Production of 67Cu by enriched 70Zn targets: first measurements of formation cross sections of 67Cu, 64Cu, 67Ga, 66Ga, 69mZn and 65Zn in interactions of 70Zn with protons above 45 MeV

Gaia Pupillo, Liliana Mou, Petra Martini, Micòl Pasquali, Alessandra Boschi, Gianfranco Cicoria, Adriano Duatti, Ferid Haddad, Juan Esposito

▶ **To cite this version:**

Gaia Pupillo, Liliana Mou, Petra Martini, Micòl Pasquali, Alessandra Boschi, et al.. Production of 67Cu by enriched 70Zn targets: first measurements of formation cross sections of 67Cu, 64Cu, 67Ga, 66Ga, 69mZn and 65Zn in interactions of 70Zn with protons above 45 MeV. Radiochimica Acta, 2020, 108 (8), pp.593 - 602. 10.1515/ract-2019-3199 . hal-02912614

HAL Id: hal-02912614
https://hal.science/hal-02912614

Submitted on 14 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Gaia Pupillo*, Liliana Mou, Petra Martini, Micòl Pasquali, Alessandra Boschi, Gianfranco Cicoria, Adriano Duatti, Férid Haddad and Juan Esposito

Production of ^{67}Cu by enriched ^{70}Zn targets: first measurements of formation cross sections of ^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga, ^{69m}Zn and ^{65}Zn in interactions of ^{70}Zn with protons above 45 MeV

https://doi.org/10.1515/ract-2019-3199
Received August 11, 2019; accepted December 26, 2019

Abstract: Despite its insufficient availability, Copper-67 is currently attracting much attention for its enormous potential for cancer therapy as theranostic radionuclide. This work aims to accurately measure the unexplored cross section ^{70}Zn(p,x)^{67}Cu in the energy range 45–70 MeV and to evaluate its potential advantages in the case of high-intensity proton beams provided by compact cyclotrons. Thin target foils of enriched ^{70}Zn were manufactured by lamination at the INFN-LNL and irradiated at the ARRONAX facility using the stacked-foils method. A radiochemical procedure for the separation of Cu, Ga and Zn contaminants and the isolation of ^{67}Cu from the irradiated material was developed. The efficiency of the chemical processing was determined for each foil by monitoring the activity of selected tracer radionuclides (^{61}Cu, ^{66}Ga and ^{69m}Zn) through γ-spectrometry. Experimental data of the ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga, ^{69m}Zn, ^{65}Zn cross sections were measured for the first time in the energy range 45–70 MeV and compared with the theoretical results obtained by using the TALYS code. The ^{67}Cu production yield by using enriched ^{70}Zn thick targets was compared with the results obtained by using ^{68}Zn targets in the same irradiation conditions.

Keywords: Cu-67, cross section measurements, nuclear reactions, radiochemistry, proton cyclotron, Zn-70 target.

1 Introduction

Theranostic radionuclides are defined as the category of radioactive isotopes that can be used as both diagnostic and therapeutic agents [1, 2]. This implies that, in order to exhibit theranostic properties, radionuclides or pair of isotopes should decay through the emission of either γ photons or β^+ for diagnostic purpose (SPECT or PET imaging) and α or β^- for eliciting the therapeutic effect. The first study with the theranostic approach was performed in 1993 by using ^{86}Y and ^{90}Y [3]. Currently, among the several radionuclides identified as theranostic isotopes [4], Copper-67 (half-life, 61.83 h) is of particular relevance because of its simultaneous emission of a γ-ray (184.58 keV), suitable for the detection by SPECT cameras, and β^- radiation (end point energy, 577 keV). Although ^{67}Cu has been studied for more than 50 years [5–8], there has been, recently, a surge of interest stimulated by the biological results observed in clinical studies with the positron emitter isotope ^{64}Cu (half-life, 12.701 h) [9]. Actually, it was found that the injection of ^{64}Cu as simple chloride salt ($^{64}CuCl_2$) [10] allows imaging of a variety of tumors, due to the overexpression of the human copper transporter protein (hCtr1) by the cancerous cells [11]. Considering that different isotopes of the same element always show an identical biological behavior, it is reasonable to expect that also $^{67}CuCl_2$ can be a potential targeting agent for cancer [12], thus opening a new avenue for the radionuclide therapy of tumors.

At present, global availability of ^{67}Cu is quite modest and this constitutes the principal factor limiting a more extensive application of this radionuclide in medical studies [13]. In the last decade, different production routes were investigated as recently summarized in a few review articles [6, 7, 14]. Albeit the ^{68}Zn(γ,p)^{67}Cu

***Corresponding author: Gaia Pupillo,** Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro (INFN-LNL), Viale dell'Università 2, Legnaro (PD), Italy, E-mail: gaia.pupillo@lnl.infn.it
Liliana Mou and Juan Esposito: Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro (INFN-LNL), Viale dell'Università 2, Legnaro (PD), Italy
Petra Martini and Micòl Pasquali: Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro (INFN-LNL), Viale dell'Università 2, Legnaro (PD), Italy; and Department of Morphology, Surgical and Experimental Medicine, University of Ferrara, Ferrara, Italy
Alessandra Boschi and Adriano Duatti: Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy
Gianfranco Cicoria: Department of Nuclear Medicine, Sant'Orsola Hospital, Bologna, Italy
Férid Haddad: GIP ARRONAX, Saint-Herblain and Laboratoire Subatech, IN2P3-CNRS, Ecole des Mines de Nantes, Université de Nantes, France

Published online February 12, 2020

reaction is now receiving increasing attention because of the possibility to carry it out with an electron LINAC [15], effective production routes rely on the interaction of charged particles in nuclear processes such as ^{70}Zn(p,α)^{67}Cu, ^{70}Zn(d,αn)^{67}Cu and ^{68}Zn(p,2p)^{67}Cu. The ^{70}Zn(p,α)^{67}Cu and ^{70}Zn(d,αn)^{67}Cu production routes can be carried out with low-energy cyclotrons and enriched ^{70}Zn targets [16, 17], whereas the ^{68}Zn(p,2p)^{67}Cu reaction is run on intermediate-energy cyclotrons [8]. Comparing the thick-target yields of these reactions, apparently the ^{68}Zn(p,2p)^{67}Cu route seems to offer the most suitable production method, although some significant discrepancies in experimental data still exist [8]. For this reason, a new measurement of the ^{68}Zn(p,2p)^{67}Cu cross section was recently performed using enriched ^{68}Zn material [18]. The ^{67}Cu production yield in the 35–70 MeV energy region, based on these latest results, was 15 % lower than the estimation reported in the International Atomic Energy Agency (IAEA) database [19]. The comparison between the two main reactions, ^{68}Zn(p,2p)^{67}Cu and ^{70}Zn(p,α)^{67}Cu, is currently possible only up to 35 MeV [19] since for the latter no experimental data are available at higher energies [20–22], where it is expected an increased trend of the (p,x) nuclear reaction due to the contribution of the various channels reported in Table 1. Thus, aim of this work was to fill this gap and to accurately measure the ^{70}Zn(p,x)^{67}Cu nuclear cross section for $E_p > 35$ MeV. To obtain an exhaustive characterization of the ^{70}Zn(p,x)^{67}Cu process, the experimental evaluation of the collateral ^{70}Zn(p,x)^{64}Cu, ^{70}Zn(p,4n)^{67}Ga, ^{70}Zn(p,5n)^{66}Ga, ^{70}Zn(p,x)^{69m}Zn and ^{70}Zn(p,x)^{65}Zn reactions was also carried out for the first time in the 45–70 MeV energy range, and compared with theoretical estimations obtained with the TALYS code (version 1.9) [24]. This work was developed in the framework of the LARAMED project [25] at INFN-LNL (Legnaro, Italy), in collaboration with the ARRONAX centre (Nantes, France) [26] and the Sant'Orsola Hospital (Bologna, Italy).

