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On the formation of non-radioactive copper during the production of ^{64}Cu via proton- and deuteron-induced nuclear reactions on enriched ^{64}Ni targets

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Abstract

Routine production of ^{64}Cu commonly exploits the ^{64}Ni(p,n) or ^{64}Ni(d,2n) reactions. Above specific threshold energies, however, non-radioactive ^{63}Cu and/or ^{65}Cu are also co-produced. The non-radioactive (cold) Cu can significantly decrease the specific activity (SA) of ^{64}Cu-labelled radiopharmaceuticals. Based on nuclear model calculations for the formation of non-radioactive Cu isotopes, theoretical specific activities (TSA) for ^{64}Cu were estimated. Reported current production methods, however, often yield SA values that are lower than the corresponding TSA predictions by more than an order of magnitude. Most of the non-radioactive Cu causing this has been found to originate from sources other than co-production, indicating that there is still significant potential for method improvement.

Keywords

^{64}Ni target, proton and deuteron reactions, ALICE 2014 calculations, TENDL 2014 library, non-radioactive Cu formation, specific activity of ^{64}Cu

Introduction

The production of radionuclides in high specific activity form, especially for application in positron emission tomography (PET) and targeted radiotherapy, is a continuous challenge for many laboratories. The desired radioisotopes would usually be contaminated to some degree, not only with other unwanted radionuclides but with stable nuclides as well. With properly selected targetry, irradiation conditions and methods for preparation, separation, and labelling, however, both the radioactive and stable contaminations can often be decreased to acceptable levels.

The unique decay properties of the radionuclide ^{64}Cu ($T_{1/2}$ = 12.7 h) make it useful for both imaging and therapy [1–3]. Two nuclear reactions have been suggested for its production with a radionuclidic purity sufficient for biomolecule labelling, namely ^{64}Ni(p,n)^{64}Cu (Q = -2.5 MeV) and ^{64}Ni(d,2n)^{64}Cu (Q = -4.7 MeV). By keeping the bombarding energies below the thresholds for ^{61}Cu ($T_{1/2}$ = 3.4 h) production via the ^{64}Ni(p,4n)^{61}Cu (Q = -30.1 MeV) and ^{64}Ni(d,5n)^{61}Cu (Q = -32.3 MeV) reactions, respectively, the only co-produced Cu contaminants are stable ^{63}Cu and ^{65}Cu. Note that ^{62}Cu ($T_{1/2}$ = 9.74 m) is, in principle, also a potential contaminant but due to its relatively short half-life, its presence can be tolerated as it will decay to an acceptably low level after a relatively short waiting time post end of bombardment (EOB), for example during the typical chemical separation time. Commercial medical cyclotrons with typical energy capability, *e.g.* 30/15 or 18/9 MeV for protons/deuterons, are therefore ideal for this purpose. There are still some concerns, however, about the presence of non-radioactive Cu in final product solutions [2–4].

Several authors developed ^{64}Cu production systems based on proton activation of highly enriched ^{64}Ni targets, and reported measured SA values [2–5]. In order to critically evaluate these SA values, we felt there was a need to compare them with corresponding theoretical specific activity (TSA) predictions as well as with the theoretical maximum specific activity (TMSA) of the relevant nuclear reactions. No measured SA values could be found in the literature for the deuteron-based production route however TSA and TMSA values for deuterons can provide a valuable comparison with the proton-based production route.

The relevant reactions for the co-production of the stable Cu radionuclides are ^{64}Ni(p,2n)^{63}Cu (Q = -10.4 MeV), ^{64}Ni(d,3n)^{63}Cu (Q = -12.6 MeV) and ^{64}Ni(d,n)^{65}Cu (Q = +5.2 MeV). In principle, the ^{64}Ni(p,γ)^{65}Cu reaction channel is always open in the proton energy region of interest, however, the cross sections for formation of ^{65}Cu via this reaction is well below 1 mb, therefore its contribution is negligible. In the case of deuterons, however, the ^{64}Ni(d,n)^{65}Cu reaction channel is always open in any production energy window due to its positive Q-value. As its excitation function is expected to reach a maximum of several hundred millibarn, which is typical for (d,n) reactions in that mass region, its contribution to stable copper formation cannot be neglected.

The basic aim of this study was to estimate the level of stable Cu contamination(s) from co-production in typical energy windows for both the proton-based and deuteron-based production routes, using yield predictions derived from the formation cross sections according to the TENDL 2014 nuclear data library

[6,7] and the ALICE 2014 nuclear model code [8]. It should be noted that the theoretical excitation functions of non-radioactive nuclides remain *inter alia* untested against experimental measurements. Thus, in order to get an idea of the typical predictive power of these codes for the relevant reactions, in the energy region up to about 30 MeV, comparisons with measured data for similar reactions in a wider mass region ($40 \leq A \leq 130$) have also been performed.

