Excitation functions of proton induced reactions on ^{68}Zn from threshold up to 71 MeV, with specific reference to the production of ^{67}Cu

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Summary. The excitation function of the ^{68}Zn$(p, 2p)^{67}$Cu reaction was measured radiochemically up to a proton energy of 71 MeV to obtain accurate data for production of the therapy related β^--emitting radioisotope ^{67}Cu ($T_{1/2} = 61.9$ h). Investigations were also made on the $(p, 2n)$ and $(p, 3n)$ reactions on ^{68}Zn. The experimental 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 compared with published data and with theoretical predictions based on the hybrid-precompound model ALICE-IPPE. Thick target yields of ^{67}Cu, ^{67}Ga ($T_{1/2} = 78.3$ h) and ^{66}Ga ($T_{1/2} = 9.4$ h) were calculated. Production of ^{67}Cu is feasible only at proton energies above 50 MeV. For the target thickness $E_p = 70 \rightarrow 50$ MeV, the yield of ^{67}Cu amounts to 16.9 MBq/μA·h.

1. Introduction

The radionuclide ^{67}Cu ($T_{1/2} = 61.9$ h; $E_{\beta^-\,(\max)} = 0.6$ MeV) is the longest-lived radioisotope of copper and is used in endoradiotherapy. In systemic therapy, it has the advantage of providing β^--particles of ideal energy which are accompanied by γ-radiation of 91 keV (7%), 93 keV (16%) and 184.6 keV (48.7%). Especially the latter γ-ray permits imaging of the radionuclide distribution during therapy. Due to this reason and because of its proper half-life, ^{67}Cu is well suited for imaging slow antibody pharmacokinetics and is used, *e.g.* in form of a porphyrin complex [cf. 1] or ceruloplasmin complex [cf. 2]. Several reports have described the ability to conjugate such complexes to polyclonal and monoclonal antibodies and small autoantigenic peptides [cf. 3]. The biodistribution characteristics of such radioimmunoconjugates, however, have not yet been well explored in animals bearing human tumors.

For the production of ^{67}Cu, several nuclear routes have been suggested. The most promising ones are the ^{68}Zn$(p, 2p)^{67}$Cu and ^{70}Zn$(p, \alpha)^{67}$Cu reactions at a cyclotron [4–7] or the ^{67}Zn$(n, p)^{67}$Cu reaction in a high flux reactor [8–10]. Another possibility of production is the spallation of ^{75}As with high energy protons [cf. 11]. This work deals with the production route ^{68}Zn$(p, 2p)^{67}$Cu. Although the method has found practical application, the cross section data are not known well. We performed a detailed radiochemical study on this reaction as well as on the competing ^{68}Zn$(p, xn)^{66,67}$Ga processes.

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2. Experimental

2.1 Samples and irradiations

Excitation functions of the ^{68}Zn$(p, 2p)^{67}$Cu and ^{68}Zn$(p, xn)^{66,67}$Ga reactions were measured using the conventional stacked-foil technique [cf. 12,13]. Thin samples of enriched ^{68}Zn (98.3%) were produced by electrolytic deposition on 10 and 12.5 μm thick Au-backings. A ^{68}Zn-solution of approximately 3 mg zinc per mL in 1 M HCl was prepared. An electrolytic cell, described earlier [14], was filled with 1 mL of the electrolytic solution which was stirred with a rotating Pt-anode. Electrolysis was carried out with a current of 0.15 mA and a voltage of 5 V for one hour. During the electrolysis some gas formation occurred and the current decreased in the end to 0.02 mA. The deposited material was rinsed with ethanol; a deposition yield of 85%–95% was obtained.

Irradiations were carried out at two cyclotrons: the injector of the cooler synchrotron (COSY) of the Forschungszentrum Jülich, Germany, [cf. 15] and the accelerator of the Paul-Scherrer Institut (PSI), Villigen, Switzerland. Several stacks were irradiated, each containing up to 12 samples and copper and aluminium foils as energy degraders and monitors for the proton beam. The beam currents were monitored *via* the well-known ^{nat}Cu$(p, xn)^{62,63}$Zn and the ^{27}Al$(p, x)^{22}$Na reactions [cf. 16]. The primary proton energies used were: 45.5 ± 0.1 MeV at COSY and 71.0 ± 0.2 MeV at PSI. Calculations on the degradation of the proton energy in each stack were based on the tables of Williamson *et al.* [17].

