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Cross-section measurement for an optimized ^{61}Cu production at an 18 MeV medical cyclotron from natural Zn and enriched ^{64}Zn solid targets

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ABSTRACT

The availability of novel medical radionuclides is a key point in the development of personalised nuclear medicine. In particular, copper radioisotopes are attracting considerable interest as they can be used to label various molecules of medical interest, such as proteins and peptides, and offer two of the most promising true theranostic pairs, namely ^{61}Cu/^{67}Cu and ^{64}Cu/^{67}Cu. Although ^{64}Cu ($t_{1/2}$ = 12.7006 h, β^+: 17.6%, β^-: 38.5%) is nowadays the most commonly used as a diagnostic radionuclide, ^{61}Cu ($t_{1/2}$ = 3.339 h, β^+: 61%) features more favourable nuclear properties, such as a higher positron decay fraction and the absence of β^- emissions. To date, the production of ^{61}Cu has been carried out irradiating highly enriched ^{61}Ni targets with a low energy proton beam. However, the use of the very expensive ^{61}Ni targets requires an efficient recovery of the target material and makes this method quite inconvenient. Another promising production route is the proton irradiation of natural Zn or enriched ^{64}Zn targets, exploiting the (p,α) nuclear reaction. Along this line, a research program is ongoing at the Bern medical cyclotron, equipped with an external beam transfer line and a solid target station. In this paper, we report on cross-section measurements of the ^{64}Zn(p,α)^{61}Cu nuclear reaction using natural Zn and enriched ^{64}Zn material, which served as the basis to perform optimized ^{61}Cu production tests with solid targets.

1. Introduction

Personalised nuclear medicine is based on the use of diagnostic techniques and therapeutic strategies that take into account the variability of the individual patient. In this framework, theranostics plays a key role as it combines the diagnostic and therapeutic aspects by means of a single radiopharmaceutical. Molecules of biomedical interest are labeled with diagnostic (β^+ or γ emitters) and therapeutic (α, β^- or Auger emitters) radionuclides with identical or very similar chemical characteristics. In this way, one isotope is used to visualise the distribution of the labeled compound, and the acquired data allow to tune the dose deposition imparted by the second isotope. The availability of novel medical radionuclides is therefore instrumental for the development of personalised nuclear medicine.

In this context, copper is attracting increasing interest as it offers an almost unique selection of radionuclides for imaging (^{60}Cu, ^{61}Cu, ^{62}Cu and ^{64}Cu) and targeted radionuclide therapy (^{64}Cu and ^{67}Cu) (Blower et al., 1996), with a varying range of half-lives and decay modes (Table 1). In particular, it provides two of the most interesting true theranostic pairs, namely ^{61}Cu/^{67}Cu and ^{64}Cu/^{67}Cu. Finally, the well-established chemistry of copper allows copper radionuclides to be linked to antibodies, proteins, peptides and other biologically relevant small molecules (Wadas et al., 2007). Among the positron emitting copper radioisotopes, ^{61}Cu is of particular interest because of its desiderable nuclear properties. With a half-life of 3.339 h, it fills the gap between the short-lived ^{60}Cu and ^{62}Cu ($t_{1/2}$ = 23.7 min and $t_{1/2}$ = 9.67 min, respectively) and the ^{64}Cu ($t_{1/2}$ = 12.7 h), allowing on the one hand to reduce the loss of radioactivity during the processing procedures and on the other hand to label relatively small molecules that have fast biokinetics (Rowshanfarzad et al., 2006), such as ^{61}Cu-TETA-octreoride for imaging of tumors of the endocrine system (McCarthy et al., 1999; Tolmachev et al., 1998). Finally, contrary with respect to ^{64}Cu, ^{61}Cu has no β^- emissions, which could contribute significantly to the radiation dose to the patient (Rowshanfarzad et al., 2006).

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Table 1
Physical properties of copper radionuclides (IAEA, 2022). The values in parentheses are the uncertainties referred to the last digits of the value. BR is the branching ratio.

Radionuclide	$t_{1/2}$	Decay mode: [%]	E_γ [keV]	BR_γ [%]
^{60}Cu	23.7(4) min	ec + β^+: 100	826.4(2)	21.7(11)
^{61}Cu	3.339(8) h	ec + β^+: 100	282.956(10)	12.7(20)
^{62}Cu	9.67(3) min	ec + β^+: 100	1172.97(10)	0.342(17)
^{64}Cu	12.7006(20) h	ec + β^+: 61.5 β^-: 38.5	1345.77(6) –	0.472(4) –
^{67}Cu	61.83(12) h	β^-: 100	184.577(10)	48.7(3)

Several ^{61}Cu production methods have been reported in the literature, including α-particle irradiation of nickel (Muramatsu et al., 1978) and cobalt (Fukumura et al., 2004) targets and the irradiation of natural nickel targets with a deuterium beam (Takács et al., 1997). Cyclotron production has also been investigated via the ^{61}Ni(p,n)^{61}Cu and ^{64}Zn(p,α)^{61}Cu reactions. In the first case, the optimum energy range is between 9 and 14.7 MeV and the use of enriched ^{61}Ni targets is required. McCarthy et al. (1999) reported a ^{61}Cu yield at the End of Beam (EoB) of 281 MBq/μAh by irradiating a > 99% ^{61}Ni enriched target (5 mm in diameter, 118 μm thick) with a 14.7 MeV proton beam. However, due to the low natural isotopic abundance of ^{61}Ni (0.14%), this production method is likely to be prohibitively expensive for clinical applications. The second production route has the advantage that both enriched ^{64}Zn targets and cheap natural zinc targets can be used, as the natural isotopic abundance of ^{64}Zn is 48.6%. In the latter case, studies investigating ^{61}Cu production using solid (Rowshanfarzad et al., 2006; Asad et al., 2012) and liquid (do Carmo et al., 2017) natural zinc targets are reported in the literature.