Theoretical calculations

Production yields for ^{63}Cu and ^{65}Cu have been calculated by deriving their excitation functions using nuclear model calculations, as measured cross-section data for these stable nuclides do not exist. For the non-radioactive Cu, ^{64}Cu and several other nuclides produced by similar reactions, predictions by means of the TALYS code [6], according to the TALYS-based evaluated nuclear data library TENDL 2014 [7], as well as the ALICE 2014 code system [8] have been employed. The ALICE 2014 code was consistently used with default parameters and no "fine tuning" of any parameters was performed. The objective was to look for order-of-magnitude predictions by observing the typical level of agreement by both TENDL 2014 and ALICE 2014 (using mainly default parameters) with experimental data, where available, in the relevant mass and energy regions, rather than to search for the most fine-tuned calculations in terms of completeness and/or accuracy that might be possible today. The default parameter choice selects the Hybrid Monte Carlo Simulation (HMS) precompound decay model of Blann [9] in conjunction with the Weiskopf-Ewing evaporation model for the subsequent decay of an equilibrated nuclear system. Precompound emission of d, t, ^{3}He and ^{7}Be clusters in addition to n, p and α-particles was selected. An energy mesh size of 0.2 MeV was specified and 100 000 cascade events were performed at each incident energy.

Results and discussion

Cross sections of proton-induced reactions

First, the prediction capabilities of the model codes in the case of the ^{64}Ni(p,n)^{64}Cu nuclear reaction, for which good experimental data exist, were checked. The results are shown in Fig. 1. Good overall agreement between the most recent experimental data of Adam Rebeles *et al*. [10] and Szelecsényi *et al*. [11], the TENDL 2014 compilation and the ALICE 2014 calculations is evident. Next, the predicted excitation functions for stable ^{63}Cu via the ^{64}Ni(p,2n)^{63}Cu reaction are shown in Fig. 2. In this case, the agreement is also acceptable although ALICE 2014 predicts a somewhat higher value at the peak maximum, which is also shifted towards higher energies. As will be explained in more detail later, spline fits through the mean values of the two sets of theoretical predictions reproduce the excitation functions of various (p,n) and (p,2n) reactions quite well up to 30 MeV. (The spline fits were performed with the well-known graphing software package Origin 9.1, by selecting either the B-spline or Akima spline options built into the code.) The same applies to the relevant deuteron-induced reactions. Figures 1 and 2 also include these spline-fit curves.

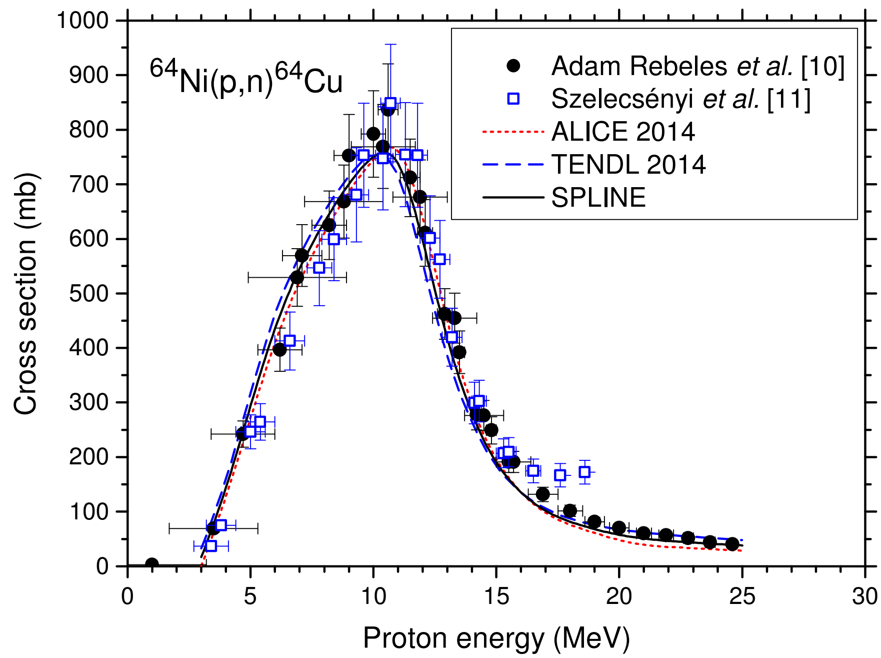

Fig. 1. Excitation functions for the production of ^{64}Cu in the bombardment of ^{64}Ni with protons.

