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Photonuclear production of medical radioisotopes ^{161}Tb and ^{155}Tb

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A B S T R A C T

The production possibility of ^{161}Tb and ^{155}Tb by irradiating of natural dysprosium with gamma rays obtained by decelerating an electron beam with an energy of 55 MeV has been demonstrated experimentally. The yield of ^{161}Tb was 14.4×10^3 Bq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}. Simultaneously, upon irradiation, ^{155}Dy is formed with the yield of 25×10^3 Bq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}, which leads to the formation of 1.6×10^3 Bq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3} of ^{155}Tb. It has been shown that the isolation of terbium radioisotopes from tens of mg of dysprosium target can be achieved by extraction chromatography, and final separation yield was 39%. The impurity of ^{160}Tb is 7.3% of the ^{161}Tb activity at EOB.

1. Introduction

The use of drugs containing radionuclides is one of the main methods for diagnosing and therapy of cancer (Hamoudeh et al., 2008). Positron emitters or emitters of soft electromagnetic radiation are usually considered as diagnostic agents, while beta, alpha emitters, emitters of conversion and Auger electrons are used for therapy. Terbium radioisotopes are among the most promising radionuclides for nuclear medicine (Müller et al., 2012), since they combine favorable nuclear properties (half-life, decay mode and energy of radiation) with the ability to form stable complexes with oxygen-containing donor groups. The availability of four terbium isotopes with different properties (^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb) enable to develop a line of radiopharmaceuticals that behave identically in the body and allow solving various medical problems. For example, ^{149}Tb is an alpha emitter that can be used to destroy small objects, such as individual cancer cells and micrometastases (Beyer et al., 2004). ^{161}Tb is considered as one of the most promising beta emitters with properties superior to ^{177}Lu (Müller et al., 2014b). ^{152}Tb is a positron emitter that can serve as a diagnostic pair for ^{149}Tb and ^{161}Tb, since it allows visualization by PET (Müller et al., 2019). ^{155}Tb emits soft photon radiation and Auger electrons, which opens up possibilities for its use in both SPECT (Müller et al., 2014a), and Auger therapy (Filosofov et al., 2021).

Terbium isotopes production has been the subject of many recent experimental studies and a recent review (Naskar and Lahiri, 2021). ^{149}Tb, ^{152}Tb and ^{155}Tb are produced in particle accelerators using proton beams (Dmitriev et al., 1989; Steyn et al., 2014; Vermeulen et al., 2012; Duchemin et al., 2016; Szelecsényi et al., 2016; Tárkányi et al., 2014) and helium ions (Zagryadskii et al., 2017; Moiseeva et al., 2020; Aliev et al., 2021b; Moiseeva et al., 2021; Dmitriev et al., 1989; Gyürky et al., 2010; Kazakov et al., 2018a). To obtain ^{155}Tb, it is also proposed to irradiate gadolinium targets with deuterons (Dmitriev et al., 1989; Tárkányi et al., 2014; Szelecsényi et al., 2016; Duchemin et al., 2016). However, these reactions do not make it possible to obtain ^{155}Tb free of ^{156}Tb impurities even at 100% enrichment of the target material (Szelecsényi et al., 2016). When using an indirect way of obtaining through ^{155}Dy, much less radioisotope impurities are formed (Moiseeva et al., 2022). It is possible to obtain ^{155}Tb without radioisotope impurities by irradiating a tantalum target with high-energy (1.4 GeV) protons with online mass separation of reaction products. After irradiation and isolation of products with a mass of 155, purification from isobars and pseudoisobars is required (Webster et al., 2019; Müller et al., 2014a).

