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A novel method for n.c.a. ^{64}Cu production by the ^{64}Zn($d, 2p$)^{64}Cu reaction and dual ion-exchange column chromatography

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Summary. A novel production method for n.c.a. ^{64}Cu based on deuteron irradiation of ^{64}Zn is presented. The production takes place through the ^{64}Zn($d, 2p$)^{64}Cu reaction using a deuteron beam of 19.5 MeV energy on highly enriched ^{64}Zn disks. An average yield over three irradiations of 31 MBq/μA h (850 μCi/μA h) and saturation yield of 575 MBq/μA (15.5 mCi/μA) at the end of the beam (EOB) was measured by γ-ray spectrometry. Two of the three runs, of low irradiation charge, were used for radiochemistry. The copper isotopes were separated from other radionuclidic impurities by the combination of cation and anion exchange chromatography. An average radiochemical yield of 90% was estimated for the two runs performed in this study, and the specific activity as determined using flame atomic absorption spectrometry was about 4 MBq/μg, 2 hours after EOB. An extrapolation of the present results to production conditions (50 μA, 10 h) indicates approximately 8 GBq/μg (220 mCi/μg) of specific activity. The overall uncertainty in these values is estimated to 15%.

1. Introduction

Tracers labeled with copper radionuclides (*e.g.* ^{61}Cu, ^{64}Cu, ^{67}Cu) are being widely studied at present because of the wide range of their useful physical properties and well known chemistry. In particular, ^{64}Cu with its half-life $t_{1/2} =$ 12.7 h. and decay scheme, EC (44%), β^- (38%), β^+ (18%) and single 1346 keV γ line (0.54%) is a promising candidate both for long-term PET imaging and therapy [1–4]. Several hypoxia (^{64}Cu-ATSM), blood perfusion (^{64}Cu-PTSM) and cancer imaging tracers (^{64}Cu-labelled antibodies and peptides) have been already studied *in vivo* [5].

Several methods for ^{64}Cu production have been developed using nuclear reactors or cyclotrons. An overview of some methods is given in Tables 1 and 2. This should allow a wide availability to researchers, but unfortunately each production method suffers from some disadvantage. Thermal neutron capture in copper targets can produce only low specific activity ^{64}Cu; however it can be increased when the Szilard-Chalmers reaction is applied [6–9] or enriched ^{63}Cu targets are irradiated. On the other hand, high purity n.c.a. ^{64}Cu can be prepared by fast neutron irradiation of ^{nat}Zn [10]. The main disadvantage of this method is the co-production of ^{65}Zn, $t_{1/2} = 244$ days, which causes difficulties with radioactive waste disposal, when the irradiations are done on a regular basis [11]. Several production methods of ^{64}Cu have been recommended previously [12]. Practical cyclotron production methods include irradiation of nickel and zinc targets. The most effective methods of ^{64}Cu production (highest yields) with a cyclotron are based on ^{64}Ni irradiation with protons [22, 23] and deuterons [25]. Of these, the ^{64}Ni(p, n)^{64}Cu process, first suggested by the Jülich group [22], is the method of choice for large scale production of ^{64}Cu [23, 24] despite the relatively high cost of enriched target material. The advantage of the (p, n) reaction is that common small-sized production cyclotrons are sufficient to produce high yields of ^{64}Cu. Methods based on deuteron irradiation of ^{nat}Zn [13–15] are considered to be a cheap alternative for n.c.a. ^{64}Cu cyclotron production, but deuterons of higher energies (above 20 MeV) are necessary to achieve reasonable yields. Interesting results can be obtained with enriched Zn targets, for example with ^{66}Zn, where a good yield of ^{64}Cu and no other radionuclidic impurities of copper were observed [15]. High amounts of ^{64}Cu side-product, from the production of ^{66}Ga by the ^{68}Zn($p, 3n$)^{66}Ga reaction, has led to the recovery of ^{64}Cu from waste solutions [19, 20]. The disadvantage here is with the ^{67}Cu impurity, which is produced when the proton energy exceeds 40 MeV [15]. Another cyclotron method based on fast neutron iradiation of zinc in d(Be) generator, was recently reported [17].

