Radiochim. Acta **90**, 845–849 (2002)

Radiochemical studies relevant to the production of ^{86}Y and ^{88}Y at a small-sized cyclotron

By K. Kettern, K.-H. Linse, S. Spellerberg, H. H. Coenen and S. M. Qaim*

Institut für Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

(Received March 4, 2002; accepted in revised form April 11, 2002)

Nuclear reaction / Excitation function / Isomeric cross section ratio / Integral yield / Production / Quality control

Summary. Excitation functions were measured by the stacked-foil technique for $^{nat}Sr(p, xn)^{88,87m,g}Y$ reactions from threshold up to 25 MeV. From the measured cross sections integral yields of ^{88}Y, ^{87m}Y and ^{87g}Y were calculated. The optimum energy range for the production of ^{88}Y is $E_p = 14 \rightarrow 9$ MeV; the ^{88}Y yield amounts to 1.75 MBq (47.3 μCi/μA·h) and the ^{87}Y and ^{87m}Y impurities to 2.0 and 4.4%, respectively. The isomeric cross section ratio for the pair ^{87m,g}Y was determined as a function of incident proton energy and the results are discussed in terms of the spins of the two isomeric states involved. Medium scale production of both ^{86}Y and ^{88}Y has been carried out more than 15 times each using the (p, n) reaction. In the former case 96.3% enriched $^{86}SrCO_3$ was used as target material, and in the latter $^{nat}SrCO_3$. The method of separation of radioyttrium has been improved. After coprecipitation with $La(OH)_3$, cation-exchange HPLC was applied to isolate radioyttrium from the carrier lanthanum. The radionuclidic and chemical purities of the products were good. Batch yields of ^{86}Y and ^{88}Y amounted to about 3.5 GBq and 35 MBq, respectively.

1. Introduction

The radionuclide ^{90}Y ($T_{1/2} = 64.1$ h, $I_{\beta^-} = 100\%$, $E_{\beta^-} = 2.3$ MeV) is one of the widely used therapeutic nuclides. However, it is not suitable for imaging. A general solution to this problem has been to substitute ^{90}Y by a γ- or β^+-emitting yttrium radioisotope. In a few studies ^{87}Y ($T_{1/2} = 79.8$ h, EC = 99.8%, $E_\gamma = 388.5$ keV (82.1%) and $E_\gamma = 484.8$ keV (89.7%)) in combination with Single Photon Emission Computed Tomography (SPECT) was used. It is produced either *via* the $^{88}Sr(p, 2n)$ reaction [cf. 1] or the $^{85}Rb(\alpha, 2n)$ process [cf. 2]. The positron emitting ^{86}Y ($T_{1/2} = 14.7$ h, $I_{\beta^+} = 33\%$, $E_{\beta^+} = 1.2$ MeV), however, has proved to be more useful because of the possibility of imaging *via* Positron Emission Tomography (PET). For its production several nuclear processes were considered and the reaction $^{86}Sr(p, n)^{86}$Y was found to be most suitable [3], partly because it could be used at a small-sized cyclotron. The method was developed to produce about 1 GBq quantities of ^{86}Y [4]. In the meantime, the longer-lived ^{88}Y ($T_{1/2} = 106.6$ d, $I_{\beta^+} = 0.2\%$, EC = 99.8%, $E_\gamma = 898$ keV (92.7%) and $E_\gamma = 1836$ keV (99.4%)) has also gained some attention with respect to the development of novel chemical syntheses and investigation of slow metabolic processes, especially in animal experiments. The aim of this work was therefore to improve the known production method of ^{86}Y and to develop a method for the production of ^{88}Y in no-carrier-added form. The radionuclide ^{88}Y has hitherto been produced in no-carrier-added form only *via* the spallation process, mainly at the Los Alamos National Laboratory, USA. We describe its production at a small-sized cyclotron.

2. Study of $^{nat}Sr(p, xn)^{88,87m,g}Y$ processes

2.1 Experimental techniques pertaining to cross section measurements

Cross sections for the formation of ^{88}Y and ^{87m,g}Y were determined *via* the activation technique. In order to obtain a large body of data from a few irradiations, the conventional stacked-foil technique [cf. 5,6] was used.

