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Reactor production of Thorium-229 ☆

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HIGHLIGHTS

- Production of ^{229}Th from irradiation of ^{226}Ra, ^{228}Ra, and ^{227}Ac is studied.
- Microgram quantities irradiated under high neutron flux for varying durations.
- Measured radionuclide yields lower than predicted but generally in uncertainty range.
- ORNL ^{229}Th reserve can be increased by 450 MBq per gram of irradiated ^{226}Ra.
- Large ^{227}Ra cross section further results in production of ^{228}Ra.

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ABSTRACT

Limited availability of ^{229}Th for clinical applications of ^{213}Bi necessitates investigation of alternative production routes. In reactor production, ^{229}Th is produced from neutron transmutation of ^{226}Ra, ^{228}Ra, ^{227}Ac and ^{228}Th. Irradiations of ^{226}Ra, ^{228}Ra, and ^{227}Ac targets at the Oak Ridge National Laboratory High Flux Isotope Reactor result in yields of ^{229}Th at 26 days of 74.0 ± 7.4 MBq/g, 260 ± 10 MBq/g, and 1200 ± 50 MBq/g, respectively. Intermediate radionuclide yields and cross sections are also studied.

1. Introduction

A large number of antibody targeted radiopharmaceuticals are in development for the treatment of blood-borne cancers, disseminated cancers and a variety of solid tumors using alpha-emitters such as ^{213}Bi, ^{225}Ac, ^{223}Ra, ^{227}Th and ^{211}At (Miederer et al., 2008; Kim and Brechbiel, 2012). The alpha emitters combine high-potency, high-linear energy transfer, and low toxicity; consequently, the initial attempts to use alpha particles from alpha emitting radioisotopes have focused on leukemia and small micrometastatic deposits of cancer cells such as lymphoma. Among possible alpha emitters for application in targeted alpha therapy (TAT), interest in ^{225}Ac ($t_{1/2} = 10.0$ days) has increased substantially since the initial supply of this radioisotope from Oak Ridge National Laboratory (ORNL) in 1997 (Boll et al., 2005a; Du et al., 2003; Mirzadeh, 1998). Since then, ORNL has been the main supplier of high-purity ^{225}Ac from decay of existing ^{229}Th stock, and since 2011 ~26 GBq of ^{225}Ac has been harvested annually from the ^{229}Th stock, typically in six campaigns per year. Supply of ^{225}Ac,

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however, remains inadequate to meet the demand if current or planned clinical studies are found to be effective. Furthermore, the success of ^{223}Ra for treatment of metastatic prostate cancer, as the first alpha-emitting radiopharmaceutical approved by the U. S. Food and Drug Administration (Colletti, 2013), will further encourage the research and development (R&D) of other alpha-emitting radiopharmaceutical therapies, including ^{225}Ac, for clinical use. Efforts to increase the current production of ^{225}Ac and evaluate alternate production routes have been considered a high priority (Nuclear Science Advisory Committee, 2015), and in recent years a significant investment has been made in R&D aimed at increasing the supply of ^{225}Ac (Mirzadeh, 2013; Jost et al., 2012; Weidner et al., 2012a, 2012b; Zhuikov et al., 2011; Apostolidis et al., 2005a, 2005b).

In this work, we report on a systematic evaluation of production of ^{229}Th via neutron irradiation of ^{226}Ra, ^{227}Ac, and ^{228}Ra targets in the ORNL High Flux Isotope Reactor (HFIR), examining the nuclear reactions involved in multiple production pathways and assessing the future capacity for reactor supply of ^{229}Th. Some preliminary data from this research were presented earlier (Boll et al., 2005b).

Production of ^{229}Th through neutron irradiation of ^{226}Ra requires three neutron captures and two β^- decays through a number of pathways, shown in Fig. 1 along with their associated nuclear data.

From the nuclear data presented in Fig. 1, it can be seen that the dominant production pathway is via:

$$^{226}\mathrm{Ra} \xrightarrow{(n,\gamma)} {}^{227}\mathrm{Ra} \xrightarrow{(\beta^-)} {}^{227}\mathrm{Ac} \xrightarrow{(n,\gamma)} {}^{228}\mathrm{Ac} \xrightarrow{(\beta^-)} {}^{228}\mathrm{Th} \xrightarrow{(n,\gamma)} {}^{229}\mathrm{Th}.$$

The amount of ^{229}Th produced from irradiation of ^{226}Ra can be calculated by solving a linked set of Bateman equations (Bateman, 1910) of the form shown in (Eqs. (1) and 2).

$$N_i(t) = \sum_{k=1}^{i} \left(\prod_{j=k}^{i-1} \Lambda_j \right) N_k^0 \sum_{j=k}^{i} a_j e^{-\Lambda_j t} \tag{1}$$

$$a_j = \prod_{m \neq j} \left(\Lambda_m - \Lambda_j\right)^{-1} (m = k,\ k+1,\ \ldots,\ i), \tag{2}$$

where

Λ_{i-1} is the formation rate constant (λ_{i-1} or $\sigma_{i-1}\phi$) of the ith species from the (i−1)th species.