Cross sections of deuteron-induced reactions

Based on the excitation-function results for the ^{64}Ni+p reactions, we expected a similar tendency for ^{64}Ni+d processes as well. Unfortunately, the ALICE 2014 and TENDL 2014 results exhibited larger differences from each other (see Figs. 3, 4 and 5). Figure 3 shows the excitation functions for the production of ^{64}Cu in the deuteron bombardment of ^{64}Ni. The TENDL 2014 values seem to overpredict the most recent experimental data of Daraban *et al.* [12] and Hermanne *et al.* [13]. In contrast, an underprediction is observable in the case of ALICE 2014. Interestingly, the spline fit through the mean values reproduces the measured data quite well. Similar behavior was found for several other (d,2n) reactions as well in the surrounding mass region. We would like to strongly state here that the adopted fitting of mean values from the two sets of calculations is by no means advocated as a suitable approach for general use. It merely seems to be a reasonable thing to do in this particular study as suitable agreement with measured data for the relevant reactions is evident in this mass and energy region.

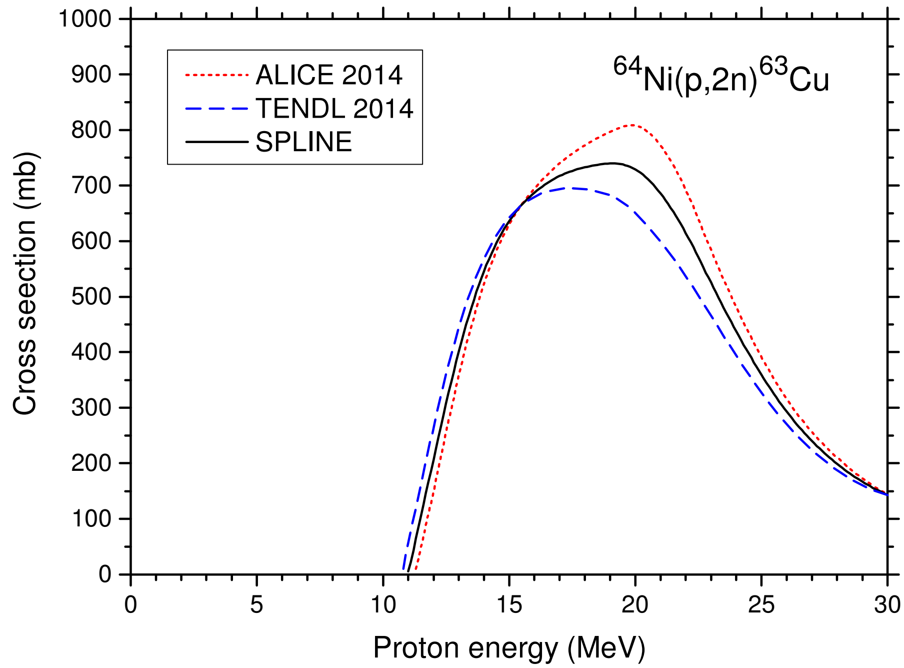

Fig. 2. Excitation functions for the production of ^{63}Cu in the bombardment of ^{64}Ni with protons.

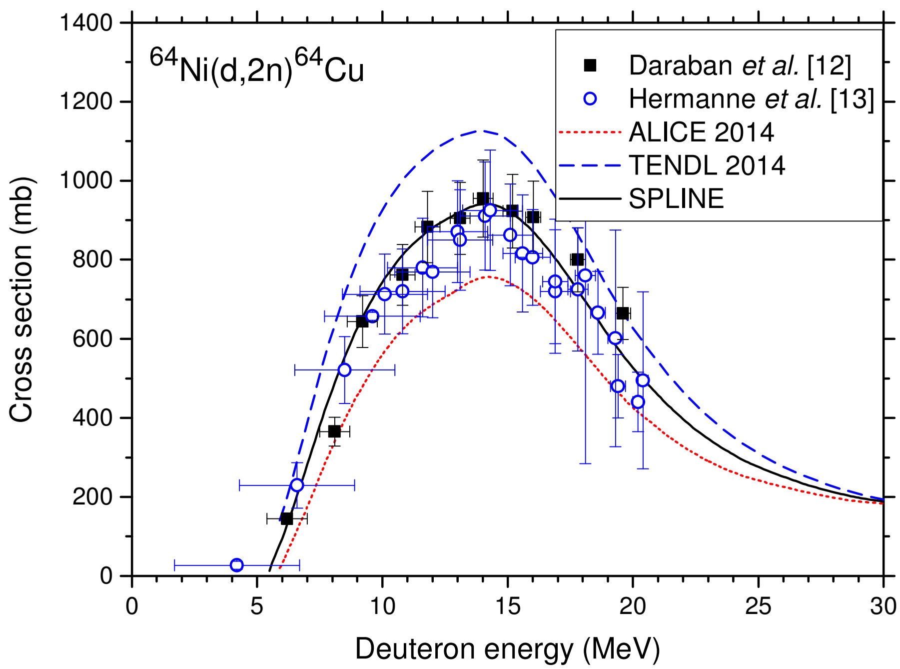

Fig. 3. Excitation functions for the production of ^{64}Cu in the bombardment of ^{64}Ni with deuterons.