In the framework of a research program focused on novel radionuclides for theranostics ongoing at the Bern medical cyclotron laboratory, ^{61}Cu production was investigated via proton irradiation of both natural Zn and enriched ^{64}Zn solid targets. In this paper we report on the cross-section measurement of the reaction ^{64}Zn(p,α)^{61}Cu, performed with the Beam Transfer Line (BTL) at the Bern medical cyclotron. These results were used to optimize the main parameters for the production of ^{61}Cu, by maximizing the production yield and the radionuclidic purity. On this basis, production irradiation tests from natural Zn and enriched ^{64}Zn solid targets were performed using the solid target station in operation at the Bern medical cyclotron.

2. Material and methods

The laboratory at the Bern University Hospital (Inselspital) hosts an IBA Cyclone 18/18 HC, providing proton beams at a nominal energy of 18 MeV with a current range from a few pA to 150 μA (Auger et al., 2015). The cyclotron features six liquid targets for ^{18}F routine production, an IBA Nirta Solid Target Station (STS) and a 6-m-long BTL (Braccini, 2013) that transports the beam to a second bunker with independent access. The BTL is equipped with several beam diagnostic systems. The beam extracted to the BTL has a mean energy of (18.3 ± 0.3) MeV with a Root Mean Square (RMS) of (0.4 ± 0.2) MeV (Nesteruk et al., 2018; Häffner et al., 2019). Although uncommon for a hospital-based facility, this solution allows performing both multi-disciplinary research activities and ^{18}F-labeled PET tracer routine production, performed by the spin-off company SWAN Isotopen AG. In particular, the BTL was used for the cross-section measurements carried out in this paper.

The STS was conceived to irradiate solid materials electroplated on a metallic disk (24 mm in diameter and 2 mm thick). To avoid overheating during the irradiation, the face of the disk hit by the beam is helium-cooled, while the back part is water-cooled.

To irradiate compressed powder pellets or solid foils, our group developed a special magnetic "coin" consisting of two aluminum halves, the lid and the cup, held together by small permanent magnets (Fig. 1).

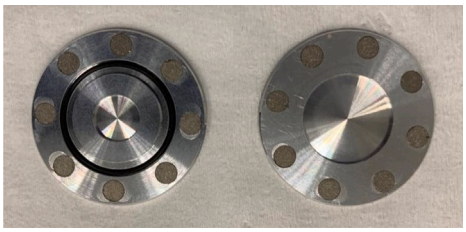

Fig. 1. The cup (left) and the lid (right) of the coin target (24 mm diameter, 2 mm thickness). The cup contains the pocket for the target and the O-ring.

Table 2
Isotopic abundance of natural Zn and of the enriched ^{64}Zn materials used in this study. (A) Metallic zinc powder by TRACE Sciences International (www.tracesciences.com) and (B) metallic zinc powder by Isoflex (http://www.isoflex.com/). The values in brackets are the uncertainties referred to the last digits of the value.

	^{64}Zn	^{66}Zn	^{67}Zn	^{68}Zn	^{70}Zn
Natural [%]	49.17	27.73	4.04	18.45	0.61
64-enr. (A) [%]	99.40(10)	0.39	0.04	0.17	0.01
64-enr. (B) [%]	99.71(10)	0.23	0.025	0.03	0.005

The cup hosts the 6-mm-diameter target and an O-ring to prevent the possible leakage of molten material or any gas produced during the irradiation. The thickness of the lid can be adjusted to set the optimal energy of the protons reaching the target material, as described later in detail. With this method, several radionuclides have been produced (Dellepiane et al., 2021), in particular ^{44}Sc (van der Meulen et al., 2020), ^{68}Ga (Braccini et al., 2022) and ^{155}Tb (Favaretto et al., 2021; Dellepiane et al., 2022a).

The STS was customized by our group to minimize the dose to the personnel. A mechanical transfer system (named Hyperloop) (Dellepiane et al., 2022b) was developed and installed to load the station without entering the cyclotron bunker. Moreover, the STS is equipped with a pneumatic solid target transfer system (STTS) by TEMA Sinergie to deliver a shuttle containing the irradiated target either to one hot-cell in the nearby GMP radio-pharmacy or to a receiving station located in the BTL bunker. The latter option is used when the target has to be transported to external research laboratories for chemical processing or transferred to the physics laboratory of the facility to assess its activity by gamma spectrometry. For this purpose, a N-type high-purity germanium (HPGe) detector featuring the Genie2K analysis software and the Microsoft Excel application Excel2Genie is used (Forgács et al., 2014). The detector efficiency at different distances was assessed using a multi-peak γ source, whose activity is known with an overall uncertainty below 1%. The production of ^{61}Cu was studied by irradiating both natural Zn and enriched ^{64}Zn powder, whose isotopic compositions are reported in Table 2. The γ-lines used to identify the activated copper isotopes are reported in Table 1.

2.1. Cross section measurements

The experimental procedure used in this work was the same as in previous studies on cross-section measurements (Braccini et al., 2022; Dellepiane et al., 2022a; Carzaniga and Braccini, 2019) and it is described in detail in Carzaniga et al. (2017). This method is based on the irradiation of the full mass of a thin target by a proton beam with a constant surface distribution and has the advantage that it does not require a uniform thickness for the target, provided that the energy of the protons can be considered constant within the mass of the target.

