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Production of scandium-44m and scandium-44g with deuterons on calcium-44: cross section measurements and production yield calculations

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Abstract

HIGHLIGHTS

- Production of Sc-44m, Sc-44g and contaminants.
- Experimental values determined using the stacked-foil technique.
- Thick-Target production Yield (TTY) calculations.
- Comparison with the TALYS code version 1.6.

Among the large number of radionuclides of medical interest, Sc-44 is promising for PET imaging. Either the ground-state Sc-44g or the metastable-state Sc-44m can be used for such applications, depending on the molecule used as vector. This study compares the production rates of both Sc-44 states, when protons or deuterons are used as projectiles on an enriched Calcium-44 target. This work presents the first set of data for the deuteron route. The results are compared with the TALYS code. The Thick-Target production Yields of Sc-44m and Sc-44g are calculated and compared with those for the proton route for three different scenarios: the production of Sc-44g for conventional PET imaging, its production for the new 3 γ imaging technique developed at the SUBATECH laboratory and the production of a Sc-44m/Sc-44g *in vivo* generator for antibody labelling.

Keywords: Ca-44 target, Sc-44m/Sc-44g *in vivo* generator, deuteron beam, stacked-foil technique, excitation function, TALYS 1.6

(Some figures may appear in colour only in the online journal)

1. Introduction

Nuclear medicine is a specialty involving the use of radionuclides for diagnosis as well as for therapy for cancers. In the last few years, the positron emission tomography (PET) diagnosis technique has been developed rapidly through the use of fluorine-18. At the same time, molecular therapy using new isotopes like Lu-177 has shown very promising results. In this case, the radionuclide must have a half-life which matches that of the vector distribution (peptide or antibody). The combination of imaging information and the therapeutic use of radionuclides is called theranostics and allows the personalization of treatment to each patient. Indeed, the diagnostic test, done prior to the treatment, permits one to follow and control the patient's response to the injected radiopharmaceutical. It allows better control of the targeting and increases the benefit/toxicity ratio as useless treatments on patients with no response to the diagnosis test are avoided. For a better description of the tracer biodistribution, pairs of radionuclides of the same element are preferable.

Scandium is a useful element for this theranostic concept. Scandium-47 can be used for therapy while Sc-43 and Sc-44 can be used for positron emission tomography (PET). Scandium-47 is a β- emitter (100%) with a half-life of $T_{1/2} = 3.3492$ d which decays to Ti-47. Its β energy makes it well suited for radionuclide therapy. Associated with its decay, a 159 keV γ-ray is emitted (branching ratio of 68%) which can be used for imaging in Single-Photon Emission Computed Tomography (SPECT). This isotope can be produced efficiently in a nuclear reactor (Müller *et al* 2014).

Scandium-43, with a half-life of 3.9 h, is a β+ emitter with a branching ratio of 88.1%. Its production is quite difficult using accelerators since it needs an expensive Ca-43 enriched target (Majkowska-Pilip and Bilewicz 2011). Scandium-44 in ground state, scandium-44g or Sc-44g, with a half-life of 3.97 h, is also a β+ emitter (branching ratio of 94%). This radioisotope can be produced via a generator system Ti-44/Sc-44g (Roesch *et al* 2012) but also directly via the irradiation of an enriched Calcium-44 target (Müller *et al* 2014, Alliot *et al* 2015). Scandium-44g has an important production advantage over scandium-43 because the starting material, Ca-44, is more abundant (2.1%) than Ca-43 (0.14%) leading to a less expensive target material. Sc-44g is complementary to other PET isotopes. Indeed, Sc-44g's half-life is between that of Ga-68 ($T_{1/2} = 67.71$ min) and Cu-64 ($T_{1/2} = 12.701$ h).

Associated with Sc-44g decay, a high-energy gamma ray at 1.157 MeV, with a high probability of occurrence (99.9%), is emitted. This γ ray can be used in addition to two 511 keV resulting from the positron annihilation, on a new three-gamma imaging technique developed at the SUBATECH laboratory (Nantes, France). The aim of this technique is to measure, on an event-by-event basis, the emitter location in three dimensions as proposed by Grignon *et al* (2007). To do that, it is necessary to combine the line of response obtained with the two gammas following the positron/electron annihilation with the arrival direction of the third gamma emitted by the radioisotope. The first device using liquid xenon as detection medium has been developed to show the feasibility of this new technique, called XEMIS for XEnon Medical Imaging System. Simulations have shown the possibility of reducing the injected dose to the patient with good energy and spatial resolution (Oger *et al* 2012). Today, an experimental device is in construction for small-animal imaging, named XEMIS 2 (Gallego Manzano *et al* 2015).

Last but not least, with scandium-44, it is possible to match the half-life of the isotope to the vector characteristics. The 3.97 h half-life of Sc-44g is well suited for the use of peptides and small molecules with rapid distribution in the body. For long biological processes like the ones induced when antibodies are used, Sc-44's metastable state, Sc-44m, can be used as an *in vivo* generator of Sc-44g. This excited state of scandium has a half-life of 58.6 h and

decays mainly by internal transition (IT) to its ground state Sc-44g. It has been shown that when a molecule is labeled with Sc-44m, the Sc-44g formed by its decay remains attached to this molecule (Huclier-Markai *et al* 2014). Sc-44m cannot be formed through the Ti-44/Sc-44 generator. It can be produced, at the same time as Sc-44g, with particle accelerators interacting on a Ca-44 enriched target. Experimental data exist on the production of scandium-44 using protons as projectiles on Ca-44 (Mitchell *et al* 1982, Levkovskij 1991, Krajewski *et al* 2013). They are in good agreement with the assessment given by the TALYS code version 1.6 (Koning and Rochman 2012). From these cross section values, the thick-target production yields (TTY) (see section 2.3) have been calculated to be 23 MBq/μA.h for Sc-44m and 2.7 GBq/μA.h for Sc-44g at 30 MeV (see figures 1).

In some cases, deuterons can be advantageously used for isotope production (Alliot *et al* 2015). This is the case for Copper-64 production from a Nickel-64 enriched target as well as for the production of Re-186g using a Tungsten-186 enriched target. In the latter case, 3.7 times more activity can be obtained with deuterons of 17.6 MeV than with protons at the same energy (Duchemin *et al* 2015). In order to investigate the potential advantage in using deuterons and due to the lack of experimental data with deuterons as projectiles, we have used the TALYS code to get hints on the best production route between protons and deuterons. The TALYS results for the Ca-44(d,2n) reactions are plotted in figure 2. The TTY calculated from these theoretical values is 65 MBq/μA.h for Sc-44m and 2.3 GBq/μA.h for Sc-44g at 30 MeV, showing a Sc-44m/Sc-44g ratio 3.3 times higher when using deuterons than when using protons for this energy.

