New production cross sections for the theranostic radionuclide ^{67}Cu

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A B S T R A C T

The cross sections of the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions were measured at the ARRONAX facility by using the 70 MeV cyclotron, with particular attention to the production of the theranostic radionuclide ^{67}Cu. Enriched ^{68}Zn material was electroplated on silver backing and exposed to a low-intensity proton beam by using the stacked-foils target method. Since ^{67}Cu and ^{67}Ga radionuclides have similar half-lives and same γ-lines (they both decay to ^{67}Zn), a radiochemical process aimed at Cu/Ga separation was mandatory to avoid interferences in γ-spectrometry measurements. A simple chemical procedure having a high separation efficiency (> 99%) was developed and monitored during each foil processing, thanks to the tracer isotopes ^{61}Cu and ^{66}Ga. Nuclear cross sections were measured in the energy range 35–70 MeV by using reference reactions recommended by the International Atomic Energy Agency (IAEA) to monitor beam flux. In comparison with literature data a general good agreement on the trend of the nuclear reactions was noted, especially with latest measurements, but slightly lower values were obtained in case of ^{67}Cu. Experimental results of the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions were also compared with the theoretical values estimated by using the software TALYS. The production yield of the theranostic radionuclide ^{67}Cu was estimated considering the results obtained in this work.

1. Introduction

Theranostics is a new treatment strategy that combines therapy and diagnostics, allowing the possibility to select patients that have a good chance to respond to the specific radiopharmaceutical. The knowledge of the uptake prior therapy, through low-dose imaging scans (PET/CT or SPECT/CT), is the ground of tailored-dose treatments by using the same radiopharmaceutical. In addition, theranostic radionuclides permit to follow the behaviour of the therapeutic agent after injection and monitor treatment efficacy in time [1]. These steps toward the personalization of medicine induce positive outcomes for patients and limit healthcare costs, avoiding expensive ineffective therapies [2]. Among the theranostic isotopes of major interest [3], ^{67}Cu is probably the most promising candidate due to the specific role of copper in several biochemical processes. The overexpression of the human copper transporter protein (hCtr1) in a variety of cancers, explaining the already observed avidity of copper by tumour cells, was recently discovered [4,5]. In addition, ^{67}Cu has been long considered an excellent nuclide for radioimmuno-therapy (RIT) [6], by means of its peculiar physical-chemical characteristics (Table 1). Its relatively long half-life (61.83 h) permits to follow the slow biodistribution of antibodies, the most used bioactive vectors for ^{67}Cu, while its β-emission (mean E_{β^-} = 141 keV) has a therapeutic effect of short-medium range on the targeted cells. The low energy γ-rays produced by ^{67}Cu decay (E_γ = 184.58 keV, 48.6%) [7] allow to follow its track and monitor tumor uptake during therapy, by using standard SPECT or SPECT/CT cameras developed for the 140 keV γ-rays of ^{99m}Tc.

In recent years the main limiting factor for a more consistent evaluation of ^{67}Cu in clinical trials was its availability [8]. Although ^{67}Cu production started in nuclear reactors about 45 years ago, over the last decades it shifted over particle accelerators, due to the higher quality of the final product that meets the specifications required for its use in targeted therapy [9,10]. In comparison with other production routes, such as ^{64}Ni(α,n), ^{70}Zn(d,αn) and ^{70}Zn(p,α) [11–15], the advantages of using the ^{68}Zn(p,2p)^{67}Cu reaction are mainly based on the cheaper price of enriched target material needed (^{68}Zn natural abundance is 18.45%, ^{70}Zn is 0.61% and ^{64}Ni is 0.9255%) and the use of intense proton beams, available by several particle accelerators, including

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Table 1
Nuclear data associated to the radionuclides of interest, extracted from the NuDat2 Database (National Nuclear Data Center, NNDC) [7].

Radionuclide	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 d (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)
^{57}Ni	35.60 h (6)	127.167 (3)	16.7 (5)
		1377.63 (3)	81.7 (24)
^{22}Na	2.6027 y (10)	1274.537 (7)	99.941 (14)

compact cyclotrons [16]. In the framework of the project LARAMED (LAboratory of RAdionuclides for MEDicine) [17], a collaboration between the ARRONAX facility (Acceleration for Research in Radiochemistry and Oncology at Nantes Atlantique) [18] and INFN-LNL (Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro) recently started, aimed at the investigation of the best production routes, based on high-performance cyclotrons, of radionuclides with relevant medical interest, including ^{67}Cu.

The accurate knowledge of the cross section is the first step forward the optimization of radioisotope production [10]: for this reason the ^{68}Zn(p,2p)^{67}Cu reaction was repeatedly measured over years but literature data present some disparities. A critical analysis of published articles showed that such an experiment is demanding, since the proton irradiation of ^{68}Zn induces the co-production of large quantity of ^{67}Ga (half-life 3.2617 d), that as ^{67}Cu decays to the stable daughter nuclei ^{67}Zn. In addition to the similar half-lives, respectively about 62 and 78 h, ^{67}Cu and ^{67}Ga present the same γ-rays emission with different relative intensities (Table 1). This fact caused the need of a radiochemical process before γ-spectroscopy measurements to efficiently separate Cu from Ga isotopes and get accurate measurements of their activity values. The separation procedure could be a possible source of discrepancy between authors, as well as the use of different target materials (natural *versus* enriched), manufacturing techniques and selected monitor reactions or not up-to-date decay data.

The purpose of this work was to provide a new accurate measurement of the ^{68}Zn(p,2p)^{67}Cu excitation function in the energy range 35–70 MeV, integrating the existing database. Highly enriched ^{68}Zn material was used and the yield of the chemical process was monitored for each irradiated target. ^{61}Cu and ^{66}Ga radionuclides were used as tracer isotopes of the separation procedure, respectively for copper and gallium elements, thanks to their characteristics γ-rays and suitable half-lives (Table 1). New data of the ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga cross sections were also obtained. Our data were compared with previous published values [19] and with theoretical estimations provided by the TALYS code [20].