The beam is flattened by the optical elements of the BTL and monitored online by means of the UniBEaM detector (Auger et al., 2016; Potkins et al., 2017). This detector is based on silica-doped fibers passing through the beam and allows for two dimensional beam profile measurements.

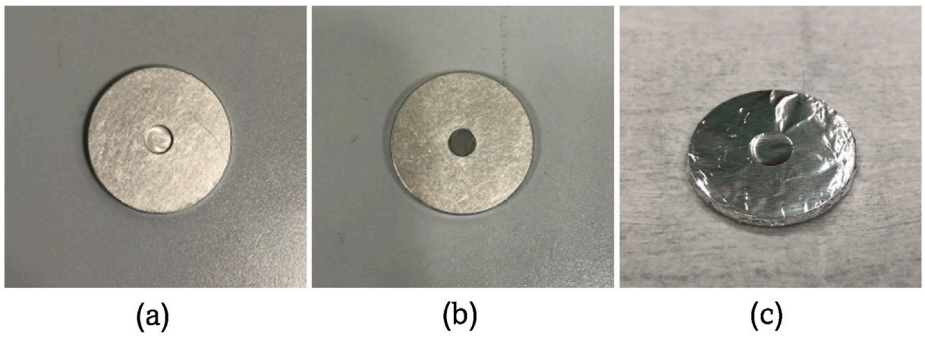

Fig. 2. Preparation procedure of targets for cross-section measurements: (a) aluminum disk with the pocket housing the target material; (b) aluminum disk filled with zinc metallic powder; (c) aluminum disk covered with a 13 μm thick aluminum foil.

To measure the beam current hitting the target material, a custom target station connected to a Keysight B2985A electrometer was designed and built. The station is also connected to a negative bias voltage in order to repel secondary electrons produced during the irradiation, that would lead to an artificial increase in the measured beam current, and provides a beam of controlled diameter by means of a collimator. To perform irradiations below 18 MeV, the beam energy was degraded by means of aluminum attenuators disks placed in front of the target and was determined using the SRIM-2013 Monte Carlo code (Ziegler and Manoyan, 2013).

After each irradiation, the produced activity was measured by gamma spectrometry with the HPGe detector.

For the cross-section measurements, several targets were prepared by the deposition method. About 1.5 mg of natural Zn and enriched ^{64}Zn (marked as (A) in Table 2) powder were suspended in distilled water and deposited in a 4.2-mm-diameter pocket of an aluminum disk (Fig. 2(a): 22.8 mm in diameter, 2 mm thick), as shown in Fig. 2(b). Once the water had completely evaporated by means of a heating plate, the deposited mass was measured with an analytical balance (Mettler Toledo AX26 DeltaRange) with a sensitivity of 2 μg and a reproducibility of 4 μg. To guarantee that the material is kept within the pocket throughout the irradiation and measurement procedure, the targets were then sealed with a 13 μm thick aluminum foil (Fig. 2(c)). With this procedure, target thicknesses of about 15 μm were achieved and the beam energy could be considered constant within the uncertainties over the full irradiated mass in all measurements. Each target was used in only one irradiation.

2.2. ^{61}Cu production tests

Production tests were performed with the STS in order to investigate the capability of producing ^{61}Cu with medical cyclotrons from solid targets in view of clinical theranostic applications. Disk-shaped pellets (6 mm in diameter, 0.3 mm thick) were prepared by compressing approximately 80 mg and 40 mg of natural Zn and enriched ^{64}Zn powder (isotopic composition marked as (B) in Table 2), respectively, and inserted in the coin pocket (Fig. 3(a)). The density of the pressed material was calculated by precisely measuring the mass and thickness of each pellet and was found to be (5.85 ± 0.01) g cm^{-3} and (5.12 ± 0.01) g cm^{-3} for the natural Zn and the enriched ^{64}Zn pellet, respectively. These values were used in all calculations and SRIM simulations.

To optimize the production yield and the radionuclidic purity, a lid with a 7-mm-diameter hole (Fig. 3(b)) was used in some production tests in order not to degrade the beam energy. In this case, a 13-μm-thick aluminum foil was placed inside the coin to prevent the target material from escaping during the irradiation (Fig. 3(c)).

Beam current measurements were performed throughout each irradiation by connecting the body of the STS to a Keysight B2985A electrometer. The effective current hitting the 6-mm-diameter pellet was assessed by measuring the 2D beam profiles with radiochromic films (Casolaro, 2021) and was known within an uncertainty of 10%.

3. Results

3.1. Cross-section measurements

Both natural Zn and enriched ^{64}Zn (isotopic composition marked as (A) in Table 2) samples were irradiated for an average of 10 min with currents of about 7 nA. The produced activity was assessed by means of the HPGe detector. In order to investigate the ^{64}Cu production from natural Zn, a second series of measurements was carried out. The targets were irradiated for about 20 min at about 7 nA and their activity measured for several days to optimize the detection of the only low-intensity γ-ray emitted by ^{64}Cu (Table 1). In all measurements, the dead time was below 1%.

The results of the ^{64}Zn(p,α)^{61}Cu nuclear reaction cross-section measurements obtained with the two materials are presented in Fig. 4; for completeness, the numerical values are reported in the Appendix (Table A.5). Our measurements are in good agreement with the data available in the literature (Szelecsényi et al., 2005; Uddin et al., 2007; Asad et al., 2014). TENDL (Koning and Rochman, 2012) predictions reproduce well our data for energies below 8 MeV, while at higher energies some discrepancies are observed.