The aim of this work is to experimentally determine the Sc-44g and Sc-44m production cross sections using deuterons on an enriched Ca-44 target in order to be able to calculate the associated production yields, and make a comparison with those of the proton route. Experimental data have been extracted up to 34 MeV for the Ca-44(d,2n)Sc-44m,Sc-44g reactions, using the stacked-foil technique and gamma-spectrometry, at the ARRONAX cyclotron. Some results on the production of K-42,43 and Sc-43 have also been obtained but not in all the targets as the main objective was to properly measure the activity of Sc-44m and Sc-44g. Based on these new data, three different scenarios for the production of Sc-44 have been defined depending on the aim of its use: the first one corresponds to the use of Sc-44g for PET imaging with small molecules as vectors. In this case, the production of the metastable-state Sc-44m has to be limited. The second one corresponds to the use of Sc-44g for the new three-gamma imaging technique, developed at the SUBATECH laboratory (Nantes, France). In this case, Sc-43 and Sc-44m will generate a background in the detection system as they don't have the third γ emission with the energy required. The third one corresponds to the use of a Sc-44m/Sc-44g *in vivo* generator to follow long biological processes. In this case, it is necessary to maximize Sc-44m production. All our results are compared with the results of the TALYS code version 1.6, as this information was used to infer potential interest in deuterons over protons.

2. Materials and methods

2.1. Experimental set-up

In this work, Sc-44g and Sc-44m are produced using an enriched Ca-44 carbonate target ($CaCO_3$) from Chemgas®. The isotopic composition of the calcium powder is reported in table 1.

99.04% of the calcium target is composed of Ca-44. Ca-40 represents the vast majority of the other Ca isotopes present in the target with 0.92%. All isotopes investigated in this

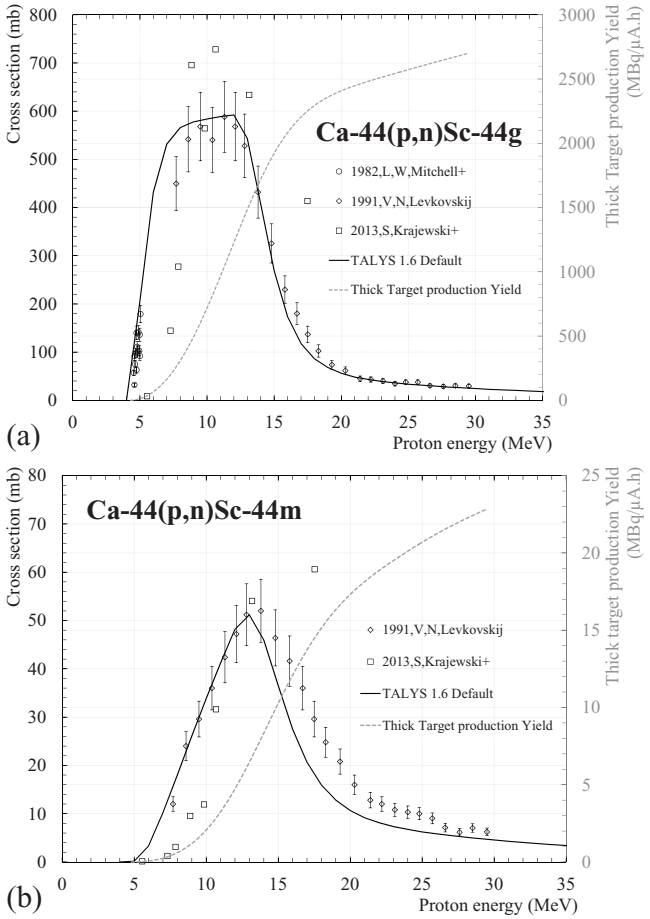

Figure 1. Experimental excitation functions for the Ca-44(p,n)Sc-44g (a) and Ca-44(p,n)Sc-44m (b) reactions with their calculated thick-target production yield, compared with TALYS 1.6 with default models.

work are not produced from Ca-40. The parasitic reactions are on Ca-43 and Ca-42. Sc-44 is produced via Ca-44(d,2n) and Ca-43(d,n) reactions. The contribution on this latter isotope is negligible since Ca-43 is present at a level of only 0.01%. The same holds for the production of Sc-43 which can be made via Ca-44(d,3n), Ca-43(d,2n) or Ca-42(d,n) (0.02%). Both Ca-43 and Ca-42 are present at a low level in the target and their contribution can be neglected. The same comments can be made for the production of K-42 and K-43. The calcium carbonate targets have been prepared at the Institut de Physique Nucléaire dOrsay (IPNO, France) by the CACAO (Chimie des Actinides et Cibles radioActives *à* Orsay) project team (Petitbon-Th'evenet 2010). The backing of our target was chosen to be 100 μm thick aluminium foils with a surface of 25×25 mm^2, manufactured by the Goodfellow Company®. The backing surface was first prepared to be sufficiently rough to insure the good adhesion of the carbonate calcium deposit. Before use, each support was cleaned with isopropanol. To perform centrifugation/sedimentation, the apparatus of the Centre de Spectrométrie Nucléaire et de Spectrométrie de Masse in Orsay (France) was used. The experimental process is expounded in the article by Durnez *et al* (2014). An amount of 6.53 mg of calcium carbonate powder was used to make each target. This value corresponds to 5.44 mg with 20% losses during the

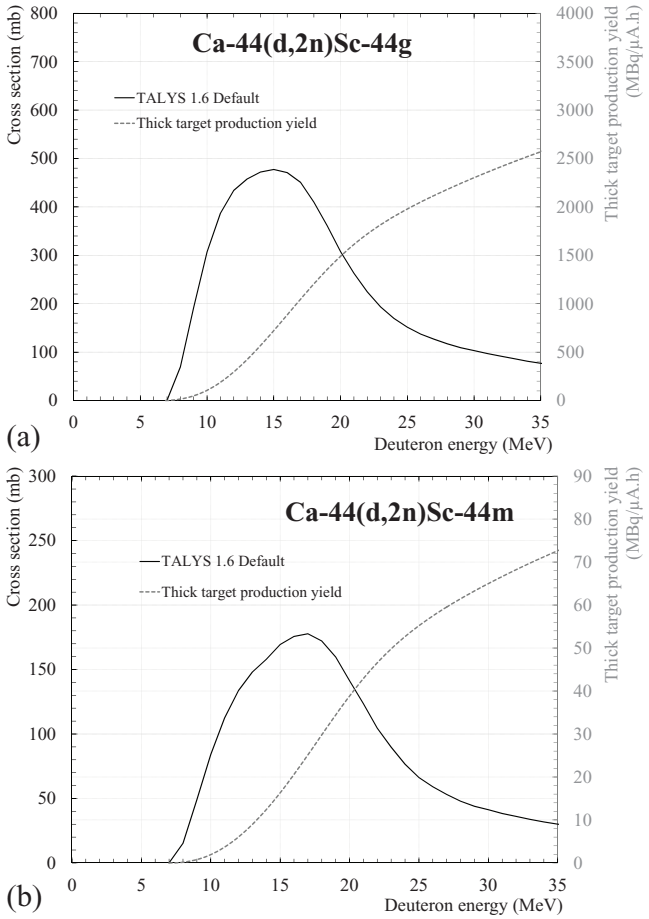

Figure 2. Estimations of the excitation functions of the Ca-44(d,2n)Sc-44g (a) and Ca-44(d,2n)Sc-44m (b) reactions from TALYS 1.6 with default parameters and the associated thick-target production yield.