Considering the increasing interest of ^{67}Cu in theranostics and the recent availability of compact cyclotrons, the thick target yield for 70 MeV proton beams and fully enriched ^{68}Zn targets was calculated.

2. Materials and methods

2.1. Experimental set-up

Eight irradiation runs were performed at the ARRONAX facility in the energy range 35–70 MeV, using the stacked-foils technique, obtaining several experimental data on each run through the simultaneous bombardment of a set of thin foils [21]. A typical stacked-foils target was made by two identical patterns composed by an enriched ^{68}Zn target foil and a monitor foil, used to measure the effective beam flux by considering a reference reaction recommended by IAEA [22]. Some aluminium foils (500 μm–1 mm thick) were used to separate the two patterns, decrease the proton beam energy and catch possible recoil atoms. Considering that ^{61}Cu was not produced into ^{68}Zn targets in case of low energy proton beams (threshold energy E_{THR} = 35.97 MeV), a natural copper foil (20 μm thick) was added to the stacked-target and later used in the chemical process as source of ^{61}Cu *via* the ^{nat}Cu(p,x) reaction. On the contrary ^{66}Ga, the tracer radionuclide of gallium isotopes, was always directly produced into ^{68}Zn targets in the energy range investigated (E_{THR} = 23.55 MeV). Stacked-foils targets were made using high purity foils (> 99%, Goodfellow Cambridge Ltd., Ermine Business Park, Huntingdon PE29 6WR, UK).

2.2. Enriched ^{68}Zn target foils

Thin deposits of enriched ^{68}Zn metallic powder purchased by CHEMGAS (Boulogne-Billancourt, France) with isotopic composition ^{64}Zn (0.18%), ^{66}Zn (0.13%), ^{67}Zn (0.55%),^{68}Zn (98.78%), ^{70}Zn (0.36%), were obtained by electroplating on a natural high-purity silver foil (25 μm thick). The plating solution was prepared dissolving the ^{68}Zn powder in 5 mol/L HNO_3, evaporating to dryness and recovering in 5 mol/L H_2SO_4, (step repeated twice); the final solution had pH = 2 and 3 g/L of zinc concentration, measured by using ICP-OES CID spectrometer (iCAP 6500, Thermo Scientific, Waltham, MA, USA), in $^{68}ZnSO_4$ form. An aliquot of 30 ml of the electrolyte solution was usually required to obtain a 1.8 cm diameter, 10 μm thick deposit, using a proper silicon mask placed on the silver support: this geometry was a compromise between the dimension of the available proton beam size and the quantity of enriched material needed to realize targets. During the electroplating process, normally 30 min long, three electrodes were employed: one was connected to the silver backing (cathode), one to a platinum rod (anode) and the third was a saturated calomel electrode, immersed in the solution and used as reference electrode. The temperature of the solution was kept at 30 °C and the applied potential was fixed at -1.6 V/ENH. In order to maintain the homogeneity of zinc concentration during the cyclic potentiostatic currents, the solution was stirred at 300 rpm with a magnetic rod. Fig. 1 shows a typical target foil with the enriched ^{68}Zn deposit on the silver backing; the monitor foil, a disc of 1.8 cm diameter, was placed on the top of the deposit.

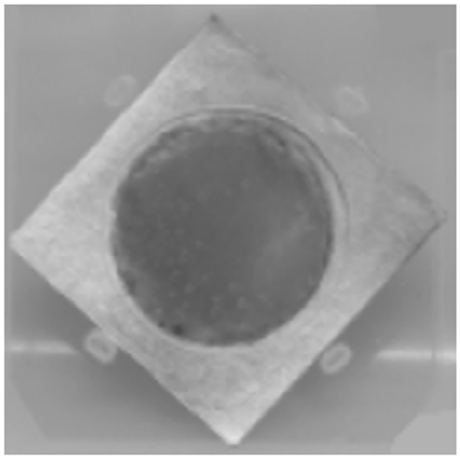

Fig. 1. Photograph of a typical target foil, composed by an enriched ^{68}Zn deposit on a silver support.

2.3. Irradiation

Electroplated target foils were inserted into the stacked-target and irradiated ranging from 35 MeV to 70 MeV proton beam provided by the ARRONAX cyclotron. A typical irradiation run had a duration of 1.5 h with a constant current of about 100–230 nA, monitored during the bombardment by using an instrumented beam dump. The beam line was under vacuum and closed with a 75 μm thick kapton foil. The stacks, containing two target foils, were located about 6.8 cm downstream in air. The proton beam energy in each layer of the stacked-target was calculated using the code SRIM-2013 [23], considering the thickness of the foils (calculated by accurately weighing their mass and measuring the dimensions), the extracted proton beam energy from the cyclotron and the energy losses in the kapton foil and air. In order to verify the general trend of the nuclear reaction, the incoming proton energies were selected to overlap data from different irradiation runs. The uncertainty on the proton beam energy was obtained by considering the uncertainty on extracted energy from the cyclotron (± 500 keV) and calculating with SRIM code the energy straggling through each layer of the stacked-target; it resulted a maximum value for the beam energy uncertainty of 750 keV.