^{64}Cu is the main impurity that is produced by irradiating a natural Zn target. It is obtained from ^{67}Zn and ^{68}Zn via the reactions ^{67}Zn(p,α)^{64}Cu and ^{68}Zn(p,αn)^{64}Zn, respectively. Having a longer half-life than ^{61}Cu, ^{64}Cu cannot be removed from the sample by exploiting the decay time. However, the use of the enriched ^{64}Zn material makes the production of ^{64}Cu negligible. The production cross section measured from natural Zn targets is reported in Fig. 5. For completeness, the numerical values are reported in the Appendix (Table A.6). TENDL predictions are in good agreement with our data; to the best of our knowledge, no data are available in the literature for this process in the energy range of interest.

For energies above 17.5 MeV, ^{60}Cu is produced from ^{64}Zn via the ^{64}Zn(p,αn)^{60}Cu reaction. Although its production cannot be avoided by using enriched ^{64}Zn material, ^{60}Cu has a short half-life and can be removed from the sample after a few hours. The results of the ^{64}Zn(p,αn)^{60}Cu nuclear cross-section measurements obtained from the two materials are presented in Fig. 6; for completeness, the numerical values are reported in the Appendix (Table A.7). Our measurements are in good agreement with the few data available in the literature in the energy range of interest (Cohen et al., 1954) and are well described by TENDL predictions.

According to TENDL-2021, ^{62}Cu should also be produced irradiating natural Zn targets with protons at energies higher than 16 MeV. However, due to the low activity produced and the low intensity of the γ-emissions, it was not possible to detect ^{62}Cu in this experiment.

The main experimental uncertainty in the ^{64}Zn(p,α)^{61}Cu cross-section measurements was due to the branching ratio of the 283 keV γ-line (~16%). For the reactions ^{nat}Zn(p,x)^{64}Cu and ^{64}Zn(p,αn)^{60}Cu the main experimental uncertainty was due to the statistical error of the

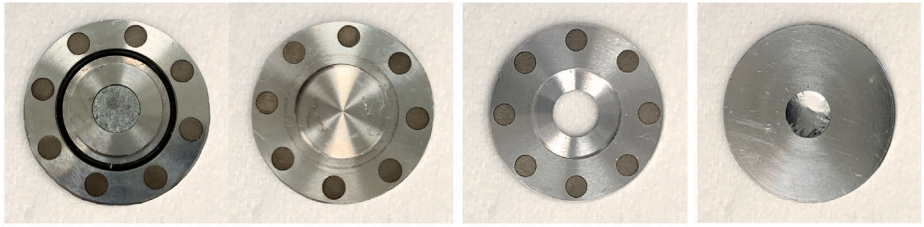

Fig. 3. (a) The cup (left) and the lid (right) of the coin target containing the 6-mm-diameter pellet; (b) lid with a 7-mm-diameter hole; (c) 13 μm-thick aluminum foil inserted in the coin to prevent the pellet from escaping during the irradiation.

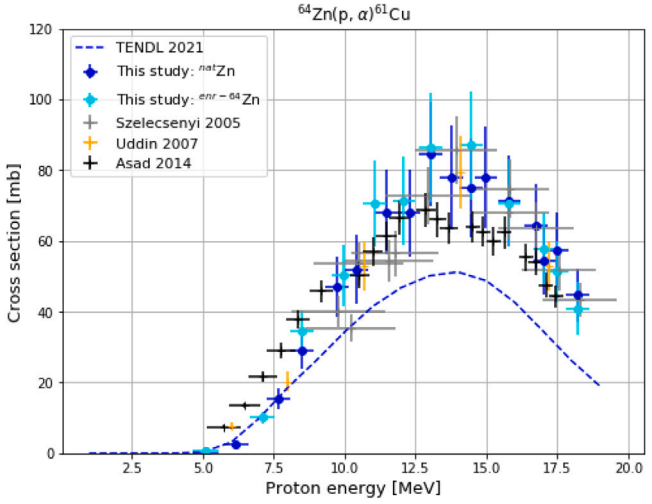

Fig. 4. ^{64}Zn(p,α)^{61}Cu cross section measured from natural and enriched ^{64}Zn targets with the isotopic composition marked as (A) in Table 2.

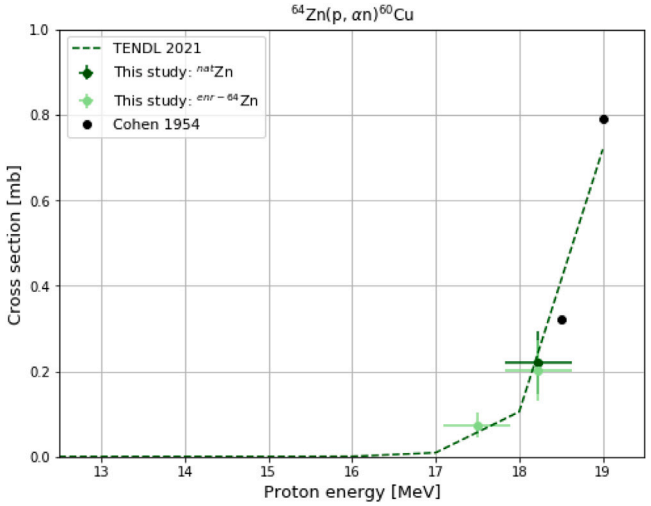

Fig. 6. ^{64}Zn(p,αn)^{60}Cu cross section measured from natural and enriched ^{64}Zn targets with the isotopic composition marked as (A) in Table 2.