The neutron-rich ^{161}Tb isotope is usually produced in a reactor by irradiating a^{160}Gd target according to the scheme ^{160}Gd (n,γ)^{161}Gd→^{161}Tb. This method was proposed by Lehenberger et al. (2011). In experiments carried out by Gracheva et al. (2019), it was possible to obtain up to 20 GBq of ^{161}Tb per irradiation. The IAEA database (IAEA, n.d.) lists 36 operating research reactors that provide a neutron flux of more than 1014 cm^{-2} × s^{-1}, suitable for the production of radionuclides, but most of them are over 40 years old, and their

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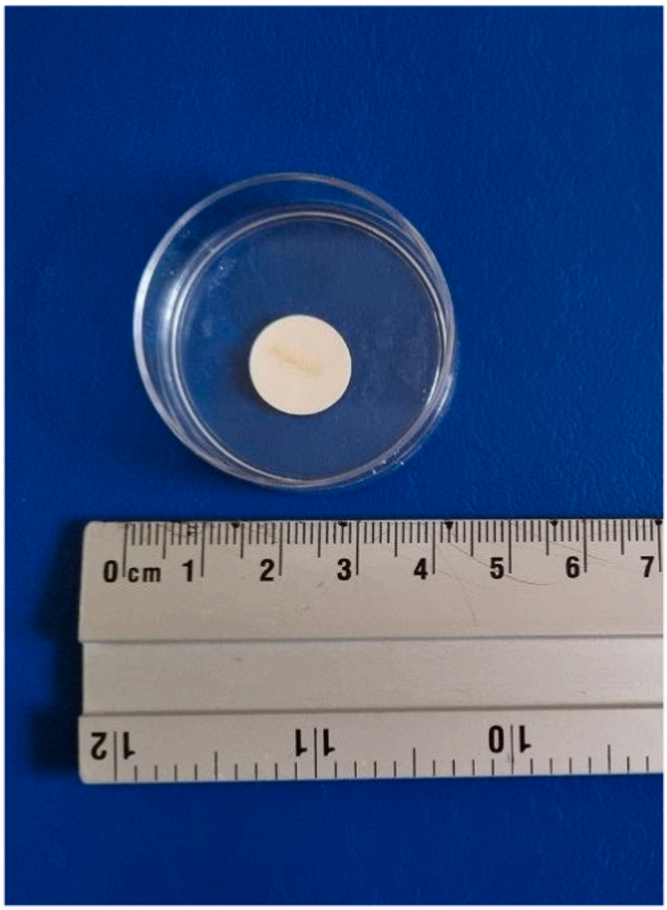

Fig. 1. Target after irradiation.

number is decreasing. This forces to look for alternative ways to obtain reactor radionuclides. Deuteron beams can be used to produce ^{161}Tb at the cyclotron. The formation proceeds in two ways: ^{160}Gd(d,n)^{161}Tb and ^{160}Gd(d,p)^{161}Gd→^{161}Tb, with the second one predominating. The maximum cross section for the formation of ^{161}Tb is ~300 mbar at ~11 MeV. Unfortunately, the side reaction ^{160}Gd(d,2n)^{160}Tb has a maximum cross section of ~700 mb at 13 MeV, i.e., it proceeds approximately in the same range (Tárkányi et al., 2013). Thus, it is not possible to obtain ^{161}Tb without a significant (10–20%) admixture of the long-lived ^{160}Tb isotope, which makes this method unsuitable.

In recent years, the photonuclear production method for producing radionuclides has attracted increasing interest. The main problem of the photonuclear production is that the main (γ,n) reaction leads to the formation of an isotope of the same element as the irradiated target. This means it is impossible to obtain a radionuclide without a carrier. Other reactions, (γ,p) and (γ,np) in particular, have relatively low cross sections, especially for nuclei with a high atomic number. Indirect ways of obtaining are the most promising, for example, (γ,n) reactions accompanied by beta decay. In recent years, it has been shown that the use of electron accelerators is a good alternative for the production of radionuclides important for medicine, such as ^{99}Mo/^{99m}Tc (Tsechanski et al., 2016; NAKAI et al., 2014; Galea et al., 2014), ^{67}Cu (Starovoitova et al., 2015; Aliev et al., 2019), ^{47}Sc (Mamtimin et al., 2015; Rotsch et al., 2018; Aliev et al., 2020), ^{225}Ac (Melville et al., 2007). It is also possible to obtain ^{177}Lu (Kazakov et al., 2018b), ^{167}Tm (Aliev et al., 2021a) and ^{195m}Pt (Bodnar et al., 2015; Dykiy et al., 2007) on a limited scale.