Table 1: Threshold energies to produce the radionuclides of interest extracted from NuDat2.7 database [23].

	Reaction channel on ^{70}Zn target	Q-value (MeV)	Threshold (MeV)
^{67}Cu	p,α	2.619	0
	p,p + t	−17.195	17.443
	p,n + ^{3}He	−17.959	18.218
	p,2d	−21.228	21.534
	p,n + p + d	−23.452	23.790
	p,2n + 2p	−25.677	26.047
^{64}Cu	p,3n + α	−23.490	23.829
	p,n + 2t	−34.822	35.324
^{61}Cu	p,4n + 2t	−62.477	63.377
^{67}Ga	p,4n	−27.682	28.081
^{66}Ga	p,5n	−38.909	39.469
^{69m}Zn	p,d	−6.994	7.094
	p,n + p	−9.218	9.351
^{65}Zn	p,3n + t	−35.528	36.039

2 Experimental

2.1 Irradiation runs

Four irradiation runs were performed at the ARRONAX facility using a proton beam with tunable energy (35–70 MeV) and stacked-foils targets, allowing the simultaneous bombardment of a set of thin metallic foils [27]. A typical stacked-foils arrangement was made of two identical patterns, each composed by one enriched ^{70}Zn (>95 %) target foil followed by one ^{nat}Al monitor foil. The ^{nat}Al foil was used to measure the effective beam flux by referring to the IAEA monitor reaction ^{nat}Al(p,x)^{24}Na [28], but also as a trap of possible recoil atoms from the target foil. Another aluminum foil (0.5–1.0 mm thick) was placed in-between the two adjacent patterns to decrease the proton beam energy. An additional enriched ^{63}Cu (99.7 %; ^{65}Cu ≤ 0.3 %) thin metal foil was positioned at the end of the whole target arrangement to produce ^{61}Cu. This radionuclide was used as a tracer isotope for the copper-elements in the chemical separation process, but its production occurs on ^{70}Zn targets only at $E_p > 63$ MeV (Table 1). The enriched ^{63}Cu target was preferred to a natural copper foil to avoid the co-production of ^{64}Cu, that might potentially affect the measurement of the ^{70}Zn(p,x)^{64}Cu cross section. The production of ^{64}Cu was of particular interest because it is the only copper radionuclide that may affect the radionuclidic purity (RNP) of ^{67}Cu-labelled radiopharmaceuticals. In fact, although ^{61}Cu may also be co-produced at $E_p > 63$ MeV, its short half-life makes this isotope not of much a concern from a practical point of view. The enriched ^{70}Zn and ^{63}Cu foils were manufactured by lamination at the INFN-LNL Target Laboratory starting from enriched metal powders. Table 2 reports the isotopic composition of the ^{70}Zn powders, purchased from Trace (Trace Science

Table 2: Isotopic composition of enriched ^{70}Zn metal powders.

	Zn-64 (%)	Zn-66 (%)	Zn-67 (%)	Zn-68 (%)	Zn-70 (%)
Trace	<0.02	<0.02	0.13	4.45	95.42
Chemotrade	0.05	0.27	0.07	4.14	95.47

International Inc., DE, USA) and Chemotrade (Chemotrade GmbH, Dusseldorf, Germany).

For an easier handling of the expensive enriched materials, a dedicated target holder (Ø = 11 mm), a graphite collimator (Ø = 9 mm) and a plastic support were designed and produced at the INFN-LNL. These devices were used to precisely define the beam size onto the target during the bombardment (Figure 1). The duration of a typical irradiation was 1.5 h with a constant beam intensity of about 100 nA. The target was placed under normal atmosphere downstream the end of the beam line. The beam-line was kept under vacuum and closed with a 75 μm thick Kapton foil. The distance from the target holder to the Kapton foil, ranging from 14.5 cm to 17.1 cm, was accurately measured for each run. The proton beam energy entering each layer of the stacked-foils target was calculated using the SRIM-2013 code [29]. In order to calculate the energy losses in the Kapton foil, in the air and across each target foil, the input parameters were the proton beam energy extracted from the cyclotron and the layers' thicknesses. As previously reported [18], the uncertainty of the proton beam energy was obtained considering the uncertainty of the beam energy extracted from the cyclotron (±500 keV) and by calculating with the SRIM code the energy straggling through each layer of the stacked-target.

2.2 Chemical separation and γ-spectroscopy

The proton irradiation of enriched ^{70}Zn yielded a variety of radionuclides including ^{67}Ga (half-life 3.2617 days). In the present study, the production of this radioisotope raised a major concern because its half-life is similar to ^{67}Cu (*ca.* 2.6 days) and both decay to ^{67}Zn, thus emitting the same γ-lines (Table 3). This suggests that it would be challenging to discriminate between these two radionuclides by simple γ-spectroscopy and, therefore, a procedure for the separation of Cu from Ga isotopes should be set up to achieve an accurate measurement of ^{67}Cu and ^{67}Ga activities. The overproduction of ^{67}Ga is an ubiquitous problem also with the ^{68}Zn(p,x)^{67}Cu route, given the dramatic difference between the cross sections of the reactions ^{68}Zn(p,x)^{67}Cu (of the order of tens mb) and ^{68}Zn(p,x)^{67}Ga (of the order of hundreds mb) [18, 30]. Since a previous work focused on the ^{70}Zn(p,α)^{67}Cu cross section measurement includes a chemical process aimed at Cu/Ga separation [22], we also developed a radiochemical procedure to be applied to the irradiated ^{70}Zn targets. The efficiency of this procedure was evaluated for each run by measuring the activity of ^{61}Cu, ^{66}Ga and ^{69m}Zn, the radionuclides selected as tracers for copper, gallium and zinc elements, respectively. This approach allowed to overcome the impossibility of distinguishing between the activities of ^{67}Cu and ^{67}Ga because of the identical γ-emission. Table 3 reports the nuclear data of the radionuclides of interest used in this work, as available on the NuDat2.7 Database [23].