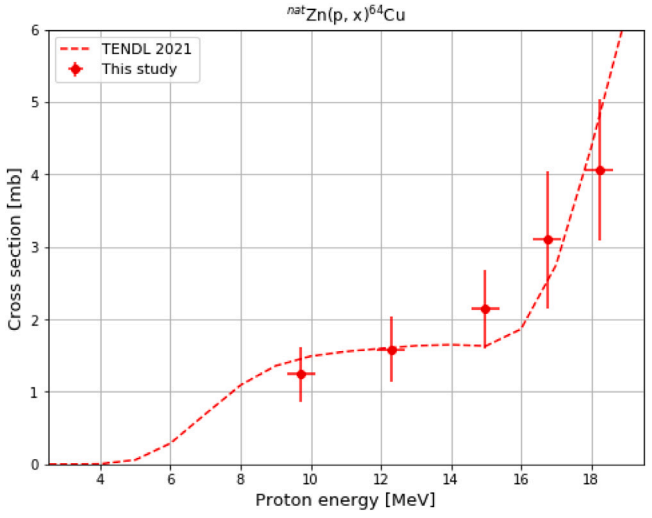

Fig. 5. ^{64}Cu production cross section measured from natural Zn targets.

γ-ray counting (up to 30% and to 20%, respectively), due to the low activities produced. Other sources of uncertainty include the flatness of the beam (5%), the beam current integration (1%), the HPGe detector efficiency (3%) and the target mass measurements (up to 5%). All the contributions were summed in quadrature to obtain the overall experimental uncertainty.

3.2. Study of ^{61}Cu production yield and purity

Aiming at an optimized production of ^{61}Cu, a study of the Thick Target Yield (TTY) and of the purity was performed on the basis of the results obtained. From the cross-section measurements, the TTY as a function of the proton energy on target (entry energy) E can be calculated using the following formula

$$TTY(E) = \frac{A(t_{EoB})}{I \cdot t_i} = \frac{(1 - e^{-\lambda \cdot t_i})}{m_{mol} \cdot q} \int_{E_{th}}^{E} \frac{\sigma(E')}{S_p(E')} dE' \quad (1)$$

where t_i is the irradiation time, I the current on target, $A(t_{EoB})$ the activity produced at EoB, λ the decay constant, $\sigma(E')$ the cross section as a function of the proton kinetic energy E', $S_p(E')$ is the mass stopping power for the target material, E_{th} is the threshold energy of the considered reaction, N_A the Avogadro constant, m_{mol} the average molar mass of the target material, η the number of target atoms of the desired species per molecule and q the charge of the projectile. The mass stopping power was calculated using SRIM.

Given a sample containing a mixture of N radioisotopes, the purity of the radionuclide of interest X is given by

$$P_X = \frac{A_X}{\sum_i^N A_i} \quad (2)$$

where A_i is the activity of the ith radionuclide.

The ^{61}Cu thick target yield and purity obtained irradiating natural Zn and enriched ^{64}Zn (isotopic composition marked as (B) in Table 2) targets are shown in Fig. 7(a) and Fig. 7(b), respectively, as a function of the entry energy.

The thick target yield was also calculated at saturation, considering an irradiation time much longer than the ^{61}Cu half-life, and is shown

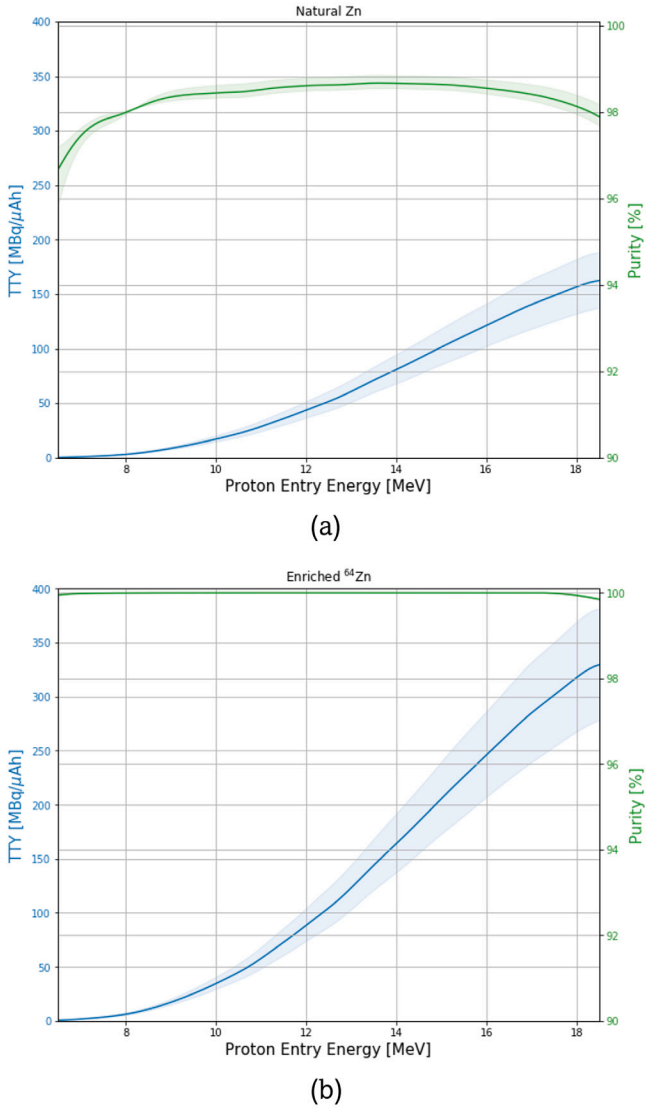

Fig. 7. ^{61}Cu thick target yield and purity for a natural Zn (a) and a 99.71% enriched ^{64}Zn (b) thick target. The bands correspond to the maximum and minimum activity calculated on the basis of the measured cross sections.

