A study of ^{225}Ac production cross section by proton, deuteron, and neutron irradiation on ^{232}Th targets based on FLUKA toolkit

Authors: Zhu, Miss Ke Ying, Zhang, Dr. Gaolong 张高龙, Zhang, Mr. Wei, Cheng, Mr. Chang, Xiaoyu Xu, Huang, Dr. Zhen, Qu, Prof. Wei-Wei, Dr. Zhen Huang

Date: 2025-08-27T00:00:00+00:00

Abstract

The limited global supply of actinium-225 remains a major bottleneck for its widespread clinical application in targeted alpha therapy, highlighting the importance of exploring alternative methods for large-scale production. In this study, the FLUKA Monte Carlo transport code was employed to simulate the irradiation of thorium targets with protons, neutrons, and deuterons in the energy range of 10 to 800 MeV per nucleon. The production cross sections of ^{225}Ac for different incident particles were systematically compared to identify the most promising production pathway for accelerator-based synthesis. Additionally, the study reports product cross section data for relevant actinides, thorium, radium, and protactinium isotopes. By comparing the simulated results with available experimental data, the reliability of the nuclear reaction models was verified, and directions for further refinement of Monte Carlo-based physical models in radionuclide production simulations were proposed.

Full Text

Preamble

A Study of 225Ac Production Cross Sections by Proton, Deuteron, and Neutron Irradiation on 232Th Targets Based on the FLUKA Toolkit

Ke-Ying Zhu,[1] Gao-Long Zhang,[2] Wei Zhang,[1] Chang Cheng,[2] Xiao-Yu Xu,[1] Zhen Huang,[1],† and Wei-Wei Qu[1],‡

[1]State Key Laboratory of Radiation Medicine and Protection, School of Radiation Medicine and Protection, Collaborative Innovation Center of Radiological Medicine of Jiangsu Higher Education Institutions, Soochow University, Suzhou

215123, China
[2]School of Physics, Beihang University, Beijing 100191, China

The limited global supply of actinium-225 remains a major bottleneck for its widespread clinical application in targeted alpha therapy, highlighting the importance of exploring alternative methods for large-scale production. In this study, the FLUKA Monte Carlo transport code was employed to simulate the irradiation of thorium targets with protons, neutrons, and deuterons in the energy range of 10 to 800 MeV per nucleon. The production cross sections of 225Ac for different incident particles were systematically compared to identify the most promising production pathway for accelerator-based synthesis. Additionally, the study reports product cross section data for relevant actinides, thorium, and protactinium isotopes. By comparing the simulated results with available experimental data, the reliability of the nuclear reaction models was verified, and directions for further refinement of Monte Carlo-based physical models in radionuclide production simulations were proposed.

Keywords: 225Ac, FLUKA simulation, Cross section, Thorium target

Introduction

Targeted radionuclide therapy (TRT) has emerged as an effective cancer treatment strategy in recent decades [1–4]. Targeted alpha therapy (TAT), in particular, offers enhanced precision in cancer treatment [5–8]. The 9.9-day half-life of actinium-225 (225Ac) makes it an excellent candidate for TAT and well-suited for antibody targeting [9]. The four α particles released during its decay chain enable multiple high-energy depositions inside targeted cells, greatly increasing treatment effectiveness [10].

It is estimated that only about 63 GBq of actinium-225 are produced annually worldwide, primarily from limited 229Th decay sources in the United States, Germany, and Russia [11]. This amount can treat fewer than 1000 patients annually, which falls far short of clinical demand [10]. The medical community desperately needs increased 225Ac supplies for clinical trials and treatment. Several alternative production methods have been proposed, including reactor-based approaches (226Ra(n, 2n)225Ra) [12], low-energy proton bombardment (226Ra(p, 2n)225Ac) [13], and electron accelerator techniques (226Ra(γ, 2n)225Ra) [14].

While these methods are promising, they rely on high-purity 226Ra targets at the gram scale. Radium is highly radioactive, rare, and expensive to handle. In this context, high-energy proton spallation (232Th(p,x)225Ac) is considered the most practical short-term solution [15, 16]. However, the current yield of this method remains insufficient for large-scale clinical use. Additionally, it produces the toxic actinide isotope 227Ac, which has a long half-life of 21.8 years [11]. The safety impact of 227Ac impurities must be carefully evaluated during treatment since 225Ac cannot be chemically separated from 227Ac.

