



# On the feasibility of producing Lu-177 in the IEA-R1 reactor via the direct route

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## ABSTRACT

Over the last years the  $^{177}\text{Lu}$  radioisotope has attracted great interest for the use in therapeutic and diagnostic procedures simultaneously, being what is now called a theranostic radioisotope, with outstanding results in prostate and neuroendocrine cancer. There are mainly two ways of producing this radioisotope, by direct neutron capture in a  $^{176}\text{Lu}$  target (the “direct route”) or by irradiating a  $^{176}\text{Yb}$  sample, producing  $^{177}\text{Yb}$  that will then decay to  $^{177}\text{Lu}$  (also referred as the “indirect route”). In this work, the technical feasibility of producing  $^{177}\text{Lu}$  in the IEA-R1 nuclear research reactor via the direct route was assessed, and the specific activity that could be obtained was estimated both experimentally and theoretically.

**Keywords:** Lu-177, radioisotope production; reactor production.

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## 1. INTRODUCTION

$^{177}\text{Lu}$  is a radionuclide of the family of the lanthanides, produced artificially in nuclear reactors, that is being applied in treatment of neoplasms worldwide in the last years, mostly in neuroendocrine and prostate cancers, revealing promising outcomes [1-3]. This radionuclide decays by low-energy  $\beta^-$  emission ( $E_{max}=497$  keV, 78.6%) followed by  $\gamma$  emission (most intense transitions, 113 keV, 6.4%, and 208 keV, 11%) [4], what is ideal for targeted radionuclide therapies, with theranostic applications:  $\beta^-$  particles kill tumor cells and gamma radiation can be detected in SPECT cameras, for diagnostic purposes.

$^{177}\text{Lu}$  can be produced by two different ways: one called the direct route, in which a  $^{176}\text{Lu}$  target is irradiated in a neutron flux, generating  $^{177}\text{Lu}$  via the nuclear reaction  $^{176}\text{Lu}(n, \gamma)^{177}\text{Lu}$ ; and other called the indirect route, in which a  $^{176}\text{Yb}$  target is irradiated, generating  $^{177}\text{Yb}$  by neutron capture, which decay via  $\beta^-$  emission to  $^{177}\text{Lu}$ . Both methods have their advantages and disadvantages, and the choice for one of them must consider the final usage purposes, besides technical and financial aspects.

Despite of its increasing importance in nuclear medicine, availability of  $^{177}\text{Lu}$  is still restricted, with commercial production limited to a few countries, like Russia and the Netherlands. In this sense, local production of this radionuclide is of great interest, since it would reduce final cost and could potentially supply larger demands. Considering this, the aim of this study is to assess the technical feasibility of production of  $^{177}\text{Lu}$  in the IEA-R1 nuclear research reactor via direct route.

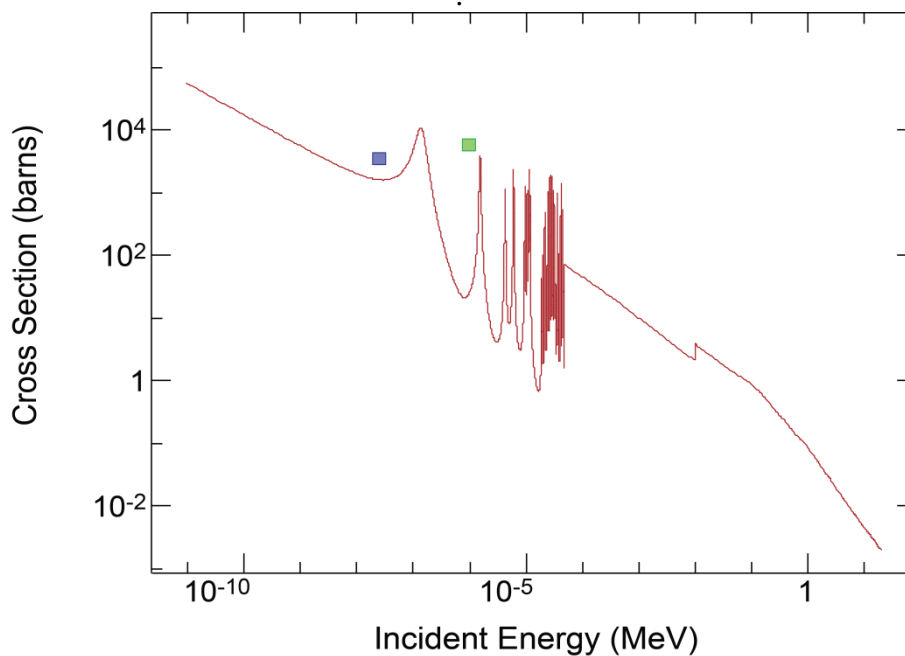
## 2. MATERIALS AND METHODS

The specific activity of  $^{177}\text{Lu}$  that would be achievable in the IEA-R1 reactor was estimated by two distinct theoretical methodologies. To validate the results, an experimental irradiation of a natural lutetium sample was performed.