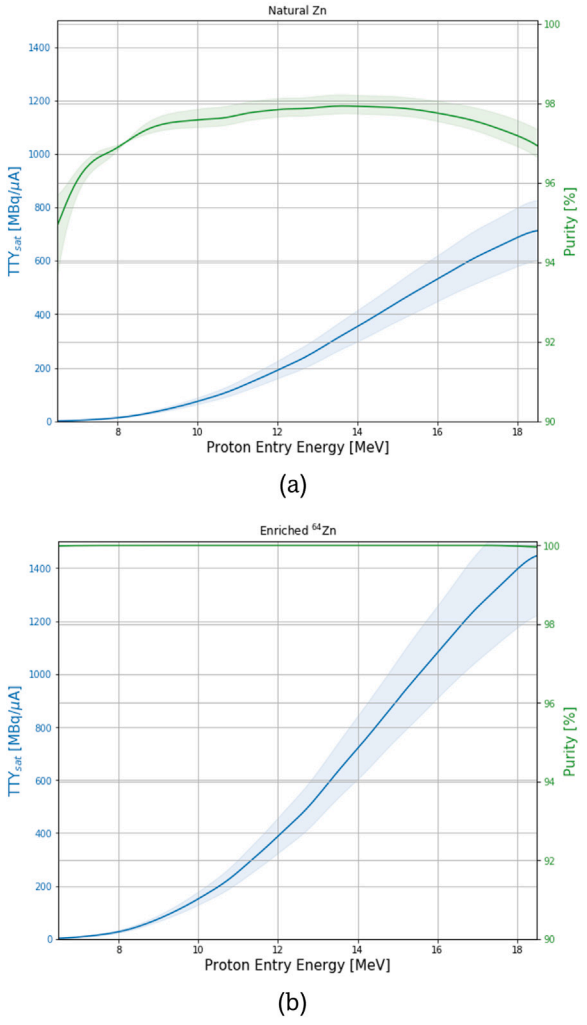

Fig. 8. ^{61}Cu thick target yield and purity at saturation for a natural Zn (a) and a 99.71% enriched ^{64}Zn (b) thick target. The bands correspond to the maximum and minimum activity calculated on the basis of the measured cross sections.

in Fig. 8(a) and Fig. 8(b) for a natural Zn and an enriched ^{64}Zn thick target, respectively. As regards the enriched ^{64}Zn material, ^{61}Cu is the only copper radioisotope produced in the irradiation as the production of the short-lived ^{60}Cu at high energies is negligible. The highest ^{61}Cu yield and isotopic purity can be obtained with the maximum achievable energy on target, which for our medical cyclotron is 17.75 MeV in the outport of the STS, if a $\sim$ 10 μm Havar beam extraction window foil is used. In this condition, a thick target saturation yield of 1359 MBq/μA with a 99.99% purity can be achieved.

For the natural Zn, the radionuclidic purity at saturation is reduced due to the co-production of the relatively long-lived ^{64}Cu. Although its highest value is obtained at about 14 MeV, an input energy of 17.75 MeV could also be evaluated. In fact, a yield and purity of 670 MBq/μA and 97.3%, respectively, can be obtained in this configuration, compared with 335 MBq/μA and 97.9% obtained at 14 MeV.

We would like to emphasize that, while for the enriched ^{64}Zn the radionuclidic purity remains constant over time, in the case of the natural Zn it decreases because of the presence of ^{64}Cu, as shown in Fig. 9 for a proton energy of 17.75 MeV.

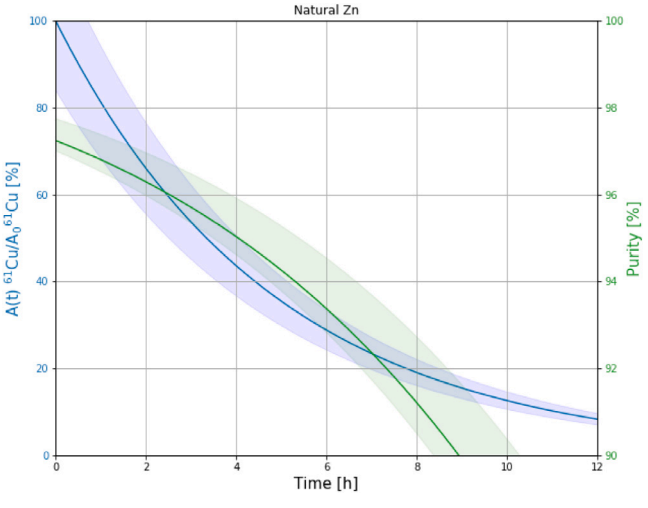

Fig. 9. ^{61}Cu activity fraction and purity as a function of time after EoB for a natural Zn thick target, given a proton energy of 17.75 MeV. The bands correspond to the maximum and minimum activity calculated on the basis of the measured cross sections.

Table 3
Irradiation parameters, ^{61}Cu yield and purity and radioisotopic impurity at EoB obtained irradiating a 0.51-mm-thick natural Zn pellet. The values in parentheses are the yield calculations based on the cross-section measurements.

E_{in} [MeV]	E_{out} [MeV]	Q $\times 10^{-4}$ [μAh]	Y(^{61}Cu) [MBq/μAh]	Y(^{64}Cu) [MBq/μAh]	P(^{61}Cu) [%]
17.3 ± 0.4	11.1 ± 0.4	3.3 ± 0.3	120 ± 18 *(115)*	2.1 ± 0.8 *(2.0)*	98.3 ± 0.7 *(98.3)*
16.0 ± 0.4	9.2 ± 0.4	3.1 ± 0.3	113 ± 17 *(111)*	1.7 ± 0.7 *(1.6)*	98.6 ± 0.6 *(98.6)*
11.4 ± 0.4	0	1.1 ± 0.1	34 ± 5 *(35)*	No signal *(0.50)*	100 *(99)*

Table 4
Irradiation parameters, ^{61}Cu yield and purity at EoB obtained irradiating a 0.31-mm-thick enriched ^{64}Zn pellet. The values in parentheses are the yield calculations based on the cross-section measurements.