2.2 Chemical separation

For studies on ^{67}Cu produced *via* the proton-induced nuclear reaction on ^{68}Zn, a radiochemical separation of stable

^{68}Zn, radiogallium and radiocopper was necessary. Since both ^{67}Ga and ^{67}Cu populate the same levels in the product nucleus ^{67}Zn, most of the γ-lines emitted in the decay of ^{67}Cu are also observed in the decay of ^{67}Ga. The half-lives of the two radionuclides are also rather similar. In addition, the cross sections of the ^{68}Zn$(p, xn)^{67,66}$Ga reactions are relatively high and those of the ^{68}Zn$(p, 2p)^{67}$Cu process very low. Therefore the amount of radiogallium present in the irradiated sample was appreciably higher than that of radiocopper.

Dithizone is among the most selective chelating agents for copper and the present separation is based on it. It is a slightly modified form of that reported by DasGupta *et al*. [18]. The steps involved were:

(i) extraction of Cu-dithizionate,
(ii) dissociation of the Cu-chelate,
(iii) removal of trace Ga by ether extraction, and
(iv) anion-exchange process for final purification.

The reagents and materials required were 7.2, 1.0, 0.5 and 0.1 M HCl, CCl_4 *pro analysi*, 0.01% dithizone solution in CCl_4, diisopropylether saturated with 7.2 M HCl and Dowex AG 1X8, 100–200 mesh size anion-exchange resin, pretreated with 6 M HCl in a column with the dimensions of 1 cm$\varnothing \times 10$ cm.

The irradiated ^{68}Zn-layer on the Au-backing was dissolved in 3 mL of conc. HCl and then the solution was evaporated. The residue was dissolved in 10 mL of 0.5 M HCl. For quantification purposes 0.1 or 0.2 mg of natural copper was added as carrier. The solution was extracted three times with 10 mL of a dark blue 0.01% dithizone solution in CCl_4, which was freshly prepared. The dithizone solution turned violet. The combined organic phases were washed with 0.1 M HCl for removing traces of Zn and the aqueous layer was stored separately for measurements of ^{66,67}Ga and recovery of the target material. The radiocopper was then re-extracted from the organic phase three times with 10 mL of 7.2 M HCl and 5–10 drops of H_2O_2. Through oxidation of the dithizone the solution turned bright orange. The combined aqueous phases were washed twice with 5 mL of CCl_4 and then three times with 10 mL of diisopropylether to remove traces of radiogallium. It was then evaporated to near dryness and transferred to the anion-exchange column. Elution was done with 10 mL of 1 M HCl which quantitatively removed copper isotopes. The eluate was evaporated nearly to dryness and counted.

The chemical yield of the copper separation was determined *via* UV-spectrometry. The absorption peak of the copper dithizone complex at 512 nm was measured with the spectrometer UV-160 A by Shimadzu against a 0.01% dithizone solution in CCl_4. The chemical yield was about 95%. The contamination from radiogallium was found to be less than 1%.

The aqueous phase containing the radiogallium was also evaporated to near dryness and counted. The ratio of the activity before and after separation gave the radiochemical yield of the radiogallium separation; it was nearly 100%.

Enriched target material ^{68}Zn was recovered by precipitation of ^{68}ZnS with Na_2S-solution from the collected respective solutions as described by Lambrecht *et al*. [19]. The precipitate was dissolved and reprecipitated with 5 N NaOH. Then it was centrifuged, decanted and annealed at 673 K in order to form ^{68}ZnO. In this chemical form the target material is storable. The recovery yield amounted to about 94%.

2.3 Measurement of radioactivity

The radioactivity of the irradiated monitor foils, chemically untreated sample foils as well as of the chemically separated samples was measured *via* γ-ray spectrometry using HPGe detectors. Counting of foils and solutions was done at various distances varying between 10 and 50 cm from the detector surface. The detector counting efficiency was determined using calibrated standard sources from PTB Braunschweig and Amersham International. The activity of ^{67}Cu was measured using the 184.6 keV (48.7%) γ-ray whereas that of ^{67}Ga ($T_{1/2} = 78.3$ h) *via* the 300.2 keV (16.8%) and the 184.6 keV (21.2%) γ-lines, the two results being consistent. For determining the activity of ^{66}Ga ($T_{1/2} = 9.4$ h) the 1039.2 keV (37%) γ-ray was used.