2.4. Separation procedure, γ-spectroscopy and data analysis

After 14 h of cooling time, a radiochemical procedure was applied to irradiated targets in order to separate gallium from copper isotopes. This procedure was based on a Cu-resin (purchased to TrisKem International, France) able to selectively retain and release copper atoms under specific conditions, *i.e.* $2 \leq pH \leq 5$ HNO_3 (absorption) and 5 M HCl (elution) [24]. Each irradiated ^{68}Zn deposit was dissolved in HNO_3 5 M; if needed, an aliquot of the HNO_3 10 M solution with the dissolved ^{nat}Cu foil was added to the previous solution; the final solution, named "*Mix*", was analyzed by γ-spectrometry. In order to remove from the solution undesired silver atoms, the precipitation of AgCl was induced by adding NaCl, filtering the solution, evaporating it to dryness and adding HNO_3 at pH 2; the resulting solution was transferred into the Cu-resin, previously preconditioned with HNO_3 at pH 2. The amount of the Cu-resin used for each target-foil was optimized considering the quantity of ^{nat}Cu added. In order to rinse the resin additional HNO_3 at pH 2 was used, obtaining a solution with all isotopes but copper elements, named "*Rinse*". The resin was then eluted with HCl 5 M, obtaining a solution with copper isotopes, named "*Eluted*". The activity of all radionuclides was measured by γ-spectrometry, using 5 ml aliquot of *Rinse* and *Eluted*; the total activity value of each radionuclide was calculated by considering the weight ratio between the aliquot and the entire solution. The yield of chemical processing (Y) was monitored for all target foils, by measuring the activities of the tracer radionuclides (^{61}Cu and ^{66}Ga for copper and gallium elements respectively), before (Act^B) and after (Act^A) the radiochemical procedure; Eq. (1) shows the calculation of the chemical yield for copper isotopes, but a similar formula was used for gallium elements:

$$Y_{Cu} = \frac{Act^A_{Cu61}}{Act^B_{Cu61}} \tag{1}$$

The ^{67}Cu activity before the separation procedure (Act^B) was estimated by using Eq. (2):

$$Act^B_{Cu67} = \frac{Act^A_{Cu67}}{Y_{Cu}} = Act^A_{Cu67}\frac{Act^B_{Cu61}}{Act^A_{Cu61}} \tag{2}$$

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 standard liquid source (purchased to Cerca-Lea, France) containing the reference radionuclides ^{241}Am, ^{109}Cd, ^{57}Co, ^{139}Ce, ^{51}Cr, ^{113}Sn, ^{85}Sr, ^{137}Cs, ^{88}Y and ^{60}Co. The typical counting time of final samples was about 2 h; two sample-detector positions (at 19 cm distance and at contact) were used to always keep the dead time below 10%. In order to quantify separation efficiency, the Minimum Detectable Activity (MDA) was calculated for the radionuclides whose γ-line was not visible in the spectra, by using Eq. (3) [25]:

$$MDA = \frac{4.653\cdot\sqrt{C_B}}{\varepsilon(E)I(E)t_L} \tag{3}$$

where C_B was the number of counts of background in the energy region of interest, $\varepsilon(E)$ the detector efficiency and $I(E)$ the intensity of the γ-line of interest, and t_L the live time of the γ-spectroscopy measurement. The activities at the end of instantaneous bombardment (EOIB) of each radionuclide of interest were calculated with the Fitzpeak spectroscopy software [26]. The well-known activation formula was used to calculate the cross section values, by considering the monitor reactions ^{nat}Ni(p,x)^{57}Ni and ^{nat}Al(p,x)^{22}Na recommended by IAEA [22], respectively for energies lower and higher than 50 MeV, as previously described [21]. The uncertainty of the reference cross section value was estimated by considering the uncertainty of the closest experimental data present in the fitting curve proposed by IAEA. Isotopic purity of the ^{68}Zn deposit and chemical purity of reference foils were taken into account in the cross section calculation; results referred to 100% enriched ^{68}Zn target. Table 1 reports the nuclear data used, selected from NuDat 2 database [7]. The uncertainty of the cross section values were evaluated in a quadratic form, considering individual uncertainties: reference cross section (≤10%), measured activity (≤8%), target thickness and decay data values (1%).

2.5. Comparison with TALYS code

The new experimental cross section values obtained in this work for ^{67}Cu, ^{67}Ga and ^{66}Ga radionuclides were compared with results from the TALYS code (version 1.6 released in December 2013) [20]. TALYS is a software that simulates nuclear reactions induced by light particles on target nuclei heavier than carbon: it incorporates theoretical models to predict observables, including cross section values, as a function of the incident particle energy (from 1 keV to 1 GeV). A combination of models, based on the best description of the whole set of available data for all nuclear reactions, were defined by the authors and put as default in the code [20]. Considering the wide range of TALYS's applications, some discrepancies of results based on default parameters may be found with experimental data for specific nuclear reactions and energy range of interest. To tackle this issue, Duchemin et al. (2015) proposed the use of a new combination of models for proton- and deuteron-induced reactions in the energy range 1–70 MeV [27]. This set included the optical potential (only for deuterons), the exciton model for pre-equilibrium reaction, numerical transition rates with an optical model for collision probability and the microscopic level densities (Skyrme force) from Hilaire's combinatorial tables [20]. Since such new combination of models showed a good reproducibility for different targets [27], in this work we used TALYS code with both combination of models without any fit to our result. Predictions based on the default set of models developed by [20] and the new combination proposed by [27] were respectively indicated as *Talys* and *Talys** on the graphs (Figs. 2–4).

3. Results and discussions

The radiochemical yield for copper and gallium isotopes, respectively Y_{Cu} and Y_{Ga}, was precisely determined by using the tracer radionuclide activities (^{61}Cu and ^{66}Ga). A large variety of chemical yield was measured from one experiment to the other, mainly due to the precipitation step. Despite this effect, the precipitation of AgCl was considered essential: it allowed to remove most of the radioactive isotopes, produced into the silver support, that might have affected γ-spectrometry measurements of *Rinse* and *Eluted* solutions due to their

