Published in final edited form as:
Appl Radiat Isot. 2012 August ; 70(8): 1526–1530. doi:10.1016/j.apradiso.2012.04.030.

Cyclotron Produced ^{44g}Sc from Natural Calcium

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Abstract

^{44g}Sc was produced by 16 MeV proton irradiation of unenriched calcium metal with radionuclidic purity greater than 95%. The thick target yield at saturation for ^{44g}Sc was 213 MBq/μA, dwarfing the yields of contaminants ^{43}Sc,^{44m}Sc, ^{47}Sc and ^{48}Sc for practical bombardment times of 1–2 h. Scandium was isolated from the dissolved calcium target by filtration, and reconstituted in small volumes of dilute HCl. Reactions with the chelate 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) indicated a reactivity of 54±14 Gbq/μmol at end-of-bombardment.

Keywords

^{44}Sc; scandium-44; isotope production; PET; radiometal; thick target yield

1. Introduction

A 3.97 h[1] half-life and 94% positron branch make ^{44g}Sc suitable for peptide radiolabeling for PET. Another scandium isotope, ^{43}Sc, has matched characteristics with a 3.89 h half-life, and 88% positron branch. Both represent PET surrogates for the therapeutic isotope ^{47}Sc, and possibly for ^{177}Lu as shown by Majkowska-Pilip and Bilewicz (2011).

Recent developments in ^{44}Ti/^{44g}Sc generator technology have intensified interest in ^{44g}Sc (Filosofov *et al.*, 2010; Pruszyński *et al.*, 2010, 2012). However, production of sufficient quantities of ^{44}Ti ($t_{1/2}$ =60 y) requires proton irradiation parameters exceeding the capabilities of most small medical cyclotrons. Therefore production is limited to the few willing facilities in the world (Zhernosekov *et al.*, 2011; Alenitzky *et al.*, 2005). In order to justify the procurement and custodianship of a long-lived generator, the need for ^{44g}Sc must be established through preclinical trials. To that end, direct production of ^{44g}Sc on small research cyclotrons is necessitated.

Abbas *et al.* (2011) investigated production *via* ^{44}Ca(p,n)^{44g}Sc and showed that Ci levels of ^{44g}Sc are possible using an enriched target. Additionally, a thin target of enriched ^{44}Ca produces the activity required for preclinical PET, and at current market prices such a target is not prohibitively expensive (currently 15 USD/mg metal mass, at 98% enrichment as carbonate; Isoflex, CA). However, to protect against the fluctuating prices of enriched

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[2]The ^{43}Sc produced from ^{44}Ca(p,2n) is not distinguished from ^{43}Ca(p,n) in this study.

[1]All nuclear physics data in this report come from *Nuclear Data Sheets* and were accessed *via* www.nndc.bnl.gov.

isotopes, especially when anticipating the demand that may arise from successful tracers, it is worthwhile to develop alternative production routes.

^{43}Sc, having lower energy concurrent gamma emissions and lower positron-branch endpoint energies than ^{44g}Sc, is produced by either the ^{43}Ca(p,n) reaction or by alpha irradiation *via* the ^{40}Ca(α,p) and ^{40}Ca(α,n) channels. The method of alpha bombardment su3ers from a similar lack of available cyclotrons as ^{44}Ti production. However with a 4-hour half-life and a production cross-section approaching 1 barn (Levkovskij, 1991), potential exists for regional distribution following mass production at a single alpha facility. The most suitable target for such irradiations is natural Ca metal, comprised at 97% by ^{40}Ca.

To date, available literature does not address ^{44g}Sc and ^{43}Sc production from a natural metal calcium target, but the properties are favorable. Calcium metal is malleable, has a melting point over 1100 K, is electrically conductive, and has a coe3cient of thermal conductivity comparable to that of aluminum (200 W/m K and 237 W/m K respectively). This is in contrast to CaO or $CaCO_3$, insulating ceramics which dissipate neither heat nor charge in su3cient quantity to allow high-power targetry. The malleability of calcium allows it to be pressed into a water-cooled target body forming good thermal contact. Additionally, the intense reactivity of calcium with water lends itself towards fast target chemistry.

The development of Ca metal targetry and subsequent chemical separation begins with proton irradiations, producing ^{44g}Sc on a preclinical scale. Owing to a large reaction cross section, an unenriched calcium metal target provides ample ^{44g}Sc–in spite of the meager 2.09% natural abundance of ^{44}Ca. Levkovskij (1991)[2] determined the production cross-sections for ^{44m}Sc, ^{44g}Sc, and ^{43}Sc. Coupling these values with the stopping power of calcium gives the expected end-of-saturation-bombardment (EOSB) yields shown in Fig. 1.

