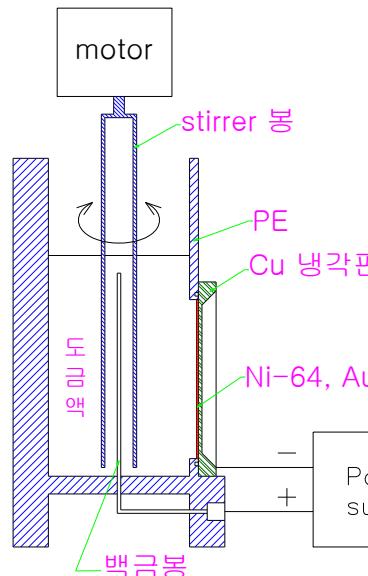
• ^{70}Zn target (Au, ^{70}Zn plating) fabrication

1) Au Plating : 0.3g $\text{KAu}(\text{CN})_2$ /3g EDTA/
2g phosphate buffer in 500mL H_2O
thickness: $\sim 8\text{mg/cm}^2$
Area: $12\text{cm}^2(1.2\text{cm} \times 10.2\text{cm})$

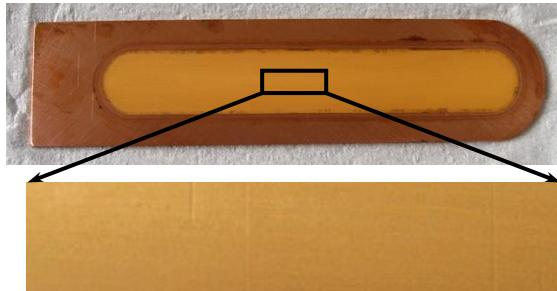
2) ^{70}Zn plating:
Electrolyte: 1.2g ^{70}Zn +0.5g boric acid+
1.0g NaCl in 80ml DM water

- Tracer: ^{65}Zn
- Current: constant 200mA on 10cm^2 target surface
- Time: 6 hr, Cathode efficiency: 71.7%
- Target thickness: 105mg/cm^2
- Recovery with cation resin

^{70}Zn electro-plating device



Au plating on Cu cooling plate



10 배 확대

^{70}Zn Target



Power supply



표적 안전성 평가를 위한 burning test (350°C heating/bending test)



- ^{70}Zn 표적 (Au, Zn plating) 제작 기술

1) Au 도금: 0.3g $\text{KAu}(\text{CN})_2$ /3g EDTA/2g KH_2PO_4 buffer in 500mL H_2O

3) Zn plating

(1) ZnCl_2 : 2g, NH_4Cl : 20g, 2ml hydrazine in 80ml H_2O
constant voltage : 1.4V, current: 100mA for 4hr
heater: 40°C, stirrer speed: 700rpm
surface: sponge, bad

(2) ZnCl_2 : 2g, boric acid: 1.5g, NaCl : 5g in 80ml H_2O
const. voltage: 3V, current: 120mA for 5hr
heater: 60°C, stirrer speed: 700rpm
surface: very good, but 630mg 도금 후 다시 녹음
pH adjustment (pH 0.5 → 3) with c-NaOH

(3) ZnCl_2 : 2g, boric acid: 1.5g, NaCl : 5g in 80ml H_2O
constant current : 100mA, voltage: 3.5 → 2.9V
pH adjustment (pH 0.5 → 3) with c-NaOH
surface: micro-crystal, not bad
Zn amount: 495mg → 441mg plating

- Isotopic abundance of the enriched ^{70}Zn target (ISOFLEX)

Isotope	^{64}Zn	^{66}Zn	^{67}Zn	^{68}Zn	^{70}Zn
Content (%)	0.054	0.047	0.005	0.361	99.533

* ^{67}Ga 계산 생산량: $0.361\% \times 8\text{mCi}/\mu\text{A}/\text{h} \times 200\mu\text{A} \times 10\text{h} = 57\text{mCi}$