Radiochemical methods for ^{64}Cu separation depend on the target material. Dry distillation [10], electrolysis [26], ion exchange chromagraphy and liquid-liquid extraction [13, 14] have all been applied. The ion exchange chromatography method is the most effective for ^{64}Cu separation from zinc target material and other impurities.

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Table 1. Reactor production methods of ^{64}Cu.

Reaction	^{64}Cu yield[a] [MBq/mg] of target material (A_{total})	Neutron flux [cm^{-2} s^{-1}] thermal	fast	Copper radionuclidic impurities at EOB	Reference
^{nat}Cu(n, γ)^{64}Cu	56 (14 GBq)	5×10^{13}		[b]	[8]
	0.7 (740 MBq)	8.5×10^{12}		10^{-6}% ^{60}Cu, 91% ^{66}Cu	[9]
^{nat}Zn(n, p)^{64}Cu	0.4[(b)]		5×10^{12}	[b]	[8]
	0.2 (925 MBq)		5×10^{12}	< 1% ^{67}Cu	[10]
	12.5 (9.5 GBq)		7×10^{13}	0.14% ^{67}Cu	[11]

a: yield normalised for 36 hour irradiation time;
b: not quantified.

Table 2. Cyclotron production methods of ^{64}Cu.

Reaction	^{64}Cu yield at EOB [MBq/μAh]	Beam energy [MeV]	Copper radionuclidic impurities at EOB	Reference
^{nat}Zn(d, x)^{64}Cu	5.3[a]	16	^{61}Cu[b], 0.09% ^{67}Cu	[13]
	17.3[a]	19	246% ^{61}Cu, ^{67}Cu[b]	[14]
	1.7[a,c]	13	^{61}Cu[b]	[15]
^{64}Zn(d, 2p)^{64}Cu	31[d]	19.5	498% ^{61}Cu	this work
	29[a,c]	19.5	1269% ^{61}Cu[c]	[16]
^{66}Zn(d, α)^{64}Cu	8[a,c]	14	not detected	[15]
^{66}Zn(p, 2pn)^{64}Cu	777[a,c]	70	156% ^{61}Cu	[18]
^{68}Zn(p, αn)^{64}Cu	12.2	26.5	0.5% ^{67}Cu	[19]
	36.4	29	< 0.44% ^{67}Cu	[20]
	28[a,c]	26	[b]	[15]
	67[c]	25	–	[18]
^{nat}Ni(p, n)^{64}Cu	7.4[a]	20	100% ^{61}Cu	[21]
^{64}Ni(p, n)^{64}Cu	236	12	0.4% ^{61}Cu, 10% ^{60}Cu	[22]
	185	15.5	27% ^{60}Cu, 0.35% ^{61}Cu	[23]
^{64}Ni(d, 2n)^{64}Cu	385[a]	19	0.3% ^{61}Cu	[25]

a: thick target yield;
b: not quantified;
c: calculated value;
d: based on 1346 keV peak abundance of 0.54% [3].

However it was reported that it had to be combined with an additional separation method for Ga removal [13].

In this work we have used an enriched ^{64}Zn target, which was considered to be a promising option for the elimination of Ga impurity production, and for a higher ^{64}Cu yield in comparison with ^{nat}Zn irradiations [16]. Also a novel separation technique for ^{64}Cu purification was developed for our purposes.

2. Experimental

Before the ^{64}Zn experiments, several ^{nat}Zn targets were irradiated for optimization of the experimental set-up and radiochemistry procedures. The irradiations of ^{nat}Zn were based on previously published data [14, 16].