The excitation-function predictions for the formation of stable ^{63}Cu in the deuteron bombardment of ^{64}Ni are shown in Fig. 4. Once again, the TENDL 2014 values are higher than the ALICE 2014 values. This was found to be a prevalent feature for various (d,2n) and (d,3n) reactions in the $40 \leq A \leq 130$ mass region. In the cases of the ^{89}Y(d,2n)^{89}Zr and ^{89}Y(d,3n)^{88}Zr reactions, for example, it was found that the spline fits reproduced the relevant experimental data [14,15,16] to the same level of agreement as exhibited in Fig. 3. In fact, not a single complete set of experimental excitation-function data that included the (d,n), (d,2n), and (d,3n) reactions on the same nucleus in the $40 \leq A \leq 130$ mass region was found in EXFOR [17]. This is because, invariably, some of the product nuclei are stable. Several cases were found, however, where data existed for two of the reactions. Unfortunately, space limitations preclude an in-depth discussion of all those results here. It was found, however, that the spline fits generally reproduce the data satisfactorily up to 30 MeV.

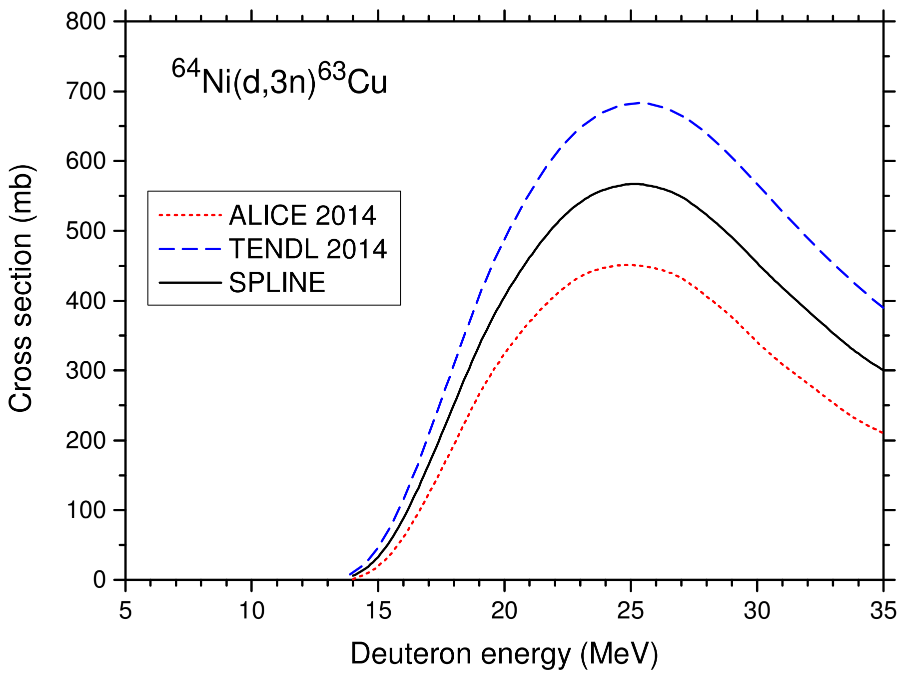

Fig. 4. Excitation functions for the production of ^{63}Cu in the bombardment of ^{64}Ni with deuterons.

A rather different trend has been observed for the (d,n) reactions. The predictions for the ^{64}Ni(d,n)^{65}Cu reaction (see Fig. 5) show the opposite trend beyond the peak region, namely that the ALICE 2014 values exhibit a probable overprediction and the TENDL 2014 values a probable underprediction. Up to the peak maximum, however, the agreement is generally good. Concerning the (d,n) reaction, it should be pointed out that experimental data on naturally mono-isotopic nuclei and/or nuclei with large natural abundances are quite sparse. The reason is because this reaction very often leads to another stable nucleus. In addition, a significant fraction of the published cross sections compiled in EXFOR [17] only cover the low energy region (*i.e*. near the threshold or not significantly beyond the peak maximum). Nevertheless, in nine data sets found (leading via the (d,n) reaction to ^{48}V, ^{55}Co, ^{59}Cu, ^{67}Ga, ^{71}As, ^{75}Br, ^{79}Rb, ^{95g}Tc and ^{123}I) the TENDL 2014 and ALICE 2014 values exhibit the same trend as in Fig. 5, with ALICE clearly overpredicting and TENDL clearly underpredicting the measured data beyond the peak region. Also, the spline fits through the mean values give a reasonable estimate of the peak region up to the onset of the high-energy plateau, making them useful for this study. Figure 6 shows the excitation function of the ^{47}Ti(d,n)^{48}V reaction as an example to illustrate this. Consequently, the decision was made to adopt these spline fits for purposes of calculating the integral yield predictions for ^{63,64,65}Cu, from which TSA and TMSA values could be derived.