The ^{44}Ca(p,n)^{44g}Sc cross-section (peaking with 588 mb at 10.9 MeV) allows 264 MBq/μA ^{44g}Sc at EOSB for 16 MeV protons on a thick, unenriched metal target. The cross-sections for creation of other scandium radioisotopes are unpublished, and a measurement of their production rate concurrent with ^{44g}Sc is of utmost interest when assessing the potential for research use.

For eventual labeling of PET tracers, recovery of the ^{44g}Sc from calcium needs to remove bulk metal and give the final product in a small volume. A fortunate fact is that small amounts of residual calcium do not interfere with DOTA chelation (Abbas *et al.*, 2011). Thus the chemical processing may be aimed at concentrating the activity rather than at rigorous purification. One such viable separation employs precipitation and filtration (Duval and Kurbatov, 1953). This approach takes advantage of the insolubility of $Sc(OH)_3$ either as a precipitate or coprecipitate, and is similar to a technique developed for purifying yttrium from strontium (Avila-Rodriguez *et al.*, 2008).

Majkowska-Pilip and Bilewicz (2011) showed that DOTA is a satisfactory candidate for bifunctional chelation of ^{44g}Sc to PET-tracer molecules. Pruszyński *et al.* (2012) report reaction conditions for labeling bifuncionalized DOTA, conjugated to octreotide (DOTATOC), with generator-produced ^{44}Sc. They achieve near quantitative yields with a ratio of ^{44}Sc to DOTATOC of roughly 9 GBq/μmol at 95 °C in pH 4 acetate bu3er for 30 min. When considering extracting ^{44g}Sc from a metallic calcium target, reactivity with DOTA in excess of 9 GBq/μmol is therefore a reasonable benchmark for evaluating the success of the chemical separation.

[2]A multiplicative correction of 0.8 was applied to all proton reaction cross-section values taken from Levkovskij (1991). The correction is discussed by Takács *et al.* (2002), arising from an incorrect value for the monitor reaction cross-section. The shapes of the excitation functions are considered valid.

For this work, we measured the thick target yields of ^{44g}Sc at 16 MeV, along with contaminants ^{44m}Sc, ^{43}Sc, ^{47}Sc, and ^{48}Sc. Additionally, we developed a filtration separation technique providing ^{44g}Sc in a small volume of dilute HCl. Finally, we determined the reactivity with DOTA by titration.

2. Materials and Methods

2.1. Cyclotron targetry and irradiations

To prepare the targets, several 100–150 mg dendritic chunks totalling 400–600 mg of natural 99.99% calcium metal (Sigma Aldrich, St. Louis MO) were pressed with a mechanical lever press into an aluminum target holder. The holder was a short 4.2 mm cylinder (3.8 cm diameter) with a 1.26 cm^2 by 2.5 mm flat-bottom cavity in the center for holding the calcium. 1.7 mm of aluminum separated the calcium target from water-jet cooling applied to the backside of the holder. A piece of 12.5 μm aluminum foil placed over the irradiated face of the target protected the cyclotron from vaporized calcium.

Irradiations were performed on the UW-Madison PET-trace at 16 MeV. Typical irradiations lasted for 1 hour at currents ranging from 5–27 μA. In order to address the concern of target oxidation, a single 770 mg target was pressed into the aluminum holder and exposed to lab air for 3.5 days. The mass of the target was measured before and after pressing and after the waiting period.

2.2. Thick target yields

A 600 mg calcium target[3], prepared as above, was irradiated for 330 s with an average current 6.1 μA at 16 MeV. The target was kept in the holder, and γ intensities were determined with a 60 cm^3 high purity germanium (HPGe) detector (Canberra C1519) in 600 s and 1800 s segments for 3.5 days. The gamma lines used to determine yields are listed in Table 1. Peaks were selected from the spectra and their associated decay curves were fit with the appropriate half-lives to determine the activity at end-of-bombardment (EOB) and the activity distribution as a function of time. Gain shifts in the detector electronics were corrected by centroid fitting, and segments with poor resolution (indicating a gain shift during counting) were discarded.

For all other irradiations, the activity at greater than 20 min post-EOB was measured with a Capintec CRC-15 Dual PET dose calibrator (setting 938) after dissolution and acidification of the target as described in Sec. 2.3.