2. Experimental

2.1. Target preparation and irradiation

$^{Nat}Dy_2O_3$ was obtained by annealing of $Dy(NO_3)_3{\cdot}6H_2O$ (Sigma). $^{Nat}Dy_2O_3$ targets (97.22% of Dy and 2.78% of Ce determined by ICP-MS) were prepared as described previously (Rösch et al., 1993). 6–7 mL of acetone and collodion (3.2 wt % of dinitrocellulose) were added to 170–180 mg of Dy_2O_3 powder, and 800–1000 μL of the suspension was dried on a 22 μm thick aluminum backing. The thickness of each target was determined by weighing. It was 37.3 mg/cm^2 in terms of Dy_2O_3, the spot diameter was 10 mm. The coating was homogeneous, had no defects, and adhered firmly to the backing. To prevent the targets from sticking together during irradiation, the surface was additionally covered with 8.3 μm aluminum foil.

The target was irradiated on the bremsstrahlung beam of the Skobeltsyn Institute of Nuclear Physics of Lomonosov Moscow State University RTM-55 for 6.9 h. The race-track microtron RTM55 - an electron accelerator with an energy of 55 MeV - was developed and built for fundamental and applied research, in particular, for studying the mechanisms of photonuclear reactions with the emission of a large number of nucleons. The output electron energy is 55.5 MeV. The accelerator operates in a pulsed mode. The accelerated beam current is 10 mA per pulse for a pulse duration of 8 μs and a pulse frequency of up to 50 Hz. The beam passes 11 times through the linear accelerator, with each revolution increasing the energy by 5 MeV. The thickness of the tungsten converter was 2.1 mm. To determine the average beam current, a metal cobalt foil (99 mg/cm^2) was simultaneously irradiated. The current was normalized according to the ^{59}Co(γ,n)^{58}Co, ^{59}Co(γ,n)^{58m}Co, and ^{59}Co(γ,2n)^{57}Co reactions. The average beam current was 183 nA. The image of the target after irradiation is shown in Fig. 1.

2.2. Radioactivity measurements and yield calculation

HP Ge detector Canberra GR3818 (USA) with a corrugated aluminum entrance window was used for radioactivity measurements. Efficiency calibration was performed using a certified ^{152}Eu, ^{137}Cs and ^{241}Am gamma ray sources with a distance between the source and detector of 1 cm. Detector relative efficiency was 38%, resolution for 1332 keV line was 1.7 keV. The detector was located inside a 10 cm thick lead passive shield. The spectrum was processed using the SpectraLine software (LSRM, Russia).

Yields were calculated from activities converted to end-of-irradiation (EOB) according to the formula:

$$Y = \frac{A\lambda}{ix(1 - e^{-\lambda t})}$$

where Y is the yield of radionuclide (kBq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}), A is the radionuclide activity (kBq), λ is the decay constant (h^{-1}), i is the electron beam current (μA), x is the target thickness (g × cm^{-2}) and t is the exposure time (h).

2.3. Extraction chromatography separation of radionuclides

The target material was removed from the aluminum backing and dissolved in 5.6 M HNO_3. The solution was evaporated to wet salts and adjusted to 2 mL of 0.5 M HNO_3. A 25 cm height column with an internal diameter of 4 mm was filled with LN Resin sorbent (100–150 μm grain size, TrisKem International) preliminarily equilibrated with 0.5 M HNO_3. For each experiment, 1 g of dry resin was taken. In total, two experiments were carried out with aliquots of the dissolved target containing different masses of stable dysprosium (No. 1, 2 mg and No. 2, 20 mg) to establish the optimal range of sorbent capacity. First, 0.5 M HNO_3 was used, then the acidity was changed to 3 M HNO_3. Fractions of 5 mL were collected and the content of radionuclides was monitored by

Table 1
Radionuclides identified in the irradiated target (Target mass 29.3 mg, irradiation for 6.9 h, current 139 nA, nuclear data was taken from IAEA Live Chart of Nuclides (https://nds.iaea.org/relnsd/vcharthtml/VChartHTML.html).