- Proton beam irradiation on ^{70}Zn target



^{70}Zn target after $200\mu\text{A}$, 23 MeV
proton beam irradiation

Beam irradiation condition

- Energy: 23MeV
- Beam current: $200\mu\text{A}$
- Time: 2hr

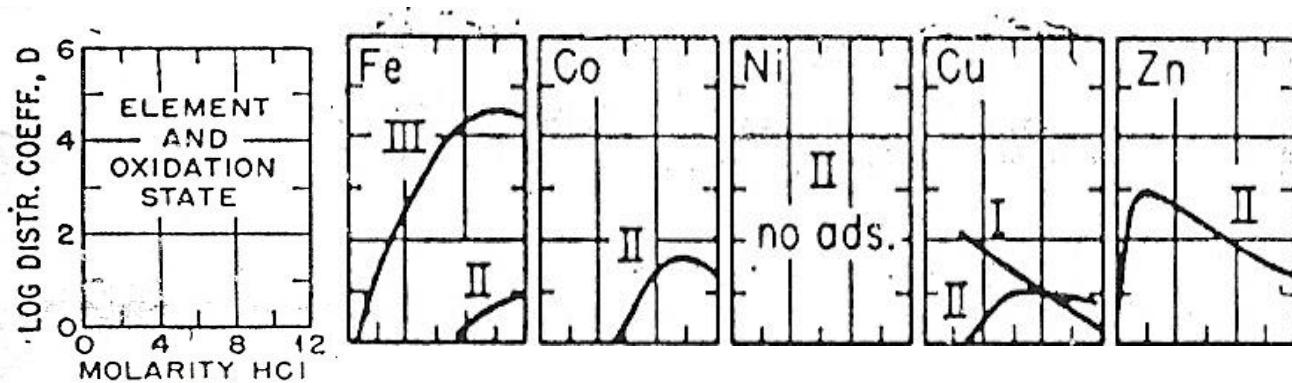
Zn의 thermal conductivity: 116W/m/k

Ni의 thermal conductivity: 90.9W/m/k

- Chemical separation :

- 1) Solvent extraction with 0.01% dithizone in CCl_4 -0.5N HCl (vol. ratio, aq:org=1:1/10)
org. phase: ^{67}Cu
Aq. phase: ^{67}Ga , ^{70}Zn 등 impurity RI

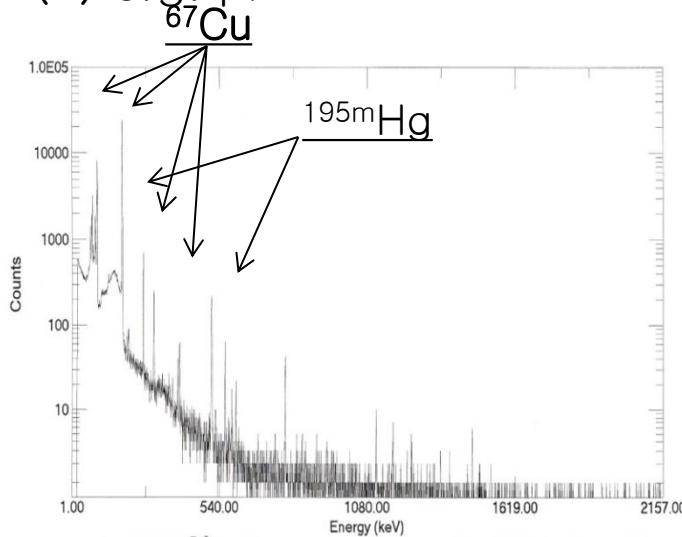
- 2) Anion resin (AG1x) 분배계수: 이동상 HCl



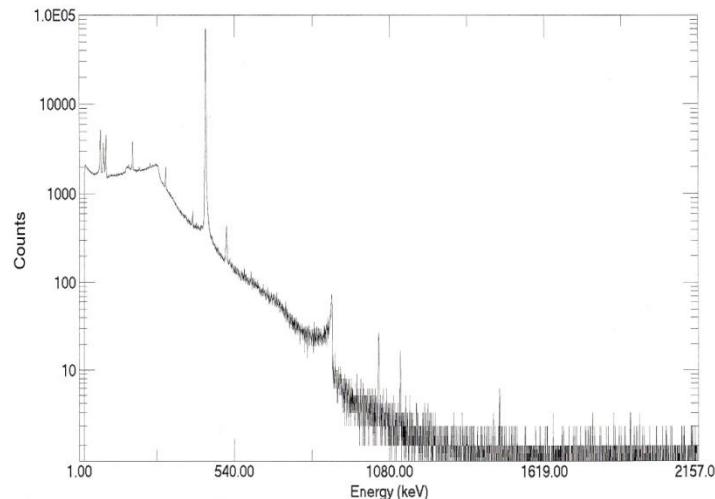
- **^{67}Cu separation from irradiated ^{70}Zn enriched target**

^{67}Cu separation from proton irradiated ^{70}Zn target
by solvent extraction (0.01% dithizone in CCl_4 – 0.5N HCl)