Table 1. Isotopic composition of the calcium carbonate powder from Chemgas®.

Isotope	Ca-40	Ca-42	Ca-43	Ca-44	Ca-46	Ca-48
%	0.92	0.02	0.01	99.04	$\leqslant 0.01$	0.01

process. One milliliter of a mix of both chloroform and polystyrene (17 g l^{-1}) as well as two milliliters of ethyl acetate was added to the powder. This mix is transferred to a bottle and placed in an ultrasonic bath for one hour to produce good-quality slurry. Then the solution was transferred to a centrifuge tube mounted with the backing. The tube with the slurry was placed in the centrifuge and was spun at 3500 revolutions per minute for one hour. After completing sedimentation, the excess solvent is removed and the target is left aside for polymerizing for 12 h. At the end of the process, the amount of the target material is defined by precise weighting. Typical values are 2.54 (12) mg.cm^{-2} for our 10 targets.

At an ARRONAX cyclotron (Haddad *et al* 2008), cross section measurements are made using the stacked-foil method (Blessing *et al* 1995, Duchemin *et al* 2015) which consists in the irradiation of a set of thin foils, grouped as patterns. Each pattern contains a target

Table 2. Irradiation conditions and energies estimated with SRIM.

Beam energy (MeV)	<Intensity> (nA)	Energy points (MeV)			
34.00 (25)	54	33.33 (28)	29.45 (44)	25.11 (54)	21.66 (60)
20.50 (25)	55	19.51 (29)	17.33 (36)	14.91 (44)	12.17 (58)
16.90 (25)	68	10.71 (49)	8.40 (61)		

to produce the isotopes of interest, a thin aluminium cover to protect the calcium carbonate deposit, a monitor foil to have information on the beam current through the use of a reference reaction recommended by the International Atomic Energy Agency and a degrador to change the incident-beam energy from one target foil to the next one. Each monitor, deposit protection and degrador foil has been weighed before irradiation using an accurate scale ($\pm 10^{-5}$ g) and scanned to precisely determine its area. The thickness is deduced from these values, assuming it is homogeneous over the whole surface. In this work, 10 μm thick titanium monitor foils and 100 to 500 μm thick aluminium degrador foils were irradiated. The titanium and aluminium foils, with a purity of 99.6% and 99%, respectively, were purchased from Goodfellow®.

The ARRONAX cyclotron delivers deuteron beams with an energy uncertainty of $\pm$0.25 MeV, as specified by the cyclotron provider using simulations. The beam line is under vacuum and closed using a 75 μm thick kapton foil. The stacks were located about 7 cm downstream in air. The energy through each foil has been determined in the middle of the thickness of the foil using the SRIM software (Ziegler *et al* 2010). Energy loss in the kapton foil and air has been taken into account. Along the stack, depending on the number of foils, the energy uncertainty calculated using the SRIM software (Ziegler *et al* 2010) increases up to $\pm$0.61 MeV due to energy straggling (see table 4). Three stacks were irradiated with a different incident energy in order to minimize this energy dispersion and cover the energy range from 34 MeV down to 8 MeV, which corresponds to the whole energy range of interest (see table 2). Irradiations were carried out with a mean beam intensity between 54 and 68 nA for 30 min. The beam current through the target has been limited knowing that $CaCO_3$ can be affected by thermal decomposition above 800 °C. In the worst case, the maximal power to the target was 7 mW cm^{-2} which is not enough to decompose the calcium carbonate. The irradiation conditions are reported in table 2.

For all the experiments, the recommended cross section of the reaction Ti-nat(d,x)V-48 (Tárkányi *et al* 2001) is used to obtain information on the beam current from the Ti monitor foils. This reaction is well known over the whole studied energy range. A Faraday cup was placed after the stack to collect charges and control intensity during the irradiation. The cross section values obtained with this measurement are in agreement with those obtained using the monitor foil within 6.5% on average. This difference is explained by the beam stop used to collect the beam current after the stack which has no electron suppression device. In the stacks, 20 μm aluminium foils were placed in front of the Ca-44 carbonate deposit, for protection. The activity on the Ca-44 was determined to measure the target and the protection cover together. The activity measurements in each foil were performed using a high-purity germanium detector from Canberra (France) with low-background lead and copper shielding. All foils were counted twice. The first measurements started the day after irradiation for one hour, for all targets, protection covers and monitor foils. The second ones were performed for a minimum of 24 h (one day) and up to 60 h (during the week-end), one week after the end of irradiation for the Ca-44 targets and after three weeks for the monitor foils, when the Scandium-48 had completely decayed. Indeed, Sc-48 ($T_{1/2}$ = 43.67 (9) h) has common gamma lines with

Table 3. Produced-radioisotope parameters (National Nuclear Data Center; (Ekström and Firestone 2004)).

Radioisotope	$T_{1/2}$ (hours)	E_γ (keV)	I_γ(%)	Contributing reaction(s)	Threshold (MeV)
Sc-44m	58.6 (1)	271.13	86.7 (3)	Ca-44(d,2n)	7.23
Sc-44g	3.927 (8)	1157.031	99.9	Ca-44(d,2n)	6.96
Sc-43	3.891 (12)	372.76	23	Ca-44(d,3n)	17.11
K-42	12.360 (3)	1524.7	18	Ca-44(d,α)	0.00
				Ca-44(d,2p + 2n)	25.13
K-43	22.3 (1)	372.76	23	Ca-44(d,d + p)	12.74
		396.861	11.85 (8)	Ca-44(d,2p + n)	15.07
		593.390	11.26 (8)		
		617.490	79.2 (6)		

the radioisotope of reference, Vanadium-48 ($T_{1/2}$ = 15.9735 (25) d). Gamma spectra were recorded in a suitable geometry calibrated in energy and efficiency with standard Co-57,60 and Eu-152 gamma sources from LEA-CERCA (France). The full widths at half maximum were 1.04 keV at 122 keV (Co-57 γ ray) and 1.97 keV at 1332 keV (Co-60 γ ray). The samples were placed at a height of 19 cm from the detector in order to reduce dead time and the effect of sum peaks. Dead time during counting was always kept below 10%.