The measurement of the activities of the different radioisotopes produced was made with γ-ray spectrometry based on a HPGe detector system (EG&G Ortec, USA). Stopping powers and ion ranges in Zn and Ti foils were calculated using the SRIM computer code [29]. Radiochemical separations were performed in a well ventilated glove-box. The enriched target material consisted of ^{64}Zn foils of 99.4% enrichment and a purity of 99.98% with max. 0.003% of Cu impurity (Isoflex, USA). The foils used were of thickness 320 μm or 325 μm. The natural target material was ^{nat}Zn 99.98% and ^{nat}Ti 99.6% for monitor foils (Goodfellow, UK). The isotopic composition of the Zn targets is summarized in Table 3. Foils, together with a 30 μm ^{nat}Ti monitor were placed in a standard aluminium target holder and fixed with a 0.7 cm diameter aluminium collimator. The irradiations were performed on the Scanditronix MC-40 cyclotron of the Joint Research Centre (Ispra, Italy) with a deuteron beam at the maximum available energy of 19.5 MeV on an external beam line equipped with a water cooling loop.

Table 3. Isotopic composition of target material.

Isotopic composition [%]	^{64}Zn	^{66}Zn	^{67}Zn	^{68}Zn	^{70}Zn
^{nat}Zn target[a]	48.6	27.9	4.1	18.8	0.6
^{64}Zn target (certificate)	99.4	0.39	0.04	0.15	0.02

a: data taken from [4].

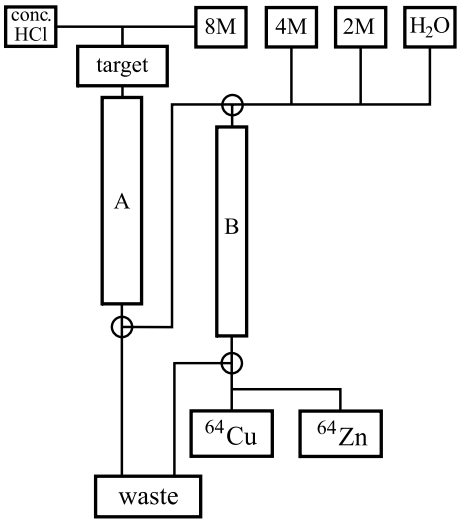

Fig. 1. Schematic drawing of the separation apparatus: A: cation exchanger column, B: anion exchanger column.

Consecutive dual ion-exchange chromatography, with a combination of strong cation and strong anion exchanger using gradient elution with 8 M, 4 M, 2 M HCl and distilled water has been applied for ^{64}Cu separation, following previously published papers [27, 28]. The possibility of automation of the separation procedure for large-scale production of ^{64}Cu was the main reason for the selection of this method. A schematic diagram of the separation apparatus is shown in Fig. 1. Dowex®-1 × 8, Dowex®-50 × 8 resins (Fluka, Switzerland), 37% fuming analytical grade HCl of 0.02 mg/kg of Cu, (Fluka, Switzerland), and disposable columns (Sigma-Aldrich, Italy) were used without further purification. 5 g of dry Dowex®-1 × 8 and 6 g of Dowex®-50 × 8 resin were preconditioned with a small amount of 8 M HCl (approx. 20 ml each). The acid was decanted subsequently, together with small amount of small-sized resin particles fraction. Dowex®-1 resin was loaded on ∅ 0.7 × 10 cm and Dowex®-50 on ∅ 1 × 10 cm Luer-Lock® ended disposable columns. The resins were washed with an additional 50 ml of 8 M HCl after column packing. Zn targets were processed 3–4 hours after EOB to allow short-lived isotopes to decay and to reduce the dose rate. The irradiated foil was transferred to a Teflon® beaker and dissolved in 1 ml of concentrated HCl. Less concentrated acid can be also used (8 M HCl), however the target weight has to be taken into account, to avoid undesired volume increase and pH shift. The solution was loaded on the cation exchanger, which served for ^{66}Ga and ^{67}Ga impurity removal in the environment of 8 M HCl. Copper and zinc were eluted in first few fractions (total volume approx. 12 ml) directly onto the anion exchanger column, with the Ga isotopes retained on the cation exchanger. Following this, the elution was continued on the anion exchanger column, by switching off the cation exchanger. All Cu and Zn was absorbed on the anion exchanger and fully retained, while ^{24}Na and ^{58}Co impurities were washed off with 4 M HCl (8 ml). Finally, ^{61}Cu and ^{64}Cu were eluted with 2 M HCl (12 ml). Switching the mobile phase to the water, the zinc isotopes were eluted at the final stage. The collected ^{64}Cu fractions (12 ml) were transferred to a Teflon® beaker and evaporated to dryness in a glove box. The [^{64}Cu]$CuCl_2$ was then re-dissolved in small amount of distilled water (1 ml) and analyzed with γ-spectrometry.