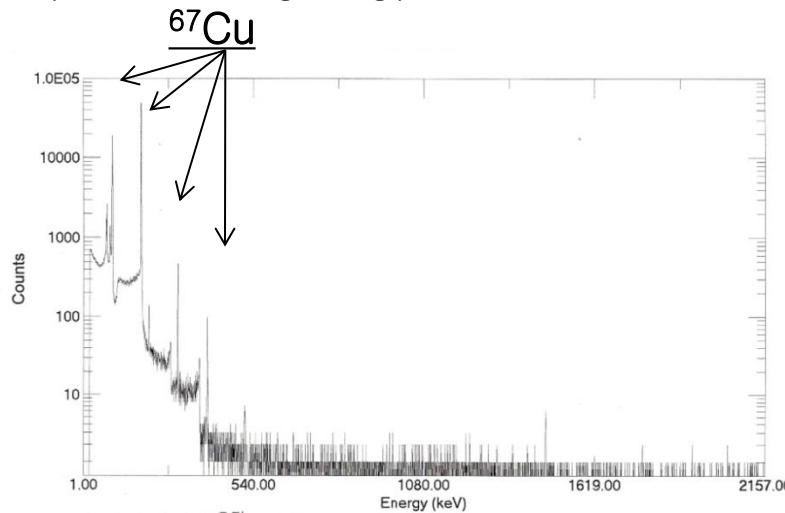
(a) org. phase



(b) aq. phase



Final ^{67}Cu solution

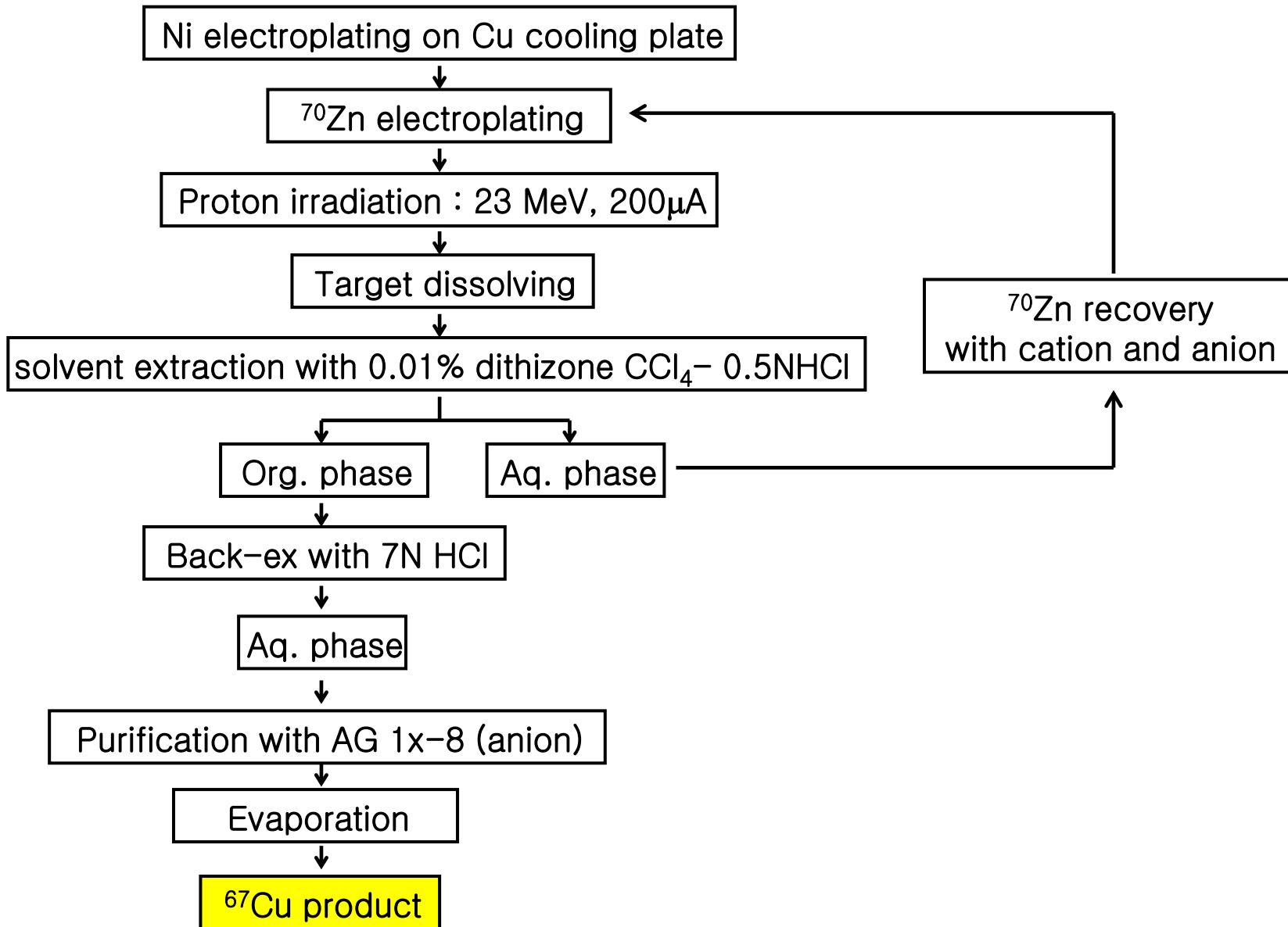


Final solution은 anion resin 후 product임.