In 2021, Burahmah et al. [17] used Monte Carlo methods to simulate 225Ac production from 232Th targets using proton, deuteron, and α beams. Their results showed that the maximum 225Ac cross section for the d+232Th system was roughly 1.8 times higher than that of the p+232Th system within the 50–200 MeV/nucleon range, implying that deuteron-induced reactions on thorium might provide a more efficient path for large-scale 225Ac production. However, deuteron-induced reactions were not thoroughly investigated in their study, and the feasibility of large-scale 225Ac production was not addressed.

The present study utilized the FLUKA Monte Carlo transport algorithm to simulate 225Ac production cross sections from proton, deuteron, and neutron irradiation on 232Th targets over the energy range of 10–800 MeV/nucleon. The purpose was to understand the enhanced cross section of 225Ac from deuteron-induced reactions and to discuss 227Ac impurity across the three reaction systems. Furthermore, cross sections of co-produced radionuclides (223,225Ra, 227,229Th, and 229,230,231Pa) were reported, and simulation results were validated against available experimental data.

II. FLUKA Simulations

The FLUKA code is a general-purpose Monte Carlo tool for the interaction and transport of hadrons, leptons, and photons from keV energies (neutrons are tracked down to thermal energies) to cosmic ray energies in any material [18]. The code is applied to radionuclide production, medical physics, dosimetry, radiation shielding and facility design, and detector and target design [19–22].

The FLUKA Monte Carlo code (version 4-5.0) was utilized in this study. FLUKA employs the PEANUT package [23] for hadron–nucleus interactions below 3–5 GeV/c, which includes the Generalised Intra-Nuclear Cascade (GINC) and the pre-equilibrium stage in detail. The built-in equilibrium processes of the FLUKA toolkit, including evaporation, fission, Fermi break-up, and gamma emission, simulate the de-excitation of residual nuclei following the PEANUT model. The PEANUT model was used in these simulations for nuclear reactions induced by protons and neutrons with incident energies above 20 MeV. For neutrons with energies below 20 MeV, FLUKA provides a full pointwise treatment based on data from widely used ENDF libraries such as JEFF, JENDL, CENDL, and BROND. In this study, the JEFF-3.3 library was used.

Various models were employed to handle deuteron-induced reactions in FLUKA simulations, depending on incident energy. The DPMJET model was applied above 5 GeV/nucleon [24]. FLUKA used the Relativistic Quantum Molecular Dynamics (RQMD) model between 150 MeV/nucleon and 5 GeV/nucleon [25, 26]. Since version 4-2.0, FLUKA has included a dedicated model to support deuteron-beam applications for energies below 150 MeV/nucleon [27]. This model accounts for four main reaction mechanisms: elastic break-up, stripping to discrete energy levels, stripping to the continuum, and complete fusion. The Serber model [28] in conjunction with the PEANUT model [23] of FLUKA was used to model stripping to the continuum process. The Distorted Wave Born Approximation (DWBA) [29] was used to describe elastic break-up and nucleon transfer to discrete states. The low-energy ion-ion inelastic interaction framework in the FLUKA toolkit was based on the Boltzmann Master Equation (BME) model, which describes the complete fusion mechanism [23].

The default PRECISIO settings were used in all simulations. In PHYSICS settings, Coalescence and the new evaporation model, which incorporates heavy fragment evaporation, were activated.

Figure 1 [Figure 1: see original paper] illustrates the simplified model for projectile beam bombardment of the thorium metal target. The simplified target model utilized pure metallic thorium enriched to 100% 232Th. The incident beam energies ranged from 10 to 800 MeV/nucleon. A cylindrical beam with a radius of 0.5 cm irradiated the target perpendicularly at its center in vacuum. The target surface was set to 10.0×10.0 cm^2, with 1.5×10^{10} particles sampled in each simulation.

Burahmah et al. [17] defined nuclear cross section as $\sigma = \phi\{int\}/\phi_0 nx$, *where* $\phi\{\text{int}\}$ represents the number of product nuclei, ϕ_0 represents the number of incident particles on the target, n represents the number of target nuclei per unit volume, and x stands for the target thickness. Usually, $\phi\{int\}$ *1, and the expression simplifies to* $\sigma = \phi\{\text{int}\}/\phi_0\text{nx}$.

Subsequently, cross sections of actinide, radium, thorium, and protactinium isotopes from proton, deuteron, and neutron irradiation of a thorium target were simulated using FLUKA. Figure 2 [Figure 2: see original paper] shows the decay relationships between relevant produced nuclides.