There are several methods for separating ^{67}Cu from irradiated zinc target, extensively reviewed [6, 31]. Among them, electrodeposition, sublimation, solvent extraction and ion exchange have been frequently employed. For example, high recovery yields of copper were reported by solvent extraction with thenoyltrifluoroacetone in benzene [6]. In this work, the chemical separation was accomplished

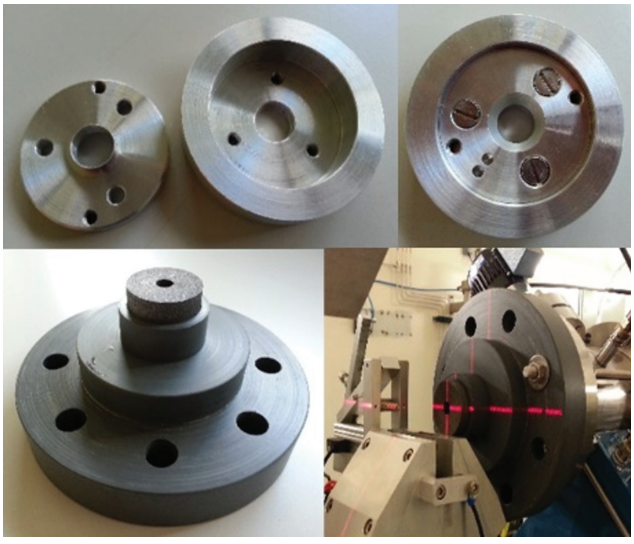

Figure 1: The opened (up left) and assembled target-holder (up right); the collimator and support (down left); the alignment procedure on the beam line at the ARRONAX facility (down right).

Table 3: Nuclear data of the radionuclides relevant for this study; uncertainties are reported in brackets [23].

	Half-life	E_γ (keV)	I_γ (%)
^{67}Cu	61.83 h (12)	184.577 (10)	48.7 (3)
		208.951 (10)	0.115 (5)
		300.219 (10)	0.797 (11)
		393.529 (10)	0.220 (8)
^{64}Cu	12.701 h (2)	1345.77 (6)	0.475 (11)
^{61}Cu	3.333 h (5)	282.956 (10)	12.2 (22)
		656.008 (10)	10.8 (20)
^{67}Ga	3.2617 days (5)	184.576 (10)	21.410 (10)
		208.950 (10)	2.460 (10)
		300.217 (10)	16.64 (12)
		393.527 (10)	4.56 (24)
^{66}Ga	9.49 h (3)	1039.220 (3)	37.0 (20)
^{69m}Zn	13.756 h (18)	438.634 (18)	94.85 (7)
^{65}Zn	243.93 days (9)	1115.539 (2)	50.04 (10)
^{24}Na	14.997 h (12)	1368.626 (5)	99.9936 (15)

according to the principles of ion-exchange solid-phase extraction chromatography since this is a simple, clean and reliable method that can afford good reproducibility and high yields [6, 31, 32]. A previously described three-step process [32] was used with slight modifications. All chemicals and reagents used were of analytical grade unless otherwise specified. After the irradiation, the ^{63}Cu foil was dissolved in HNO_3 (6 M, 0.5 mL) and the resulting solution was evaporated to dryness; the residue was dissolved in 1 mL of HCl (10 M). Similarly, the ^{70}Zn foil was dissolved in 4.5 mL of HCl (10 M). A 0.5 mL aliquot of the ^{63}Cu solution was mixed with the ^{70}Zn solution. This mixture, hereafter referred to as *Mix* solution, was passed through a cation exchange resin AG50W-X4 (hydrogen form, 100–200 mesh, BioRad, Hercules, CA, USA) preconditioned with HCl (10 M) in a glass column for chromatography (Ø = 1.2 cm, height = 20 cm). From this column, Cu and Zn-elements were collected by elution with HCl (10 M, 10 mL), whereas Ga isotopes were recovered by passing 20 mL of a acetone/HCl (0.05 M) mixture (97.56 % acetone). The Cu/Zn solution was evaporated to dryness using a dedicated evaporation system and the residue redissolved to adjust HCl concentration at 2 M. Meanwhile, a 5 mL aliquot of the solution with gallium isotopes, named *xGa*, was stored for spectrometry measurements. Finally, separation of Cu isotopes from zinc bulk was performed by anion exchange using a AG1-X8 resin (chloride form, 100–200 mesh, BioRad, Hercules, CA, USA), previously packed and conditioned in a glass column for chromatography (Ø = 1.2 cm, height = 20 cm). Recovery of Cu isotopes from the column was obtained by passing HCl (2 M, 20 mL), whereas zinc was eluted from the same column using diluted HCl (0.005 M, 20 mL). A 5 mL aliquot of each solution, named *xCu* and *xZn*, was stored for spectroscopy. The radiochemical separation process is schematically shown in Figure 2. The complete procedure lasted approximately 4 h. For activity determination, a homogeneous 5 mL aliquot was withdrawn from each of the three final solutions (*xCu*, *xGa* and *xZn*). The collected samples were analyzed by γ-spectrometry. Aluminium monitor foils were directly dissolved into the spectrometry vial by adding 5 mL of HCl (10 M). As already described [18], the yield of chemical processing was monitored for all target foils by measuring the activity of the tracer radionuclides (^{61}Cu, ^{66}Ga and ^{69m}Zn for copper, gallium and zinc elements, respectively) before and after the radiochemical separation procedure. All samples were measured with the same high-purity germanium (HPGe) detector (10 % relative efficiency, FWHM 1.0 keV at 122 keV, Canberra GC1020), previously calibrated with 5 mL reference liquid source (Cerca-Lea, France). To keep the dead time below 10 %, two sample-detector positions (19 cm far from and

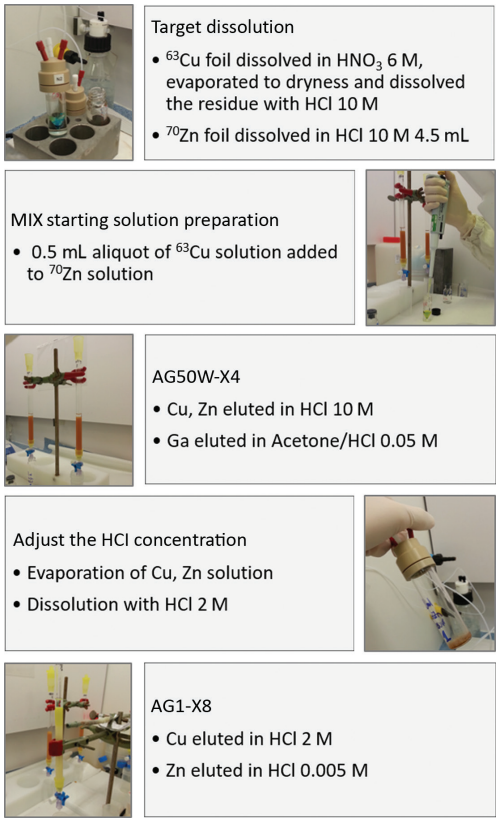

Figure 2: Schematic representation of the main steps of the radiochemical separation process.

in contact with the sample) were used. The typical counting time of final samples was approximately 2 h.