2.2. Data processing

The activity values of the produced radioisotopes were derived from the γ spectra and the nuclear decay data (National Nuclear Data Center; (Ekström and Firestone 2004)) given in table 3 using the FitzPeaks spectroscopy software (FitzPeaks Gamma Analysis and Calibration Software version 3.66 1981). Knowing the precise thickness of the foil and the activity value of the produced isotope, its production cross section is calculated using the activation formula (1) with the appropriate beam current:

$$\sigma = \chi \cdot \frac{\mathrm{Act} \cdot A}{\Phi \cdot N_a \cdot M \cdot (1 - \mathrm{e}^{-\lambda t})} \tag{1}$$

In this equation, the production cross section σ of a radioisotope depends on its measured activity reported at the end of irradiation (Act), its decay constant (λ), its atomic mass (A), its areal density (M), its chemical and isotopic purity (χ), the irradiation duration (t) and the beam current (Φ).

In our experiment, each target foil received the same beam current as the monitor foil that follows. It is then easier to use the relative equation (2) in which the knowledge of the beam current is no longer necessary. In this equation, the prime parameters are associated with V-48 while the others relate to the radioisotope produced in the target (i.e. Sc-44m, Sc-44g, Sc-43, K-42 and K-43).

$$\sigma = \sigma' \cdot \frac{\chi' \cdot \mathrm{Act} \cdot A \cdot M' \cdot (1 - \mathrm{e}^{-\lambda' t})}{\chi \cdot \mathrm{Act}' \cdot A' \cdot M \cdot (1 - \mathrm{e}^{-\lambda t})} \tag{2}$$

The cross section uncertainty is estimated with a propagation error calculation. Since all the parameters of equation (2) are independent, the total error is expressed as a quadratic sum (equation (3)). The main error sources come from the recommended cross section, the activity

values of each produced radioisotope and the foil thickness uncertainties. An uncertainty around 11% is applied to the recommended cross section values given by the uncertainty of the nearest experimental value. The uncertainties on the activity of the radioisotopes produced on the Ca-44 targets depend on different parameters such as the gamma line branching ratio and energy, half-life etc, described afterwards. These uncertainties are, on average, 3.5% for Sc-44m activity, 16% for Sc-44g, 20% for K-42, 18% for K-43 and up to 30% for Sc-43. The uncertainty on the activity of V-48 is 4% on average. Around 1% of uncertainty is calculated for the areal density. The contribution of the irradiation time uncertainty is not significant and has been neglected.

$$\frac{\Delta\sigma}{\sigma} = \sqrt{\left(\frac{\Delta\sigma'}{\sigma'}\right)^2 + \left(\frac{\Delta\mathrm{Act}}{\mathrm{Act}}\right)^2 + \left(\frac{\Delta\mathrm{Act}'}{\mathrm{Act}'}\right)^2 + \left(\frac{\Delta M}{M}\right)^2 + \left(\frac{\Delta M'}{M'}\right)^2} \tag{3}$$

2.3. Thick-target production yield (TTY)

Using the cross section values obtained in this work or those in databases as a function of the energy $\sigma(E)$, we have calculated the associated Thick-Target production Yield in Bq/μA.h, also called production yield or integral yield. The values are obtained as a function of the projectile energy, using the relation (4).

$$\mathrm{TTY} = \Phi.\chi.\frac{N_a.\rho}{A}(1 - \mathrm{e}^{-\lambda.t}) \int_{E\mathrm{min}}^{E\mathrm{max}} \frac{\sigma(E)}{\frac{\mathrm{d}E}{\mathrm{d}x}}\mathrm{d}E \tag{4}$$

In relation (4), ϕ is set to be the number of particles per second delivered in 1 μA. χ corresponds to the isotopic and chemical purity of the target and N_a is the Avogadro number. The TTY results presented in this article are obtained using the density ρ and the atomic mass A of a calcium-44 carbonate target. The density is provided by the CACAO team who prepared the target, and fixed at 2.71 g.cm^{-3}. All the TTY calculation is done taking into account one hour of irradiation, which is less than the time when the activity of the investigated radionuclides is saturated. $\frac{\mathrm{d}E}{\mathrm{d}x}$ is the specific energy loss of the projectile in the target material (MeV. cm^{-1}). In a thick target, the incident particle energy decreases with the penetration depth. E_{max} corresponds to the incident projectile's energy when it enters into the target whereas E_{min} corresponds to its energy when it leaves the target. TTY is also called production yield or integral yield.

2.4. Comparison with the TALYS 1.6. code

In this work, all experimental cross section values are compared with the latest version (1.6) of the TALYS code released in December, 2013 (Koning and Rochman 2012). TALYS is a nuclear reaction program for simulating the reaction induced by light particles on nuclei heavier than carbon. It incorporates theoretical models to predict observables including theoretical cross section values as a function of the incident particle energy (from 1 keV to 1 GeV). A combination of models that better describe the whole set of data available for all projectiles, targets and incident energies has been defined by the authors of the code and put as default in the code. This way, the code can be launched with minimum information in the input file: the projectile's type and its incident energy, the target's type and its mass. The experimental data obtained in this work are compared to TALYS with default models (named TALYS 1.6 Default in the graphs).

Table 4. Experimental cross section values (mb) for Ca-44(d,2n)Sc-44m,Sc-44g, Ca-44(d,3n)Sc-43 and Ca-44(d,x)K-42,K-43 reactions.

Energy (MeV)	σ Sc-44m (mb)	σ Sc-44g (mb)	σ Sc-43 (mb)	σ K-42 (mb)	σ K-43 (mb)
33.33 ± 0.28	35.63 ± 4.42	120.05 ± 24.25	80.25 ± 25.98	13.51 ± 9.50	27.86 ± 4.32
29.45 ± 0.44	57.29 ± 6.74	156.12 ± 42.62			17.74 ± 3.77
25.11 ± 0.54	104.01 ± 12.71	223.06 ± 67.61			10.82 ± 3.71
21.66 ± 0.60	132.97 ± 16.14	350.52 ± 56.88	43.44 ± 15.49		2.98 ± 0.61
19.51 ± 0.29	176.10 ± 22.53	482.57 ± 78.80			
17.33 ± 0.36	184.46 ± 25.73			37.00 ± 12.05	
14.91 ± 0.44	138.25 ± 15.76	538.49 ± 77.97		36.52 ± 8.41	
12.17 ± 0.58	89.64 ± 10.26	448.59 ± 67.96		58.78 ± 9.47	
10.71 ± 0.49	52.49 ± 6.37	267.88 ± 60.57		49.96 ± 8.76	
8.40 ± 0.61	4.16 ± 0.63	27.05 ± 5.09		38.59 ± 6.87	

3. Results and discussion

Production cross sections are needed to obtain the thick-target production yield for a produced radioisotope. In the first part, new results on deuteron-induced Sc-44 production cross sections on Ca-44 will be revealed, as well as the contaminant cross sections. In the second part, the Sc-44m and Sc-44g TTY will be calculated and compared with those of the proton routes for different production scenarios.