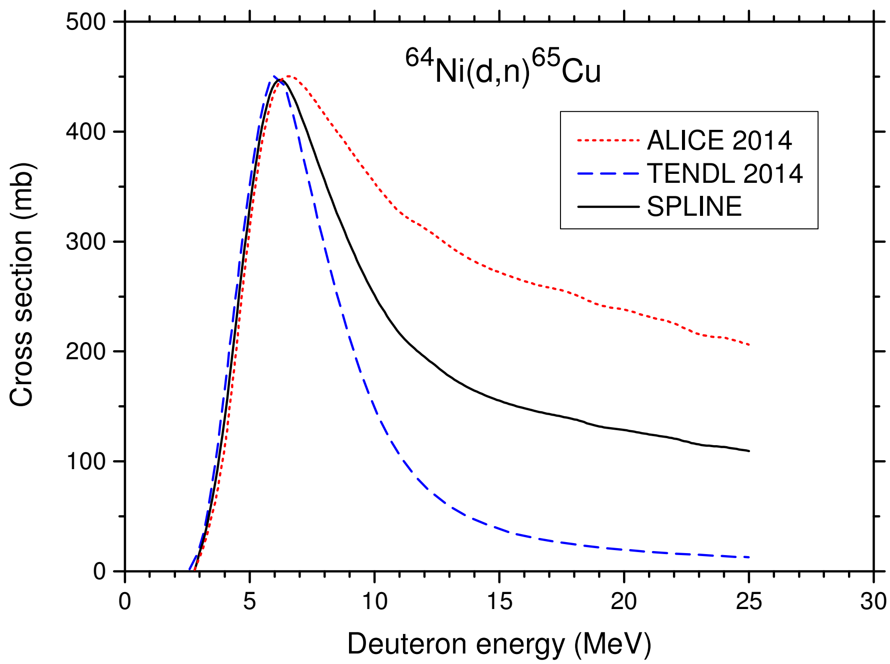

Fig. 5. Excitation functions for the production of ^{65}Cu in the bombardment of ^{64}Ni with deuterons.

Yield and TSA calculations

^{64}Ni+p reactions

Based on the spline fits of the cross sections for the ^{64}Ni(p,n)^{64}Cu and the ^{64}Ni(p,2n)^{63}Cu reactions, we calculated the absolute number of nuclei produced of each Cu species per unit charge (*i.e.* physical number yield of nuclei/Coulomb – see Fig. 7) as well as the corresponding TSA values, as a function of the bombarding energy. It is evident that above 10 MeV the number of ^{63}Cu nuclei increases sharply and

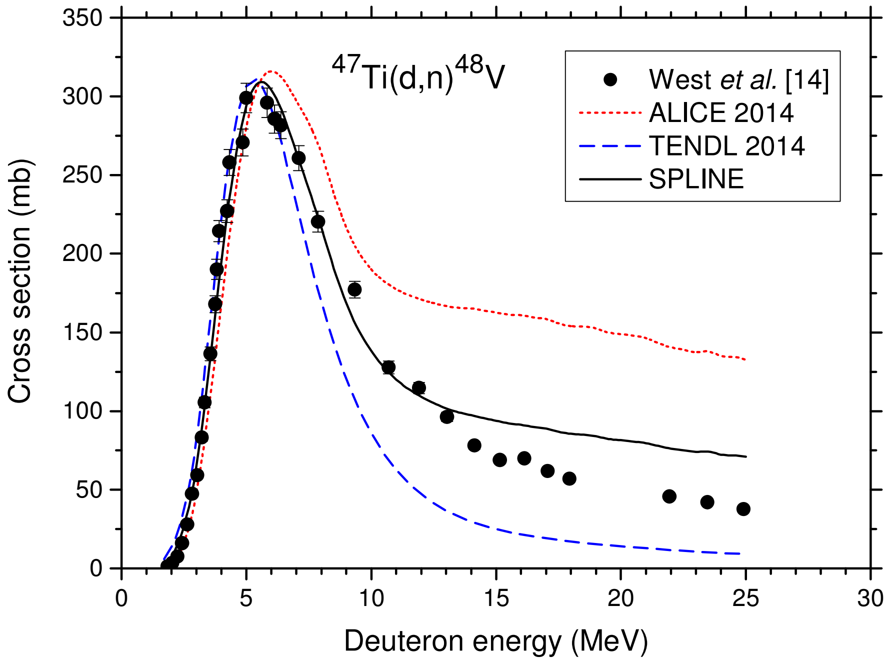

Fig. 6. Excitation functions for the production of ^{48}V in the bombardment of ^{47}Ti with deuterons.