2.3 Data analysis

The activities at the End Of Instantaneous Bombardment (Act_{EOIB}) were calculated using the equation [33]:

$$Act_{EOIB} = \frac{C}{\varepsilon(E)\cdot I(E)\cdot t_L}\cdot e^{\lambda t_D}\cdot\left(\frac{\lambda t_{IRR}}{1-e^{-\lambda t_{IRR}}}\right)\cdot\left(\frac{\lambda t_R}{1-e^{-\lambda t_R}}\right)$$

where C is the number of counts, $\varepsilon(E)$ the detector efficiency, $I(E)$ the intensity of the γ-line of interest, λ the decay constant of the radionuclide, t_L and t_R the live and real time of the γ-spectroscopy measurement, t_D the decay time occurred from the end of irradiation to the start of the γ-spectroscopy measurement, t_{IRR} the irradiation time. The activity at EOIB of the tracer radionuclides was calculated from the spectra of the *Mix* solution and directly used for the cross sections calculations. The activity at EOIB of the radionuclides of interest (^{67}Cu, ^{64}Cu, ^{67}Ga and ^{65}Zn) was calculated from the spectra of each separated solution (*xCu*,

xGa and *xZn*), considering the chemical yield of the tracer radionuclide (Y = Yield) and the Weight Factor correction (*WF*), representing the weight ratio of the 5 mL aliquot and the entire solution. When the γ-lines of the tracer radionuclides were not visible in a spectrum, the Minimum Detectable Activity (MDA) was calculated [34]. Since the 1039 keV γ-line of ^{66}Ga was visible in the spectra of the *xCu* solution, the calculation of ^{67}Cu activity took into account the residual contribution of ^{67}Ga activity by using the branching ratio correction (*BR* = Branching Ratio). Given that the total number of counts attributed to the 184 keV and 300 keV γ-lines (C^{184} and C^{300}) were due only to the ^{67}Cu and ^{67}Ga activities (Act_{Cu67} and Act_{Ga67}), the *BR* correction consisted in the solution of the following two equations system:

$$\begin{cases} C^{184} = k_1 Act_{Cu67} + k_2 Act_{Ga67} \\ C^{300} = k_3 Act_{Cu67} + k_4 Act_{Ga67} \end{cases}$$

$$k_1 = \varepsilon^{184} I^{184}_{Cu67}\, t_L \quad k_2 = \varepsilon^{184} I^{184}_{Ga67}\, t_L$$
$$k_3 = \varepsilon^{300} I^{300}_{Cu67}\, t_L \quad k_4 = \varepsilon^{300} I^{300}_{Ga67}\, t_L$$

$$Act_{Ga67} = \frac{k_1 C^{300} - k_3 C^{184}}{k_4 k_1 - k_3 k_2}$$

$$Act_{Cu67} = \frac{k_4 C^{184} - k_2 C^{300}}{k_4 k_1 - k_3 k_2}$$

Recoil of atoms jumping out one foil and trapped in the following one was measured. For ^{69m}Zn, the maximum value of the recoil effect was 2.3 %, for Ga and Cu radionuclides was 2.6 % and for ^{24}Na 21.1 %. The activities of the radionuclides of interest were corrected for this effect (R = Recoil). Table 4 summarises all the corrections applied to obtain the real activities at the EOIB.

After applying the described corrections to the activity at EOIB, the following activation formula was used to calculate the nuclear cross section σ:

$$\sigma = \sigma' \cdot \frac{Act'_{\mathrm{EOIB}}}{Act_{\mathrm{EOIB}}} \cdot \frac{N'_B}{N_B} \cdot \frac{\lambda'}{\lambda}$$

Table 4: Corrections applied to obtain the activity at EOIB for all the radionuclides of interest.

	Solution	Weight Factor (WF)	Chemical Yield (Y)	Branching Ratio (BR)	Recoil (R)
^{67}Cu	*xCu*	x	x	x	x
^{64}Cu	*xCu*	x	x		x
^{66}Ga	*Mix*				x
^{67}Ga	*xGa*	x	x		x
^{69m}Zn	*Mix*				x
^{65}Zn	*xZn*	x	x		x

Table 5: The IAEA ^{nat}Al(p,x)^{24}Na monitor reaction values and related uncertainties [28].

Energy (MeV)	Reference cross section (mb)
44.4 ± 0.7	2.9 ± 0.7
47.5 ± 0.6	4.4 ± 0.3
50.7 ± 0.5	6.3 ± 0.5
55.7 ± 0.5	9.0 ± 0.6
56.0 ± 0.8	9.2 ± 0.7
60.7 ± 0.5	10.8 ± 0.5
67.7 ± 0.6	11.6 ± 0.5

where σ' is the reference monitor reaction, ^{nat}Al(p,x)^{24}Na, recommended by IAEA [28], and Act'_{EOIB} and λ' are the activity and the decay constant of the reference radionuclide; N'_B and N_B are the effective densities of atoms for the reference and target foils respectively, calculated with the equation:

$$N_B = \frac{x \rho P N_A}{A}$$

where x is the thickness, ρ the density, P the purity, A the mass number of the foil and N_A the Avogadro constant. The amount of ^{68}Zn content (<4.5 % as reported in Table 2) into the enriched ^{70}Zn targets was taken into account, by including this residual contribution in each cross section estimation. In the case of ^{67}Cu, ^{67}Ga and ^{66}Ga radionuclides, the most recently measured values of the excitation functions from ^{68}Zn targets were considered [18]; for ^{64}Cu, the IAEA recommended cross section was used [19] and for the ^{65}Zn radionuclide the only available experimental data [35] on the EXFOR database [20] were taken into account. The ^{69m}Zn radionuclide, that is not produced by proton-beams in ^{68}Zn targets, did not need this correction. Cross-sections of all the radionuclides of interest were reported to 100 % enriched ^{70}Zn. The uncertainty of the measured cross-sections was evaluated in a quadratic form, including all the corrections applied to the measured radionuclide activities and target thicknesses, including also the monitor reaction uncertainty. Table 5 reports the values of the reference cross section with related uncertainty [28] for the investigated energy range (45–68 MeV). The uncertainty varies from 5 % to 8 %: this was the major contribution to the uncertainty of the measured cross sections.

3 Results and discussion

3.1 Radiochemical separation

Table 6 reports the mean recovery yield values and standard deviations (sd) resulting from the separation procedure applied to the seven irradiated target foils.

Table 6: Results of the radiochemical separation procedure applied to the target foils (n = 7).