## 2.1. Theoretical prediction of the $^{177}\text{Lu}$ production

The capture cross section of  $^{176}\text{Lu}$  is rather high ( $2090 \pm 70$  b [5]); however, the estimation of the activity produced when  $^{176}\text{Lu}$  is irradiated with neutrons is rather tricky, due to a very intense resonance below 1 eV (see Figure 1). For that reason, the use of the usual Høgdahl convention is not directly possible, as it assumes a  $1/E$  dependence on the cross section [6].

**Figure 1:** Neutron capture cross section for  $^{176}\text{Lu}$



Source: NGATLAS [7]

One way to overcome this limitation was proposed by Koyama [8], who calculated temperature dependent *effective cross sections* for many “non- $1/E$  nuclides” - in the case of the IEA-R1 reactor, where the pool water temperature around of the irradiation devices is approximately  $40^\circ\text{C}$ , the  $^{176}\text{Lu}$  capture cross section to be used in the Høgdahl convention [9] is, then, 3885 b; a second alternative is to use the simplified Westcott convention [10], which requires several additional parameters from

the irradiation facility, not all of which are readily available for our site – in our paper, in order to check for the validity of each approach, calculations were performed by both methods.

### 2.1.1 Høgdahl convention using the effective cross section

As the resonance integral of  $^{176}\text{Lu}$  is smaller than the cross section, and in IEA-R1 reactor the epithermal neutron flux is almost one order of magnitude lower than the thermal one, we decided to neglect the contribution of epithermal neutrons in this first calculation, so the specific activity of  $^{177}\text{Lu}$  after an irradiation time  $t$  will be given by Equation 1 [9],  $N_A$  is the Avogadro constant ( $6.02214076 \times 10^{23} \text{ mol}^{-1}$ ), and the remaining nuclear data used in the calculation are presented and described in Table 1. It should be noted that, as it is an approximated calculation, no error propagation was performed, and both self-shielding and burn-up were neglected; moreover, up to this point all calculations were performed assuming a natural Lu target.

$$\frac{A_0}{m} = \frac{\varphi_{th} \times \sigma_{th}^* \times F_m \times N_A}{M} \times (1 - e^{-\lambda \times t}) \quad (1)$$

**Table 1:** Nuclear parameters used in the calculation using the Høgdahl convention.

Parameter	Description	Value
$\sigma_{th}^*$	Effective thermal cross section	3885 b [8]
$F_m$	Isotopic fraction	2.599% [11]
$M$	Atomic mass	174.9668 Da [11]
$\lambda$	Decay constant	$0.1042797 \text{ h}^{-1}$ [4]
$\varphi_{th}$	Thermal neutron flux	$1.09 \times 10^{13} \text{ cm}^{-2} \text{ s}^{-1}$

### 2.1.2 Simplified Westcott convention

To estimate the final specific activity of  $^{177}\text{Lu}$  using the simplified Westcott convention [10], with the due burn-up corrections [6], one needs to evaluate Equation 2:

$$\frac{A_0}{m} = \frac{\varphi_{th} \times \sigma_{th} \times k \times N \times \lambda}{\lambda - \sigma_{th} \times k \times \varphi_{th}} \times (e^{-\sigma_{th} \times k \times \varphi_{th} \times t} - e^{-\lambda \times t}) \quad (2)$$

where most symbols are the same used for the Høgdahl convention,  $N$  is the number of  $^{176}\text{Lu}$  nuclei per gram:

$$N = \frac{F_m \times N_A}{M} \quad (3)$$

and  $k$  is the so-called  $k$  factor, defined in Equation 4. This formalism requires many more detailed data on the irradiation facility and nuclide, as  $T_n$  and  $T_0$  are, respectively, the standard temperature for which cross sections are tabulated, ( $20^\circ\text{C}$ ) the actual temperature in the irradiation facility ( $40^\circ\text{C}$ );  $G_{th}$  and  $G_r$ , the thermal and epithermal self-shielding factors, both set to one in the present work, as an infinitely diluted sample is assumed, and the remaining parameters are defined in Table 2.

