Cyclotron production of ^{67}Cu: a new measurement of the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga nuclear cross sections

Gaia Pupillo[*1,2], Thomas Sounalet[3], Nathalie Michel[4], Férid Haddad[3,4], Liliana Mou[1], Luciano Canton[5], Andrea Fontana[6], Juan Esposito[1] and Adriano Duatti[2]

[1] Istituto Nazionale di Fisica Nucleare (INFN), Laboratori Nazionali di Legnaro (LNL), Italy
[2] Università degli Studi di Ferrara, Ferrara, Italy
[3] Laboratoire Subatech, IN2P3-CNRS, Ecole des Mines de Nantes, Nantes, France
[4] GIP ARRONAX, Nantes, France
[5] Istituto Nazionale di Fisica Nucleare (INFN), Sezione di Padova (PD), Italy
[6] Istituto Nazionale di Fisica Nucleare (INFN), Sezione di Pavia (PV), Italy
pupillo@fe.infn.it

Abstract

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 alow-intensity proton beam by using the stacked-foils target method. Since ^{67}Cu and ^{67}Ga radionuclides have similar half-lives and sameγ-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 nuclear reaction code TALYS. The production yield of the theranostic radionuclide ^{67}Cu was estimated considering the results obtained in this work.

Key words: *radioisotope production, cyclotron, copper-67, radiochemistry, cross section.*

Producción de ^{67}Cu en ciclotrón: una nueva medición de secciones eficaces nucleares de ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga y ^{68}Zn(p,3n)^{66}Ga

Resumen

Las secciones eficaces de las reacciones ^{68}Zn (p, 2p) ^{67}Cu, ^{68}Zn (p, 2n) ^{67}Ga y ^{68}Zn (p, 3n) ^{66}Ga se midieron en la instalación ARRONAX utilizando el ciclotrón 70 MeV, con especial atención a la producción del radionucleidos teranóstico ^{67}Cu. El material enriquecido ^{68}Zn se galvanizó sobre soporte de plata y se expuso a un haz de protones de baja intensidad utilizando un blanco de láminas apiladas. Como los radionucleidos ^{67}Cu y ^{67}Ga tienen periodos de semidesintegración y líneas γ similares (ambos se desintegran a ^{67}Zn), un proceso radioquímico dirigido a la separación Cu / Ga fue obligatorio para evitar interferencias en las mediciones de espectrometría γ. Se desarrolló un procedimiento químico simple con una alta eficiencia de separación (> 99%) durante cada procesamiento de la lámina, gracias a los isótopos trazadores ^{61}Cu y ^{66}Ga. Las secciones eficaces nucleares se midieron en el rango de energía de 35-70 MeV utilizando reacciones de referencia recomendadas por el Organismo Internacional de Energía Atómica (OIEA) para monitorear el flujo del haz. Al comparar con los datos de la literatura, se observó una buena concordancia en general con la tendencia de las reacciones nucleares, particularmente con las últimas mediciones, pero se obtuvieron valores ligeramente inferiores en el caso de ^{67}Cu. Los resultados experimentales de las reacciones ^{68}Zn (p, 2p) ^{67}Cu, ^{68}Zn (p, 2n) ^{67}Ga

y ^{68}Zn (p, 3n) ^{66}Ga también se compararon con los valores teóricos estimados usando el código de reacción nuclear TALYS. El rendimiento de producción del radionucleido teranóstico ^{67}Cu se estimó considerando los resultados obtenidos en este trabajo.

Palabras clave: *producción de isotopos; generadores de radisótopos; ciclotrones; secciones eficaces; cobre 67.*

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. Among the theranostic isotopesof major interest [1], ^{67}Cu is probably the most promising candidate due to the specific role of copper in several biochemical processes. In addition, ^{67}Cu has been long considered an excellent nuclide for radioimmuno-therapy (RIT), 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 $E_{\beta-}$ = 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%) [2] allow to follow its uptake, by using standard SPECT or SPECT/CTcameras 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. In the framework of the LARAMED (LAboratory of RAdionuclides for MEDicine) [3] project , a collaboration between the ARRONAX facility (Acceleration for Research in Radiochemistry and Oncology at Nantes Atlantique) [4] and INFN-LNL (Istituto Nazionale di Fisica Nucleare, Laboratori Nazionali di Legnaro) started, aimed at investigating 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 towards the optimization of radioisotope production: acritical analysis of previous data available on EXFOR library [5] showed that there are some discrepancies. In fact, during the proton irradiation of ^{68}Zn target there is 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 hours, ^{67}Cu and ^{67}Ga present the same γ-rays emission with different relative intensities (Table 1). This fact requested 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. 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.