Solution	Tracers percentage (mean ± sd)		
	^{61}Cu	^{66}Ga	^{69m}Zn
xCu	95% ± 2 %	2% ± 1 %	<MDA
xGa	<MDA	79% ± 12 %	<MDA
xZn	<MDA	(<0.5 %)	84% ± 3 %

The copper isotopes were quantitatively recovered in the *xCu* solution and no trace amounts were found in the other samples. On the contrary, few percent of the total activity of the tracer radionuclide ^{66}Ga were detected in the *xCu* solution, thus indicating that some residual ^{67}Ga was left over. This contribution was included in data analysis for cross section determination with the *BR* correction. Some residual amounts of Ga and Zn radionuclides were also retained onto the resin after elution. The amount of these elements was not quantified, but only detected qualitatively by γ-spectrometry. Presumably, the variability in the results of the separation process could be attributed to the manual procedure adopted. However, it is reasonable to affirm that this process can be easily automated and remotely controlled to ensure effective operator's radioprotection and to maximize the reproducibility of the separation process. Most importantly, it could be potentially adapted and standardized for pharmaceutical applications.

3.2 Cross section on ^{70}Zn targets: experimental data and TALYS calculations

Table 7 and Figures 3–8 report the experimental cross sections obtained for the ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga, ^{69m}Zn, ^{65}Zn reactions, referred to 100 % enriched ^{70}Zn. The maximum value for the beam energy uncertainty, including the energy straggling, was 770 keV.

Results for the various irradiation runs show a regular trend for all the measured ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga, ^{69m}Zn, ^{65}Zn cross sections (Figures 3–8). No literature data are available in the energy range investigated in this work (45–70 MeV) [20]. Previous measurements at lower energies are reported on the graphs for reference purposes. In case of the ^{70}Zn(p,α)^{67}Cu reaction the IAEA recommended cross section, calculated up to 40 MeV [19], is also shown in Figure 3. Our experimental data were also compared with the calculations obtained using the TALYS nuclear code (version 1.9) [24]. In Figures 3–8, the calculation obtained by using the default set of parameters is represented as dotted line and indicated as *TALYS* on the legend; the estimation resulting from the set of parameters proposed by Duchemin et al. [36] is reported with a dashed-dotted line on the graphs and indicated with *TALYS** on the legend. This new set of parameters showed a good reproducibility for different nuclear reactions, including the ^{68}Zn(p,2p)^{67}Cu cross section [18]. Such a good performance presumably originated from the different ingredients included in the code as compared to the default calculation. Among the main phenomena involved, the optical potential, the pre-equilibrium emission and the level density are worthy to be mentioned [36].

3.3 ^{70}Zn (p,x)^{67}Cu,^{64}Cu

Results of the ^{70}Zn(p,x)^{67}Cu cross section are illustrated in Figure 3. Different irradiation runs showed a regular increasing trend of the reaction, that is well described by the TALYS calculation with the default set of parameters, even if with an overestimation of the cross section in the energy range investigated in this work. Notably, in order to link the new data collected here at high energies with the previous estimation of the (p,α) channel, it would be necessary to perform a dedicated measurement in the energy range 30–45 MeV. At this moment, it is not possible to predict the entire trend of the reaction.

Table 7: Cross sections of the ^{70}Zn(p,x)^{67}Cu, ^{64}Cu, ^{67}Ga, ^{66}Ga, ^{69m}Zn, ^{65}Zn reactions referred to 100% enriched ^{70}Zn targets.

Energy (MeV)	^{67}Cu (mb)	^{64}Cu (mb)	^{67}Ga (mb)	^{66}Ga (mb)	^{69m}Zn (mb)	^{65}Zn (mb)
44.7 ± 0.7	8.0 ± 1.3	48.0 ± 4.6	281.2 ± 42.8	3.2 ± 0.6	84.3 ± 7.4	6.2 ± 1.2
47.7 ± 0.6	10.8 ± 1.9	57.3 ± 5.3	214.0 ± 33.8	4.1 ± 0.8	71.5 ± 6.3	7.1 ± 1.3
50.8 ± 0.5	12.7 ± 2.2	51.1 ± 5.3	172.1 ± 27.0	11.4 ± 2.1	66.5 ± 5.6	8.2 ± 1.5
55.8 ± 0.5	16.8 ± 3.0	45.2 ± 4.0	120.1 ± 18.6	31.4 ± 6.1	60.5 ± 4.7	11.9 ± 2.1
56.0 ± 0.8	18.7 ± 3.4	48.0 ± 4.5	135.6 ± 21.0	37.2 ± 7.3	68.6 ± 5.1	14.3 ± 2.6
60.8 ± 0.5	20.1 ± 3.6	33.0 ± 2.7	97.3 ± 14.2	46.8 ± 8.5	65.7 ± 4.1	28.2 ± 4.7
67.8 ± 0.6	21.5 ± 4.0	23.2 ± 1.7	59.7 ± 7.7	34.5 ± 5.1	54.8 ± 2.8	65.3 ± 10.5

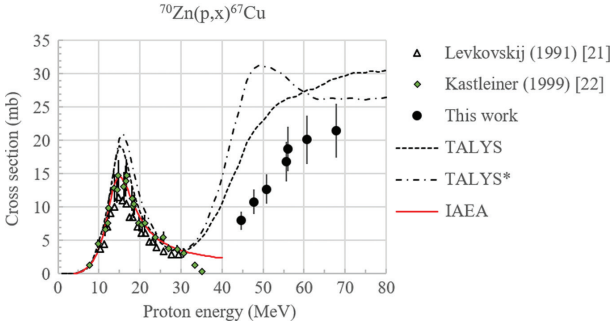

Figure 3: Results of the ^{70}Zn(p,x)^{67}Cu nuclear cross section.

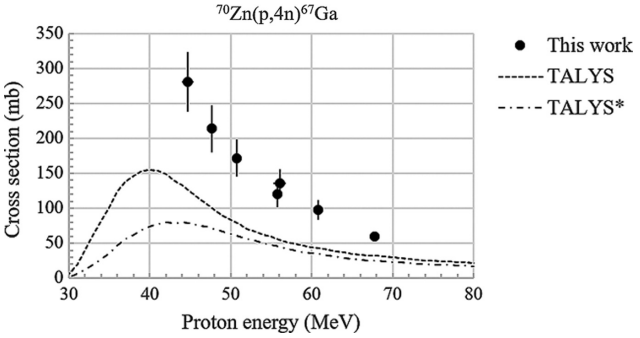

Figure 6: Results of the ^{70}Zn(p,4n)^{67}Ga nuclear cross section.

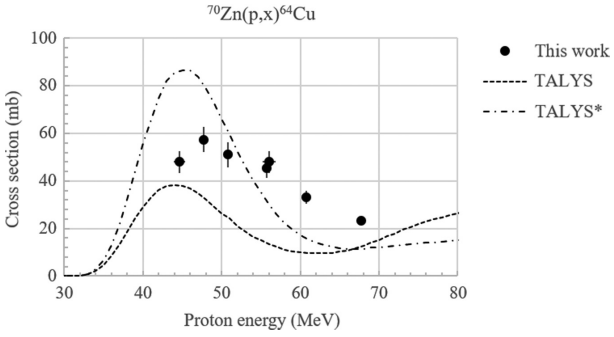

Figure 4: Results of the ^{70}Zn(p,x)^{64}Cu nuclear cross section.