 ^{195}mHg 는 anion으로 제거하였음.

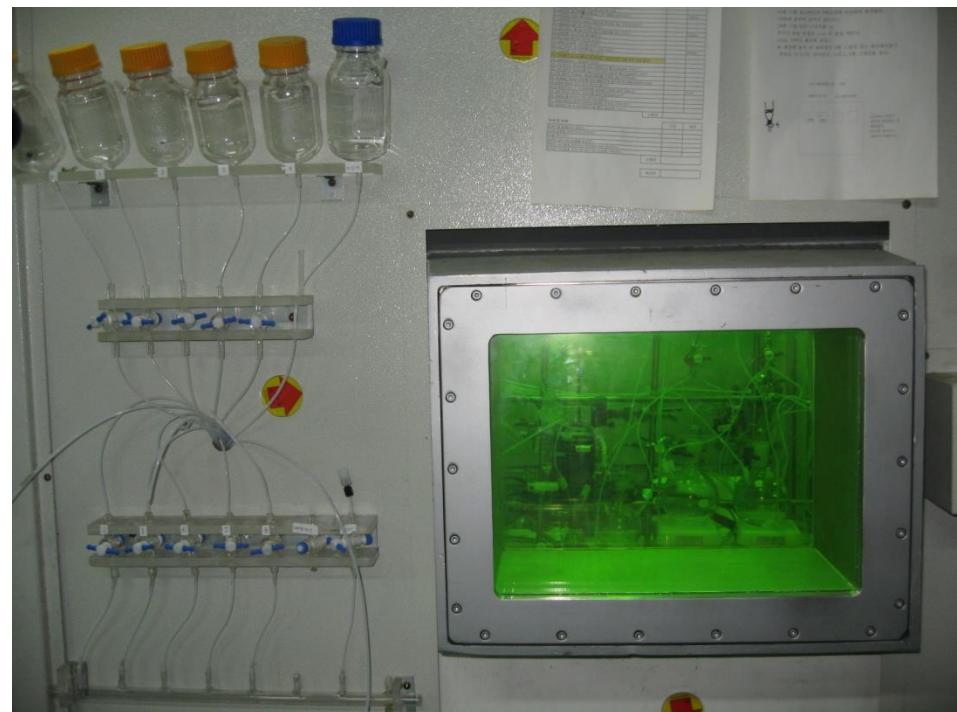
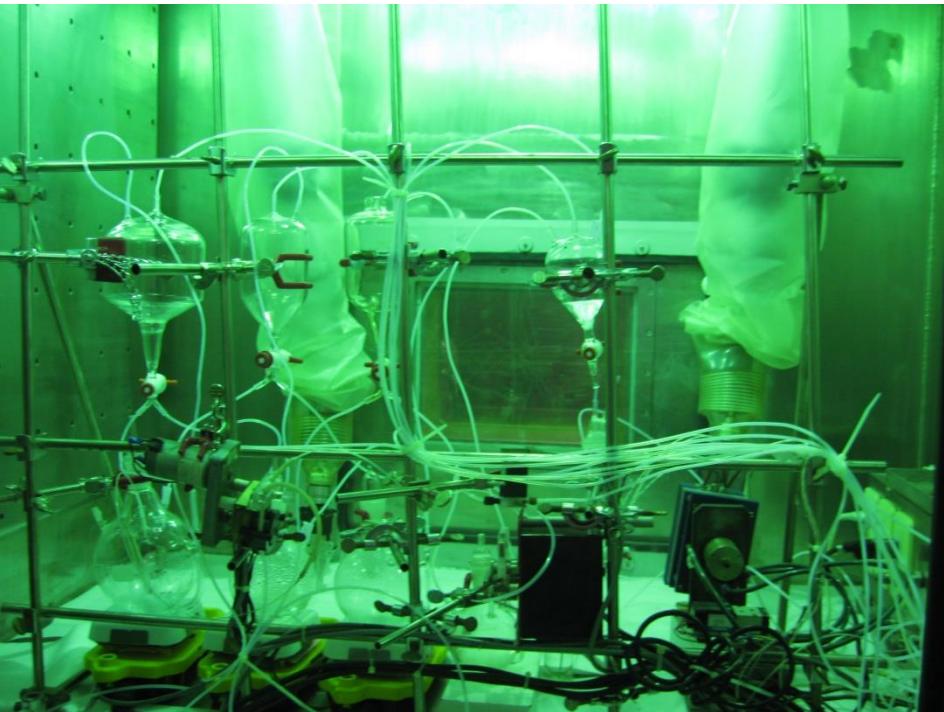
- Radionuclides in proton beam irradiated ^{70}Zn target