The thin samples of $SrCO_3$ required for these measurements were prepared *via* a special sedimentation method described earlier [3]. A suspension of very fine strontium carbonate powder in water-free acetone (about 50 mg carbonate per mL acetone) was obtained by mixing and stirring. Additionally, cellulose nitrate was added in concentration of 3%–5% with respect to the metal carbonate. About 200 μL of the suspension was then transferred to the sedimentation device placed in a desiccator. The suspension evaporated slowly at room temperature. After 2–3 hours the device was opened carefully and the homogeneous and mechanically stable deposit on a 25 μm thick Cu-backing (∅ = 13 mm) was removed. The surface of the deposit was covered with a 25 μm thick Al foil. The prepared sample was then used for irradiation.

Several stacks, each consisting of about 5 samples and a few monitor foils, were irradiated at the Jülich compact cyclotron CV 28 at a beam current of about 100 nA. The irradiation time in each case was 60 min. One stack was irradiated at the PSI in Villigen (Switzerland) for 7.7 h at a beam current of 40 nA. The beam currents were determined *via* the monitor reactions $^{nat}Cu(p, xn)^{62,63}$Zn and

*Author for correspondence (E-mail: s.m.qaim@fz-juelich.de).

^{nat}Ti(p, xn)^{48}V [7]. The primary proton energies used at the CV 28 were: 12.0 ± 0.2, 16.0 ± 0.2 and 20.0 ± 0.2 MeV. The primary proton energy at the PSI injector was 45.0 ± 0.2 MeV. It was degraded in the stack so that the calculated energy on the first sample amounted to 25.6 MeV. We determined the effective energy *via* a ratio of monitor reactions [cf. 6]. The two energy values agreed within ± 0.4 MeV. The energy degradation in each stack was calculated using a program based on the tables given by Williamson *et al*. [8].

The activity of each sample and monitor foil was measured non-destructively *via* γ-ray spectrometry. For this purpose a 145 cm^3 HPGe-detector coupled to an Ortec 4 K MCA Plug-in Card was used. The card was connected to an IBM-compatible PC-AT. The peak area analysis was carried out using EG&G Ortec software (Gamma Vision 5.00). Irradiated samples were counted at a distance of at least 10 cm from the detector. The detector counting efficiency at various distances was determined using standard sources (error $< 3\%$) obtained from the PTB Braunschweig and Amersham International.

The count rates were converted to decay rates by correcting for the γ-ray intensities and the efficiency of the detector. The decay data of the radioactive products investigated in this work were taken from [9] and are listed in Table 1. The cross sections were then calculated using the well-known activation formula. The overall uncertainties in the cross section values were obtained by taking the square root of the sum of the squares of individual uncertainties. The individual uncertainties (in %) considered were as follows:

- Target thickness, *i.e*. number of nuclei in the target ($\sim 2\%$)
- Inhomogeneity in target thickness ($\sim 5\%$)
- Bombarding beam intensity ($\sim 10\%$)
- Detector efficiency and sample-detector geometry ($\sim 5\%$)
- Peak area analysis ($\sim 5\%$)

For the ^{nat}Sr(p, xn)-reactions investigated the typical overall uncertainty was 13%.

2.2 Cross section data

The measured cross sections of the ^{nat}Sr(p, xn)-reactions and their uncertainties are given in Table 2. All values describe elemental cross sections, *i.e*. they refer to Sr of natural isotopic composition. The data up to 18.8 MeV were measured at the CV 28 and those in the higher energy region at the PSI injector. A few energy points between 10 and 19 MeV were covered at both the cyclotrons to ascertain the consistency in the data.

The measured cross sections are shown as a function of proton energy in Fig. 1. The formation of ^{88}Y starts at

Table 1. Decay data of the product nuclei studied[a].