2.3. Radiochemical separation

Irradiated calcium targets (400–600 mg) were removed from the target holder and dropped into 10 ml cold water in a 50 ml centrifuge tube resting in an ice bath. The calcium reacted on contact with the water creating a white sludge of CaO and $Ca(OH)_2$. This was dissolved by addition of 2.5 ml concentrated trace-metals-grade HCl (Aristar Ultra, VWR, West Chester PA). For some of the dissolutions the calcium was dissolved with 2M HCl added 2–4 ml at a time instead of water. This had the effect of keeping the calcium in solution as hydrolysis commenced, reducing its propensity to bubble over. After dissolution, the pH was adjusted to 6.5–9.0 by addition of the appropriate volume of 1 M NH_4OH (Optima, Fisher Scientific, Fair-lawn NJ). pH values were monitored during the procedure with an ion-sensitive field-effect transistor (ISFET) probe (I.Q. Scientific Instruments, Carlsbad CA). The solution was then pushed through a 0.22 μm Millex-GV 13 mm diameter syringe filter (Millipore Corporation, Billerica MA) where the majority of the activity was retained. To

[3]A thick target for 16 MeV protons in calcium is 400 mg/cm^2 (Ziegler, 1985), or ≥ 504 mg for the geometry described.

recover activity adhered to the tube walls, 2 ml 4M HCl was added to the dissolution vessel, vortexed, and the pH was readjusted to 6.5–9.0. This liquid was also pushed through the same filter. Then the filter was washed with 10 ml 0.1M ammonium hydroxide that had been adjusted to pH 8–9 with HCl.

Elution was performed slowly with 0.1 M HCl, at a rate of 150 μl/min at 70–90°C. In order to maximize the activity concentration, each 150 μl fraction was pulled back through the filter 2–3 times before it was finally expelled.

The entire process was also performed with a non-irradiated Ca target (462 mg), and an eluted sample was analyzed by ICP-MS at the State Hygiene Lab of Wisconsin for metal impurities.

2.4. Reactivity measurements

The pH of the first eluted fraction (0.1M HCl, 150 μl) was adjusted to 4.8 with 0.2 M ammonium acetate. This bu3ered solution was split into 9 fractions, each mixed with 100 μl of aqueous DOTA (Macrocyclics, CA) solutions of known concentrations ranging from 0.1 to 1000 nM, along with a no-DOTA control vial. The solutions were incubated at 80 °C for 30 min, and then spotted onto aluminum backed silica gel instant thin-layer liquid chromatography (ITLC) plates (EMD Chemicals, Gibbstown NJ). The plates were developed with water solvent for 15 min and dried. The activity distribution on the plates was assessed with a Packard Cyclone Phosphor-Plate imaging system.

3. Results

3.1. Cyclotron targetry and irradiations

Oxidation of the calcium target during handling was negligible. In all cases, no oxidation of the targets was observed during the short time that they were exposed to air before and after irradiation. The 770 mg target that was left out for 3.5 days gained only 40 mg mass, indicating minimal oxidation for the routine 5–20 minute target-prep procedure. All other targets gained no mass between pressing and irradiation.

The calcium targets were tested at successively higher beam currents between 5 μA and 27 μA. No adverse effects on the target occurred until 27 μA, where the aluminum foil over the target face oxidized and an insignificant layer of calcium was deposited, through vaporization, on the target body. All irradiations afterwards were limited to 25 μA.

3.2. Thick target yields

Table 2 lists the EOSB yields for the long-lived products of calcium irradiation. Reported uncertainties in the measurements consist of a 4% systematic uncertainty from the detector/source geometry and e3ciency calibration added in quadrature with counting statistics. Total yields from all thick target irradiations, as measured by the Capintec dose calibrator (setting 938), give an EOSB ^{44g}Sc yield of 215 ± 15 MBq/μA, consistent with the HPGe measurement.

3.3. Radiochemical separation

In the 11 separations performed, 73±14% of the activity was collected on the filter. Untrapped activity was split between breakthrough (11±9%) and retention on the walls of the dissolution vial (16 ± 13%). When eluted, 73 ± 12% of the activity retained on the filter was recovered in under 1 ml of 0.1 M HCl. The average elution profile is shown in Fig. 2. Clearly the highest activity concentration occurs in the first 150 μl fraction, representing

55% of the trapped activity, or 40% of the total produced scandium. The entire separation typically concluded less than one hour post-EOB.

ICPMS of the first eluted fraction in the non-irradiated separation indicated that the most significant metal impurities were calcium (2.3 mM), iron (43 μM), and aluminum (107 μM). Using this final calcium concentration along with the original mass of the non-irradiated target (462 mg) and the typical 40% Sc recovery in 150 μl, gives a separation factor of 1.4×10^4.

3.4. Reactivity measurements

ITLC of the DOTA titration showed a peak at $R_f = 0.8 – 0.9$ consistent with the production of Sc-DOTA, *i.e.* the activity in the peak increased with increasing DOTA concentration and was not present in the control. A representative titration using 99.99% calcium is shown in Fig. 3. The y-values show the % of ^{4x}Sc activity in the $R_f = 0.8 – 0.9$ (Sc-DOTA) peak, along with the expected curve for carrier-free complexation. The reactivity is estimated using the assumption that 50% chelation yield occurs when the molar ratio of chelate to DOTA-binding metal impurities is 1:2. Here, the 99.99% curve implies an reactivity of 51 GBq/μmol. Overall, the reactivity was 54 ± 14 GBq/μmol (n=4) corrected to EOB. Fig. 3 also shows a representative titration when 99% pure calcium was used for production. An almost ten-fold increase in reactivity was observed when using 99.99% calcium over the less pure metal.