III. Results

Radionuclides are typically produced through two pathways: direct production (described by independent cross section) and indirect production via the decay of all precursor nuclei coproduced during irradiation (described by cumulative cross-section). FLUKA calculated independent cross sections without considering precursor decay contributions or the decay of the produced nuclide.

A. Proton Projectiles

The excitation function of 225Ac under proton irradiation on a thorium target is shown in Fig. 3 Figure 3: see original paper. FLUKA simulations agree well with experimental data throughout the entire energy range of 0–800 MeV. However, at an incident energy of 450 MeV, the FLUKA toolkit slightly overestimates the experimental data by Robertson et al. [30]. At incident energies up to 800 MeV, it slightly underestimates the cross section measured by Weidner et al. [31]. Further attention was paid to the energy range of 20–200 MeV, where abundant experimental data made comparisons with simulation results more reliable. When the incident energy was less than 80 MeV, FLUKA greatly underestimated the data reported by Weidner et al. [32] and Ermolaev et al. [33]. However, the predictions were in good agreement with data from Griswold et al. [34] and Zhuikov et al. [35] in the energy range of 80–200 MeV.

During 225Ac production, the highly toxic and long-lived 227Ac was generated simultaneously and also requires special attention. Figure 3(b) presents the excitation function over the energy range of 0–800 MeV, and the simulated values by FLUKA agreed well with experimental data when the incident energy was less than 500 MeV. At incident energies up to 800 MeV, the FLUKA simulation was significantly lower, approximately 70% of the result reported by Weidner et al. [31]. While FLUKA underestimated cross sections when the incident energy was less than 70 MeV and greater than 140 MeV, it agreed well with results in the 70–140 MeV range measured by Ermolaev et al. [33], Engle et al. [36], and Griswold et al. [34].

As the major 225Ac source in the world today, 229Th serves as a generator of 225Ac and its parent 225Ra ($t_1/_2$ = 14.9 d) [30]. Figure 3(c) shows the excitation function of the 232Th(p,x)229Th reaction with incident energy up to 800 MeV. The FLUKA simulations and experimental data reported by Griswold et al. [37] showed certain discrepancies when the incident energy was less than 40 MeV. This discrepancy arose because the cross sections measured by Griswold et al. [37] represent cumulative cross sections over the 23–33 MeV range, where the cumulative yield was mostly impacted by the 232Th(p,x)229Pa reaction [37]. In contrast, FLUKA calculated independent cross sections that exclude contributions from precursor nuclide decay and subsequent decay of the produced nuclides. At an incident energy of 150 MeV, FLUKA simulations were in good agreement with experimental data reported by Lefort et al. [38].

Simulation of the production cross section of 225Ra was also important as it represents a significant source of 225Ac [39]. Figure 3(d) presents the excitation function of 225Ra under proton irradiation of 232Th over the energy range of 0–800 MeV. FLUKA simulations show good agreement with data by Weidner et al. [32] at 150 MeV incident energy, but were slightly lower than experimental data reported by Steyn et al. [40], Lefort et al. [38], and Hogan et al. [41] at energies below 100 MeV. At high incident energies up to 800 MeV, the measurement by Weidner et al. [31] was slightly higher than the predicted value, while experimental results by Robertson et al. [30] at 450 MeV incident energy were much higher than the simulations.

Moreover, 223Ra and 227Th have also been considered promising TAT candidates [10]. Figure 3(e) shows the excitation functions for 223Ra production under proton irradiation on 232Th with incident energies up to 800 MeV. FLUKA consistently underestimated the reported experimental cross sections of 223Ra from Weidner et al. [32], Lefort et al. [38], Hogan et al. [41], and Weidner et al. [31], similar to those in 225Ra production. For the 232Th(p,x)227Th reaction, the overall trend of the excitation functions over the incident energy range of 0–800 MeV is shown in Fig. 3(f), where FLUKA predictions generally agreed with the experimental trend. The model demonstrated good agreement in low to middle energy regions but showed noticeable underestimation at higher incident energies, particularly around 450 MeV and 800 MeV. In the incident energy range of 20–200 MeV, where more experimental data were available for comparison, FLUKA simulations agreed well with data from Hogan et al. [41], Griswold et al. [34], and Ermolaev et al. [33], and accurately reproduced results between 50 and 120 MeV. However, measurements by Weidner et al. [32] were significantly higher than both FLUKA predictions and other experimental data in the 80–200 MeV range, probably due to the use of a thicker target composed of thorium foils (0.065 mm) in a 12-layer stacked configuration, which was significantly thicker than in previous investigations. This enhanced the probability of proton-thorium reactions and thus increased the yield of 227Th [32].