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.

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) 208.951 (10) 300.219 (10) 393.529 (10)	48.7 (3)
^{64}Cu	12.701 h (2)	1345.77 (6)	0.475 (11)
^{61}Cu	3.333 h (5)	282.956 (10) 656.008 (10)	12.2 (22) 10.8 (20)
^{67}Ga	3.2617 d (5)	184.576 (10) 208.950(10) 300.217(10) 393.527(10)	21.410 (10) 2.460 (10) 16.64 (12) 4.56 (24)
^{66}Ga	9.49 h (3)	1039.220 (3)	37.0 (20)
^{57}Ni	35.60 h (6)	127.167 (3) 1377.63 (3)	16.7 (5) 81.7 (24)
^{22}Na	2.6027 y (10)	1274.537 (7)	99.941 (14)

Materials and methods

The 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. 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 [6]. 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., UK). The ^{68}Zn target foils were obtained by electrodeposition 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%); a natural high-purity silver foil (25 μm thick) was used as support (Figure 1).

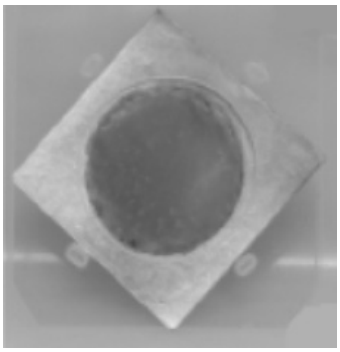

Fig. 1. Photograph of a typical target foil with enriched ^{68}Zn deposit on a silver support.

Electroplated target foils were inserted into the stacked-target and irradiated by the proton beam provided by the ARRONAX cyclotron with energy ranging from 35 MeV to 70 MeV. A typical irradiation run had a duration of 1.5 hours with a constant current of about 100-230 nA, monitored during the bombardment by using an instrumented beam dump. After 14 hours 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. Further details of the radiochemical procedure can be found in [7]. The yield of chemical processing was monitored for all target foils, by measuring the activities of the tracer radionuclides, before and after the radiochemical 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 standard liquid source. Two sample-detector positions (at 19 cm distance and at contact) were used to always keep the dead time below 10%. The well-known activation formula was used to calculate the cross section values, by considering the monitor reactions ^{nat}Ni(p,x)57Ni and ^{nat}Al(p,x)^{22}Na recommended by IAEA [6], respectively for energies lower and higher than 50 MeV.The isotopic purity of the ^{68}Zn deposit and the chemical purity of reference foils were taken into account in the cross section calculation; results of the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions referred to 100% enriched ^{68}Zn target. The uncertainty of the cross section values were evaluated in a quadratic form, considering individual uncertainties: reference cross section (≤ 10%), measured activity (≤ 8%), target thickess and decay data values (1%).

Results

The radiochemical yield for copper and gallium isotopes was precisely determined by using the tracer radionuclide activities (^{61}Cu and ^{66}Ga). The efficiency of the separation procedure was calculated measuring the presence of ^{61}Cu (and thus copper isotopes) into the gallium solution and viceversa. It was found thatthe ^{66}Ga activity (and thus ^{67}Ga activity) into the copper solution was about 0.2% of its initial activity (i.e.before the chemical process), while ^{61}Cu activity (and thus ^{67}Cu) into the gallium solution was always below the Minimum Detectable Activity (MDA), corresponding to less than 1% of ^{61}Cu initial activity. These results showed a high yield of separation Cu/Ga isotopes, assuring a proper measurement of ^{67}Cu and ^{67}Ga activity values.

Figure 2, Figure 3 and Figure 4 reported the results obtained in this work respectively for the ^{68}Zn(p,2p)^{67}Cu, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga nuclear reactions. Literature data available from EXFOR database [5] were reported on figures without error bars for clarity; TALYS estimations, obtained by using both default (Talys) and new set of models (Talys*) [7, 8], were also shown as dashed and dotted lines (Figure 2-4).