3. Results and discussion

The ^{64}Zn irradiation parameters and measured ^{64}Cu yields for all runs are given in Table 4. Foil thicknesses of 54% and 55% of calculated thick target value caused approximately 5% reduction in the ^{64}Cu yield, so the losses were almost insignificant. The yield values differ somewhat from each other due to different experimental conditions and uncertainties (target and monitor foil thicknesses, energy windows, beam currents, activity measurement, *etc.*). The production yields of copper isotopes and main radionuclidic impurities for the longer irradiation are summarized in Table 5. Some nuclide species were checked by half-life measurements. No Ga impurities should be produced for irradiation of a pure ^{64}Zn target, however small amounts are present

Table 4. Irradiation parameters and yields of ^{64}Cu.

Run #	Irradiation time [min]	Beam current [μA]	^{64}Zn foil		Energy window [MeV]	^{64}Cu at EOB	
			Weight [mg]	Thickness [μm]		Activity [MBq]	Yield [MBq/μAh]
1	150	0.6	128.8	325	19.5 → 12.1	57.4	40
2	30	0.5	128.8	325	19.1 → 11.5	6.4	28
3	30	0.4	84.1	320	19.5 → 12.2	4.7	26

Table 5. Production yields of main isotopes in Run 1.

Isotope	^{64}Cu	^{61}Cu	^{65}Zn	^{69m}Zn	^{66}Ga	^{67}Ga	^{24}Na	^{58}Co
Half-life[a]	12.70 h	3.33 h	244.26 d	13.76 h	9.49 h	3.26 d	14.96 h	70.82 d
Measured half-life [hours]	13.02 ± 0.33	3.36 ± 0.06	[b]	13.59 ± 0.18	9.49 ± 0.03	[b]	15.30 ± 0.27	[b]
Yield at EOB [MBq/μAh]	40	199	0.4	0.1	2.2	0.1	0.01	0.01

a: data taken from [4];
b: not measured.

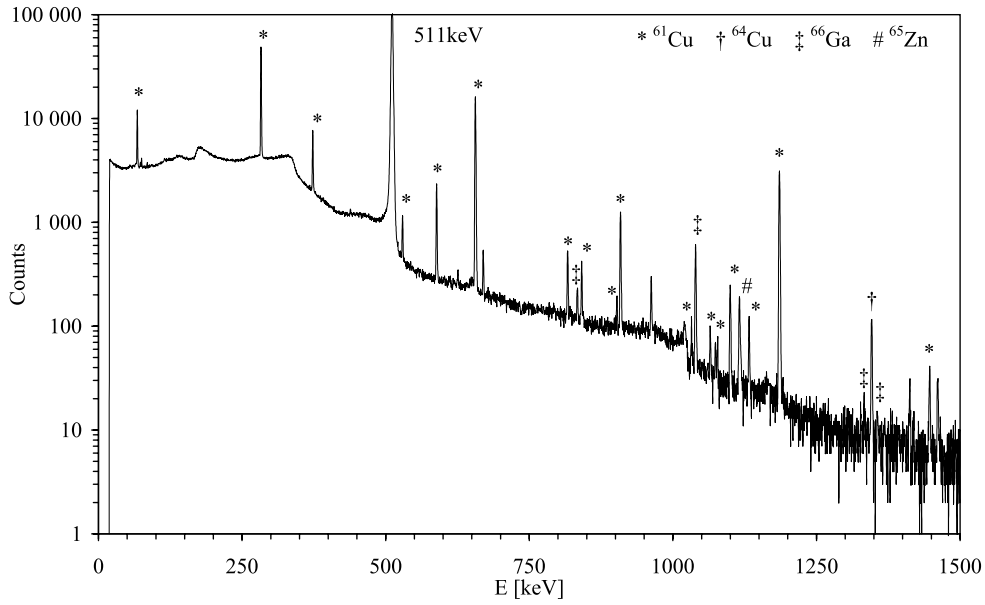

Fig. 2. Typical spectrum of an irradiated ^{64}Zn target, showing the main ^{61}Cu and ^{64}Cu peaks as well as peaks from activation products of trace nuclides and ^{64}Zn.