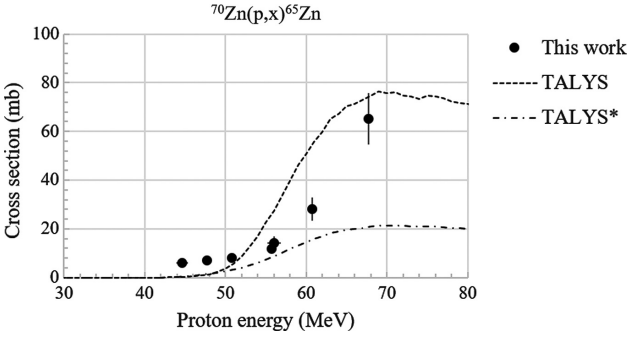

Figure 7: Results of the ^{70}Zn(p,x)^{65}Zn cross section.

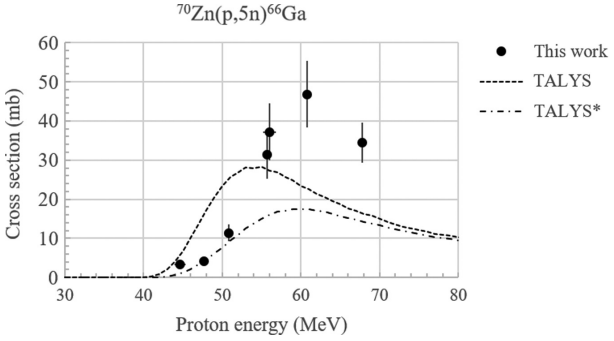

Figure 5: Results of the ^{70}Zn(p,5n)^{66}Ga nuclear cross section.

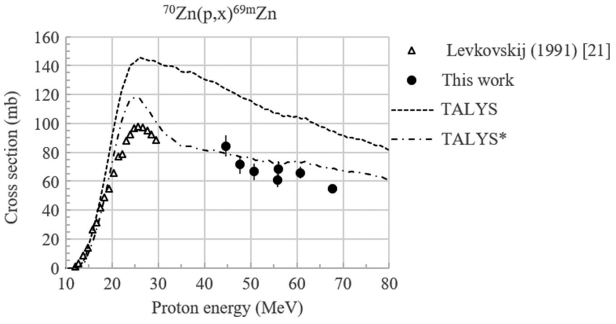

Figure 8: Results of the ^{70}Zn(p,x)^{69m}Zn cross section.

The experimental values obtained by Kastleiner et al. [22] at $E_p = 33–35$ MeV are not in agreement with the IAEA fit [19], neither with the TALYS results obtained with both set of parameters (Figure 3). Following the method described by Qaim et al. [37], data by Levkovski [21] are rescaled by a factor of 0.77 in order to take into account the recent IAEA evaluation [28] of the ^{nat}Mo(p,x)$^{96g+m}$Tc monitor cross section used by the author (250 mb vs. 192.82 mb at $E_p = 30$ MeV).

Figure 4 reports the first experimental data of the ^{70}Zn(p,x)^{64}Cu nuclear reaction, showing a regular trend in the energy range investigated. The discrepancy of the measured values with TALYS calculations is evident. It is interesting to note that the trend of the ^{70}Zn(p,x)^{64}Cu reaction declines when $E_p > 48$ MeV (Figure 4), whereas it increases for the ^{70}Zn(p,x)^{67}Cu reaction (Figure 3). However, the cross section values for ^{64}Cu production are always higher than those for ^{67}Cu.

3.4 ^{70}Zn (p,x)^{67}Ga,^{66}Ga

First experimental results of the ^{70}Zn(p,5n)^{66}Ga and ^{70}Zn(p,4n)^{67}Ga cross sections are shown in Figures 5 and 6, respectively. As in the case of ^{64}Cu, TALYS estimations do not appropriately describe the measured trend. The ^{70}Zn(p,5n)^{66}Ga reaction shows a 50 mb peak around 61 MeV, while the ^{70}Zn(p,4n)^{67}Ga reaction apparently shows a peak at lower energy ($E_p < 45$ MeV).

In view of a potential use of enriched ^{70}Zn targets to produce ^{67}Cu, it is surely of importance to estimate the production of ^{66}Ga and ^{67}Ga radionuclides since they have to be considered in the development of the radiochemical procedure necessary for copper separation and purification.

3.5 ^{70}Zn (p,x)^{65}Zn,^{69m}Zn

Figure 7 reports the first measurement of the ^{70}Zn(p,x)^{65}Zn cross section. The experimental data are not properly described by the TALYS calculations in the entire energy range, including the initial trend of the reaction, that has 36 MeV as threshold energy (Table 1). Considering that the ^{65}Zn activity is measured from the *xZn* solution, which contains only zinc isotopes, no interference with the 1115 keV γ-line from ^{65}Ni can occur.

In case of ^{70}Zn recovery, the measurement of ^{65}Zn production (the longest-lived radioactive contaminant present in the irradiated material) is of particular interest since it provides an estimation of the suitable decay time before re-processing.

Figure 8 plots the results of the ^{70}Zn(p,x)^{69m}Zn cross section, together with literature data [21], rescaled by a factor of 0.77 (as previously described for the ^{70}Zn(p,x)^{67}Cu reaction), and TALYS estimations. A general agreement in the trend of the ^{70}Zn(p,x)^{69m}Zn cross section can be observed between TALYS results with the new set of parameters and the measurements, even if there is a lack of data in the 30–45 MeV energy region.

3.6 ^{67}Cu production yield with ^{70}Zn target

Figure 9 shows the fitting curve (dotted line) of our new experimental data for the ^{70}Zn(p,x)^{67}Cu nuclear reaction, compared with the IAEA recommended cross section [19] of the ^{68}Zn(p,2p)^{67}Cu reaction (continuous line). The cross section at 70 MeV on ^{70}Zn targets (approximately 22 mb) is twice that of the recommended value with ^{68}Zn targets (approximately 11 mb). Accordingly, in the energy range

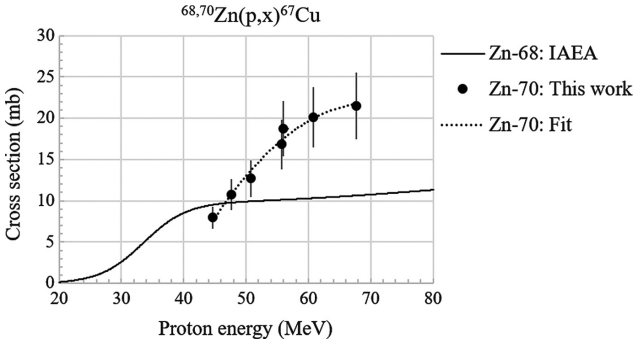

Figure 9: Comparison of the ^{70}Zn(p,x)^{67}Cu nuclear reaction (experimental data and fit) with the ^{68}Zn(p,2p)^{67}Cu cross section recommended by the IAEA [19].