The measured reactivity, divided by the activity concentration, gives a value for the concentration of non-radioactive, competitive, metal impurities in the product solution of 28±15 μM. This is consistent with the ICP-MS value for iron contamination of 43 μM.

4. Discussion

The 2% natural abundance of ^{44}Ca is not prohibitive to production of ^{44g}Sc on a medical cyclotron. The targets presented here routinely yielded over 650 MBq for 1 hour irradiations at 20 μA, more than enough for preclinical PET imaging studies.

Fig. 4 shows the radionuclidic purity of ^{44g}Sc as a function of irradiation time. The purity exceeds 95% for irradiations up to 7 hours. Additionally, Fig. 5 shows the activity balance of Sc isotopes for a 1 hour irradiation. Notably, only two positron emitters are present, ^{44g}Sc and ^{43}Sc. The comparable decay characteristics make ^{43}Sc a non-interfering nuclide. Other impurities, ^{44m}Sc, ^{47}Sc, and ^{48}Sc, are limited by their longer half-lives and the lower isotopic abundances of their respective calcium feedstocks. Such impurities are tolerable for preclinical PET, especially considering that the combined activities of the three nuclides accounts for less than 3% of total decays at early timepoints. The contribution from these nuclides does not exceed 10% of the total activity until 10 hours post-EOB.

The separation of radioscandium by filtration is fast and e3cient, routinely trapping 70% of the produced activity. More than 70% of this can be eluted in a small volume of 0.1M HCl and immediatly used for radiolabeling. The reactivity of ^{44g}Sc for DOTA is over 1 Ci/μmol which is su3cient to label DOTA-bearing peptides. Target recycling is unnecessary, and the procedure requires minimal investment in equipment and time.

Acknowledgments

GWS and JWE gratefully acknowledge the support of the NIH Radiological Sciences Training Grant # 5T32CA9206-33. HFV is supported through the SciMed GRS Advanced Opportunity Fellowship.

We would like to thank Dr. Martin Shafer and everyone in the trace metals group at the State Hygiene Lab of Wisconsin for the ICP-MS study and analysis.

References

Majkowska-Pilip A, Bilewicz A. J Inorg Biochem. 2011

Filosofov DV, Loktionova NS, Rösch F. Radiochim Acta. 2010; 98:149.

Pruszyński M, Loktionova N, Filosofov D, Rösch F. Appl Radiat Isotopes. 2010; 68:1636.

Pruszyński M, Majkowska-Pilip A, Loktionova N, Eppard E, Rösch F. Appl Radiat and Isotopes. 201210.1016/j.apradiso.2012.03.005

Zhernosekov K, Bunka M, Hohn A, Schibli R, Türler A. J Labelled Compd Rad. 2011; 54:S239.

Alenitzky, YG.; Novgorodov, AF.; Skripnik, AV.; Filosofov, DV.; Kaplun, VG.; Suzikov, AG.; Eliseev, IA.; Rösch, F. Tech Rep. Institute of Nuclear Chemistry, University of Mainz; 2005. ^{44}Ti: Investigation of target preparation, irradiation and yields in the ^{45}Sc(p,2n) process.

Abbas K, Cydzik I, Simonell F, Krajewski S, Kasperek A, Bilewicz A. J Labelled Compd Rad. 2011; 54:S53.

Levkovskij VN. *Activation cross section for nuclides with masses A* = 40 – 100 *by protons and alpha-particles with energies* 10–50 MeV. 1991 accessed via EXFOR: entry A0510.

Takács S, Tárkányi F, Sonck M, Hermanne A. Nucl Instrum Meth B. 2002; 198:183.

Ziegler, JF. The Stopping and Ranges of Ions in Matter. Pergamon; 1985.

Duval JE, Kurbatov MH. J Am Chem Soc. 1953; 75:2246. http://pubs.acs.org/doi/pdf/10.1021/ja01105a065.

Avila-Rodriguez MA, Nye JA, Nickles RJ. Appl Radiat Isotopes. 2008; 66:9.

- Unenriched calcium metal is a viable target material for cyclotron production of ^{44g}Sc.
- The thick target yield for ^{nat}Ca(p,*)^{44g}Sc is 213MBq/μA (projected to saturation).
- For short 16.4MeV proton irradiations of natural calcium, the radionuclidic purity of ^{44g}Sc exceeds 95%
- Filtration separates radioscandium from near-neutral pH calcium matrices.
- The reactivity of cyclotron-produced, filtration-separated, ^{44g}Sc with the bifunctional chelate DOTA is 54 GBq/μmol.