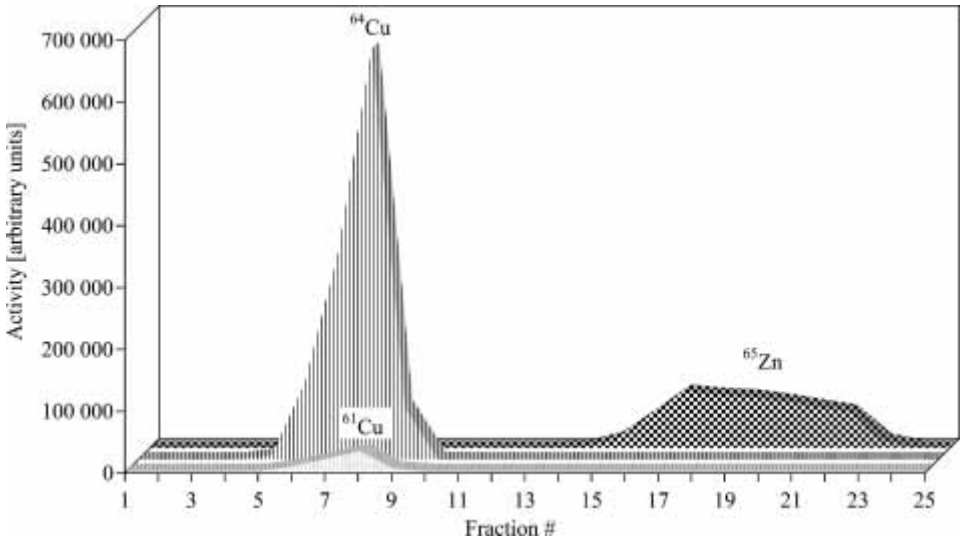

Fig. 3. Separation profile on Dowex®-1 × 8 column performed after partial decay of ^{61}Cu.

as side products resulting from (d, xn) reactions on residual ^{66}Zn and ^{68}Zn present in the target material, as shown in Fig. 2. The origin of ^{24}Na and ^{58}Co contaminants can be explained by the ^{27}Al$(d, x)^{24}$Na side reaction on the target holder and the ^{nat}Fe$(d, xn)^{58}$Co reaction on Fe trace impurity, respectively.

The irradiated target foil dissolution was a fast (usually < 1 min.) exothermic reaction. To avoid activity losses, the only manual liquid transfer step was the loading of the target solution on the cation exchanger. The Cu and Zn separation profile on Dowex®-1 resin is shown in Fig. 3. Gravitation force elution was accelerated with a small application of air-pressure. The apparatus design was sufficient to separate copper isotopes from other radionuclidic impurities both for ^{nat}Zn and ^{64}Zn targets as shown in Fig. 4. With remote controlled valves, gas pressure supply and radiation detectors, the apparatus could serve for large scale ^{64}Cu production. The ^{64}Cu separation yields, corrected for decay were 81% and 98% respectively, for the radiochemical separations performed with ^{64}Zn. Enriched target material can be recycled after the chromatographic separation of the ^{64}Cu. Measurement of ^{65}Zn contaminant activity makes the monitoring of the ^{64}Zn recovery easy and reliable. The recovery of $^{64}ZnCl_2$ was greater than 95% (determined radiometrically as ^{65}Zn). Collected solution was not processed at time; however after further processing ^{64}ZnO may be recovered [30] and directly irradiated or may serve as source material for ^{64}Zn electrodeposition.