Radionuclide	$T_{1/2}$	Mode of decay (%)	E_γ [keV]	I_γ [%]
^{87}Y	79.8 h	EC (99.8)	388.5	82.1
		β^+ (0.2)	484.8	89.7
^{87m}Y	13.4 h	IT (99.7)	380.8	79.3
		EC (0.3)		
^{88}Y	106.6 d	EC (99.8)	898.0	93.7
		β^+ (0.2)	1836.1	99.2

a: Taken from [9].

Table 2. Cross sections for the formation of some radioisotopes of yttrium in proton induced nuclear reactions on ^{nat}Sr.

		Cross section σ [mb]		
E_p [MeV]	Accelerator	^{nat}Sr(p, n)^{88}Y	^{nat}Sr(p, xn)^{87}Y	^{nat}Sr(p, xn)^{87m}Y
25.6 ± 0.5	PSI	43 ± 7	601 ± 78	354 ± 46
23.0 ± 0.5	PSI	64 ± 10	615 ± 80	323 ± 42
20.2 ± 0.5	PSI	142 ± 22	537 ± 70	298 ± 39
18.8 ± 0.3	CV 28	143 ± 22	433 ± 56	312 ± 41
17.9 ± 0.3	CV 28	210 ± 33	479 ± 62	333 ± 43
17.7 ± 0.6	PSI	392 ± 62	286 ± 37	139 ± 18
16.4 ± 0.3	CV 28	326 ± 51	296 ± 38	
15.8 ± 0.6	PSI	502 ± 79	72 ± 9	
15.2 ± 0.3	CV 28	606 ± 95	152 ± 20	94 ± 12
14.4 ± 0.3	CV 28	642 ± 101	72 ± 9	54 ± 7
14.3 ± 0.6	PSI	553 ± 87	57 ± 7	
13.3 ± 0.3	CV 28	657 ± 103		
12.8 ± 0.6	PSI		42 ± 5	
12.4 ± 0.3	CV 28	662 ± 98	33 ± 4	36 ± 5
10.9 ± 0.3	CV 28	612 ± 96	40 ± 5	37 ± 5
10.8 ± 0.3	CV 28	524 ± 83	34 ± 4	28 ± 4
10.6 ± 0.7	PSI		26 ± 3	
10.2 ± 0.3	CV 28	585 ± 92	33 ± 4	34 ± 4
9.0 ± 0.4	CV 28	510 ± 80	35 ± 5	29 ± 4
8.4 ± 0.4	CV 28	412 ± 73	24 ± 3	25 ± 3
7.1 ± 0.4	CV 28	325 ± 51	23 ± 3	18 ± 2
6.6 ± 0.5	CV 28	15 ± 34	17 ± 2	14 ± 2
4.5 ± 0.5	CV 28	29 ± 5	5 ± 1	3 ± 0.5

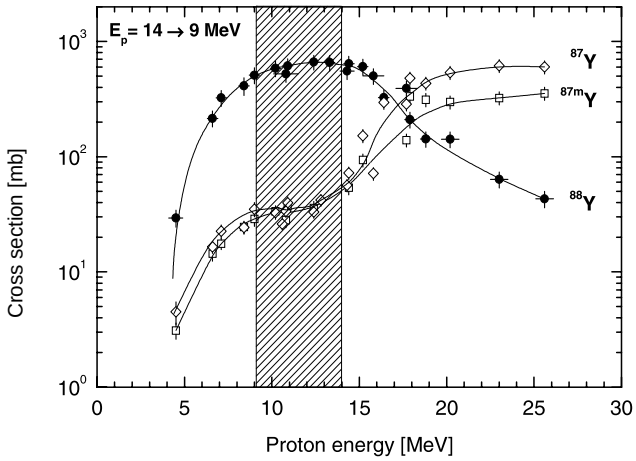

Fig. 1. Excitation functions of ^{nat}Sr(p, xn)-processes leading to the formation of ^{88}Y, ^{87}Y and ^{87m}Y. The solid lines are eye-guides. The shaded area gives a suitable energy range for the production of ^{88}Y.

a threshold energy of about 4.0 MeV and reaches a maximum cross section of 662 mb at 12.4 MeV. The shape of the curve shows that it is formed *via* the ^{88}Sr(p, n)^{88}Y reaction. The curves for the formation of ^{87m}Y and ^{87}Y suggest that possibly two components are involved, up to 13 MeV the ^{87}Sr(p, n) reaction and thereafter a sum of ^{87}Sr(p, n) and ^{88}Sr(p, $2n$) reactions.