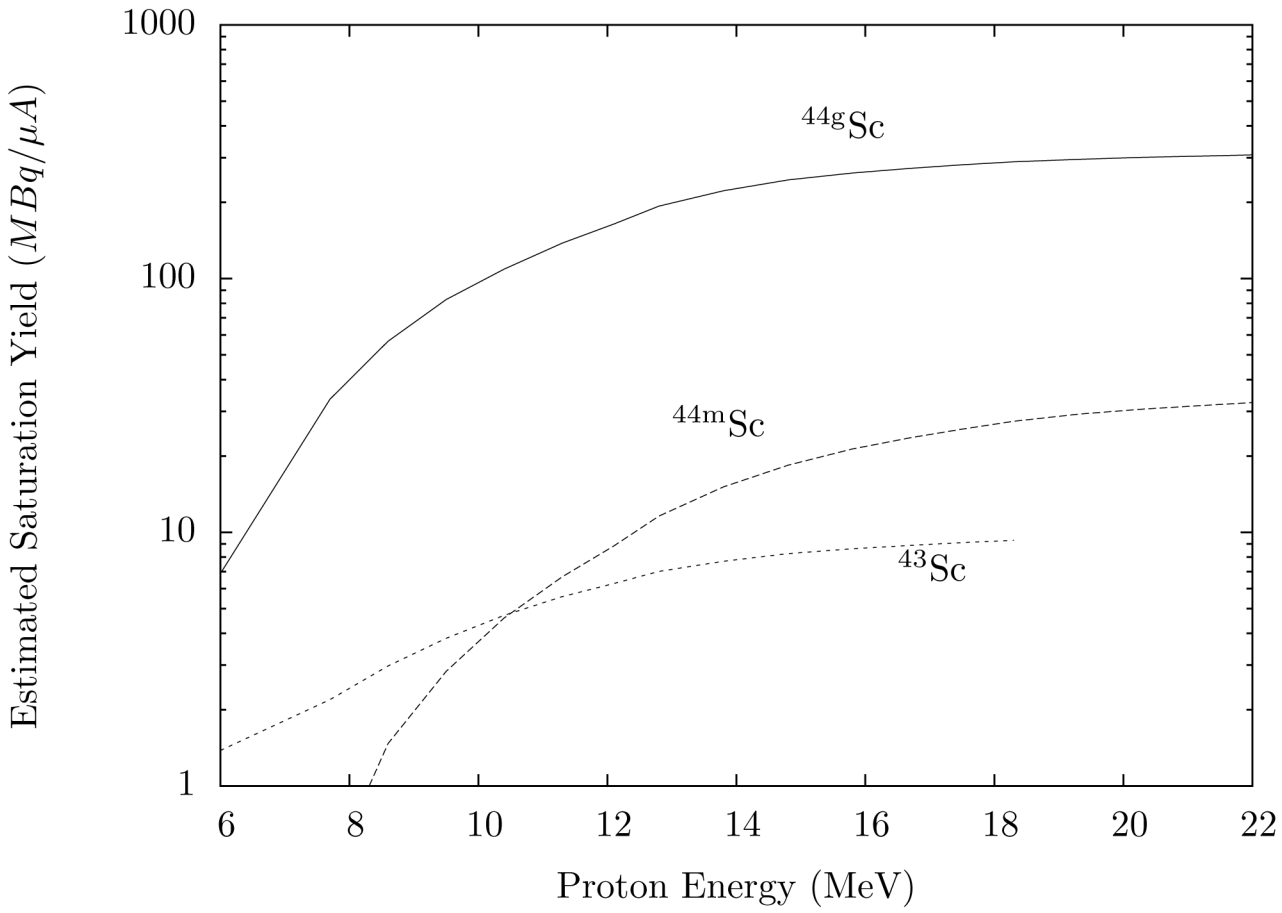

Figure 1.

Estimated thick target EOSB yields for production of ^{44g}Sc, ^{44m}Sc and ^{43}Sc as a function of proton bombardment energy. This represents yields from an unenriched natural calcium metal target with the isotopic ratios listed in Table 2. The values curves were calculated using the cross-section data from Levkovskij (1991) and proton ranges from SRIM (Ziegler, 1985). **Note:** This graph shows *saturation* yields. When estimating a *production* yield, irradiation time must be considered.