Λ_i is the total depletion rate constant ($\lambda_i + \sigma_i\phi$) of the ith species.

Table 1
Hydraulic tube fluxes by axial location.

Hydraulic tube position[a]	Thermal flux (n cm^{-2} s^{-1})	Thermal – Epithermal ratio
1	1.00×10^{15}	40
2	1.45×10^{15}	35
3	1.80×10^{15}	30
4	2.00×10^{15}	25
5	2.05×10^{15}	20
6	1.95×10^{15}	25
7	1.65×10^{15}	30
8	1.20×10^{15}	35

[a] Position 5 is located at the HFIR core mid-plane.

Throughout this paper, these equations are solved using a Java tool, "IsoChain" (Almanza et al., 2006; Mirzadeh and Walsh, 1997), using the nuclear data given in Fig. 1, and the previously measured neutron fluxes in the HFIR hydraulic tube facility, listed in Table 1 (Mahmood et al., 1995). In this table and in all future references, the thermal to epithermal ratio, R, refers to the ratio of the thermal flux to the flux in the energy range 0.5 eV and 0.1 MeV divided by the logarithm of the energy difference of that energy range, which is known as the flux per unit lethargy.

$$R = \frac{\varphi_{th}}{\varphi_{ep} / ln\left(\frac{E_{Upper}}{E_{lower}}\right)} \tag{3}$$

In our computation, any unknown cross sections are assigned a value of 1 barn.

2. Estimating isotope yields, sensitivities and uncertainties

An initial calculation was performed to assess the potential for production of ^{229}Th from ^{226}Ra using a thermal neutron flux of 2.0×10^{15} n cm^{-2} s^{-1} and a thermal to epithermal flux ratio of 25, representing the neutron flux in a typical target irradiation position near the mid-plane of the HFIR. This calculation was performed for 12 time steps of 25 days irradiation, with 35 days of decay between each time step, which is representative of ~two years' (12 cycles') worth of irradiation in HFIR. The production of ^{229}Th over time is shown in Fig. 2. in units of GBq ^{229}Th per g ^{226}Ra in the initial target.

From Fig. 2, it can be seen that the production of ^{229}Th is slow

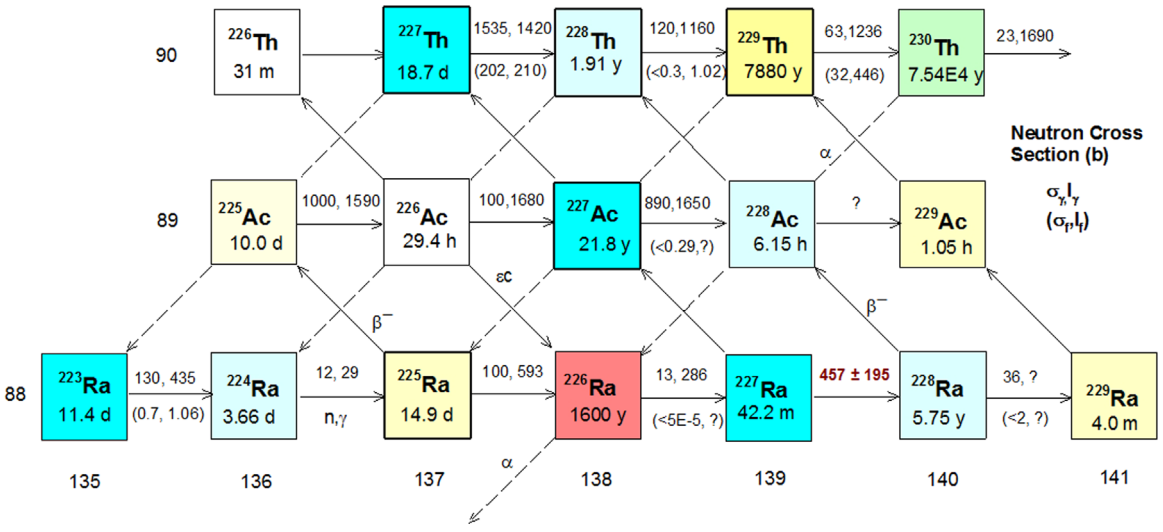

Fig. 1. Transmutation pathways from ^{226}Ra to ^{229}Th and approximate neutron cross sections. As indicated, the first term of cross section refers to thermal and second term to resonance integrals. The values in parenthesis are fission cross sections at thermal and epi-thermal neutrons, respectively.