2.4 Calculation of cross section and estimation of its uncertainty

The measured count rates were converted to decay rates, taking into account the γ-ray emission probability [20] and the efficiency of the detector. From the known decay rate and the proton flux the cross section was calculated using the usual activation formula. The total uncertainty in the measured cross section was obtained by adding all the individual uncertainties in quadrature. The individual uncertainties considered were: target thickness (1.4%), target inhomogeneity (5%), detector efficiency (5%) peak area analysis and counting statistics (5%–7%), beam current (10%) and chemical yield (5%). The total uncertainty amounted to about 16%. The uncertainty in the energy scale was generally small since well-defined primary proton energies were used and the stacks were not very thick. Only in the last samples of the stack the energy uncertainty was higher.

3. Nuclear model calculation

Reaction cross sections were also calculated using the nuclear model code ALICE-IPPE. It is a modified version of the exciton model code ALICE, originally developed by Blann [21]. The modifications introduced by the Obninsk group [22] and used here include:

(a) treatment of the level density in the frame of the generalized superfluid model,
(b) consideration of the preequilibrium cluster emission (d, t, ^{3}He, ^{4}He),
(c) estimation of direct interactions in cluster emission,
(d) calculation of γ-ray emission.

The code has been succesfully applied to the calculation of (p, x)-reaction cross sections on medium mass targets [cf. 23,24]. In the present work, the excitation functions of the three nuclear reactions under consideration were calculated from their respective thresholds up to 67 MeV.

4. Results and discussion

4.1 Experimental data

The measured cross sections of the ^{68}Zn$(p, 2p)^{67}$Cu, ^{68}Zn$(p, 2n)^{67}$Ga and ^{68}Zn$(p, 3n)^{66}$Ga reactions together with the estimated total uncertainties are listed in Table 1. Measurements were perfomed using 98.3% enriched ^{68}Zn and the data were extrapolated to 100% enrichment of the target.

The results for the ^{68}Zn$(p, 2p)^{67}$Cu reaction are shown in Fig. 1 as a function of the proton energy. The available literature data are also given. McGee *et al.* [25] studied this reaction using enriched material and a radiochemical separation, but no details are given. Those data are somewhat lower than our values. A report by Levkovskii [26] lists some cross sections on this reaction up to 30 MeV. However, no experimental details are available in the open literature. Thus we believe that our work presents the first detailed systematic study on this reaction up to 71 MeV,

Table 1. Measured cross sections of the ^{68}Zn(p, x) reactions.

Proton energy [MeV]	Cross section [mb] ^{68}Zn$(p, 2p)^{67}$Cu	^{68}Zn$(p, 2n)^{67}$Ga	^{68}Zn$(p, 3n)^{66}$Ga
70.8 ± 0.2	9.9 ± 1.7	84 ± 13	
68.9 ± 0.2			23 ± 4
67.9 ± 0.2	9.8 ± 1.7	78 ± 13	
66.1 ± 0.2			15 ± 3
64.5 ± 0.3		79 ± 13	
63.0 ± 0.3	10.0 ± 1.9		23 ± 4
61.0 ± 0.4		89 ± 14	
59.6 ± 0.3	9.1 ± 1.8		21 ± 3
57.1 ± 0.4	9.6 ± 1.6	90 ± 14	
56.0 ± 0.4	10.7 ± 1.6		27 ± 4
53.2 ± 0.4	9.9 ± 1.7	109 ± 18	
52.0 ± 0.4	10.6 ± 1.4		34 ± 5
49.1 ± 0.5	9.7 ± 1.7	123 ± 20	
47.8 ± 0.5	10.3 ± 1.5		61 ± 10
45.4 ± 0.2	5.9 ± 1.0		
45.3 ± 0.5		142 ± 23	
45.1 ± 0.2	9.2 ± 1.6		
45.0 ± 0.2	5.7 ± 0.9		
44.1 ± 0.2	5.6 ± 0.9		
44.0 ± 0.5	9.0 ± 1.3		103 ± 16
43.6 ± 0.2	7.2 ± 1.2		121 ± 19
43.1 ± 0.2	5.2 ± 0.9		
42.1 ± 0.6	8.4 ± 1.4	144 ± 23	
42.0 ± 0.2	8.7 ± 1.5	140 ± 22	
41.1 ± 0.3	5.6 ± 0.9		
41.0 ± 0.3	8.0 ± 1.4		120 ± 19
39.3 ± 0.3	4.1 ± 0.7		
39.2 ± 0.3		155 ± 25	
38.0 ± 0.7	6.2 ± 1.0	219 ± 35	
37.9 ± 0.3	7.0 ± 1.2		154 ± 25
37.8 ± 0.3	4.6 ± 0.8		
36.1 ± 0.3	3.9 ± 0.6		156 ± 25
35.6 ± 0.3	3.8 ± 0.6		177 ± 28
32.6 ± 0.4	3.7 ± 0.6		
30.3 ± 0.4	1.5 ± 0.3	363 ± 58	109 ± 17
30.2 ± 0.4	2.8 ± 0.5		
28.6 ± 0.5	1.9 ± 0.3	414 ± 66	62 ± 10
27.1 ± 0.5	1.0 ± 0.2		
26.7 ± 0.5	0.8 ± 0.1	475 ± 76	31 ± 5
25.7 ± 0.6	0.7 ± 0.1	591 ± 95	14 ± 2
24.9 ± 0.6	0.8 ± 0.1		
19.7 ± 0.6		588 ± 94	