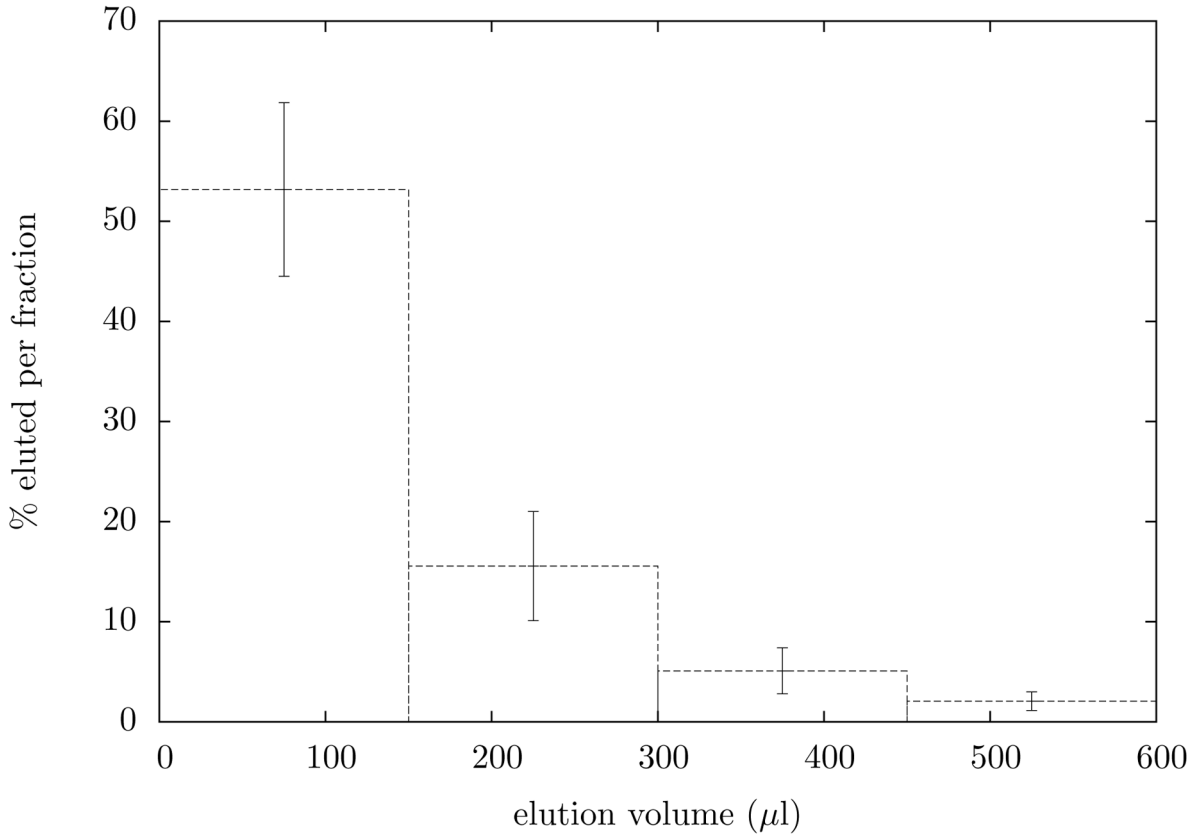

Figure 2.
The average elution profile of ^{44g}Sc from the membrane filter. Elution is performed with hot 0.1 M HCl, roughly 150μl at a time.