3.1. Production cross sections for deuteron-induced reactions

The production cross sections of the produced radioisotopes are plotted in figures 3–7 as full circles and the associated numerical values are reported in table 4.

3.1.1. Production cross section of Sc-44m. Sc-44m ($T_{1/2}$ = 58.6 (1) h) mainly decays by internal transition (IT), at 98.80 (7)%, to its ground state Sc-44g ($T_{1/2}$ = 3.97 (4) h) by emitting an intense γ ray at 271.13 keV (table 3). It also decays by the electron capture (EC) process (1.20 (7)%) to Ca-44 (stable) by emitting three γ rays of 1001.83 (1.20%), 1126.06 (1.20%) and 1157.031 keV (1.20%). The high branching ratio of the 271.13 keV gamma line allows its use for extracting the Sc-44m production cross section plotted in figure 3, with the results of the TALYS code version 1.6 with the default parameters.

The Sc-44m production cross section shows the maximum at 17.3 MeV with a value of 185 mb (see figure 3). The TALYS code gives cross section values slightly shifted to lower energies as compared to those that are experimentally determined (see figure 2(a)). The magnitude of the cross section is of the same order for both the experimental and TALYS results.

3.1.2. Direct-production cross section of Sc-44g. Sc-44g ($T_{1/2}$ = 3.97 (4) h) is a 100% EC/β+ emitter which decays to Ca-44 (stable). It emits an intense gamma ray at 1157.031 keV (99.9%), used to determine its activity. The measured activity and the cross section obtained in this work correspond to the direct production of Sc-44g in a Ca-44 carbonate target. As Sc-44m decays to Sc-44g, its contribution has been determined and removed from the Sc-44g activity, as well as the contamination by the direct decay of Sc-44m to Ca-44 in the gamma line at 1157 keV, which is common to Sc-44m (I_γ = 1.2%) and Sc-44g. The experimental Sc-44g production cross section is plotted in figure 4.

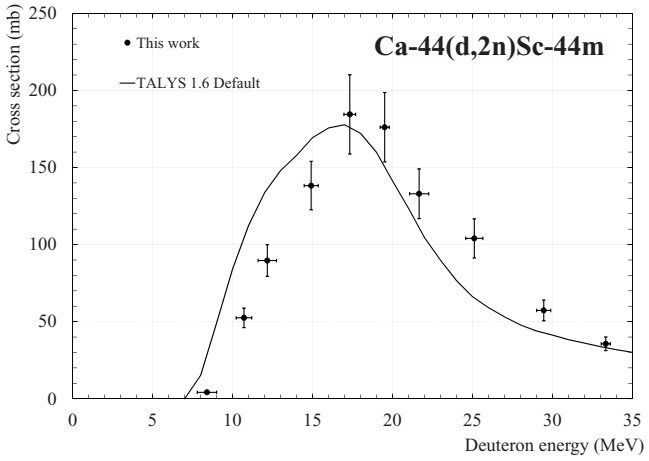

Figure 3. Excitation function for the Ca-44(d,2n)Sc-44m reaction.

In figure 4, the experimental data show a broader peak with its maximum 10% higher than the results obtained using the TALYS calculations. The maximum of the experimental cross section is found to be 538 mb at 14.9 MeV, against 470 mb with TALYS for the same incident deuteron energy. In this case, there is no energy shift between TALYS and the experimental results.

3.1.3. Production cross section of K-42. K-42, with a half-life of 12.260 (3) h, decays by the β- process (100%) to Ca-42 (stable). It emits one main γ ray at 1524.7 keV with a branching ratio of 18%. This gamma line has been used to determine K-42 activity and deduce its production cross section, plotted in figure 5. K-42 activity has not been obtained for all energies as it was not the main objective of this study. The TALYS code is not able to reproduce the excitation function for this reaction.

3.1.4. Production cross section of K-43. K-43 has a half-life of 22.3 (1) h and decays by β- emission at 100% to Ca-43 (stable), emitting four gamma rays with a branching ratio higher than 11% (see table 3). Among these gammas, one is common to Sc-43. The three other gamma lines have been used to extract the cross section values. They have also permitted the deduction of the K-43 contribution in the gamma line (372.9 KeV), which is common to Sc-43. In figure 6, we can see that our experimental data are in agreement with the reaction energy threshold at 15.07 MeV. The TALYS code is not able to reproduce the experimental trend and amplitude for this reaction.

3.1.5. Production cross section of Sc-43. Sc-43 has a half-life of $T_{1/2} = 3.891$ (12) h. It is an 88% β+ emitter and decays to Ca-43 (stable), by emitting a γ ray at 372.9 keV (see table 3) with a branching ratio of 22.5%. This gamma line is common to K-43 which is also produced in the target (see section 3.1.4).

The activity of Sc-43 has been deduced from this peak using the other detectable gammas emitted by K-43, resulting in an additional uncertainty source for the determination of Sc-43 activity. As there is some cooling time of 14 h between the end of irradiation and the activity measurements, the short half-life of Sc-43 and its low production cross section don't permit the detection of Sc-43 in every irradiated target. When activity was high enough to be detected, the uncertainty on the peak fit was up to 30%. Only two cross section values at

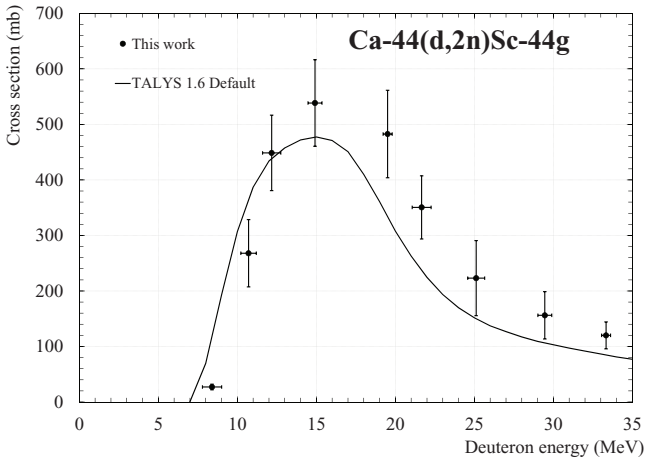

Figure 4. Excitation function for the Ca-44(d,2n)Sc-44g reaction (direct production).