almost the same amount of ^{63}Cu and ^{64}Cu nuclei are formed already at 19 MeV. Consequently, the TSA value at 19 MeV is only about 50% of the TMSA value of 9130 GBq/µmol (1.43 x 10^{17} Bq/g). Taking into account the decay of ^{64}Cu during longer activations, the actual SA values will in practice always be lower than the corresponding TSA values. The TSA reaches the TMSA value below the formation threshold of ^{63}Cu, the latter value of which is always a physical upper limit. Naturally, the separation, labelling and transportation times also lead to a decrease in the SA available for biomolecule labelling.

^{64}Ni+d reactions

Due to the inevitable co-formation of ^{65}Cu in ^{64}Ni+d reactions, the ^{64}Cu cannot be produced in non-radioactive copper contamination-free form in the whole investigated energy region, as shown in Fig. 8. The contamination ratio reaches its minimum at about 17 MeV, where the TSA curve reaches a peak maximum (*i.e.* the TMSA value) of 6648 GBq/µmol (1.04 x 10^{17} Bq/g). Unfortunately, the majority of hospital-based accelerators are capable of accelerating deuterons only up to 9 MeV, therefore only about 57% of TMSA (*i.e.* 3846 GBq/µmol or 6.02 x 10^{16} Bq/g) is theoretically available on such machines. Similar to the (p,n) production route, the contamination level increases with increasing irradiation time and practical SA values are correspondingly lower. It is also interesting to note that the TMSA value of the (d,2n) reaction was found to be lower, estimated to be 72.8% of the TMSA value of the (p,n) reaction.

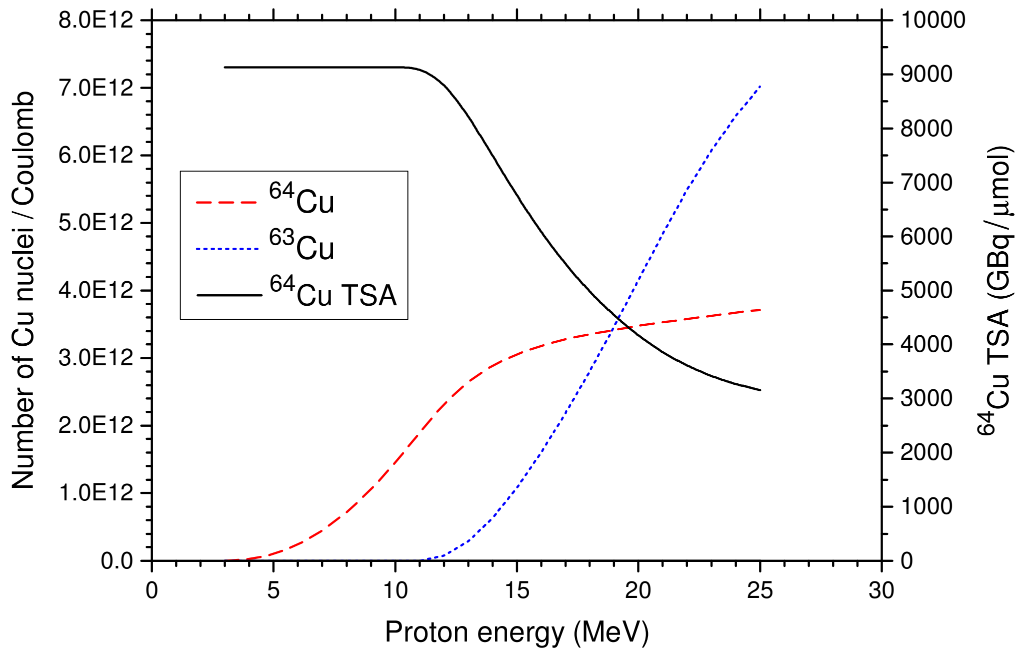

Fig. 7. Absolute number of ^{63}Cu and ^{64}Cu nuclei produced per unit charge, as well as the corresponding ^{64}Cu theoretical specific activity (TSA), as a function of proton energy.