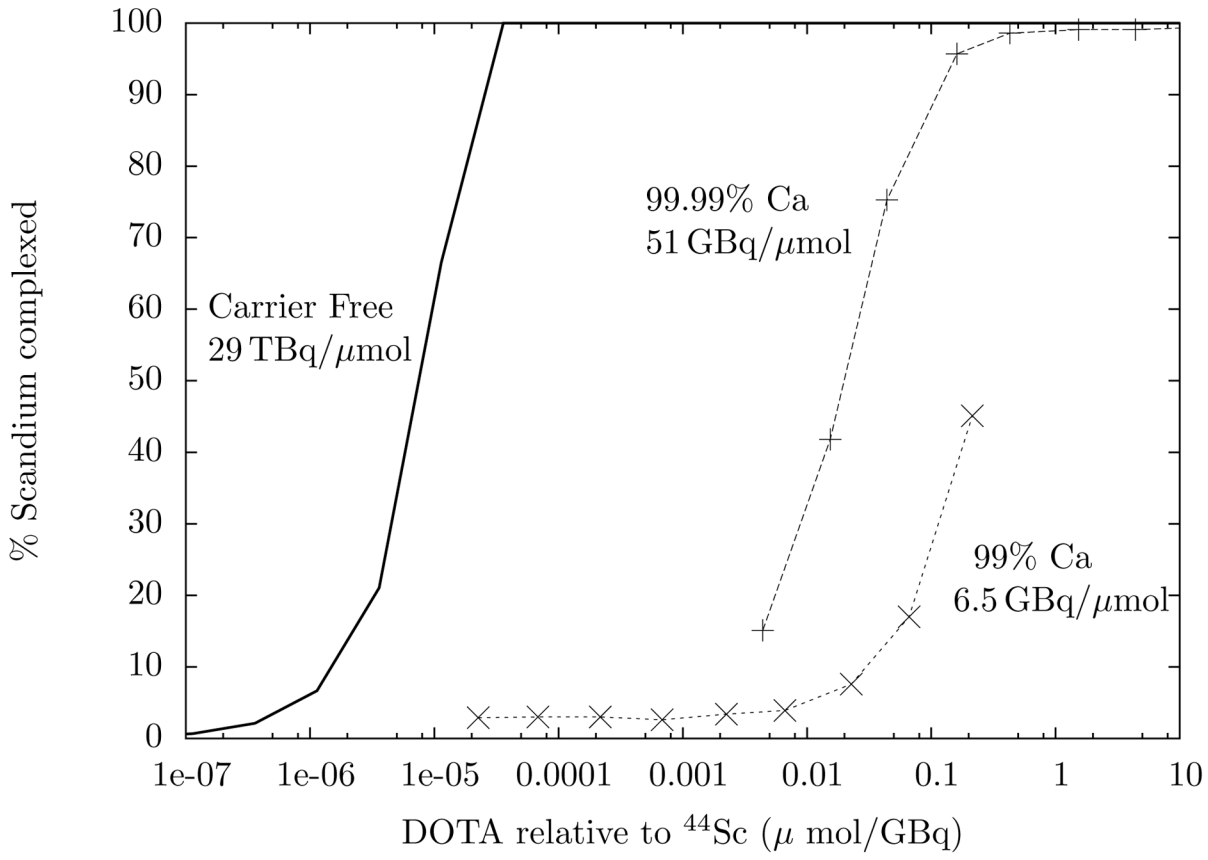

Figure 3.

Representative results of DOTA-Sc titrations with two di3erent grades of calcium target, along with the expected curve for carrier-free ^{44g}Sc. The reactivity of each measured sample is listed next to the curve, corrected to EOB. The carrier-free curve assumes log $k = -26$ and 75 μCi ^{44g}Sc in 200 μl bu3er.

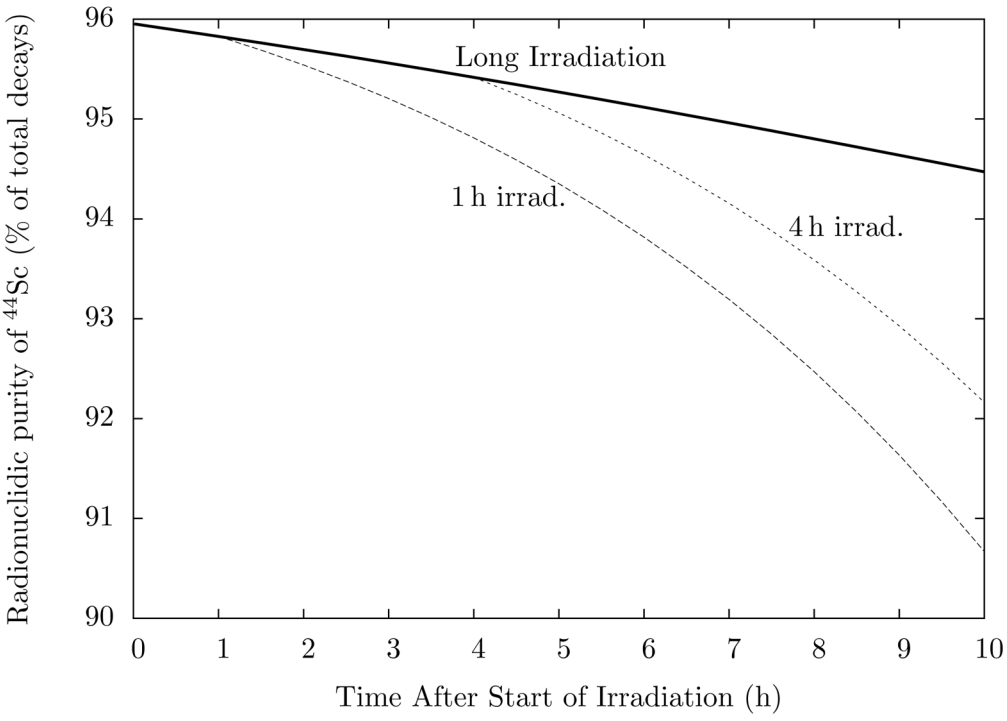

Figure 4.
Radionuclidic purity of ^{44g}Sc as a function of time after start of irradiation. The bold line represents the radionuclidic purity as a function of irradiation time, and the dashed lines show the purity of decaying samples after 1 hour and 4 hour irradiations.