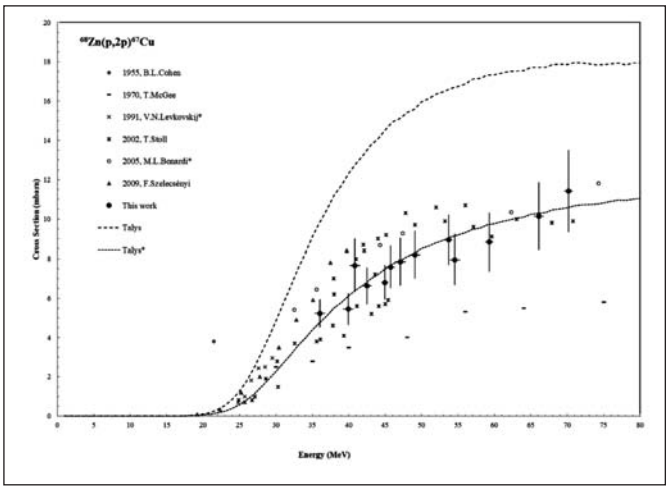

Fig. 2. Cross section of the ^{68}Zn(p,2p)^{67}Cu nuclear reaction

Figure 2 reported the ^{68}Zn(p,2p)^{67}Cu cross section measured in this work in the energy range 35-70 MeV, compared with literature [5] and TALYS estimations. 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. Bonardi et al. (2005) irradiated a natural zinc target: their data in Figure 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) 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) were rescaled by an appropriate factor to correct the use of an over-estimated reference reaction, as reported in EXFOR database [5]. Previous data

were considered not reliable, due to the large discrepancy with other authors; in particular, results by McGee et. al. (1970) did not reproduce the expected shape of the excitation function even after the adjustment needed to account for up-to-date IAEA monitor data.

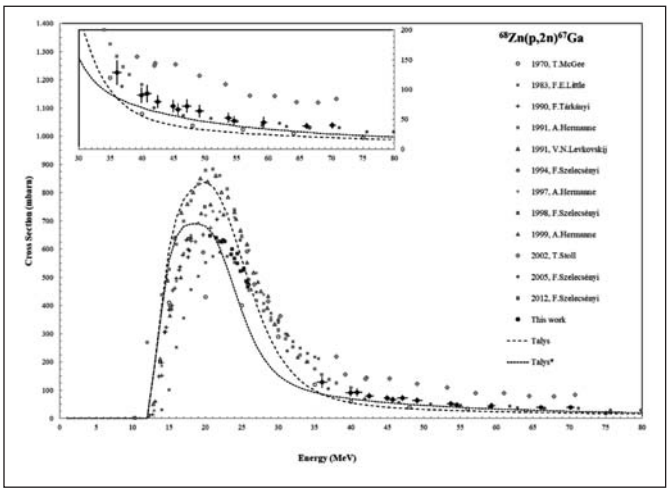

Fig. 3. Cross section of the ^{68}Zn(p,2n)^{67}Ga nuclear reaction

Figure 3 showed the measurements of the ^{68}Zn(p,2n)^{67}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 (Figure 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) in the entire energy range (35-70 MeV) and, in the energy region 35-45 MeV, with data by Hermanne et al. (1991). The same author repeated the measurement up to 33 MeV, confirming previous results. The only discrepancy at high energy was the data set by Stoll et. al. (2002), that seemed to almost double the cross section values in the entire energy range (38–71 MeV).

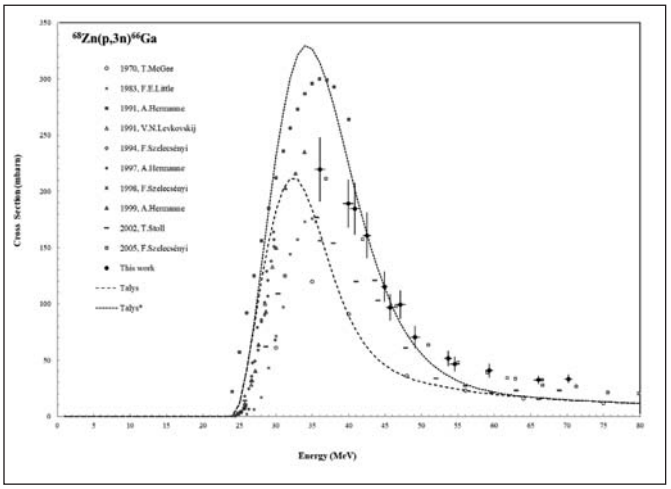

Fig. 4. Cross section of the ^{68}Zn(p,3n)^{66}Ga nuclear reaction

Figure 4 reported the measurements of the ^{68}Zn(p,3n)^{66}Ga cross section: as in case of ^{67}Ga, 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) in the entire energy range (35-70 MeV). Measurements by Stoll et al. (2002) 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) measured a very high peak value (around 290 mb at 34 MeV), but the same authors repeated the experiment in 1999 and these later data are in good agreement with results obtained in this work.