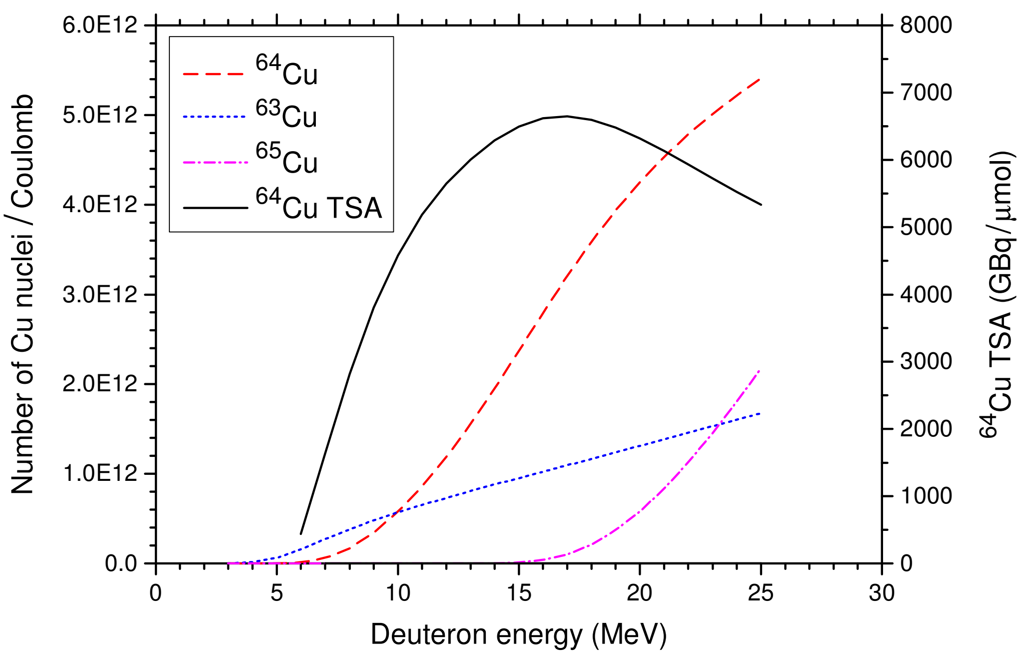

Fig. 8. Absolute number of ^{63}Cu, ^{64}Cu and ^{65}Cu nuclei produced per unit charge, as well as the corresponding ^{64}Cu theoretical specific activity (TSA), as a function of deuteron energy.

Comparison with measured specific activities

Table 1 presents some measured SA values for ^{64}Cu productions utilizing highly enriched ^{64}Ni (> 95%) electroplated onto gold backings and irradiated with protons. During bombardment the gold backings are cooled with water. Although there are many differences in the details of the targetry, *e.g.* target layer thickness and diameter, backing thickness and methods of preparation, other target holder materials, cooling geometry, etc., it is nevertheless interesting to compare these SA values with the corresponding TSA values.

As can be seen from Table 1, only one group activated their samples with an energy (15.5 MeV) that is higher than the threshold of the ^{64}Ni(p,2n)^{63}Cu reaction [2]. At this energy, the expected TSA would be 6412 GBq/µmol, which is more than an order of magnitude higher than most of the results presented by those authors. The best result reported by McCarthy *et al.* [2] is a SA value at EOB which is still more than a factor of 8 lower than the corresponding TSA value (734 GBq/µmol). The high amount of total Cu prompted further investigations into the detail of possible sources of non-radioactive Cu. This group pointed out that cleaning the targets after irradiation (with 1.0 N HNO_3, Milli-Q water, hexane and with ethanol) dramatically increases (up to twenty times) the SA. They found that the cooling media could always be a major source of non-radioactive Cu. Additionally, targets prepared from re-used ^{64}Ni material produced higher SA than targets prepared from new material. This is a very significant finding and can be explained by the fact that previous separation chemistry purified the target material from its initial non-radioactive Cu content. It was also shown that the chemical separation can release Cu contaminants from the gold backings.

Table 1. Reported specific activities in ^{64}Cu productions using targets of highly enriched ^{64}Ni (> 95%) electroplated onto gold backings.

Incident energy (MeV)	Bombardment time	SA at EOB* (GBq/µmol)	TSA (GBq/µmol)	Reference
15.5	2–3 h	223–734	6412	McCarthy *et al.* [2]
10	2–3 h	861–1685	9130	Thieme *et al.* [3]
11.7	100–120 min	13.1– 28.9	9130	Jeffery *et al.* [4]
11.1	Not given	977– 2021	9130	Walther *et al.* [5]

*Minimum and maximum SA values reported by these authors.

Thieme *et al*. [3] and Walther *et al*. [5] reported on a positive effect on the SA by using thinner gold backings (in fact, gold foils on Al backings). The latter group also investigated Pt backings but those results showed similar SA values to the targets with Au backings. Both groups also reported best results where the SA values significantly exceed 1.5 TBq/µmol. They also reported that further investigation is ongoing and that there is potential for improvement. Based on the findings of this study it seems that these groups are on the right track.