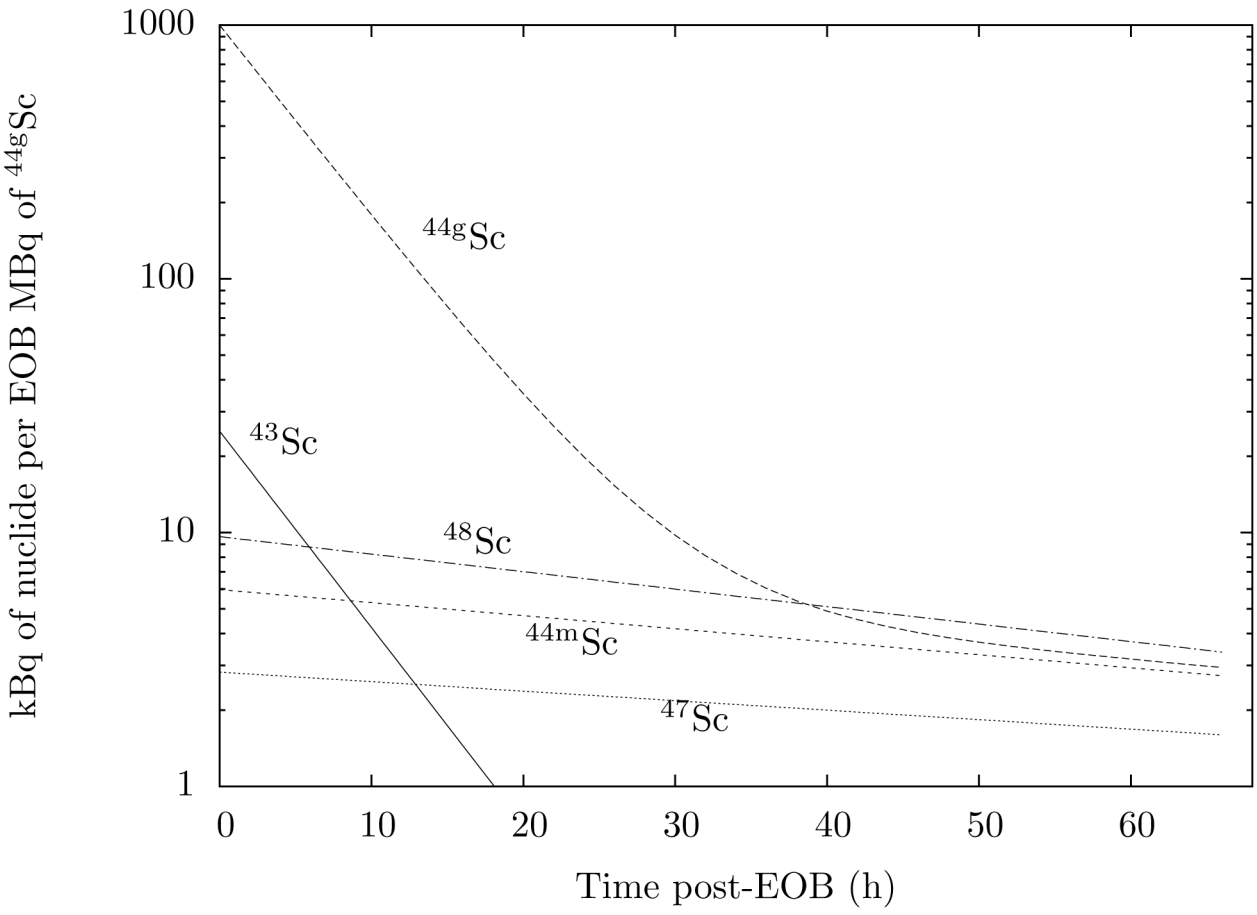

Figure 5.
Activity balance of scandium radioisotopes as a function of time after a 1 hour irradiation of a thick target at 16 MeV.

Table 1

Gamma emissions from the long-lived scandium radioisotopes used for determining the yields from proton irradiation of ^{nat}Ca.

Nuclide	γ Energy (keV)	Branch (γ's per decay)
^{43}Sc	373	0.23
^{44g}Sc	1157	1.0
^{44m}Sc	271	0.87
^{46}Sc	889	1.0
^{47}Sc	159	0.68
^{48}Sc	1038	0.98

Table 2

Natural abundances of calcium isotopes, and their long-lived reaction products after proton bombardment at 16 MeV.

Target	%	Product	$t_{1/2}$ product	EOSB meas. (MBq/μA)	Yield @ 1 h (MBq/μA)
^{40}Ca	96.94%	-	-	-	-
^{42}Ca	0.647%	-	-	-	-
^{43}Ca	0.135%	^{43}Sc	3.89 h	5.3 ± 0.4	0.85
^{44}Ca	2.09%	^{44g}Sc	3.97 h	213. ± 9.	34.1
		^{44m}Sc	58.6 h	17.3 ± 0.6	0.21
^{46}Ca	0.004%	^{46}Sc	83.8 d	*unobs.*	-
^{48}Ca	0.187%	^{48}Sc	43.7 h	20.9 ± 0.9	0.33
		^{47}Sc	80.4 h	11.2 ± 0.4	0.09