2.3 Comparison of present data with the literature data

The formation of ^{88}Y in proton induced reactions on ^{nat}Sr occurs only *via* the ^{88}Sr(p, n) reaction. Thus, from the elemental cross section given in this work, we could also deduce the real cross section of the ^{88}Sr(p, n)^{88}Y reaction. Previously three groups studied this reaction: Blaser *et al.* [10] up to 8 MeV, Levkovskii [11] up to 30 MeV and Sachdev *et al.* [12] over the energy range of 7 to 85 MeV. Our measurements agree with the results of Blaser *et al.* and Sachdev *et al.* up to 15 MeV and provide a more detailed data set around the maximum of the excitation function. Our values also agree with the Levkovskii data except around the maximum and above 22 MeV where the latter are too high (Fig. 2).

Regarding the formation of ^{87m,g}Y, complete datasets for the two contributing reactions, *viz.* ^{87}Sr(p, n)^{87m,g}Y and ^{88}Sr(p, $2n$)^{87m,g}Y, have not been reported. The ^{87}Sr(p, n)^{87}Y reaction was investigated by Blaser *et al.* [10] up to 8 MeV and Levkovskii [11] up to 18 MeV. The ^{87}Sr(p, n)^{87m}Y reaction was studied only by Levkovskii up to 30 MeV. The ^{88}Sr(p, $2n$)^{87m,g}Y process was investigated by Levkovskii [11] and by Sachdev *et al.* [12] over the energy range up to about 33 MeV. From all those measurements, however, it is not possible to deduce the elemental cross section for the formation of ^{87m,g}Y; hence a comparison with our data is not possible.

2.4 Calculated yields of yttrium isotopes

The yields of yttrium radioisotopes at end of bombardment (EOB) formed *via* the ^{nat}Sr(p, xn) processes were calculated from the experimentally measured excitation function curves given in Fig. 1 and the stopping power of ^{nat}Sr. An irradiation time of one hour and a beam current of 1 μA were assumed. The calculated integral yields are shown in Fig. 3 as a function of proton energy.

2.5 Optimum conditions for the production of ^{88}Y

Because of its long half-life the radionuclide ^{88}Y ($T_{1/2}$ = 106.6 d) could be produced covering the whole energy range from threshold up to 25 MeV; the shorter-lived ^{87}Y ($T_{1/2}$ = 79.8 h) and ^{87m}Y ($T_{1/2}$ =13.4 h) would decay out completely after about 40 days. However, if application of ^{88}Y is desired soon after EOB, then the contamination from ^{87}Y has to be reduced *via* a selection of the energy range effective in the target. From the excitation functions and yield curves given above it is evident that the optimum energy range for the production of ^{88}Y is $E_p = 14 \rightarrow 9$ MeV. Over this energy range the thick target yield of ^{88}Y amounts to 1.75 MBq (47.3 μCi)/μA·h and the levels of the ^{87}Y and ^{87m}Y impurities to 2.0 and 4.4%, respectively.

2.6 Isomeric cross section data

The isomeric pair ^{87m,g}Y has interesting spin states. The metastable state has the spin $9/2^+$ and the ground state $1/2^-$.