The specific activity of ^{64}Cu was determined by the measurement of copper content by flame atomic absorption spectrometry (Varian, SpectrAA 280ET) and corresponds with our estimation. The copper concentration in the collected solution ($V = 12$ mL, fractions No. 5–10) was of order of 0.1 mg/L. Therefore the specific activity of ^{64}Cu in runs 2 and 3 is estimated to be about 4 MBq/μg, 2 hours after the EOB. Because only short irradiations were performed and standard analytical grade chemicals were used, the specific activity could be increased. The essential limiting factor is the Cu impurity, which comes from the target material. An average yield over three irradiations of 31 MBq/μA h (850 μCi/μA h) was determined at EOB.

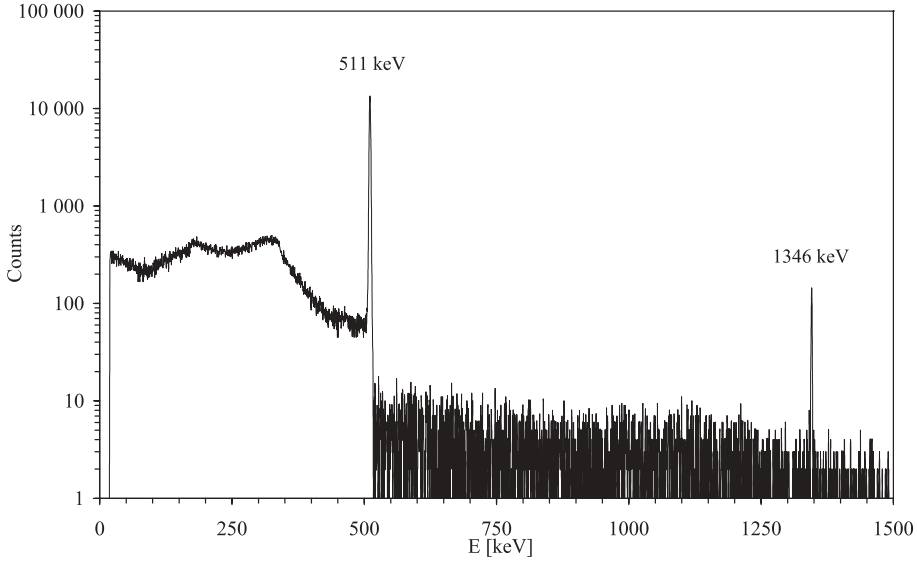

Fig. 4. Spectrum of pure ^{64}Cu fraction (after decay of ^{61}Cu), produced by the irradiation of ^{64}Zn.

4. Conclusion

We have developed a novel technique for ^{64}Cu production, based on the ^{64}Zn(d, 2p)^{64}Cu reaction. Separation of copper isotopes from ^{64}Zn target material and radionuclidic impurities based on cation and subsequent anion exchange separation was demonstrated, and may be applied also for ^{nat}Zn target processing. This method is reliable and suitable for automatization after small modifications. In comparison with the ^{nat}Zn production method, the ^{64}Zn irradiation yields more ^{64}Cu with a higher amount of the shorter half-life ^{61}Cu impurity. No other radionuclidic impurities were detected in the final product. ^{61}Cu impurity may be acceptable to enhance PET in early scans for multiple imaging. A disadvantage of the ^{64}Zn irradiation method may be in target recovery, where the long-lived ^{65}Zn is accumulated. Based on an average measured yield value of 31 MBq/μA h a production irradiation at specified conditions (50 μA, 10 hours, thick ^{64}Zn target) can be roughly estimated to produce about 12 ± 3 GBq (320 ± 80 mCi) of ^{64}Cu at the EOB, which would yield after 2 hours of radiochemical processing about 10 GBq (270 mCi) of ^{64}Cu of a specific activity of 8 GBq/μg (220 mCi/μg), this being sufficient for labeling studies and medical applications. Of course this extrapolated value would need to be ascertained experimentally under appropriate conditions. In 24 hours the ^{64}Cu activity decreases to 25% and the ^{61}Cu impurity content in the final product to less than 15%.

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