E_{in} [MeV]	E_{out} [MeV]	Q $\times 10^{-4}$ [μAh]	Y(^{61}Cu) [MBq/μAh]	P(^{61}Cu) [%]
17.3 ± 0.4	14.2 ± 0.4	2.3 ± 0.2	130 ± 18 *(123)*	100 *(100)*
16.0 ± 0.4	12.7 ± 0.4	2.7 ± 0.3	142 ± 20 *(131)*	100 *(100)*
11.4 ± 0.4	6.0 ± 0.4	1.1 ± 0.1	74 ± 10 *(70)*	100 *(100)*

In this study, natural Zn and enriched ^{64}Zn pellets with a thickness of 0.51 mm and 0.31 mm, respectively, were used for ^{61}Cu production tests. Since the protons are not stopped in the target, the production yield Y(E) can be defined as

$$Y(E) = TTY(E) - TTY(E_{out}) \quad (3)$$

where E_{out} is the proton energy after the target, calculated by using SRIM.

The ^{61}Cu production yield and purity as a function of the input energy, considering a 0.51-mm-thick natural Zn and a 0.31-mm-thick enriched ^{64}Zn target, are shown in Fig. 10(a) and Fig. 10(b), respectively. In both cases, the optimal impinging energy for ^{61}Cu production is around 16 MeV and the production tests were performed around this value.

3.3. ^{61}Cu production with solid targets

On the basis of the obtained results, the optimal conditions for the production of ^{61}Cu were assessed. Two series of tests were performed at proton energies around 16 MeV, irradiating the 0.51-mm-thick natural Zn and the 0.31-mm-thick enriched ^{64}Zn pellet (isotopic composition marked as (B) in Table 2). After each irradiation the pellets were let to decay completely.

The incident energies, the irradiation parameters and the activities obtained from the two series of measurements are reported in Tables 3 and 4.

The production yield of ^{61}Cu calculated in our irradiation conditions from Eq. (3) and the experimental results are shown in Fig. 10 as a function of the proton energy. In the case of the 11 MeV production test from natural Zn, ^{64}Cu could not be measured with the HPGe detector and the experimental purity was overestimated. In all other cases, a good agreement was found between the experimental measurements and the predictions based on our cross sections.

It is important to point out that only copper radioisotopes produced in irradiation, which cannot be eliminated by radiochemical separation, were considered in the calculation of radionuclide purity. Gallium radionuclides do not affect the purity of ^{61}Cu but may make target handling difficult due to radiation protection issues.

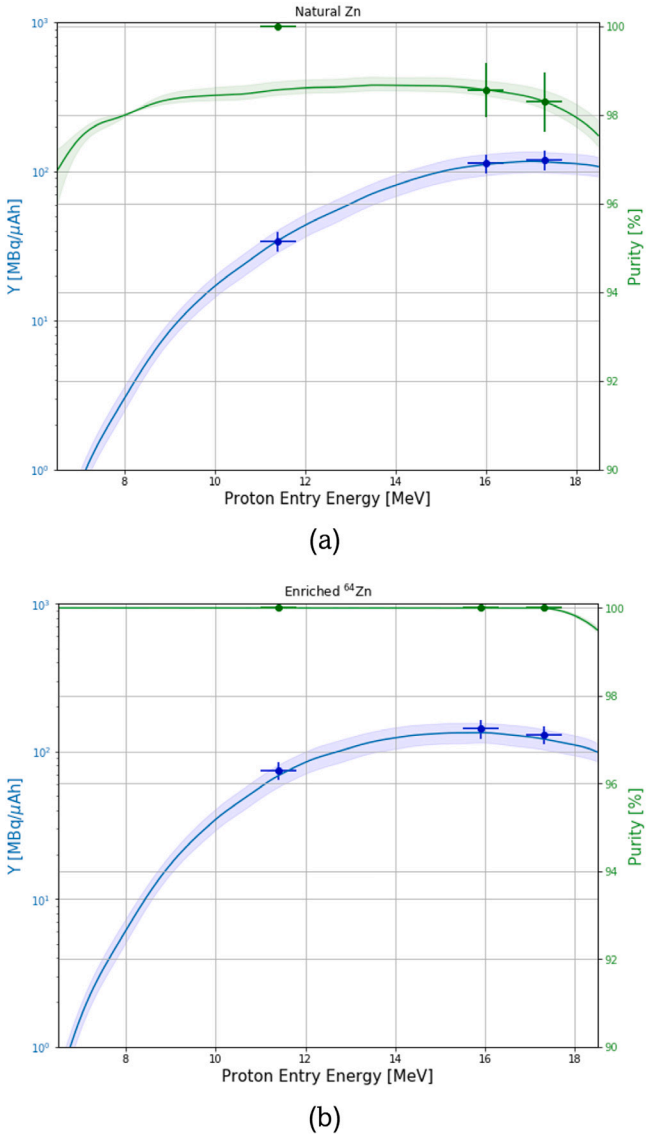

Fig. 10. ^{61}Cu production yield and purity calculated from the measured cross sections in our irradiation conditions compared to the experimental results for the 0.51-mm-thick natural Zn (a) and the 0.31-mm-thick 99.71% enriched ^{64}Zn (b) pellet. The bands correspond to the maximum and minimum activity calculated on the basis of the measured cross sections.