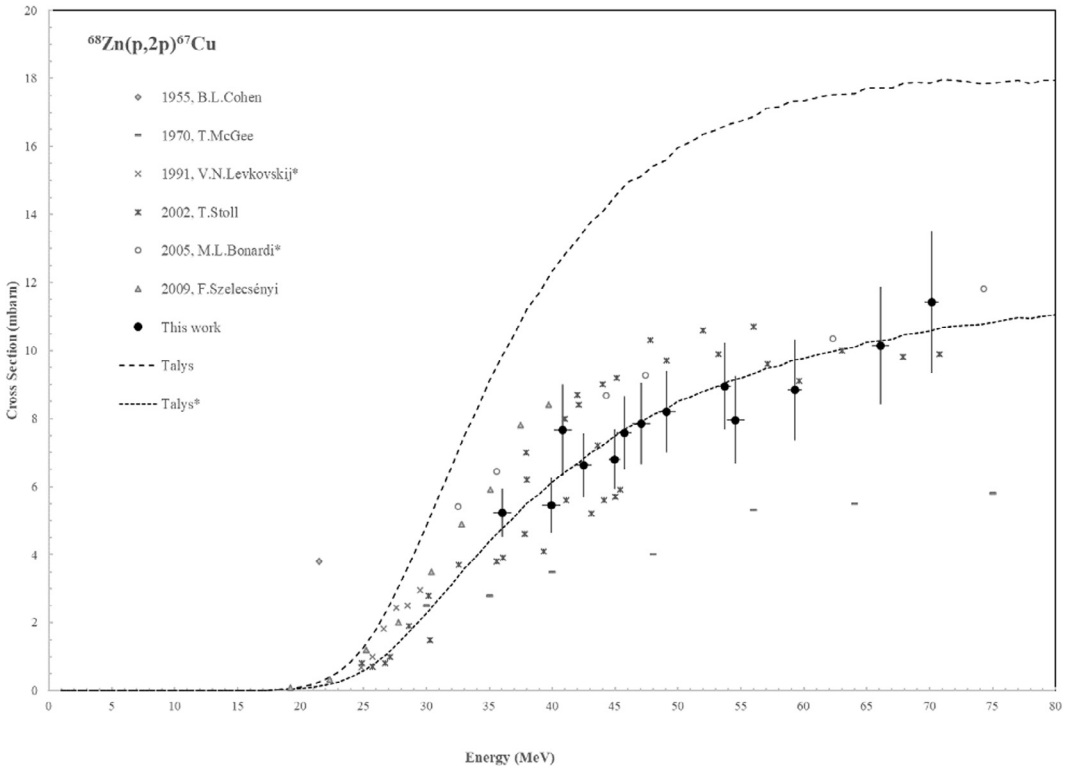

Fig. 2. Cross section of the $^{68}Zn(p,2p)^{67}Cu$ nuclear reaction.

high activity values. The efficiency of the separation procedure was calculated considering the contamination of copper isotopes into the *Rinse* solution and, viceversa, the presence of gallium isotopes in the *Eluted* solution. In this work the activity of ^{66}Ga (and thus ^{67}Ga) into *Eluted* solution was about 0.2% of its initial activity into *Mix* solution, while the ^{61}Cu activity (and thus ^{67}Cu) into *Rinse* solution was always below the Minimum Detectable Activity (MDA), corresponding to less than 1% of its initial activity into *Mix* solution. These results showed a high yield of separation Cu/Ga isotopes, assuring a proper measurement of ^{67}Cu and ^{67}Ga activity values respectively in *Eluted* and *Rinse* solutions.

Figs. 2–4 respectively reported results obtained in this work for the

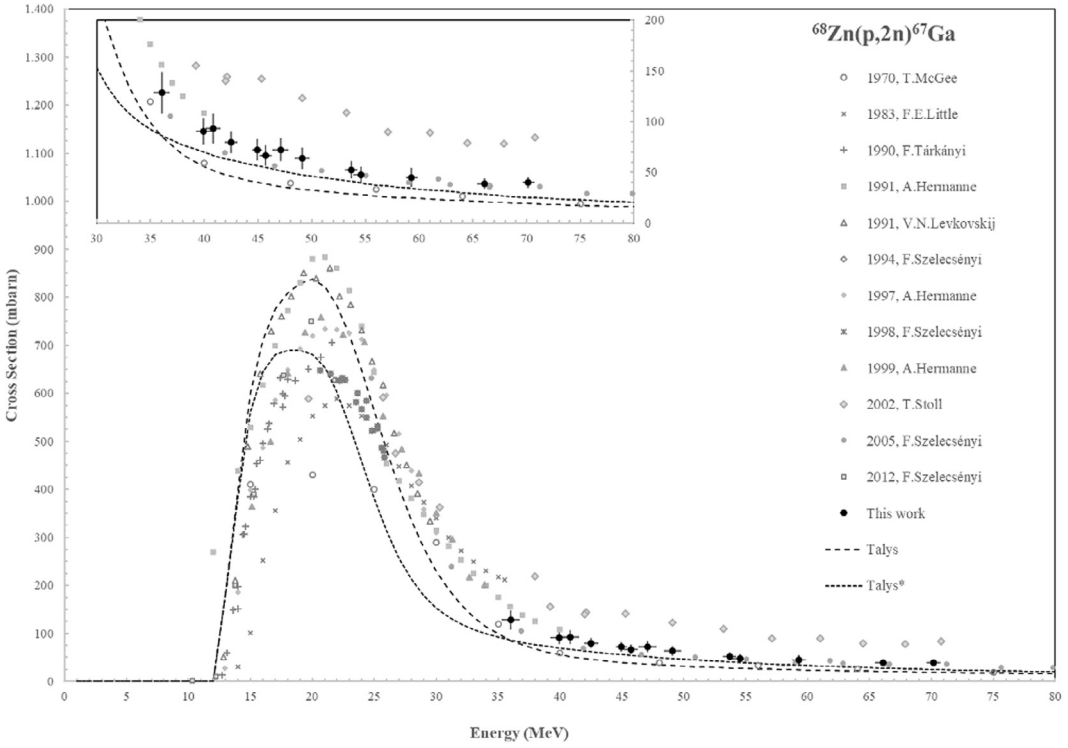

Fig. 3. Cross section of the $^{68}Zn(p,2n)^{67}Ga$ nuclear reaction.