$$k = [G_{th} \times g(T_n) + R_r \times r(\alpha) \times \sqrt{T_n/T_0} \times s_0 \times (\overline{E_r})^{-\alpha}] \quad (4)$$

**Table 2:** Nuclear parameters used in the calculation using the Westcott convention.

Parameter	Description	Value
$g(T_n)$	Westcott factor	1.8922 [12]
$r(\alpha) \times \sqrt{T_n/T_0}$	Spectral index	0.03 <sup>(1)</sup>
$\alpha$	Epithermal shape factor	0 <sup>(2)</sup>
$s_0$	Westcott s-factor	1.67 [13]
$\overline{E_r}$	Effective resonance energy	0.158 eV [13]

(1)  $r(\alpha)$  hasn't been determined for our irradiation position yet, so we used an estimate given by the local k0-INAA group.

(2). The local k0-INAA group has experimentally determined that  $\alpha$  is mostly compatible with 0.

## 2.2. Experimental validation

For the experimental validation of the specific activity estimates obtained by either method, 50  $\mu\text{L}$  of a 1 g/L natural Lutetium certified solution were pipetted in Whatman 40 filter paper; after drying, the paper was folded and placed inside a small polyethylene bag ( $\sim 1 \text{ cm} \times 1 \text{ cm}$ ). This sample was then placed inside an aluminum container and irradiated for 8 h in irradiation position 14A/4 of the IEA-R1 reactor. The sample came out too radioactive, so it had to decay for 15 days before counting in order to achieve a counting dead time below 15%.

The sample was counted in a Canberra GX4019 HPGe detector for 3600 s; then, the efficiencies ( $\epsilon$ ) determined using Canberra's LABSOCS software were used to determine the activity of the radioisotope by means of Equation 5, where  $I_\gamma$  are the transition intensities and  $cps$  are the observed count rates.

$$A = \frac{cps}{\epsilon \times I_\gamma} \quad (5)$$

As the irradiation produces both the desired ground state  $^{177}\text{Lu}$  ( $T_{1/2} = 6.647 \text{ d}$ ) and a 160 d  $^{177m}\text{Lu}$  isomer, the activity of the longer-lived isotope also had to be determined; this was achieved by a weighted average of the activity values obtained using the gamma transitions that are exclusive to it (see Table 3 for the gamma-ray energies employed in this study). As no transitions are exclusive to the ground-state  $^{177}\text{Lu}$ , the activity of this isomer was calculated by determining the expected counts using Equation 6 (where  $A$  is the activity determined for  $^{177m}\text{Lu}$ ,  $I_\gamma$  are the intensities of the common gamma transitions and  $\epsilon$  the detection efficiency at those energies) and subtracting them from the real counts. The experimental activity obtained for  $^{177}\text{Lu}$  was then corrected for the decay since the end of irradiation.

$$cps = A \times I_\gamma \times \epsilon \quad (6)$$

**Table 3:** Gamma transitions observed and their absolute intensities in the decay of either  $^{177}\text{Lu}$  isomer (from [4]).

Energy (keV)	$I_{\gamma}$ ( $^{177m}\text{Lu}$ ) (%)	$I_{\gamma}$ ( $^{177}\text{Lu}$ ) (%)
55.15	$1.78 \pm 0.10$	
71.646	$0.90 \pm 0.04$	$0.154 \pm 0.008$
112.9498	$20.4 \pm 0.4$	$6.4 \pm 0.3$
136.7248	$1.40 \pm 0.05$	$0.048 \pm 0.002$
153.2843	$16.9 \pm 0.3$	
208.3664	$57.7 \pm 1.1$	$11.0 \pm 0.6$
228.4838	$37.0 \pm 0.7$	
249.6741	$6.14 \pm 0.18$	$0.212 \pm 0.011$
281.7873	$14.1 \pm 0.3$	
327.6829	$18.1 \pm 0.5$	
378.5029	$29.7 \pm 1.2$	
413.6636	$17.4 \pm 0.6$	
418.5391	$21.3 \pm 0.8$	
465.8416	$2.35 \pm 0.12$	

### 3. RESULTS AND DISCUSSION

The specific activities determined by the Høgdahl and Westcott conventions for an 8-hour irradiation are presented in Table 4 together with the experimental results obtained. The results obtained using both formalisms were compatible within 5%, while the experimental result was 15% lower than the theoretical estimate, which can be considered acceptable, given the assumptions made in the calculations. The experimental specific activity of  $^{177m}\text{Lu}$  determined was  $(4.65 \pm 0.20) \times 10^6$  Bq/g (of natural lutetium), which is  $(4.2 \pm 0.3) \times 10^{-5}$  times smaller than that of the ground state  $^{177}\text{Lu}$ , which is rather lower than the findings in [14] ( $1.5 \times 10^{-4}$ ), who irradiated for 7 days.