45–70 MeV the ^{67}Cu thick-target yield on 100 % enriched ^{70}Zn material is 38 MBq/μAh, nearly 70 % higher than that calculated by using fully enriched ^{68}Zn targets, i. e. 23 MBq/μAh [19]. To reasonably estimate the ^{67}Cu yield at EOB, a 62 h irradiation run (corresponding to one ^{67}Cu half-life) was considered for both target materials, resulting in a ^{67}Cu activity of 1.7 GBq/μA for ^{70}Zn and 1.0 GBq/μA for ^{68}Zn targets. In both cases, ^{64}Cu is also produced: 7.5 GBq/μA for ^{70}Zn and 5.6 GBq/μA in case of ^{68}Zn. However, considering the shorter half-life of ^{64}Cu, its eventual contamination can be minimized to the desired value by waiting an appropriate decay time before starting any labelling procedure with ^{67}Cu.

4 Conclusions

Results obtained with 45–70 MeV protons on ^{70}Zn targets demonstrate a regular trend for all the measured radionuclides (^{67}Cu, ^{64}Cu, ^{66}Ga, ^{67}Ga, ^{69m}Zn, ^{65}Zn), although the experiments were conducted over a year period. The cross sections presented in this work were also calculated with the TALYS code, run with two different sets of parameters. In general, the nuclear reactions trends were not adequately described by the TALYS results. Only for ^{67}Cu and ^{69m}Zn the trend of the theoretical cross section was in agreement with experimental data, respectively by using the default and the new set of parameters. These findings indicate that additional work on parameters optimization is desirable, since a reliable nuclear code may help in the estimation of those radionuclides whose cross sections are difficult to measure, such as fast decaying and stable isotopes. In particular, the formation of ^{63}Cu and ^{65}Cu has also to be taken into account because these isotopes may affect the final isotopic purity of ^{67}Cu-labelled radiopharmaceuticals.

From the measured ^{70}Zn(p,x)^{67}Cu cross section we calculated the ^{67}Cu yield, obtaining a 70 % higher value than the one available with ^{68}Zn targets from the IAEA database, using the same 45–70 MeV energy range. It is worth noting that ^{70}Zn enriched material is about 4 times more expensive than the ^{68}Zn one, due to its lower natural abundance (^{70}Zn: 0.61 %, ^{68}Zn: 18.45 %). However, the promising outcome of this work may contribute to promote further studies aimed at developing a reliable and efficient procedure for ^{67}Cu production, also including the technology for the recovery of irradiated targets. In turn, this will stimulate future pre-clinical and clinical studies with this very attractive theranostic radionuclide eagerly awaited by the medical community.

Acknowledgements: This work was funded by INFN within the scope of the research project COME (COpper MEasurement, CSN3, Dotazioni LNL) and it was also included in the framework of the IAEA Coordinated Research Project (CRP) on "Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc)" (IAEA CRP No. F22053). It was also partially supported by a grant from the French National Agency for Research called "Investissements d'Avenir", Equipex Arronax-Plus (ANR-11-EQPX-0004), Labex IRON (ANR-11-LABX-18-01) and ISITE NExT (ANR-16-IDEX-0007). Authors would like to thank Massimo Loriggiola (Target Laboratory at INFN-LNL) for manufacturing target foils and the staff at the ARRONAX facility for arranging all irradiation runs. Contribution from Dr. Thomas Sounalet (University of Nantes), Dr. Licia Uccelli (University of Ferrara) and Prof. Mario Marengo (S. Orsola Hospital in Bologna) for practical work in radiochemistry is gratefully acknowledged. Authors are also grateful to Prof. Giovanni Fiorentini (University of Ferrara) and Dr. Carlos Rossi Alvarez (INFN-LNL) for helpful discussion and to Dr. Pier Paolo Buso, Dr. Gian Pietro Bezzon, Dr. Alessandro Zanon, Dr. Stefania Canella and Dr. Sara Carturan (INFN-LNL) for their constant support.

References

1. Srivastava, S.: Paving the way to personalized medicine: production of some theragnostic radionuclides at Brookhaven National Laboratory. Radiochim. Acta **99**, 635 (2011).
2. Srivastava, S.: A Bridge not too Far: Personalized Medicine with the use of Theranostic Radiopharmaceuticals. Postgrad. Med. Edu. Res. **47**(1), 31 (2013).
3. Herzog, H., Rösch, F., Stöcklin, G., Lueders, C., Qaim, S. M., Feinendegen, L.: Measurement of pharmacokinetics of ^{86}Y radiopharmaceuticals with PET and radiation dose calculation of analogous ^{90}Y radiotherapeutics. J. Nucl. Med. **34**, 2222 (1993).
4. Qaim, S. M., Scholten, B., Neumaier, B.: New developments in the production of theranostic pairs of radionuclides. J. Radioanal. Nucl. Chem. **318**, 1493 (2018).
5. Shikata, E.: Research of radioisotope production with fast neutrons (VI) Preparation of Cu-67. J. Nucl. Sci. Technol. **1**(5), 177 (1964).
6. Smith, N., Bowers, D., Ehst, D.: The production, separation, and use of ^{67}Cu for radioimmunotherapy: a review. Appl. Radiat. Isot. **70**(10), 2377 (2012).
7. Qaim, S. M.: The present and future of medical radionuclide production. Radiochim. Acta **100**, 635 (2012).
8. Qaim, S. M.: Nuclear data for production and medical application of radionuclides: present status and future needs. Nucl. Med. Biol. **44**, 31 (2017).
9. Boschi, A., Martini, P., Janevik-Ivanovska, E., Duatti A.: The emerging role of copper-64 radiopharmaceuticals as cancer theranostics. Drug Discovery Today **23**(8), 1489 (2018).
10. Peng, F., Lu, X., Janisse, J., Muzik, O., Shields, A.: PET of human prostate cancer xenografts in mice with increased uptake of $^{64}CuCl_2$. J. Nucl. Med. **47**(10), 1649 (2006).
11. Cai, H., Wu, J., Muzik, O., Hsieh, J., Lee, R., Peng, F., Reduced ^{64}Cu uptake and tumor growth inhibition by knockdown of human copper transporter 1 in xenograft mouse model of prostate cancer. J. Nucl. Med. **55**(4), 622 (2014).
12. Sugo, Y., Hashimoto, K., Kawabata, M., Saeki, H., Sato, S., Tsukada, K., Nagai, Y.: Application of ^{67}Cu produced by ^{68}Zn(n,n'p + d)^{67}Cu to biodistribution study in tumor-bearing mice. J. Phys. Soc. Jpn. **86**(2), 023201 (2017).
13. Rowshanfarzad, P., Sabet, M., Jalilian, A., Kamalidehghan, M.: An overview of copper radionuclides and production of ^{61}Cu by proton irradiation of ^{nat}Zn at a medical cyclotron. Appl. Radiat. Isot. **64**(12), 1563 (2006).
14. Qaim, S. M., Spahn, I.: Development of novel radionuclides for medical applications. J. Label. Compd. Radiopharm. **61**, 126 (2018).
15. Aliev, R., Belyshev, S., Kuznetsov, A., Dzhilavyan, L., Khankin, V., Aleshin, G., Kazakov, A., Priselkova, A., Kalmykov, S., Ishkhanov, B.: Photonuclear production and radiochemical separation of medically relevant radionuclides: ^{67}Cu. J. Radioanal. Nucl. Chem. **321**(1), 125 (2019).
16. Jamriska, D. S., Taylor, W., Ott, M., Heaton, R., Phillips, D., Fowler, M.: Activation rates and chemical recovery of ^{67}Cu produced with low-energy proton irradiation of enriched ^{70}Zn targets. J. Radioanal. Nucl. Chem. **195**, 263 (1995).
17. Hilgers, K., Stoll, T., Skakun, Y., Coenen, H., Qaim, S. M.: Cross section measurements of the nuclear reactions ^{nat}Zn(d,x)^{64}Cu; ^{66}Zn(d,α)^{64}Cu and ^{68}Zn(p,αn)^{64}Cu for production of ^{64}Cu and technical developments for small-scale production of ^{67}Cu via the ^{70}Zn(p,α)^{67}Cu process. Appl. Radiat. Isot. **59**, 343 (2003).
18. Pupillo, G., Sounalet, T., Michel, N., Mou, L., Esposito, J., Haddad, F.: New production cross sections for the theranostic radionuclide ^{67}Cu. Nucl. Instrum. Methods Phys. Res. Sect. B **415**, 41 (2018).
19. IAEA, IAEA website on Therapeutic Radionuclides" [Online]. available at: https://www-nds.iaea.org/radionuclides/. [Accessed in May 2019].
20. EXFOR, "Experimental Nuclear Reaction Data" [Online]. available at: https://www-nds.iaea.org/exfor/exfor.htm. [Accessed in May 2019].
21. Levkovskij, V. N.: Middle mass nuclides (A = 40–100) activation cross sections by medium energy (E = 10–50 MeV) protons and