Radionuclide	$T_{1/2}$	Formation routes	Gamma lines, keV (%)	Activity at EOB, Bq	Yield, kBq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}
^{155}Dy	9.9 h	^{156}Dy(γ,n) ^{158}Dy(γ,3n)	226.918 (68.7); 184.564 (3.39); 905.8 (2.46); 999.7 (2.45); 664.173 (2.25); 1155.47 (2.10); 498.617 (1.76); 1166.22 (1.70)	940 ± 170	25 ± 4
^{157}Dy	8.14 h	^{158}Dy(γ,n) ^{160}Dy(γ,3n)	326.336 (93); 182.424 (1.33); 265.469 (0.17)	8800 ± 500	249 ± 15
^{155}Tb	5.32 d	^{155}Dy→^{155}Tb ^{156}Dy(γ,p) ^{158}Dy(γ,p2n)	105.318 (25.1)	44.9 ± 5.9	1.6 ± 0.3[a]
^{160}Tb	72.3 d	^{161}Dy(γ,p) ^{162}Dy(γ,pn) ^{163}Dy(γ,p2n)	879.378 (30.1); 298.578 (26.1); 966.166 (25.1)	48.5 ± 3.2	1.0 ± 0.1
^{161}Tb	6.89 d	^{162}Dy(γ,p) ^{163}Dy(γ,pn) ^{164}Dy(γ,p2n)	25.651 (23.2); 74.567 (10.2)	668 ± 15	14.4 ± 0.3
^{163}Tb	19.5 min	^{164}Dy(γ,p)	351.2 (26); 389.8 (24); 494.5 (22.5); 421.9 (11.5); 533.0 (9.5); 316.4 (8.3); 250.8 (6.7); 347.8 (6.2); 338.5 (4.5)	7000 ± 900	2200 ± 300

[a] ^{155}Tb activity is calculated 40 h after EOB when ^{155}Tb accumulation from ^{155}Dy reaches a maximum based on ^{155}Dy yield.

gamma spectrometry using the 25.65 keV (^{161}Tb) and 326.16 keV (^{157}Dy) lines. Fractions 5–9 (25 mL) from experiment 2 containing 43% of ^{161}Tb and about 8% of dysprosium were combined, evaporated near dryness, and adjusted to 1 mL of 0.5 M HNO_3. Then the separation procedure was repeated (experiment No. 3). The combined fraction of ^{161}Tb from experiment 3 was evaporated to 5 mL and the long exposition gamma spectrum was measured.

3. Results and discussion

3.1. Nuclear reactions and main products

Radionuclides of dysprosium ^{155}Dy and ^{157}Dy, and terbium ^{155}Tb, ^{160}Tb, ^{161}Tb, ^{163}Tb were identified in a target made of dysprosium oxide of natural isotopic composition irradiated with bremsstrahlung photons with energies up to 55 MeV (Table 1). Radionuclides of dysprosium are formed in reactions with the elimination of neutrons (γ,xn), while terbium radionuclides are formed through photoproton channels (γ, pxn). In addition, ^{155}Tb is formed during the decay of ^{155}Dy. Fig. 2 shows a fragment of the nuclide chart, which illustrates the content of dysprosium isotopes in a natural mixture, as well as the main reaction products and formation routes. Gamma spectrum of the irradiated target is presented in Fig. 3.