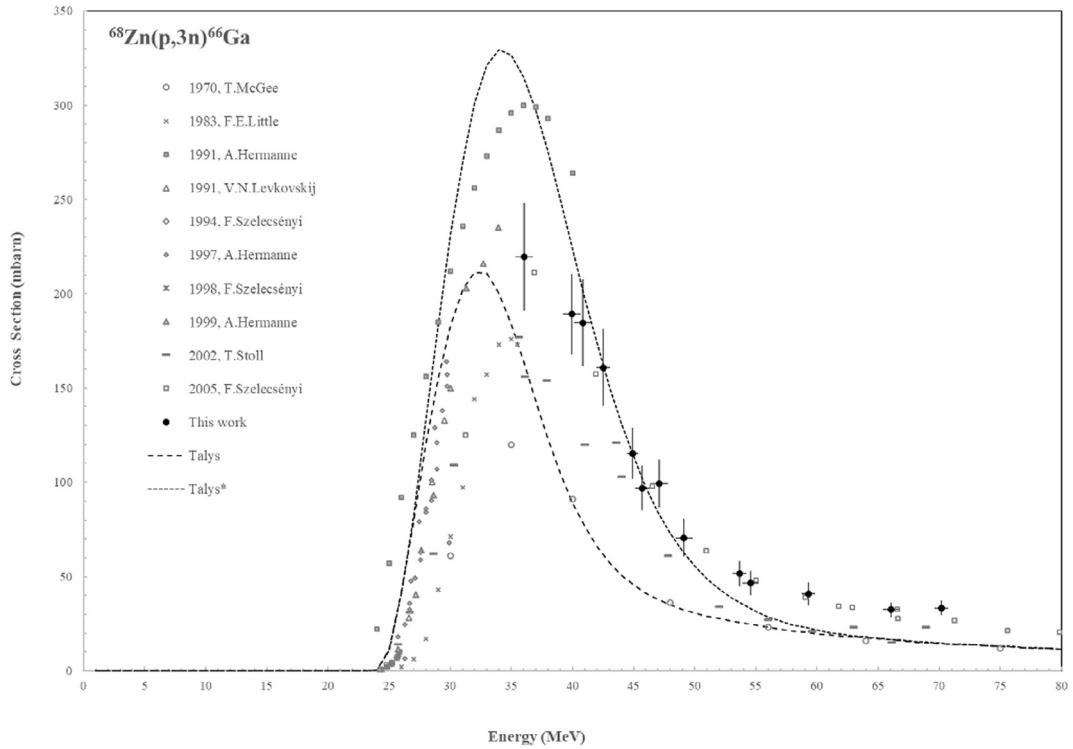

Fig. 4. Cross section of the ^{68}Zn(p,3n)^{66}Ga nuclear reaction.

Table 2
Experimental cross section values for the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions and the monitor reactions ^{nat}Ni(p,x)^{57}Ni and ^{nat}Al(p,x)^{22}Na values used [22]

Energy (MeV)	^{67}Cu (mbarn)	^{67}Ga (mbarn)	^{66}Ga (mbarn)	Monitor Reaction (mbarn)
36.0 ± 0.7	5.2 ± 0.7	128.3 ± 20.7	219.8 ± 28.5	92.1 (^{57}Ni)
39.9 ± 0.7	5.5 ± 0.8	90.5 ± 13.0	189.2 ± 21.5	86.0 (^{57}Ni)
40.8 ± 0.7	7.7 ± 1.3	92.8 ± 14.5	184.7 ± 23.1	84.5 (^{57}Ni)
42.5 ± 0.6	6.6 ± 0.9	79.7 ± 10.8	160.8 ± 20.4	81.9 (^{57}Ni)
44.9 ± 0.4	6.8 ± 0.9	72.2 ± 10.5	115.4 ± 13.4	78.3 (^{57}Ni)
45.7 ± 0.6	7.6 ± 1.1	66.5 ± 10.3	97.0 ± 11.7	77.7 (^{57}Ni)
47.1 ± 0.7	7.8 ± 1.2	72.2 ± 11.4	99.3 ± 12.6	41.6 (^{22}Na)
49.1 ± 0.7	8.2 ± 1.2	63.6 ± 10.4	70.6 ± 9.9	39.0 (^{22}Na)
53.7 ± 0.6	8.9 ± 1.3	52.5 ± 8.4	51.5 ± 6.5	32.9 (^{22}Na)
54.6 ± 0.7	8.0 ± 1.3	47.7 ± 8.1	46.5 ± 6.1	31.9 (^{22}Na)
59.3 ± 0.6	8.8 ± 1.5	45.0 ± 9.5	40.9 ± 6.1	27.2 (^{22}Na)
66.1 ± 0.7	10.1 ± 1.7	38.9 ± 5.1	32.4 ± 3.7	23.5 (^{22}Na)
70.2 ± 0.6	11.4 ± 2.1	39.7 ± 5.3	33.3 ± 3.8	22.1 (^{22}Na)

^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga nuclear reactions. Literature data were reported on figures without error bars for clarity; TALYS estimations, obtained by using both default (*Talys*) and new set of models (*Talys**), were also shown as dashed and dotted lines (Figs. 2–4). Numerical values of the production cross sections of ^{67}Cu and other radionuclides of interest (^{67}Ga and ^{66}Ga) were listed in Table 2.