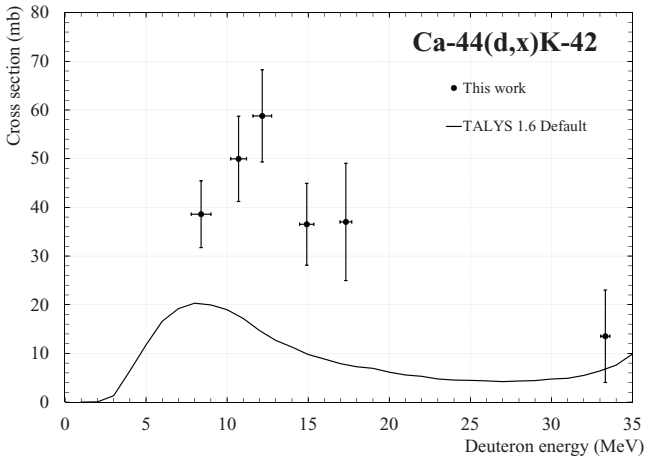

Figure 5. Excitation function for the Ca-44(d,x)K-42 reaction.

21.66 and 33.33 MeV were measured and are reported in table 4. These values are plotted in figure 7 with the results of the TALYS code with the default parameters. As no experimental data are available around the maximum plotted by TALYS, the amplitude of the curve cannot be verified. However, our existing experimental data points are in good agreement compared to the TALYS values. In addition, Sc-43 is produced by a (d,xn) as well as Sc-44 for which the TALYS code shows a good reproduction of the trend.

3.2. Thick-target production yield of Sc-44

Sc-44 can be produced using Ca-44 with protons or deuterons as projectiles. The thick-target production yields of Sc-44g and Sc-44m using deuterons have been obtained from the experimental production cross sections determined in this work. They are plotted in figures 8(a) and (b), respectively. These data are compared with the proton route, calculated from the results summarized in databases (National Nuclear Data Center 2013).

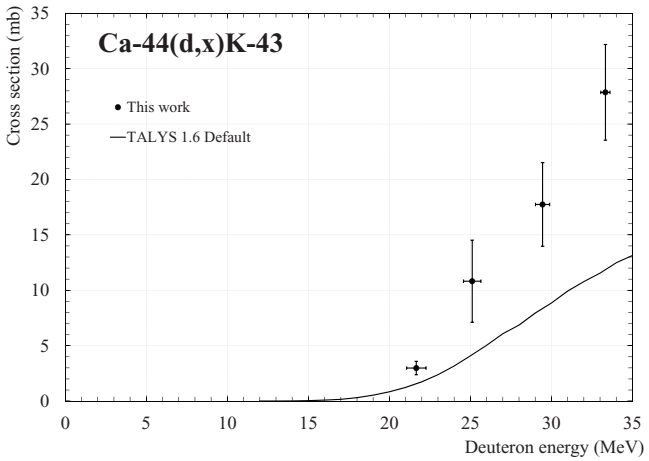

Figure 6. Excitation function for the Ca-44(d,x)K-43 reaction.

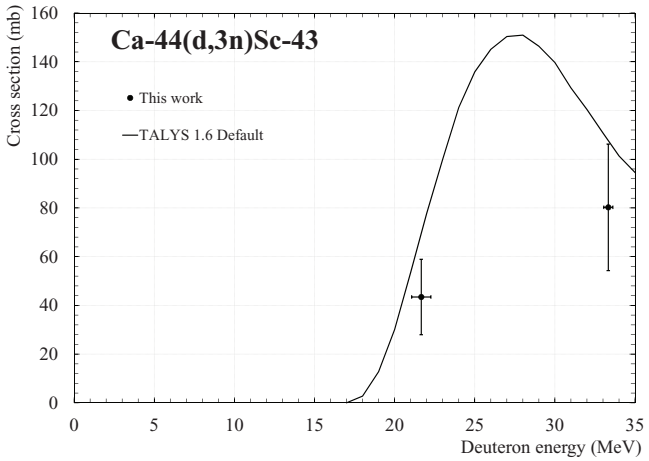

Figure 7. Excitation function for the Ca-44(d,3n)Sc-43 reaction.

Using protons as projectiles at 30 MeV, the Sc-44g TTY calculated from the experimental cross section values of Mitchell *et al* (1982), Levkovskij (1991) and Krajewski *et al* (2013), is 2.7 GBq/μA.h (see figure 8(a)). In this work, we calculate from our new cross section values obtained with deuterons a TTY of 2.9 GBq/μA.h at 30 MeV, which is close to the value calculated in the case of protons. The cross section values obtained with the TALYS code lead to a TTY of 2.3 GBq/μA.h (figure 2(a)), i.e. 21% lower than the experimental value.

For the production of Sc-44m, the TTY is 23 MBq/μA.h with protons at 30 MeV (see figure 8(b)). From our data using deuterons, the TTY is 70 MBq/μA.h with the same incident energy i.e. 3 times higher than the one obtained with protons. With the TALYS code results, the TTY is calculated to be 65 MBq/μA.h, 7% lower than the experimental one.

These results show that a higher Sc-44g production rate is obtained using protons instead of deuterons up to 27 MeV. With 30 MeV protons and deuterons, a similar amount of Sc-44g is produced with 2.7 and 2.9 MBq/μA.h, respectively. It must be taken into account that the smallest amount of carbonate calcium material is necessary with deuterons at 30 MeV as compared to protons with the same energy. Indeed, the target thickness has to be 2.3 mm using