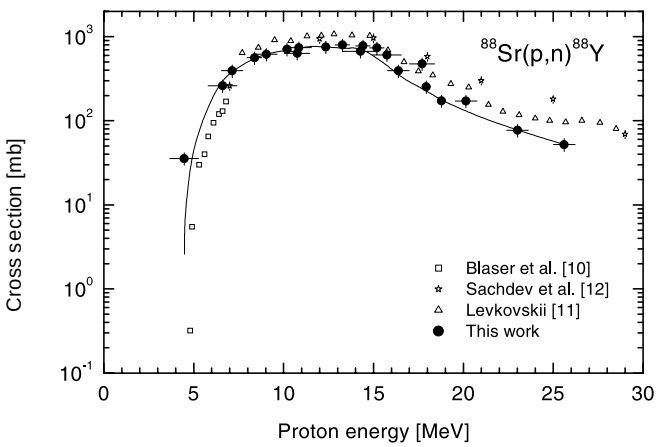

Fig. 2. Excitation function of the ^{88}Sr(p, n)^{88}Y reaction. The smooth curve is an eye-guide through our data points.

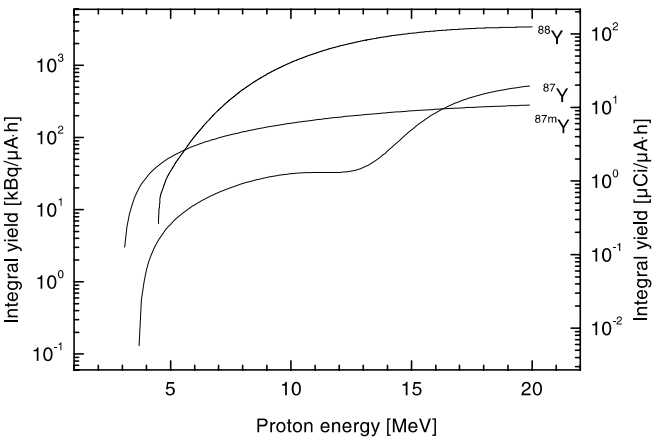

Fig. 3. Calculated integral yields of some radioisotopes of yttrium *via* the ^{nat}Sr(p, xn)-processes shown as a function of the projectile energy.

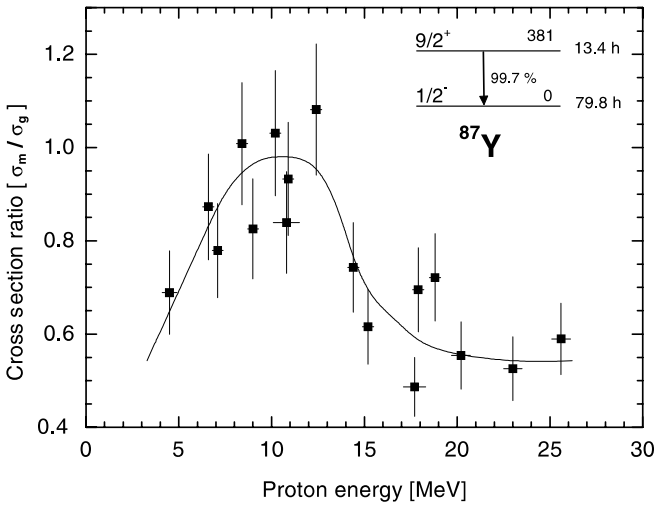

Fig. 4. Isomeric cross section ratio (σ_m/σ_g) for the isomeric pair ^{87m,g}Y in the ^{nat}Sr(p, xn)-process as a function of the projectile energy. The curve is an eye-guide.

The cross section ratio (σ_m/σ_g) determined in this work is shown in Fig. 4 as a function of proton energy. The ratio is relatively small at low incident particle energies due to the high spin of the metastable state. With the increasing energy the ratio increases and attains a value of about 1.0 at 10.0 MeV. Above 10 MeV the ratio decreases and reaches a minimum value of about 0.5 at 22.5 MeV. Thereafter it tends to remain constant. This changing trend is attributed to the competition between (p, n)- and (p, $2n$)-reactions, both of which contribute to the formation of the two isomeric states.