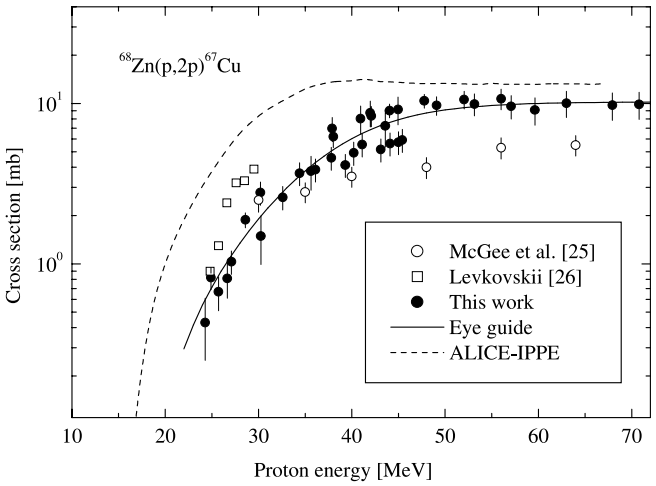

Fig. 1. Excitation function of the ^{68}Zn$(p, 2p)^{67}$Cu reaction.

although the reaction itself has already been utilized for production purposes [cf. 5,6]. It should also be mentioned that Morrison and Caretto [4] measured the cross section over the proton energy range of 80 to 450 MeV, and Mirzadeh *et al.* [5] at 200 MeV. The cross section increases with the increasing proton energy and is about 15 mb at 200 MeV.

Our results for the ^{68}Zn$(p, 2n)^{67}$Ga reaction are given in Fig. 2. For this reaction the data are well known up to energies of about 35 MeV [cf. 26–29] but not beyond. The present measurements in the energy range below 30 MeV are consistent with the known data and add confidence to the new results described here. In comparison to our data, the data of McGee *et al.* [25], also shown in Fig. 2, are somewhat lower, just as in the case of the ^{68}Zn$(p, 2p)^{67}$Cu reaction depicted in Fig. 1. They fit rather good to the calculated curve but the trend does not proceed in accordance with the recommended curve.

The excitation function of the reaction ^{68}Zn$(p, 3n)^{66}$Ga is shown in Fig. 3. For this reaction as well extensive investigations have been reported up to about 35 MeV [cf. 26–28]. Beyond that energy, however, only some results were given

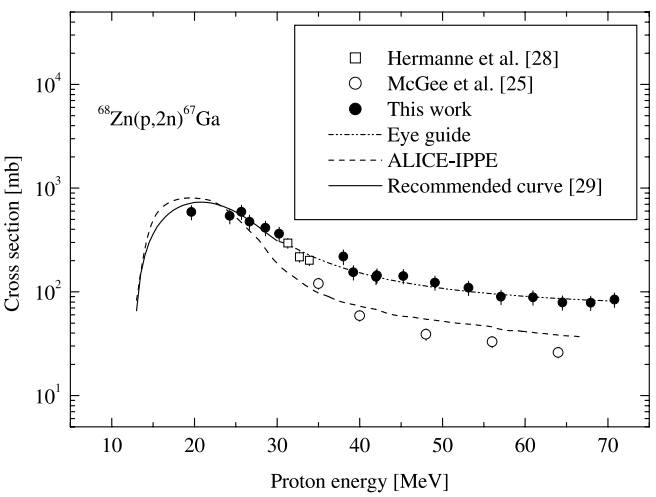

Fig. 2. Excitation function of the ^{68}Zn$(p, 2n)^{67}$Ga reaction. The recommended curve up to about 30 MeV is based on an evaluation of the rather extensive existing data [29].