3.1. The ^{68}Zn(p,2p)^{67}Cu cross section

Fig. 2 reported the ^{68}Zn(p,2p)^{67}Cu cross section measured in this work in the energy range 35–70 MeV; literature data available on EXFOR library [19] were also shown, without error bars for clarity. The new set of data obtained in this work was in good agreement with previous measurements, in particular with the latest ones. Szelecsényi et al. (2009) measured the cross section from the threshold energy up to 40 MeV, describing the rising region of the nuclear reaction [28]. Bonardi et al. (2005) [29] irradiated a natural zinc target and their data in Fig. 2 were rescaled to a 100% enriched ^{68}Zn material, thus including the additional contribution of (p,x) reactions on ^{70}Zn (0.61% natural abundance). Stoll et al. (2002) [30] investigated the energy range 25–71 MeV, obtaining two series of values in the energy range 35–45 MeV. It has to be noted that data obtained by Levkovskij et al. (1991) [31] were rescaled by an appropriate factor to correct the use of an over-estimated reference reaction, as reported in EXFOR database [19]. Previous data [32,33] were considered not reliable, due to the large discrepancy with other authors; in particular, as reported by IAEA [34], results by McGee et al. (1970) [33] did not reproduce the expected shape of the excitation function even after the adjustment needed to account for up-to-date IAEA monitor data.

Estimations of the ^{68}Zn(p,2p)^{67}Cu nuclear reaction performed with the TALYS code by using default (*Talys*) and different (*Talys**) set of models were also shown in Fig. 2. Results showed that the new set of models proposed by Duchemin et al. (2015) [27] properly describes the experimental values, including the new data obtained in this work. On the contrary, the default set of parameters overrated the nuclear reaction, almost doubling it, even if the trend was correctly described.

3.2. The ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga cross sections

Figs. 3 and 4 respectively showed the measurements of the ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga cross sections obtained in this work, also reporting literature data and estimations performed with TALYS software and the two set of models.

The ^{68}Zn(p,2n)^{67}Ga nuclear reaction has an intense peak value (about 700 mbarn) at energies lower than 25 MeV (Fig. 3). Data measured in this work described the decreasing part of the reaction: there is an excellent agreement with values obtained by Szelecsényi et al. (2005) [35] in the entire energy range (35–70 MeV) and, in the energy region 35–45 MeV, with data by Hermanne et al. (1991) [36]. The same author repeated the measurement up to 33 MeV, confirming previous results [37]. The only discrepancy at high energy was the data set by Stoll et al. (2002) [30], that seemed to almost double the cross section

values in the entire energy range (38–71 MeV).

Fig. 3 showed that the two estimations of the $^{68}Zn(p,2n)^{67}Ga$ nuclear reaction performed with the TALYS code mainly differed on the peak value: default parameters provided about 840 mb, while varied models about 690 mb. Even experimental data presented some discrepancy in this energy region, but latest measurements estimated the peak value to about 750 mb [35,38]. Considering that the peak region is the most sensitive area to test a code prediction, the default set of models seemed to better describe the shape of the $^{68}Zn(p,2n)^{67}Ga$ reaction, although the maximum value may be overrated.

Fig. 4 reported the measurements of the $^{68}Zn(p,3n)^{66}Ga$ cross section: as in case of ^{67}Ga reaction, results obtained in this work described the decreasing part of the nuclear reaction. There was an excellent agreement with latest values by Szelecsényi et al. (2005) [35] in the entire energy range (35–70 MeV); measurements by Stoll et al. (2002) [30] were in good agreement for energies higher than 43 MeV, while at lower energies these previous data seemed to underestimate the nuclear reaction. Hermanne et al. (1991) [36] measured a very high peak value (around 290 mb at 34 MeV), but the same authors repeated the experiment in 1999 [37] and these later data are in good agreement with results obtained in this work.

Fig. 4 showed that the estimations of the $^{68}Zn(p,3n)^{66}Ga$ reaction obtained with TALYS software presented as major discrepancy the maximum peak value and the width of the peak. Default parameters provided a better description of the maximum peak value but showed an energy shift of about 10 MeV in comparison with latest experimental data, including results obtained in this work. The prediction based on the set of models proposed by [27] seemed to better describe the nuclear reaction for energies higher than 40 MeV, however they overrated the maximum peak value, giving about 330 mb at 34 MeV. This discrepancy of TALYS estimations and experimental data underlined the need of further work on nuclear models for specific reactions and energy range of interest.

3.3. Copper-67 production yield

Considering the recent availability of compact cyclotrons, able to provide intense proton beams of high energy, the production yield of ^{67}Cu was calculated. The yield value of ^{67}Cu in the energy range 70–35 MeV, based on the experimental data of the $^{68}Zn(p,2p)^{67}Cu$ cross section obtained in this work, is 24.25 MBq/μAh. This value is 15% lower than the IAEA estimation in the same energy region (28.46 MBq/μAh) [34].

In order to maximize the production of the radionuclide of interest it is possible to extend the calculation to a larger energy range. In view of the good agreement of our data for the $^{68}Zn(p,2p)^{67}Cu$ cross section with the results obtained by using TALYS code with the set of models proposed by [27], it is possible to extend the yield calculation in the energy range 70–19 MeV, i.e. the starting energy of the nuclear reaction of interest. This thick target yield value is 25.95 MBq/μAh, i.e. the increase is 7% in respect of the yield in the energy range 70–35 MeV. On the other hand the increase of the thickness of the target material needed is around 28%. Considering the cost of the enriched material and the final use of ^{67}Cu radionuclide, the best energy range should be evaluated for each specific case, taking into account also the targetry and its cooling system.

4. Conclusion

In this work the new cross section data of the $^{68}Zn(p,x)^{67}Cu$, ^{67}Ga, ^{66}Ga reactions were presented. Experiments were performed at the ARRONAX facility by using 70 MeV proton cyclotron. A simple chemical procedure was applied to the irradiated targets, composed by enriched material, in order to accurately measure ^{67}Cu and ^{67}Ga activity values by γ-spectrometry. The separation yield of the radiochemical process was determined during each separation process by using ^{61}Cu and ^{66}Ga radionuclides as tracer isotopes, respectively for copper and gallium elements. Reference reactions proposed by IAEA were used to monitor beam flux and calculate the cross sections. The new set of data obtained in this work for all the radionuclides of interest were in good agreement with the latest measurements. The TALYS software was used to estimate the nuclear reaction of interest, considering the default set of models and the one recently proposed by [27]. Results showed that in case of the $^{68}Zn(p,2n)^{67}Cu$ the new set of models suitably described data obtained in this work. On the other hand, both theoretical predictions of the (p,2n) and (p,3n) reactions presented some discrepancies with experimental values in the peak energy region: this fact highlighted the need of further work on nuclear models for specific reactions and energy range of interest.