3.2. Chromatographic separation of Dy and Tb

Ln Resin sorbent based on Di-(2-ethylhexyl)phosphoric acid (HDEHP), traditionally used for the separation of lanthanides, was chosen for the separation of Dy and Tb (Horwitz and Bloomquist, 1975; Monroy-Guzman and Salinas, 2015; Ward et al., 2021). REE capacity factors *k'* were previously determined (Horwitz et al., 2006). The bond strength with the sorbent increases with atomic number growth due to the lanthanide contraction. In the case of photonuclear production of lanthanide radioisotopes, the separation process is complicated since the heavier and more strongly retained element is present as a macro-component. The separation of terbium and dysprosium was previously studied in the processing of cyclotron targets (Moiseeva et al., 2022) and it was found that the optimal concentration of nitric acid was in the range of 0.5–0.8 M. The possibility of separation was tested at two different masses loaded onto the column: 2 and 20 mg in terms of metallic dysprosium. A solution containing 2 mg of dysprosium was used in the first separation (Fig. 4).

It was shown that the separation was successful for 2 mg of dysprosium. When the mass of dysprosium was increased to 20 mg, the chromatographic behavior of both macro- and microcomponents changed dramatically and the separation of Dy and Tb was not observed, which may be due to the excess of the resin maximum capacity (Fig. 5).

Therefore, it was decided to carry out the separation in two steps. After experiment No. 2, fractions containing 43% of ^{161}Tb and no more than 2 mg of dysprosium were collected (fractions from 30 to 50 mL, highlighted by a dashed line). These fractions were combined and separation process was repeated. The chromatogram was identical to that shown in Fig. 4. Final separation yield was 39%. After the second separation, the fractions containing terbium were combined, evaporated to a volume of 5 mL, and measured on a gamma spectrometer (Fig. 6). Peaks of ^{161}Tb (25.63; 74.73), ^{160}Tb (298.46), and ^{155}Tb (105.40) were identified.

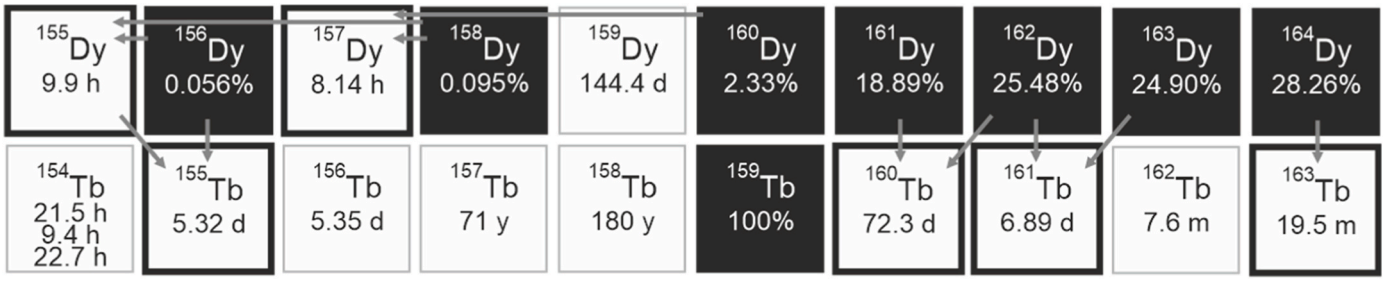

Fig. 2. A fragment of a nuclide chart illustrating the reactions taking place and the nuclei formed when natural dysprosium is irradiated with photon energies up to 55 MeV.