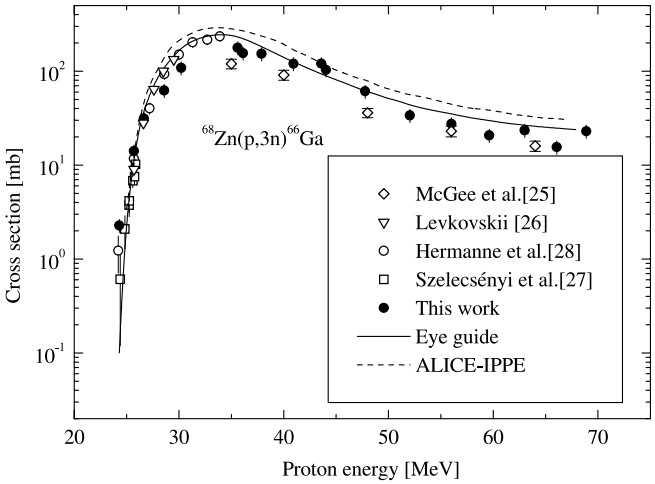

Fig. 3. Excitation function of the ^{68}Zn$(p, 3n)^{66}$Ga reaction.

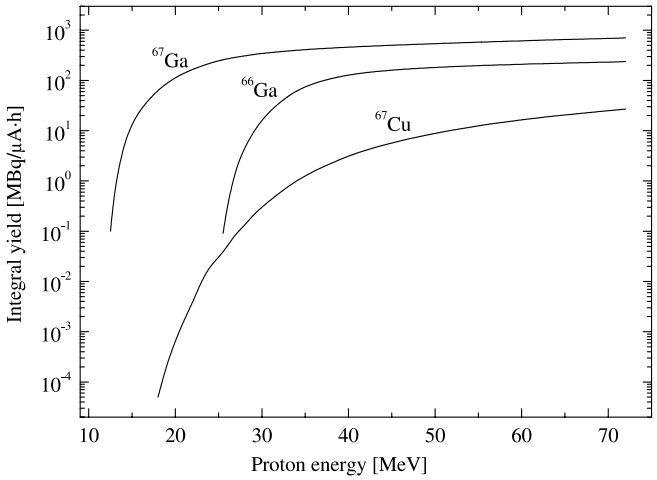

Fig. 4. Calculated integral yields of ^{67}Ga, ^{66}Ga and ^{67}Cu in the ^{68}Zn$(p, 2n)^{67}$Ga, ^{68}Zn$(p, 3n)^{66}$Ga and ^{68}Zn$(p, 2p)^{67}$Cu reactions, respectively.

by McGee *et al.* [25]. Our results are more detailed than those data. For this reaction the agreement between our data and the literature data is fairly good.

4.2 Calculated excitation functions

The results of the nuclear model calculations are given in Figs. 1 to 3 together with the experimental data. For (p, xn) reactions good agreement is observed between the calculation and the experimental data in the region of the threshold. For the $(p, 2n)$ reaction (Fig. 2) the maxima also agree but in the high-energy region some discrepancies are observed. The calculated curve is consistently lower than our experimental data. On the other hand, in the case of the $(p, 3n)$ reaction (Fig. 3), the calculated and experimental data show fairly good agreement.

The calculated excitation function of the $(p, 2p)$ reaction (Fig. 1) agrees in shape with the experimental curve. In absolute terms, however, it is appreciably higher than the experimental data, especially in the region of the threshold. Evidently, some improvements in the model are needed to describe the two proton emission process. The shape of the excitation function indicates that this is at least not a precompound reaction over the whole energy range; it is likely that the reaction partly proceeds *via* a knock-out mechanism [cf. 4].

In nuclear model calculations, the level density formalism plays an important role. Therefore in this work, besides using the generalized superfluid model of level density, described above, calculations were also performed using the Fermi-gas model. This made no difference to the $(p, 2p)$ reaction cross section. The resulting (p, xn) reaction cross sections were, however, about 10 to 25% higher at proton energies > 50 MeV. In the case of the $(p, 2n)$ reaction this meant a slight improvement in the agreement between experiment and theory; for the $(p, 3n)$ reaction no significant change was noticed.