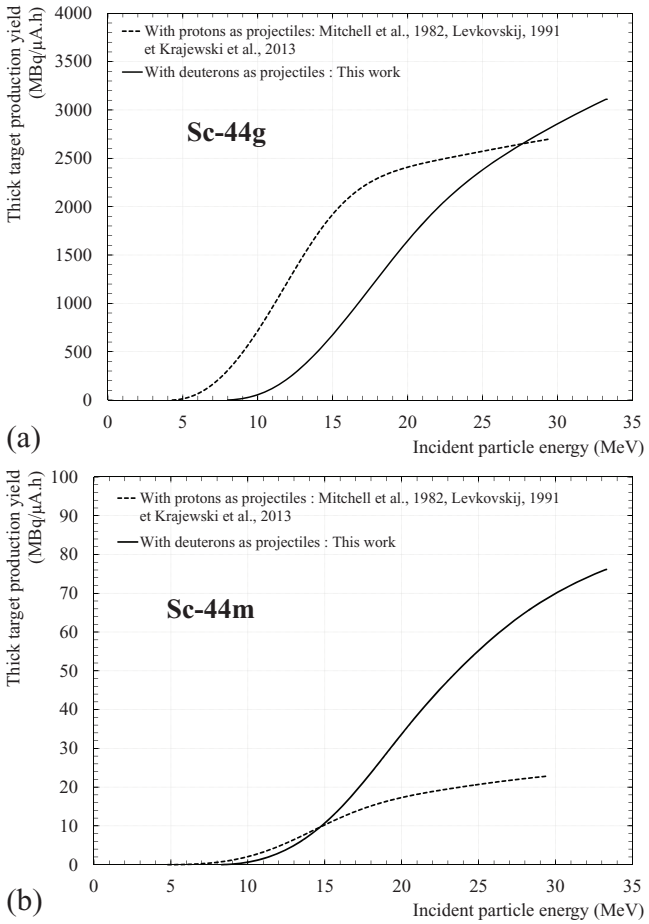

Figure 8. Thick-target production yields for the Ca-44(d,2n)Sc-44g (a) and Ca-44(d,2n) Sc-44m (b) reactions, calculated with the cross section values of this work. Comparison with the Ca-44(p,n)Sc-44g (a) and Ca-44(p,n)Sc-44m (b) reactions.

deuterons against 4.1 mm using protons. In addition, the production of Sc-44m can significantly be increased using deuterons as projectiles instead of protons.

3.3. Sc-44 production scenarios

Three production scenarios can be set and are presented below, depending of the use of Sc-44 and the cyclotron characteristics of the commercially available machine (15 MeV, 30/15 MeV and 70/35 MeV proton/deuteron).

3.3.1. Production of Sc-44g for conventional PET imaging with small vector molecule. The first scenario is the production of scandium-44g for conventional PET imaging for which Sc-44m has to be limited. Sc-43 is also of interest for PET and emits positrons with energies close to those of Sc-44g. Avoiding the production of Sc-43 is not an issue for this production scenario. Figure 8(b) shows that the production of Sc-44m with protons is lower than that with deuterons on the whole investigated energy range. This way, the use of protons is the best choice, compared with deuterons, to produce Sc-44g for PET imaging.

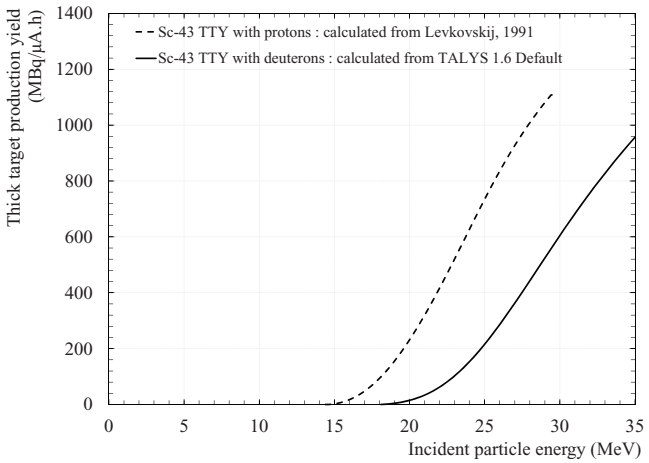

Figure 9. Thick-Target production Yields for the Ca-44(d,3n)Sc-43 and the Ca-44(d,2n) Sc-43 reactions, calculated with the cross section values of Levkovskij (1991) for the proton route and with the TALYS 1.6 default results for the deuteron route.

3.3.2. Production of Sc-44g for the new 3 γ imaging technique. The second scenario is the production of scandium-44g for the new 3 gamma imaging technique using peptides or small molecules with rapid distribution in the body. In this case, Sc-44g is the radionuclide to produce in high quantity. The production of Sc-44m and Sc-43 is not necessary as they don't have the third high-energy γ required for this new diagnostic technique. They will add noise to the detection system and an additional unnecessary dose to the patient. Sc-44m and Sc-43 cannot be separated from Sc-44g in the target, in contrast to potassium isotopes (see figures 5 and 6).

With a 15 MeV proton cyclotron. As shown in figure 8(a), 1.9 GBq/μA.h of Sc-44g is directly produced with 15 MeV protons. Figure 9 shows the Sc-43 TTY calculated for protons as projectiles using the values published by Levkovskij (1991), and for deuterons using the TALYS 1.6 Default values plotted in figure 7. Irradiating the target with a 15 MeV proton beam leads to a Sc-43 production yield of 2.4 MBq/μA.h and 10.5 MBq/μA.h for Sc-44m (see figure 8(b)). For these conditions of irradiation, the Sc-43 and Sc-44m production yields at the end of irradiation represent, respectively, 0.1% and 0.6% of the Sc-44g activity directly produced.

*With a 30 MeV proton—15 MeV deuteron cyclotron.*With 15 MeV deuterons, the amount of Sc-44g produced in the calcium-44 carbonate target is 680 MBq/μA.h (see figure 8(a)). For this energy, no Sc-43 can be produced as the Ca-44(d,3n)Sc-43 reaction threshold is 17.1 MeV. 11 MBq/μA.h of Sc-44m will be produced (see figure 8(b)) which is 1.6% of the Sc-44g activity. With 30 MeV protons, 2.7 GBq/μA.h of Sc-44g is produced. The production yield is 1.2 GBq/μA.h for Sc-43 (see figure 9) and 23 MBq/μA.h for Sc-44m, which represent respectively 44% and 0.9% of the Sc-44g activity.

With a 30 MeV deuteron cyclotron. With 30 MeV deuterons, the Sc-44g TTY is 2.9 GBq/μA.h, close to that obtained with 30 MeV protons. The amounts of Sc-44m and Sc-43 produced are, respectively, 70 MBq/μA.h and 600 MBq/μA.h. These correspond to 2.4 and 20.7% of the Sc-44g activity.

3.3.3. Production of Sc-44m/Sc-44g in vivo generator for antibody labelling. The last scenario is about the production of a Sc-44m/Sc-44g *in vivo* generator for antibody labelling.