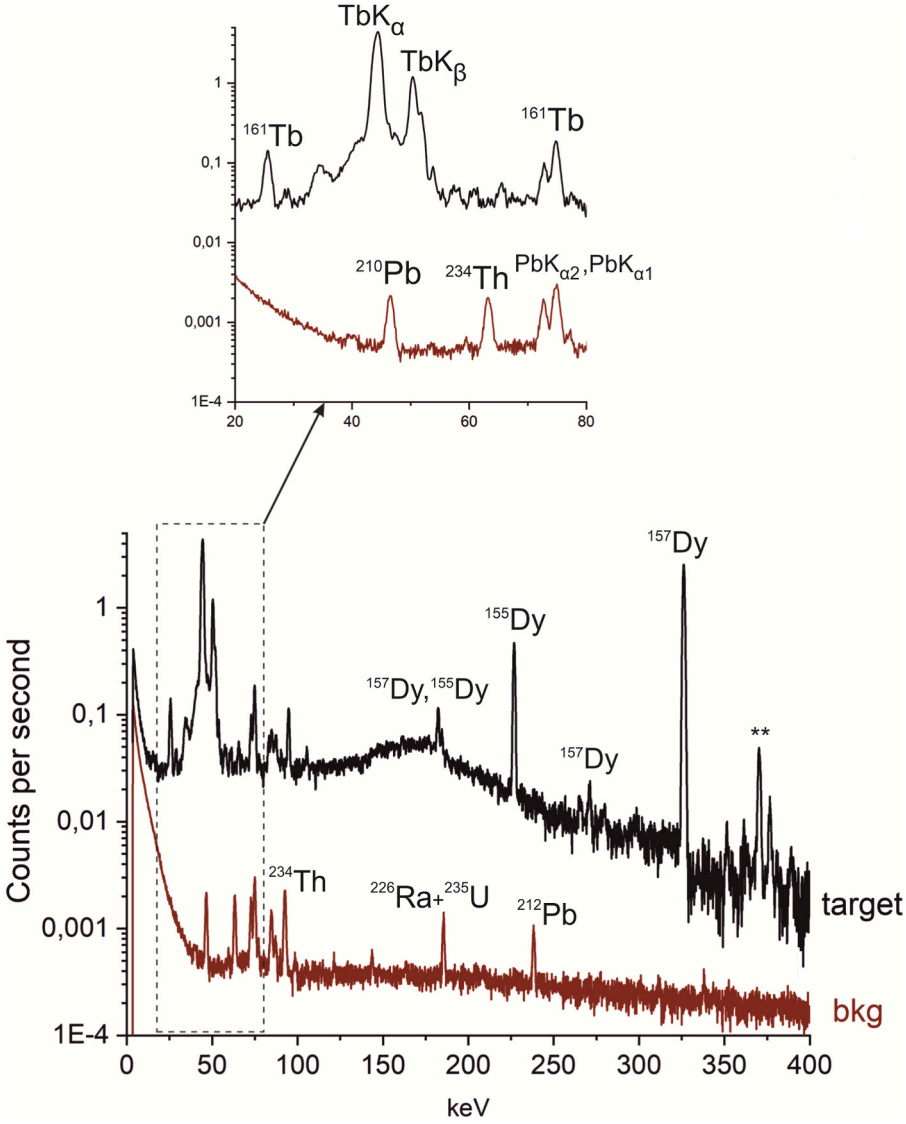

Fig. 3. Gamma ray spectrum of irradiated target measured ~90 min after EOB. Acquisition time ~1500 s. The asterisks mark the peaks corresponding to summation of gamma and X-ray quanta: 326.3 keV (^{157}Dy)+ ~44 keV (TbK$_\alpha$) and 326.3 keV (^{157}Dy)+~50 keV (TbK$_\beta$).

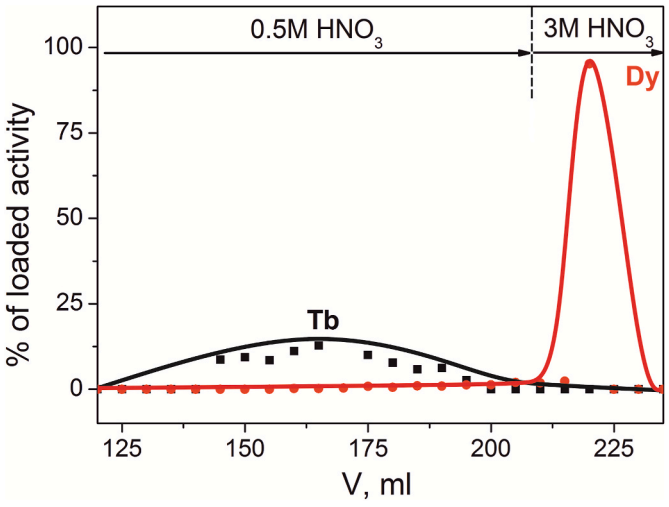

Fig. 4. Dy and Tb elution profiles for 2 mg of target material.