4.3 Calculated thick target yields

From the eye-guide curves shown in Figs. 1, 2 and 3, the integral yields of ^{67}Cu, ^{66}Ga and ^{67}Ga were calculated for an irradiation time of 1 h and a beam current of 1 μA. The results for the gallium isotopes and those for ^{67}Cu are plotted in Fig. 4. The yield of ^{67}Ga up to 30 MeV is exactly the same as given in Ref. [29]. It is obvious that the yields of ^{66}Ga and ^{67}Ga formed *via* the (p, xn) reactions are more than an order of magnitude higher than the yield of ^{67}Cu *via* the $(p, 2p)$ reaction. The chemically separated ^{67}Cu samples, however, did not show any measurable radiogallium impurities. Therefore the nuclide is available right from the threshold energy, though the yield is small. With higher proton energy, a higher ^{67}Cu yield is expected. With 40 MeV protons, for example, the expected yield of ^{67}Cu amounts to 3.1 MBq/μA·h, but with 70 MeV protons it increases to 26.9 MBq/μA·h.

4.4 Comparison of theoretical and experimental yields

It may be useful to consider the theoretical yields of ^{67}Cu given here in comparison to the practical yields reported in three experiments: (1) Using highly enriched ^{68}Zn as target material and an incident proton energy of 26.5 MeV, Boothe [30] obtained a value of $(10.7 \pm 2.2) \times 10^4$ Bq/μA·h. This result is comparable to the value of $(7 \pm 1) \times 10^4$ Bq/μA·h reported by us. (2) For a ^{nat}Zn-target of thickness $E_p = 68 \rightarrow 55$ MeV, Schwarzbach *et al.* [6] obtained a ^{67}Cu-yield of about 1 MBq/μA·h. This value is comparable to the yield of about 1.8 MBq/μA·h deduced for ^{nat}Zn from our theoretical curve. (3) The third experiment was done in the high energy range. For a ^{nat}Zn-target of thickness $E_p = 200 \rightarrow 190$ MeV, Mirzadeh *et al.* [5] obtained 1.24 MBq ^{67}Cu/μA·h. A comparison with that result is not possible since our studies were limited up to 71 MeV.

5. Conclusions

The experimental and theoretical study described in this work has extended and strengthened the data base of the three reactions, *viz* ^{68}Zn$(p, 2p)^{67}$Cu, ^{68}Zn$(p, 2n)^{67}$Ga and ^{68}Zn$(p, 3n)^{66}$Ga up to 71 MeV. As far as the production of ^{67}Cu is concerned, the ^{68}Zn$(p, 2p)$ route appears to

be suitable only at proton energies above 50 MeV. Below that energy the contribution of ^{66,67}Ga is very high. A radiochemical separation removes the radiogallium but the yield of ^{67}Cu is very low. For the target thickness $E_p = 70 \rightarrow 50$ MeV, for example, the expected yield of ^{67}Cu amounts to 16.9 MBq/μA·h and the yields of ^{66}Ga and ^{67}Ga to 53 and 149 MBq/μA·h, respectively. The radiogallium is then not too much in excess, and a radiochemical separation of ^{67}Cu for production purposes appears worthwhile. A 6 h irradiation at 20 μA could lead to about 1.8 GBq (∼ 50 mCi) of ^{67}Cu after chemical separation. The yield would be higher if protons of higher energy would be available [4, 5].

It may be interesting to compare the theoretical yields of ^{67}Cu from the ^{70}Zn$(p,\alpha)^{67}$Cu and ^{68}Zn$(p,2p)^{67}$Cu processes [7, this work]. The yield *via* the low-energy ^{70}Zn$(p,\alpha)^{67}$Cu reaction amounts to 2 MBq/μA·h at $E_p = 18 \rightarrow 8$ MeV and 4 MBq/μA·h at $E_p = 30 \rightarrow 8$ MeV. In contrast the yield *via* the ^{68}Zn$(p,2p)^{67}$Cu reaction at $E_p = 70 \rightarrow 50$ MeV amounts to 17 MBq/μA·h. Evidently, the choice of the reaction for production of ^{67}Cu would depend on the available cyclotron.

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