Based on the data obtained in this work the yield of ^{67}Cu was calculated for thick targets and it was found to be 15% lower than the IAEA estimation in the same energy region (70–35 MeV). This difference is relevant in order to plan a sustainable production of ^{67}Cu for medical purpose.

The increase of ^{67}Cu yield for 70–19 MeV thick targets in comparison with 70–35 MeV targets is only 7%, but the thickness increment is higher than 28%. Specific evaluations about the optimal irradiation conditions, taking into account the cost of enriched target material and the specific final use of ^{67}Cu-labelled radiopharmaceuticals, are recommended. In order to plan a sustainable production of ^{67}Cu for preclinical and clinical use it is important also to consider the recovery and reuse of irradiated material through definite radiochemical procedures.

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References

[1] S.C. Srivastava, A bridge not too far: personalized medicine with the use of theragnostic radiopharmaceuticals, J. Postgraduate Med. Educ. Res. 47 (1) (2013) 32–46, http://dx.doi.org/10.5005/jp-journals-10028-1054.

[2] D. Taïeb, R.J. Hicks, K. Pacak, Nuclear medicine in cancer theranostics: beyond the target, J. Nucl. Med. 57 (2016) 1659–1660, http://dx.doi.org/10.2967/jnumed.116.178343.

[3] IAEA CRP on “Therapeutic Radiopharmaceuticals Labelled with New Emerging Radionuclides (67Cu, 186Re, 47Sc)” and supported by the IAEA, Vienna, Austria, CRP code: F22053, 2016. http://cra.iaea.org/cra/explore-crps/all-active-by-programme.html.

[4] F. Peng, X. Lu, J. Janisse, O. Muzik, A.F. Shields, PET of human prostate cancer xenografts in mice with increased uptake of $^{64}CuCl_2$, J. Nucl. Med. 47 (2006) 1649–1652.