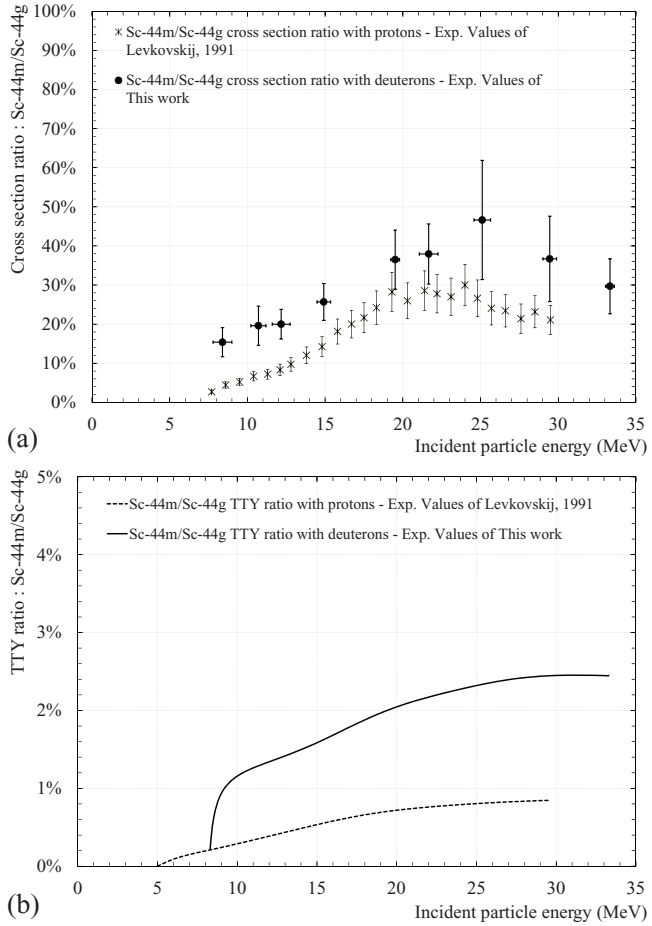

Figure 10. Experimental Sc-44m/Sc-44g cross section (a) and calculated TTY (b) ratios using protons and deuterons as projectiles.

A study has shown that a Sc-44m/Sc-44g generator labelled with a DOTA-peptide is chemically stable and that Sc-44g stays attached to the chelator after the decay of its parent radionuclide Sc-44m (Huclier-Markai *et al* 2014). The *in vivo* generator permits the extension of the Sc-44 lifetime in the patient's body. Sc-44m can then be used for antibody labelling for both conventional PET and 3 γ imaging. For this purpose, the direct production of Sc-43 and Sc-44g is useless since the transit time of antibodies is long as compared to their half-lives.

Figure 10 shows that the Sc-44m/Sc-44g cross section ratio (a) and the Sc-44m/Sc-44g TTY ratio(b) are higher when using deuterons instead of protons.

In the specific case where a Sc-44m/Sc-44g *in vivo* generator is used, a deuteron beam has to be preferred.

From a 15 MeV deuteron beam, no Sc-43 can be produced and 680 MBq/μA.h of Sc-44g is produced. The Sc-44m TTY for this energy is 11 MBq/μA.h. It is 62 times less than the Sc-44g activity.

With a 30 MeV deuteron beam, 70 MBq/μA.h of Sc-44m is produced. Figure 11 shows the decay of Sc-44m, Sc-44g and Sc-43 taking into account the initial activity produced with a 30

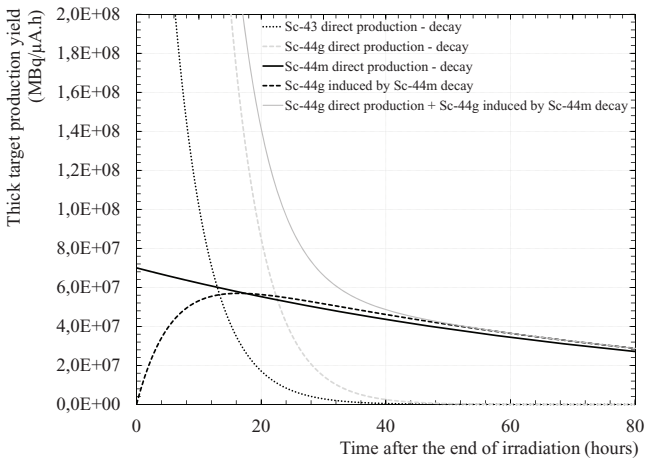

Figure 11. Sc-44m, Sc-44g and Sc-43 decay from an initial activity produced with a 30 MeV deuteron beam.

MeV deuteron beam. The secular equilibrium between Sc-44m and Sc-44g is reached after 50 h, which is close to one Sc-44m half-life, i.e. 2.44 d. Waiting for this time after the end of irradiation, Sc-43 production decreases to 18 kBq/μA.h (0.05% of the Sc-44m activity) and Sc-44g direct production decreases to 2.3 kBq/μA.h.

Sc-44m production, waiting for 2.44 d after the end of irradiation, reaches 35 MBq/μA.h, which is 3.2 times higher than the one obtained with 15 MeV deuterons at the end of irradiation.

However, only few accelerators in the world are able to deliver 30 MeV deuterons, but the technology is available. This type of cyclotron permits the production of a higher amount of Sc-44m than using 15 MeV deuterons or a proton beam.

4. Conclusion

New experimental cross section values have been presented for Ca-44(d,x)Sc-44m, Sc-44g reactions with some information on the Sc-43, K-42 and K-43 contaminants. The TALYS results are close to the experimental values for the Ca-44(p,n) and Ca-44(d,2n) reactions. New measurements dedicated to Sc-43 with deuterons as projectiles are needed to obtain experimental values on this contaminant production cross section, and validate, or not, the trend made by the TALYS code. However, TALYS with the default models is not able to reproduce the data for the production of potassium isotopes.

These new sets of experimental data allow the calculation of Thick-Target production Yields and the comparison of the proton and deuteron routes for three different Sc-44 production scenarios. This article shows that the use of a proton beam is the best choice, as compared to deuterons, to produce Sc-44g for PET imaging using peptides or small molecules with rapid distribution in the body. For the new 3 γ imaging technique developed at the SUBATECH laboratory, Sc-44g has to be produced with protons of 15 MeV to limit the background generated by Sc-44m and Sc-43 decay.

The production of the Sc-44m/Sc-44g *in vivo* generator for antibody labelling required the highest Sc-44m production rate, with a limited amount of Sc-44g directly produced. Our new experimental results have shown that the Sc-44m/Sc-44g cross section and TTY ratios

are higher with deuterons than with protons, whatever the incident beam energy. The production of Sc-44m for the *in vivo* generator is advantageous with deuterons as projectiles, using a calcium-44 carbonate target. Sc-44m can be produced with a 15 MeV deuteron beam but a higher amount of Sc-44m is produced with a 30 MeV deuteron beam. With the latter energy value, some cooling time before the extraction and separation processes permits one to more significantly reduce the contribution of directly produced Sc-44g activity and thereby obtain a negligible level of Sc-43.

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