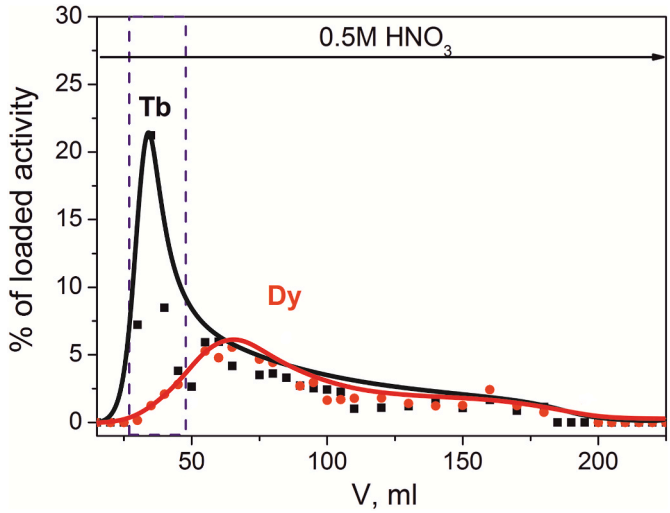

Fig. 5. Dy and Tb elution profiles for 20 mg of target material. Tb fraction used for further purification is highlighted by a dashed line.