3. Medium-scale production of ^{86}Y and ^{88}Y

3.1 Irradiation and chemical separation

The target used for ^{86}Y production *via* the ^{86}Sr(p, n) reaction on $^{86}SrCO_3$ pellet has been described [4]. The same system with a slight modification was now employed for the production of ^{88}Y. Instead of enriched $^{86}SrCO_3$ the target material used was $^{nat}SrCO_3$. About 300 mg $SrCO_3$ was pressed into a pellet of 13 mm diameter and placed into a groove in a target holder made of aluminium. The groove was closed by a sliding Al lid. This sliding lid allowed an easy removal of the pellet from the groove after irradiation. The target fitted in a 4π-water cooled target head [cf. 13]. Irradiations were done at the Jülich compact cyclotron CV 28 at beam currents of about 5 μA. The primary proton energy used was either 19 or 20 MeV.

The method for separation of radioyttrium was essentially the same as described earlier [4]. However, several optimisation steps have been introduced. In short, they consist of the following.

After dissolution of the target material in 0.5 mL hydrochloric acid, 8 mL water containing 2 mg La(III) carrier are added. Thereafter $La(OH)_3$ is precipitated by adding some drops of concentrated ammonia, whereby radioyttrium is quantitatively coprecipitated. After centrifugation the solution is kept for recovery of the enriched $^{86}SrCO_3$ (but not in case of $^{nat}SrCO_3$) and the precipitate is dissolved in 20 μL HCl. This solution is then diluted with 200 μL of 1 M α-hydroxyisobutyric acid (α-HIB), pH 4.6, 100 μL of water and 150 μL of 1 M NH_4OH solution. As earlier [cf. 4] the radioyttrium is separated from the carrier La by means of cation-exchange chromatography but now using an Aminex A9 column (column length = 200 mm, ∅ = 10 mm) and 0.5 M α-HIB (pH 4.6) as the eluting agent at 70 °C. This separation involves high performance liquid chromatography (HPLC) and the whole separation apparatus is remotely controlled in a lead cell. The eluate from the column is evaporated to dryness and the α-HIB-complex is destroyed with perchloric acid. The residue is finally dissolved in 0.1 M HCl. The final solution is ready for radiolabelling work.

3.2 Yield and purity

The production of both ^{86}Y and ^{88}Y using the new separation methodology has now been carried out more than 15 times each. In a typical run covering the energy range $E_p = 16 \rightarrow 10$ MeV and irradiation at 5 μA for 4 h, the batch yield of ^{86}Y (at EOB) amounted to 3.5 GBq (95 mCi). The yield has thus been increased by a factor of about three compared to the earlier report [4]. For ^{88}Y production the irradiation conditions were the same but the irradiation time was 6 h. The typical batch yield of ^{88}Y (at EOB) was 35 MBq (0.96 mCi). These practical yields amount to about 60% of the respective theoretical values.

The radionuclidic quality control was done *via* γ-ray spectrometry. In ^{88}Y samples the level of ^{87}Y and ^{87m}Y impurities amounted to 2.0 and 4.4% at EOB, respectively. These values are exactly the same as those expected from the excitation functions (see Sect. 2.5). The radionuclidic impurities found in ^{86}Y were the same as described earlier [4], *i.e.* ^{87m,g}Y amounted to < 3%.

The chemical purity of the product was checked *via* ICP-MS analysis of the sample after complete decay of the radioactive species. The amounts of the suspected chemical impurities were found to be: Fe (2.3 ng/mL), Sr (2.6 ng/mL), Y (< 0.02 ng/mL) and La (< 0.01 ng/mL). The product was therefore of high chemical purity.

For the separation of ^{86}Y, recently an electrolytic method has also been described [14]. It appears to be elegant and the separation yield of ^{86}Y is slightly better than in our work. However, the batch yield achieved in that work [14] is not so high as in this work. Furthermore, in the electrolytic method [14] so far only the Sr-impurity level has been determined (< 0.1 ppm). It needs to be demonstrated whether in the electrolytic method the level of other inactive impurities is as low as in the coprecipitation/cation-exchange chromatography, used in this laboratory.

4. Conclusion

From the cross section and yield data presented in this work it is concluded that both ^{86}Y and ^{88}Y can be produced on a medium scale using the (p, n) reaction at a small-sized cyclotron. If larger amounts of the two radionuclides are needed, high current target development would be mandatory.