4. Conclusions and outlook

Copper radioisotopes are of increasing interest in nuclear medicine as they provide two of the most promising true theranostic pairs, namely ^{61}Cu/^{67}Cu and ^{64}Cu/^{67}Cu.

In particular, ^{61}Cu has ideal nuclear characteristics for its use in PET diagnostics and can be efficiently produced with a medical cyclotron through the ^{64}Zn(p,α)^{61}Cu reaction from natural Zn or enriched ^{64}Zn targets, avoiding the use of expensive enriched nickel targets.

To identify the optimal irradiation conditions, the cross section of the ^{64}Zn(p,α)^{61}Cu nuclear reaction was measured at the Bern University Hospital cyclotron laboratory, irradiating both natural Zn and enriched ^{64}Zn targets. In the case of natural Zn, the impurity ^{64}Cu is also produced and, having a longer half-life than ^{61}Cu, cannot be removed from the sample by means of decay time. Although not easy to detect due to the low intensity of the emitted γ-ray, ^{64}Cu has several β-emissions that would cause an increase in the dose deposited in the patient and its production must therefore be minimised. For this reason,

a study of the thick target yield and of the radionuclidic purity was carried out to assess the beam energy leading to the optimal production of ^{61}Cu.

On this basis, several production tests were successfully performed irradiating a 0.51-mm-thick natural Zn and a 0.31-mm-thick 99.71% enriched ^{64}Zn sample with a solid target station. In both cases, the optimal entry energy was found to be 16 MeV, allowing to achieve a ^{61}Cu EoB yield of 113 MBq/μAh with a purity of 98.6% and of 142 MBq/μAh with a purity of 100%, respectively.

For the enriched ^{64}Zn, thicker targets and higher energies can be evaluated to improve these results. In particular, considering a thick target and an entry energy of 17.75 MeV, a yield of 308 MBq/μAh with a purity of almost 100% can be achieved at EoB. Moreover, ^{61}Cu is the only copper radioisotope produced and the radionuclidic purity remains constant over time.

In contrast, as far as natural Zn is concerned, the use of thicker targets would not lead to major benefits, while higher energies provide a higher yield but cause a decrease in radionuclidic purity due to the production of ^{64}Cu. Furthermore, the radionuclidic purity decreases over time due to the presence of ^{64}Cu in the sample. Despite these considerations, it must be emphasized that the cost of natural zinc is considerably lower with respect to enriched ^{64}Zn and this would allow ^{61}Cu to be more widely used in nuclear medicine. Further studies will be required to establish the impact of ^{64}Cu in a hypothetical clinical setting by investigating how this radioisotope can affect the patient from a dosimetry perspective.

These results are in line with previous findings reported in Szelecsényi et al. (2005) and confirm the excellent prospects for the production of ^{61}Cu with medical cyclotrons, paving the way towards its widespread use for PET diagnostics and theranostic in nuclear medicine.

CRediT authorship contribution statement

Gaia Dellepiane: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pierluigi Casolaro:** Writing – review & editing, Investigation. **Isidre Mateu:** Writing – review & editing, Investigation. **Paola Scampoli:** Writing – review & editing, Investigation, Conceptualization. **Naomi Voeten:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Saverio Braccini:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix

See Table A.5-Table A.7.

Table A.5
^{64}Zn(p, α)^{61}Cu reaction cross sections measured from natural Zn and enriched ^{64}Zn (marked as (A) in Table 2) targets.

E [MeV]	^{64}Zn(p, α)^{61}Cu (nat) [mbarn]	^{64}Zn(p, α)^{61}Cu (enr) [mbarn]
5.1 ± 0.5	No signal	0.6 ± 0.1
6.2 ± 0.4	2.4 ± 0.5	–
7.1 ± 0.4	–	10 ± 2
7.7 ± 0.4	15 ± 3	–
8.5 ± 0.4	29 ± 5	35 ± 6
9.7 ± 0.4	47 ± 9	–
10.0 ± 0.4	–	50 ± 9
10.4 ± 0.4	52 ± 10	–
11.1 ± 0.4	–	71 ± 12
11.5 ± 0.4	68 ± 12	–
12.1 ± 0.4	–	71 ± 12
12.3 ± 0.4	68 ± 12	–
13.0 ± 0.4	85 ± 15	86 ± 15
13.8 ± 0.4	78 ± 14	–
14.5 ± 0.4	75 ± 14	87 ± 15
15.0 ± 0.4	78 ± 14	–
15.8 ± 0.4	71 ± 13	71 ± 12
16.8 ± 0.4	64 ± 12	–
17.1 ± 0.4	54 ± 9	58 ± 10
17.5 ± 0.4	57 ± 11	51 ± 9
18.2 ± 0.4	45 ± 8	41 ± 7

Table A.6
^{nat}Zn(p,x)^{64}Cu production cross sections measured from natural Zn targets.

E [MeV]	^{nat}Zn(p,x)^{64}Cu [mbarn]
9.7 ± 0.4	1.2 ± 0.4
12.3 ± 0.4	1.6 ± 0.5
15.0 ± 0.4	2.1 ± 0.6
16.8 ± 0.4	3.1 ± 0.9
18.2 ± 0.4	4.1 ± 1.0

Table A.7
^{64}Zn(p, αn)^{60}Cu reaction cross sections measured from natural Zn and enriched ^{64}Zn (marked as (A) in Table 2) targets.

E [MeV]	^{64}Zn(p, αn)^{60}Cu (nat) [mbarn]	^{64}Zn(p, αn)^{60}Cu (enr) [mbarn]
17.5 ± 0.4	No signal	0.07 ± 0.02
18.2 ± 0.4	0.22 ± 0.07	0.20 ± 0.07

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