[5] H. Cai, J. Wu, O. Muzik, J. Hsieh, R.J. Lee, F. Peng, 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 (2014) 622–628, http://dx.doi.org/10.2967/jnumed.113.126979.
[6] I. Novak-Hofer, P.A. Schubiger, Copper-67 as a therapeutic nuclide for radioimmunotherapy, Eur. J. Nucl. Med. 29 (2002) 821–830, http://dx.doi.org/10.1007/s00259-001-0724-y.
[7] National Nuclear Data Center (NNDC), Information extracted from the NuDat2 Database, 2016. http://www.nndc.bnl.gov/nudat2/.
[8] P. Rowshanfarzad, M. Sabet, A.R. Jalilian, M. Kamalidehghan, 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) (2006) 1563–1573.
[9] H.A. O'Brien, The preparation of ^{67}Cu from ^{67}Zn in a nuclear reactor, Int. J. Appl. Radiat. Isot. 20 (1969) 121–124, http://dx.doi.org/10.1016/0020-708X(69)90149-5.
[10] S.M. Qaim, Nuclear data for production and medical application of radionuclides: present status and future needs, Nucl. Med. Biol. 44 (2017) 31–49, http://dx.doi.org/10.1016/j.nucmedbio.2016.08.016.
[11] S. Kastleiner, H.H. Coenen, S.M. Qaim, Possibility of production of ^{67}Cu at a small-sized cyclotron via the (p, α) reaction on enriched ^{7}0Zn, Radiochim. Acta 84 (1999) 107–110.
[12] R. Schwarzbach, K. Zimmermann, I. Novak-Hofer, P.A. Schubiger, A comparison of ^{67}Cu production by proton (67 to 12 MeV) induced reactions on ^{nat}Zn and enriched ^{68}Zn/^{70}Zn, J. Labelled Compd. Radiopharm. 44 (2001), http://dx.doi.org/10.1002/jlcr.25804401284.
[13] K. Hilgers, T. Stoll, Ye. Skakun, H.H. Coenen, S.M. Qaim, Cross section measurements of the nuclear reactions natZn(d, x)64Cu, 66Zn(d, α)64Cu, 68Zn(p, αn)64Cu for production of 64Cu and technical developments for small scale production of 67Cu via the 70Zn(p, α)67Cu process, Appl. Radiat. Isot. 59 (2003) 343–351, http://dx.doi.org/10.1016/S0969-8043(03)00199-4.
[14] Ye. Skakuna, S.M. Qaim, Excitation function of the ^{64}Ni(α,p)^{67}Cu reaction for production of ^{67}Cu, Appl. Radiat. Isot. 60 (2004) 33–39, http://dx.doi.org/10.1016/j.apradiso.2003.09.003.
[15] J. Kozempel, K. Abbas, F. Simonelli, A. Bulgheroni, U. Holzwarth, N. Gibson, Preparation of ^{67}Cu via deuteron irradiation of ^{70}Zn, Radiochim. Acta 100 (2012) 419–423, http://dx.doi.org/10.1524/ract.2012.1939.
[16] S.M. Qaim, New trends in nuclear data research for medical radionuclide production, Radiochim. Acta 101 (2013) 473–480, http://dx.doi.org/10.1524/ract.2013.2069.
[17] M. Maggiore, D. Campo, P. Antonini, A. Lombardi, M. Manzolaro, A. Andrighetto, A. Monetti, D. Scarpa, J. Esposito, L. Silvestrin, SPES: a new cyclotron-based facility for research and applications with high-intensity beams, Mod. Phys. Lett. A 32 (17) (2017) 1740010, http://dx.doi.org/10.1142/S0217732317400107.
[18] F. Haddad, L. Ferrer, A. Guertin, T. Carlier, N. Michel, J. Barbet, J.F. Chatal, ARRONAX, a high-energy and high-intensity cyclotron for nuclear medicine, Eur. J. Nucl. Med. Mol. Imaging 35 (2008) 1377–1387, http://dx.doi.org/10.1007/s00259-008-0802-5.
[19] Experimental Nuclear Reaction Data (EXFOR), Information Extracted from the Database, 2016. https://www-nds.iaea.org/exfor/exfor.htm.
[20] A.J. Koning, D. Rochman, Modern nuclear data evaluation with the TALYS code system, Nucl. Data Sheets 113 (12) (December 2012) 2841–2934.
[21] G. Pupillo, J. Esposito, M. Gambaccini, F. Haddad, N. Michel, Experimental cross section evaluation for innovative ^{99}Mo production via the (α, n) reaction on ^{9}6Zr target, J. Radioanal. Nucl. Chem. 302 (2) (2014) 911–917, http://dx.doi.org/10.1007/s10967-014-3321-9.
[22] IAEA-TECDOC-1211, Charged particle cross section database for medical radioisotope production: diagnostic radioisotopes and monitor reactions, IAEA, Vienna, 2001. https://www-nds.iaea.org/medical/monitor_reactions.html.
[23] J.F. Ziegler, M.D. Ziegler, J.P. Biersack, SRIM – the stopping and range of ions in matter, Nucl. Instr. Meth. Phys. Res. Sec. B 268 (2010) 1818–1823.
[24] C. Dirks, B. Scholten, S. Happel, A. Zulauf, A. Bombard, H. Jungclas, Characterization of a Cu selective resin and its application to the production of ^{64}Cu, J. Radioanal. Nucl. Chem. 286 (2010) 671–674, http://dx.doi.org/10.1007/s10967-010-0744-9.
[25] G.R. Gilmore, Practical Gamma-ray Spectrometry, second ed., John Wiley & Sons Ltd, 2008 ISBN: 978-0-470-86196-7.
[26] FitzPeaks Gamma Analysis and Calibration Software Version, 3.66, produced by J. F. Computing Services (UK), based on methods presented, Nucl. Instrum. Methods 190 (1981) 89–99.
[27] C. Duchemin, A. Guertin, F. Haddad, N. Michel, V. Métivier, Production of medical isotopes from a thorium target irradiated by light charged particles up to 70 MeV, Phys. Med. Biol. 60 (2015) 931–946, http://dx.doi.org/10.1088/0031-9155/60/3/931.
[28] F. Szelecsényi, G.F. Steyn, S.G. Dolley, Z. Kovács, C. Vermeulen, T.N. van der Walt, Investigation of the ^{68}Zn(p,2p)^{67}Cu nuclear reaction: new measurements up to 40 MeV and compilation up to 100 MeV, Nucl. Instr. Meth. Phys. Res. Sec. B 267 (2009) 1877–1881, http://dx.doi.org/10.1016/j.nimb.2009.03.097.
[29] M.L. Bonardi, F. Groppi, H.S. Mainardi, V.M. Kokhanyuk, E.V. Lapshina, M.V. Mebel, B.L. Zhuikov, Cross section studies on ^{64}Cu with Zinc target in the proton energy range from 141 down to 31 MeV, J. Radioanal. Nucl. Chem. 264 (1) (2005) 101–105, http://dx.doi.org/10.1007/s10967-005-0681-1.
[30] T. Stoll, S. Kastleiner, Y.N. Shubin, H.H. Coenen, S.M. Qaim, Excitation functions of proton induced reactions on ^{68}Zn from threshold up to 71 MeV and with specific reference to the production of ^{67}Cu, Radiochim. Acta 90 (2002) 309–313, http://dx.doi.org/10.1524/ract.2002.90.6.309.
[31] V.N. Levkovskij, 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.
[32] B.L. Cohen, E. Newman, T.H. Handley, (P, PN) + (P,2N) and (P,2P) cross sections in medium weight elements, Phys. Rev. 99 (1955) 723–727.
[33] T. McGee, C.L. Rao, G.B. Saha, L. Yaffe, Nuclear interactions of Sc-45 and Zn-68 with protons of medium energy, Nucl. Phys. Sect. A 150 (1970) 11–29.
[34] IAEA Bibliography of experimental data on 68Zn(p,2p)67Cu, https://www-nds.iaea.org/radionuclides/zn867cu0.html.
[35] F. Szelecsényi, G.F. Steyn, Z. Kovács, T.N. van der Walt, K. Suzuki, K. Okada, K. Mukai, New cross-section data for the 66Zn(p, n)66Ga, 68Zn(p,3n)66Ga, natZn(p, x)66Ga, 68Zn(p,2n)67Ga and natZn(p, x)67Ga nuclear reactions up to 100 MeV, Nucl. Instr. Meth. Phys. Res. Sect. B 234 (4) (2005) 375–386, http://dx.doi.org/10.1016/j.nimb.2005.02.011.
[36] A. Hermanne, N. Walravens, O. Cicchelli, Optimization of isotope production by cross section determination, Conference on Nuclear Data for Science and Technology, Juelich 1991, p.616-618.
[37] A. Hermanne, F. Szelecsényi, M. Sonck, S. Takács, F. Tárkányi, P. Van Den Winkel, New Cross Section Data on ^{68}Zn(p,2n)^{67}Ga and ^{nat}Zn(p, xn)^{6}7Ga Nuclear Reactions for the Development of a Reference Data Base, J. Radioanal. Nucl. Chem. 240 (1999) 623, http://dx.doi.org/10.1007/BF02349423.
[38] F. Szelecsényi, Z. Kovács, K. Nagatsu, K. Fukumura, K. Suzuki, K. Mukai, Investigation of direct production of ^{68}Ga with low energy multiparticle accelerator, Radiochim. Acta 100 (2012) 5, http://dx.doi.org/10.1524/ract.2011.1896.