Acknowledgment. We thank the crews of the Compact Cyclotron CV 28 and the accelerator at PSI for irradiations and the "Zentralabteilung

für Chemische Analysen (ZCH)" of the Forschungszentrum Jülich for ICP-MS analysis of the yttrium-86 sample. Part of this work was done under the COST Action No. D 18/0004 (Lanthanides in Therapy).

References

1. Janssen, A. G. M., Claessens, R. A. M. J., Van den Bosch, R. L. P., De Goeij, J. J. M.: A rapid and high-yield preparation method for ^{87}Y/^{87m}Sr generators, using the ^{88}Sr(p, 2n) reaction. Appl. Radiat. Isot. **37**, 297 (1986).
2. Kutzner, J., Hahn, K., Beyer, G. J., Grimm, W., Bockisch, A., Rösler, H. P.: Szintigraphische Verwendung von ^{87}Y bei der ^{90}Y-Therapie von Knochenmetastasen. Nuklearmedizin **31**, 53 (1992).
3. Rösch, F., Qaim, S. M., Stöcklin, G.: Nuclear data relevant to the production of the positron emitting radioisotope ^{86}Y *via* the ^{86}Sr(p, n)- and ^{nat}Rb(^{3}He,xn)-processes. Radiochim. Acta **61**, 1 (1993).
4. Rösch, F., Qaim, S. M., Stöcklin, G.: Production of the positron emitting radioisotope ^{86}Y for nuclear medical application. Appl. Radiat. Isot. **44**, 671 (1993).
5. Qaim, S. M., Stöcklin, G., Weinreich, R.: Excitation functions for the formation of neutron deficient isotopes of bromine and krypton *via* high-energy deuteron induced reactions on bromine: Production of ^{77}Br, ^{76}Br and ^{79}Kr. Int. J. Appl. Radiat. Isot. **28**, 947 (1977).
6. Piel, H., Qaim, S. M., Stöcklin, G.: Excitation functions of (p, xn)-reactions on ^{nat}Ni and highly enriched ^{62}Ni – possibility of production of medically important radioisotope ^{62}Cu at a small cyclotron. Radiochim. Acta **57**, 1 (1992).
7. Tárkányi, F., Takács, S., Gul, K., Hermanne, A., Mustafa, M. G., Nortier, M., Oblozinský, P., Qaim, S. M., Scholten, B., Shubin, Yu. N., Youxiang Zhuang: Beam monitor reactions. In *Charged-particle cross section database for medical radioisotope production: diagnostic radioisotopes and monitor reactions*. IAEA-TECDOC-1211 (2001) pp. 49–152.
8. Williamson, C. F., Boujot, J. P., Picard, J.: Tables of range and stopping power of chemical elements for charged particles of energy 0.5 to 500 MeV. Rapport CAE-R 3042 (1966).
9. Browne, E., Firestone, R. B.: *Table of radioactive isotopes*. (Shirley, V. S. Ed.) John Wiley and Sons, New York (1986).
10. Blaser, J. P., Boehm, F., Marmier, P., Scherrer, P.: Fonctions d'Excitation de la Reaction (p, n), part I, II, III. Helv. Phys. Acta **24**, 441 (1951).
11. Levkovskii, V. N.: *Middle mass nuclides ($A = 40$–100) activation cross sections by medium energy ($E = 10$–50 MeV) protons and α-particles (experiment and systematics)*. Inter-Vesi, Moscow (1991) pp. 147–148.
12. Sachdev, D. R., Porile N. T., Yaffe L.: Reactions of ^{88}Sr with protons of energies 7 to 85 MeV. Can. J. Chem. **45**, 1149 (1967).
13. Michael, H., Rosezin, H., Apelt, H., Blessing, G., Knieper, J., Qaim, S. M.: Some technical improvements in the production of ^{123}I *via* the ^{124}Te(p, 2n)^{123}I reaction at a compact cyclotron. Int. J. Appl. Radiat. Isot. **32**, 581 (1981).
14. Reischl, G., Rösch, F., Machulla, H.-J.: Electrochemical separation and purification of yttrium-86. Radiochim. Acta **90**, 225 (2002).