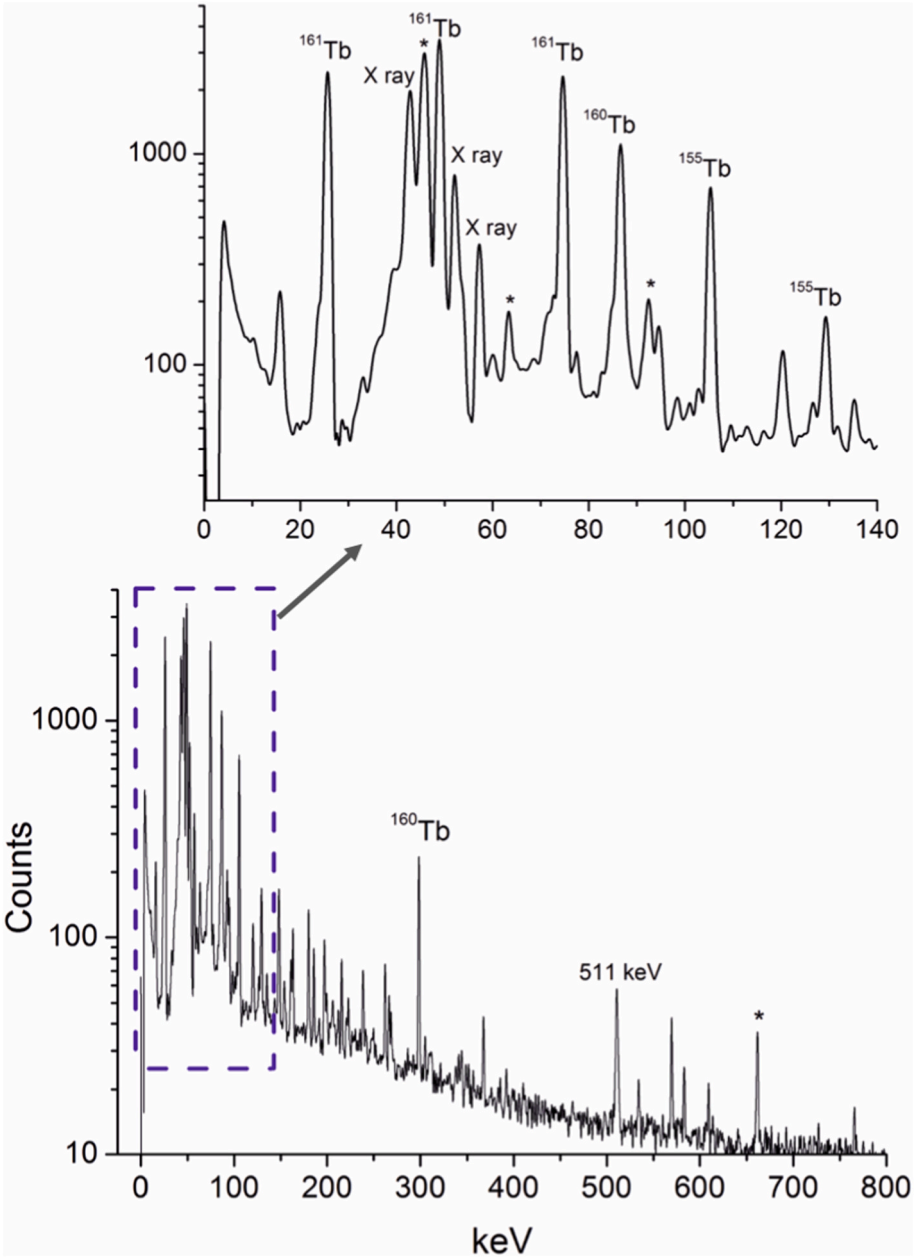

Fig. 6. Gamma ray spectrum of ^{161}Tb sample measured ~5 d after EOB. Acquisition time ~18 h. The asterisk marks the peaks corresponding to the natural background.

4. Conclusion

In the present work, dysprosium of natural isotopic composition was irradiated with a beam of bremsstrahlung gamma rays with energies up to 55 meV. The fundamental possibility of obtaining ^{161}Tb and ^{155}Tb by the photonuclear method was shown. The yield of (γ,p) reactions on heavy nuclei is low due to the Coulomb barrier, and ^{162}Dy(γ,p) route is no exception. Under the experimental conditions (thin target and thin converter), the yield of ^{161}Tb was 14.4 kBq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}. The use of a target with a natural isotopic composition does not allow to achieve high isotopic purity. The content of the long-lived impurity, ^{160}Tb, was 7.3% of the ^{161}Tb activity at EOB, which is somewhat better than when deuterons are used. However, it can be expected that the use of a target enriched in ^{162}Dy and optimization of the beam energy will manage to increase the radioisotopic purity, since (γ,p) reactions, as a rule, have much higher cross sections than (γ,np). This method is unlikely to be promising for the production of ^{161}Tb in medical quantities, but may be useful for obtaining small quantities for experiments *in vitro* in cases when ^{161}Tb from reactor is not available.

The yield of ^{155}Dy was 25 kBq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3}, from which ^{155}Tb is formed with the yield of 1.6 kBq × μA^{-1} × h^{-1} × cm^2 × g^{-1}_{Dy2O3} at the time of maximum accumulation (40 h after EOB). In the case of ^{155}Tb, the transition to an ^{156}Dy isotopically enriched target can have a significant positive effect, since the formation of ^{155}Tb occurs along the (γ,n) channel through the intermediate formation of ^{155}Dy. Moreover, the half-life of ^{155}Dy makes it possible to carry out the radiochemical isolation of the intermediate product, and thereby get rid of possible isotopic impurities formed through (γ,pxn) channels. The problem that limits the practical use of the proposed method is the low content of ^{156}Dy (0.056%) in the natural mixture of isotopes.

CRediT authorship contribution statement

A.O. Fedotova: Writing – original draft, Investigation, Data

curation. **R.A. Aliev:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **B.V. Egorova:** Writing – review & editing, Investigation, Formal analysis, Data curation. **E.S. Kormazeva:** Resources. **A.L. Konevega:** Supervision, Project administration. **S.S. Belyshev:** Resources, Investigation, Data curation. **V.V. Khankin:** Resources. **A.A. Kuznetsov:** Data curation. **S.N. Kalmykov:** Writing – review & editing, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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