Nuclide	Half-life	Gamma-ray	Nuclear reaction
^{67}Cu	61.83h	91(7), 93(16.1), 184(48.7) 208(0.12), 300(0.80)	$^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$
$^{67}\text{Ga}^*$	78.28h	91(3), 93(38.8), 184(21.4), 208(2.5), 300(16.6), 393(4.6)	$^{68}\text{Zn}(\text{p},2\text{n})^{67}\text{Ga}$
^{62}Zn	9.19h	507(14.8), 548(15.3), 596(26)	$^{64}\text{Zn}(\text{p},3\text{n})^{62}\text{Ga} \rightarrow ^{62}\text{Zn}$
^{69m}Zn	13.76h	438(94.8)	$^{70}\text{Zn}(\text{p},\text{pn})^{69m}\text{Zn}$
^{195m}Hg	41.6 h	261(31), 560(7.1)	$^{197}\text{Au}(\text{p},3\text{n})^{195m}\text{Hg}$
^{195}Hg	10.53 h	585(2.04), 599(1.8), 1111(1.5)	$^{197}\text{Au}(\text{p},3\text{n})^{195m}\text{Hg}$

- Flow chart of ^{67}Cu production with ^{70}Zn enriched target



- Chemical process unit in hot-cell



- Zn target on Ni coated Cu cooling plate.
- Ni plating on Cu cooling plate.



- 200 μ A proton beam irradiation
No melting on Zn target

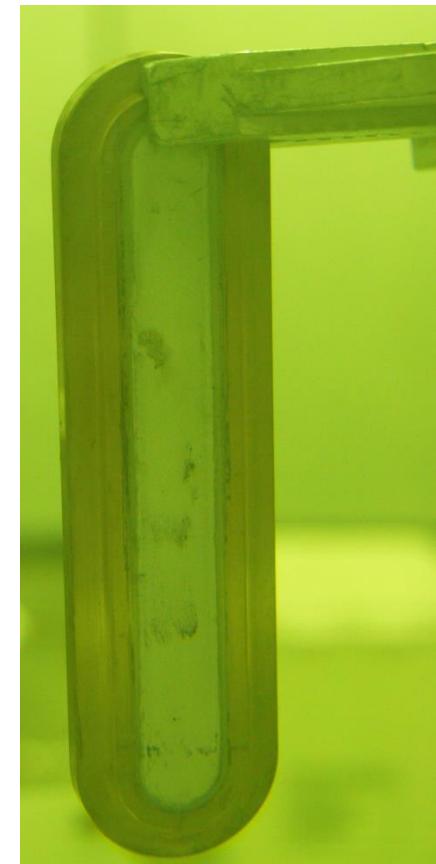
Electrolyte : NiCl_2 4.3g, boric acid 0.5g, NaCl 2g
in 500ml H_2O
200mA constant current



- Zn plating on Ni coated Cu cooling plate.



Electrolyte : ZnCl_2 4.2g, boric acid 1.0g, NaCl 1g
in 90ml H_2O
100mA constant current
200mg Zn plating



• Conclusions

- 67Cu mass production:

Cyclone-30 (<30MeV): $^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$

100MeV LINAC (>70MeV): $^{68}\text{Zn}(\text{p},2\text{p})^{67}\text{Cu} + ^{70}\text{Zn}(\text{p},\alpha)^{67}\text{Cu}$,

- 67Cu expected yields:

23MeV : 330mCi at EOB with 200 μA for 10hr irradi.

dual beam irradiation : 660mCi (= 330mCi x 2)

- 70Zn Target: Ni coated Cu plate,

no melting at 200uA proton beam irradiation

- Separation method (Solvent extra. + chromato.)

- solvent extraction: 0.01% dithizone in CCl_4-HCl

- ion chromatography: AG1x-8