An important finding by Jeffery *et al.* [4] is that not only non-radioactive Cu is problematic but that other non-radioactive metals are also accumulating with successive irradiation and recycling of the target material. They concluded that future work should focus on refining the ^{64}Ni recycling process.

Admittedly, the uncertainties in the TSA and TMSA predictions may be significant and their assessment with a very high level of confidence does not appear feasible in the context of the present study. It is unlikely, however, that such uncertainties will significantly exceed the overall level of disagreement between integrated yields derived from the nuclear model calculations as compared to the corresponding yields derived directly from spline fits through the experimental excitation-function data. Observed differences do not exceed 30%, which is significantly less than the differences observed between actual measured SA values and the corresponding TSA predictions (see Table 1). To conclude, it is worthwhile mentioning the conclusion by Lapi et al. [18] that progress over the last 30 years on obtaining high specific activity radionuclides and radiopharmaceuticals is disappointing. While this particular statement was pertaining more to ^{11}C and ^{18}F agents, the same is certainly true also for ^{64}Cu, however, recent advances in the field are reassuring.

Conclusion

Based on theoretical predictions by means of the ALICE and TALYS codes, ^{64,63}Cu and ^{65,64,63}Cu physical yields were calculated for the ^{64}Ni+p and ^{64}Ni+d reactions, respectively. For both reactions the formation of non-radioactive ^{63}Cu (above 10 and 13 MeV, respectively) significantly decreases the SA of the final ^{64}Cu product. In addition, the deuteron-based route always co-produces stable ^{65}Cu together with the ^{64}Cu regardless of the selected energy window. For this reason, the TMSA value for ^{64}Cu obtained from a proton-based production route is higher than for a deuteron-based production route. Nevertheless, a more important consideration for any production system is to constrain the amount of non-radioactive Cu from sources other than co-production. While progress has clearly been made in recent years, further experimental work is necessary to reach higher SA values, which is important for increasing the effectiveness of receptor binding studies.

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References

1. Qaim SM (2015) J Radioanal Nucl Chem, DOI 10.1007/s10967-014-3923-2 (published online, in press) and references therein
2. McCarthy DW, Shefer RE, Klinkowstein RE, Bass LA, Margeneau WH, Cutler CS, Anderson CJ, Welch MJ (1997) Nucl Med Biol 24:35–43
3. Thieme S, Walther M, Pietzsch H-J, Henniger J, Preusche S, Mading P, Steinbach J (2012) Appl Radiat Isot 70:602–608
4. Jeffery CM, Smith SV, Asad AH, Chan S, Price RI (2012) AIP Conf. Proc. 1509:84–90
5. Walther M, Preusche S, Fuechtner F, Pietzsch HJ, Steinbach J (2012) AIP Conf. Proc. 1509:81–83
6. Koning AJ, Rochman D (2012) Nuclear Data Sheets 113:2841–2934
7. Koning AJ, Rochman D, van der Marck D, Kopecky SJ, Sublet JCh, Pomp S, Sjöstrand H, Forrest R, Bauge E, Henriksson H, Cabellos O, Goriely S, Leppanen J, Leeb H, Plompen A, Mills R (2014) TENDL 2014: TALYS-based evaluated nuclear data library, available from www.talys.eu
8. Blann M, Konobeev AY, Wilson WB, Mashnik SG, Manual for Code Alice, July 2008; ALICE 2014: RSICC Code Package PSR-550, available from https://rsicc.ornl.gov
9. Blann M (1996) Phys Rev C 54:1341–1349
10. Adam Rebeles R, van den Winkel P, Hermanne A, Tárkányi F (2009) Nucl Instr and Meth. B 267:457–461
11. Szelecsényi F, Blessing G, Qaim SM (1993) Appl Radiat Isot 44: 575–580
12. Daraban L, Adam Rebeles R, Hermanne A (2009) Appl Radiat Isot 67:506–510
13. Hermanne A, Tárkányi F, Takács S, Kovalev SF, Ignatyuk A (2007) Nucl Instr and Meth B 258:308–312
14. West HI, Lanier RG, Mustafa MG, Nuckolls RM, Nagle RJ, O'Brien H (1993) Report UCRL-ID-115738 (1993) p 3-1–3-17
15. Uddin MS, Baba M, Hagiwara M, Tárkányi F, Ditrói F (2007) Radiochim Acta 95 187–192
16. Tárkányi F. Ditrói F, Takács S, Csikai J, Mahunka I, Uddin MS, Hagiwara M, Baba M, Ido T, Hermanne A, Sonck M, Shubin Yu, Dityuk AI (2005) AIP Conf. Proc. 769:1658–1661
17. Experimental Nuclear Reaction Data Library (EXFOR), Database Version of March 16, 2015, available from http://www-nds.iaea.org
18. Lapi SE, Welch MJ (2013) Nucl Med Biol 40:314–320