α-particles (experiment and systematics), Inter-Vesti, Moscow (1991).
22. Kastleiner, S., Coenen, H. H., Qaim, S. M.: Possibility of production of ^{67}Cu at a small-sized cyclotron via the (p,α)-reaction on enriched ^{70}Zn. Radiochim. Acta **84**, 107 (1999).
23. N. N. D. C. (NNDC), NuDat2.7 database [Online]. available at: http://www.nndc.bnl.gov/nudat2/.
24. Koning, A., Rochman, D.: Modern nuclear data evaluation with the TALYS code system. Nucl. Data Sheets **113**(12), 2841 (2012).
25. Esposito, J., Bettoni, D., Boschi, A., Calderolla, M., Cisternino, S., Fiorentini, G., Keppel, G., Martini, P., Maggiore, M., Mou, L., Pasquali, M., Pranovi, L., Pupillo, G., Rossi Alvarez, C., Sarchiapone, L., Sciacca, G., Skliarova, H., Favaron, P., Lombardi, A., Antonini, P., Duatti, A.: LARAMED: a laboratory for radioisotopes of medical interest. Molecules **24**(1), 20 (2019).
26. Haddad, F., Ferrer, L., Guertin, A., Carlier, T., Michel, N., Barbet, J., Chatal, J.: ARRONAX, a high-energy and high-intensity cyclotron for nuclear medicine. Eur. J. Nucl. Med. Mol. Imaging **35**, 1377 (2008).
27. Pupillo, G., Esposito, J., Gambaccini, M., Haddad, F., Michel, N.: Experimental cross section evaluation for innovative ^{99}Mo production via the (α,n) reaction on ^{96}Zr target. J. Radioanal. Nucl. Chem. **302(**2), 911 (2014).
28. IAEA, "IAEA website on Monitor Reactions 2017" [Online]. available at: https://www-nds.iaea.org/medical/monitor_ reactions.html.
29. Ziegler, J., Ziegler, M., Biersack, J., SRIM – the stopping and range of ions in matter. Nucl. Instrum. Methods Phys. Res. Sect B **268**, 1818 (2010).
30. Stoll, T., Kastleiner, S., Shubin, Y. N., Coenen, H. H., Qaim, S. M.: Excitation functions of proton induced reactions on ^{68}Zn from threshold up to 71 MeV, with specific reference to the production of ^{67}Cu. Radiochim. Acta **90**, 309 (2002).
31. Schwarzbach, R., Zimmermann, K., Bläuenstein, P., Smith, A., Schubiger A.: Development of a simple and selective separation of ^{67}Cu from irradiated zinc for use in antibody labelling: a comparison of methods. Appl. Radiat. Isot. **46**(5), 329 (1995).
32. Medvedev, D., Mausner, L., Meinken, G., Kurczak, S., Schnakenberg, H., Dodge, C., Korach, E., Srivastava, S.: Development of large scale production of ^{67}Cu from ^{68}Zn at the high energy proton accelerator: closing the ^{68}Zn cycle. Appl. Radiat. Isot. **70**, 423 (2012).
33. Manenti, S., Alí Santoro, M. D. C., Cotogno, G., Duchemin, C., Haddad, F., Holzwarth, U., Groppi, F.: Excitation function and yield for the ^{103}Rh(d,2n)^{103}Pd nuclear reaction: optimization of the production of Palladium-103. Nucl. Med. Biol. **49**, 30 (2017).
34. Gilmore, G.: Practical gamma-ray spectrometry. 2nd ed. John Wiley & Sons Ltd, Warrington, UK (2008).
35. McGee, T., Rao, C., Saha, G., Yaffe, L.: Nuclear interactions of ^{45}Sc and ^{68}Zn with protons of medium energy. Nucl. Phys. A **150**, 11 (1970).
36. Duchemin, C., Guertin, A., Haddad, F., Michel, N., Métivier, V.: Production of medical isotopes from a thorium target irradiated by light charged particles up to 70 MeV. Phys. Med. Biol. **60**(3), 931 (2015).
37. Qaim, S. M., Sudár, S., Scholten, B., Koning, A., Coenen, H. H.: Evaluation of excitation functions of ^{100}Mo(p,d + pn)^{99}Mo and ^{100}Mo(p,2n)^{99m}Tc reactions: estimation of long-lived Tc-impurity and its implication on the specific activity of cyclotron-produced ^{99m}Tc. Appl. Radiat. Isot. **85**, 101 (2014).