To further assess FLUKA' s models for predicting corresponding cross sections, this study simulated excitation functions for various protactinium isotopes, considering the abundance of experimental data on protactinium isotope production from proton-induced reactions on thorium targets. Figure 3(g) presents the energy-dependent production cross sections of 229Pa under proton irradiation of 232Th over the incident energy range of 0–160 MeV. FLUKA simulations showed excellent agreement with experimental data reported by Griswold et al. [34] and Shigekawa et al. [42] when the incident energy was less than 35 MeV. In the 35–40 MeV energy range, FLUKA predictions deviated from measurements of Griswold et al. [34] by a factor of 1–5. FLUKA results were in good agreement with experimental data by Lefort et al. [38] at 150 MeV incident energy.

Figure 3(h) shows the excitation functions for 230Pa production under the same experimental conditions. FLUKA significantly underestimated experimental cross sections [34, 40, 43, 44] when the incident proton energy was less than 40 MeV. This discrepancy may originate from the odd-odd structure of 230Pa, which FLUKA might not predict accurately, and requires further investigation. Figure 3(i) shows the excitation function for the 232Th(p,2n)231Pa reaction. FLUKA predictions showed good agreement with experimental data by Kudo et al. [44] and Celler et al. [45] at incident energies below 14 MeV. FLUKA generally overestimated measurements of Celler et al. [45] by a factor of approximately 1–2, although it still matched results of Kudo et al. [44] at incident energies above 14 MeV.

The comparisons presented in this section demonstrate that FLUKA provides good agreement with experimental data for proton-induced reactions on thorium targets, confirming the reliability of its predictive capability. Therefore, this validated computational framework can be extended to similar systems where experimental data are lacking, such as deuteron- or neutron-induced reactions on thorium targets.

B. Deuteron Projectiles

Experimental data for deuteron-induced reactions on thorium targets remain scarce. Figure 4 [Figure 4: see original paper] presents a comparison between simulation results and experimental data of the 232Th(d,4n)230Pa reaction reported in Refs. [46–48], revealing significant discrepancies. When incident energies were less than 50 MeV, FLUKA systematically underestimated cross sections and exhibited anomalous trends inconsistent with experimental data, requiring further investigation.

The low-energy deuteron reaction model in FLUKA accounts for four main reaction mechanisms, as described in Section II. Among these, only stripping to the continuum and complete fusion processes can produce 230Pa. A statistical model code PACE-4, a Monte Carlo-based tool for calculating cross sections for complete fusion reactions [49, 50], was employed to investigate this discrepancy. Although the PACE-4 model overestimates the cross section, as shown in Fig. 4, it reproduces the peak structure of the 230Pa production cross section. Based on this, the discrepancy was assumed to result from FLUKA's inadequate modeling of the complete fusion process in deuteron-induced reactions. Improvements in FLUKA predictions for low-energy deuteron reactions are needed.

C. Neutron Projectiles

Due to the current lack of experimental data on isotope production cross sections for neutron-induced reactions on thorium targets, only a brief overview of neutron reaction modeling in FLUKA is provided here. Since neutrons have no charge, they are unaffected by the Coulomb potential and can induce production of high-energy photons or charged particles through reactions like capture, even at very low incident energies.

In FLUKA, neutrons with energies below 20 MeV are designated as low-energy neutrons. Low-energy neutron reactions are complex and rich in structure, making theoretical models insufficient. Instead, experimentally evaluated nuclear data files must be used. The neutron simulations in FLUKA were based on expert evaluations of available experimental data (ENDF libraries), with a pointwise treatment for low-energy neutrons. Based on energy-dependent cross sections, a probability distribution was constructed to randomly sample reaction types such as elastic scattering, radiative capture, inelastic reactions, and fission. Nuclear models (PEANUT) handle neutron interactions at higher energies.

IV. Discussion

To determine the optimal projectile type for producing the medicinal isotope 225Ac, reactions between various incident particles (protons, deuterons, and neutrons) on thorium targets with varying beam energies were simulated using the FLUKA code. Figures 5(a)–(i) show the excitation functions for production of relevant isotopes when different incident particles bombard a 232Th target. Both deuteron and neutron bombardments show higher yields for isotopes such as 225Ac, 227Ac, 227Th, 229Th, 223Ra, and 225Ra. In contrast, proton bombardment cross sections for production of protactinium isotopes such as 229Pa, 230Pa, and 231Pa were higher than those for deuterons across the entire energy range.