Discussion

Considering the recent availability of compact cyclotrons, able to provide intense proton beams of high energy, the production yield of ^{67}Cu was also 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) [9]. 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 [8], 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 (i.e. contaminant co-production), the best energy range should be carefully evaluated, taking into account also the target design and its cooling system.

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, enriched ^{68}Zn and applying a simple chemical procedure to accurately measure ^{67}Cu and ^{67}Ga activity values by γ-spectrometry. The separation yield 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: in case of the ^{68}Zn(p,2n)^{67}Cu the new set of models suitably described data obtained in this work but TALYS 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. 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.

Acknowledgments

Authors would thank Prof. Mauro Gambaccini (University of Ferrara) for the support during the PhD thesis of G. Pupillo, Prof. Adriano Duatti (University of Ferrara), Prof. Giovanni Fiorentini (University of Ferrara and INFN-LNL) and Dott. Carlos Rossi Alvarez (INFN-LNL) for many helpful suggestions and comments on this topic. This work was promoted by the University of Ferrara with a financial support for the research activities (Progetto RaMe, Fondi 5 x 1000 Anno 2009) and by the European Commission through an Erasmus Placement fund that G. Pupillo spent at ARRONAX facility. The ARRONAX cyclotron is a project promoted by the Regional Council of Pays de la Loire financed by local authorities, the French government and the European Union. This work has been, in part, supported by a grant from the French National Agency for Research called “Investissements d’Avenir”, Equipex Arronax-Plus No. ANR-11-EQPX-0004 and Labex No. ANR- 11-LABX-0018-01.

References

[1] IAEA. Therapeutic radiopharmaceuticals labelled with new emerging radionuclides (^{67}Cu, ^{186}Re, ^{47}Sc). Vienna: IAEA, 2016.

[2] National Nuclear Data Center (NNDC). Information extracted from the NuDat2 Database. 2016. Disponible en: http://www.nndc.bnl.gov/nudat2/.

[3] MAGGIORE M, CAMPO D, ANTONINI P, LOMBARDIET A, et. al. SPES: a new cyclotron-based facility for research and applications with high-intensity beams. Modern Physics Letters A. 2017; 32(17): 1740010. doi: 10.1142/S0217732317400107.

[4] HADDAD F, FERRER L, GUERTIN A, CARLIER T, et. al. ARRONAX, a high-energy and high-intensity cyclotron for nuclear medicine. Eur J Nucl Med Mol Imaging. 2008; 35(7): 1377-1387. doi: 10.1007/s00259-008-0802-5.

[5] Experimental Nuclear Reaction Data (EXFOR). Information extracted from the database. 2016. Disponible en: https://www-nds.iaea.org/exfor/exfor.htm

[6] IAEA. Charged particle cross section database for medical radioisotope production: diagnostic radioisotopes and monitor reactions. IAEA-TECDOC-1211. Vienna: IAEA, 2001. Disponible en: https://www-nds.iaea.org/medical/monitor_reactions.html.

[7] PUPILLO G, SOUNALET T, MICHEL N, MOU L, et. al. New production cross section for the theranostic radionuclide ^{67}Cu. Nuclear Inst. and Meth Phys Res B. 2018; 415(15): 41-47. doi: https://doi.org/10.1016/j.nimb.2017.10.022

[8] DUCHEMIN C, GUERTIN A, HADDAD F, MICHEL N, et. al. Production of medical isotopes from a thorium target irradiated by light charged particles up to 70 MeV. Phys Med & Biol. 2015; 60(3): 931-946. doi: 10.1088/0031-9155/60/3/931.

[9] IAEA. Bibliography of experimental data on ^{68}Zn(p,2p)^{67}Cu. Vienna, IAEA. Disponible en: https://www-nds.iaea.org/radionuclides/zn-867cu0.html

Recibido: 13 de febrero de 2018
Aceptado: 29 de mayo de 2018