The simulation results for 225Ac (see Fig. 5 Figure 5: see original paper) suggest that in the incident energy range of 100–200 MeV per nucleon, cross sections for deuteron- and neutron-induced reactions are significantly higher than those for proton bombardment. While neutron irradiation yields can be up to five times larger than those from protons, deuteron yields can be up to four times higher. As incident energy increases, cross sections of the 232Th(d,x) and 232Th(n,x) reactions gradually approach those of the 232Th(p,x) reaction. This trend was also observed for other actinide, thorium, and radium isotopes (such as 227Ac, 227Th, 229Th, 223Ra, and 225Ra as shown in Fig. 5(b)–(f)).

In practical 225Ac production, cumulative yield must be considered. This yield includes both direct production of 225Ac and indirect contributions from the decay of all precursor nuclides produced during irradiation, as well as the decay of 225Ac itself. The decay chains in Fig. 2 show how 225Ra, 229Th, and 229Pa contribute to the cumulative yield of 225Ac. Among these, the short-lived ($T_1/_2$ = 14.2 d) nuclide 225Ra is the primary parent of 225Ac since it fully decays into 225Ac via β^- decay. As illustrated in Fig. 5(f), deuteron-induced reactions on a 232Th target show the highest cross section for 225Ra, with a peak around 150 MeV/nucleon that is significantly higher than those from proton- or neutron-induced reactions. As a long-lived ($T_1/_2$ = 7880 y) nuclide, 229Th can steadily decay into 225Ra, making it a "permanent" generator of 225Ac and one of the most important sources of this isotope worldwide today. As shown in Fig. 5(d), the production cross section of 229Th from deuteron or neutron irradiation was nearly three times larger than that from proton-induced reactions. In contrast, simulation results for 229Pa shown in Fig. 5(g) present an opposite trend. The cross section from proton-induced reactions was roughly five times higher than that from deuterons at 30 MeV incident energy. However, 229Pa contributes very little to the cumulative yield of 225Ac since only 0.48% of its decays proceed via α decay to produce 225Ac. Considering both direct production of 225Ac and indirect contributions through precursor decay, deuterons and neutrons demonstrate a clear advantage for increasing total yield, indicating strong potential for practical applications.

Production of 227Ac must be carefully controlled since it is toxic, has a long half-life of 22 years, and remains challenging to separate chemically from 225Ac. Figure 6 [Figure 6: see original paper] shows how the cross section ratio of 227Ac/225Ac changes with incident energy when a 232Th target is bombarded by protons, deuterons, and neutrons. Simulation results show that at low incident energies (less than 70 MeV/nucleon), proton and neutron bombardment produce more 227Ac. The ratio rises sharply to more than 10, reducing 225Ac purity. In contrast, deuteron bombardment results in a smoother and generally lower ratio across the entire incident energy range, indicating less 227Ac production alongside 225Ac. Therefore, the deuteron beam is a better choice for 225Ac production since it combines high yield with high purity.

V. Conclusion

This study employed the FLUKA Monte Carlo transport algorithm to simulate 225Ac production cross sections for proton, deuteron, and neutron irradiation of 232Th targets over the incident energy range of 10–800 MeV/nucleon. The overall agreement between simulation results and available experimental data supports the suitability of the FLUKA toolkit as a practical tool for assessment and comparison of accelerator-based production routes for medical radionuclides.

Detailed analysis of the simulation outcomes indicates that deuteron- and neutron-induced reactions on 232Th show significantly higher production cross sections for the α-therapy radionuclides 225Ac, 223Ra, and 227Th compared with proton-induced reactions. Between deuteron and neutron irradiation, the deuteron-induced reaction produces lower 227Ac impurity in 225Ac, making it comparatively more favorable under certain purity requirements. It is suggested that, under appropriate beam energy and target configurations, deuteron irradiation could serve as a promising production pathway for high-purity 225Ac in large-scale medical applications.

Beyond production performance, the comparative analysis between simulations and measured data also reveals energy regions and reaction channels where current nuclear reaction models may need refinement. Addressing these gaps will require new, high-precision experimental measurements, particularly in under-explored energy ranges, to validate and further improve transport codes. These enhancements would increase predictive accuracy, enabling more efficient design and optimization of isotope production facilities, and ultimately accelerate the availability of α-emitting radionuclides for targeted cancer therapy.

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Note: Figure translations are in progress. See original paper for figures.