**Table 4:** Specific activity of  $^{177}\text{Lu}$  after 8 hours of irradiation calculated using both the Høgdahl and the Westcott formalisms compared to the specific activity obtained experimentally, (in Bq/g of natural lutetium).

Høgdahl	Westcott	Experimental result
$1.30 \times 10^{11}$	$1.35 \times 10^{11}$	$(1.13 \pm 0.04) \times 10^{11}$

As both formalisms reached similar results, the activities that could be obtained in longer reactor cycles were determined using only the Westcott formalism, where a burn-up correction is included. In these simulations, two situations were considered: a cycle with 8 h/day for 3 consecutive days (the present operational status of the IEA-R1 reactor) and a cycle with 60 consecutive hours of irradiation, as the IEA-R1 used to operate previously. Moreover, as the practical production of high activities of  $^{177}\text{Lu}$  should require the use of isotopically enriched targets, the specific activities in this case were calculated per gram of  $^{176}\text{Lu}$ . These results are shown in Table 5.

**Table 5:** Specific activity of  $^{177}\text{Lu}$  calculated using the Westcott formalism for two distinct operation cycles (in TBq/g of  $^{176}\text{Lu}$ ).

Irradiation cycle	Specific activity (TBq/g)
8 h/day for 3 consecutive days	5.4
60 consecutive hours	34
14 consecutive days in a $10^{14} \text{ cm}^{-2} \cdot \text{s}^{-1}$ position	800

Comparing the specific activities results with the ones in [14,15], for instance, indicates that while these values would be useful for bone pain treatment, they would be still below the minimum requirements for Peptide Receptor Radionuclide Therapy (PRRT) – Chakraborty *et al* [15] state that for that purpose a minimum of 740 TBq/g should be obtained. In our reactor, it could be possible to use an irradiation position with a higher flux (maybe up to one order of magnitude higher), but even



then to reach those specific activities the reactor would need to operate continuously for the whole week – the situation is shown in the last line of Table 5, but it must be stressed that at that high flux position the parameters used in the calculations would be different, so this should be taken simply as a rough estimate.

#### 4. CONCLUSION

In this study we assessed the technical possibility of producing  $^{177}\text{Lu}$  for nuclear medicine in the IEA-R1 reactor via the direct neutron capture route. The production yield was calculated both using the Høgdahl convention with a modified “effective” cross section and the Westcott convention, in both cases making some simplifying assumptions, and both calculations agreed within 5%. An experimental measurement was made to validate those calculations, and agreed to the calculated values within 15%, which is reasonable given the assumptions made (most specifically, to the lack of a self-shielding correction).

Using the Westcott approach, it was possible to estimate the specific activities that could be obtained for production purposes, supposing a 100%-enriched  $^{176}\text{Lu}$  target, in  $\sim 5$  TBq/g for the present operating cycle of the IEA-R1 reactor, and in  $\sim 34$  TBq/g for a 60-straight-hour cycle. While both values are clearly more than sufficient for bone pain treatment, they are still below the requirements for Peptide Receptor Radionuclide Therapy, which could only be obtained using the highest flux position available, and even then only if the reactor operated continuously and the targets were irradiated for 14 straight days.

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## REFERENCES

- [1] DAS, T. ;BANERJEE, S. Theranostic Applications of Lutetium-177 in Radionuclide Therapy, **Curr Radiopharm** v.9, p. 94–101, 2016.
- [2] JING, L.; SHI, J.; FAN, D.; LI, Y.; LIU, R.; DAI, Z.; WANG, F.; TIAN, J.<sup>177</sup>Lu-Labeled Cerasomes Encapsulating Indocyanine Green for Cancer Theranostics, **ACS Appl. Mater. Interfaces**,v. 7, p. 22095–22105, 2015.
- [3] PERSSON, M.; JUHL, K.; RASMUSSEN, P.; BRANDT-LARSEN, M.; MADSEN, J.; PLOUG, M.; KJAER,A. uPAR Targeted Radionuclide Therapy with <sup>177</sup>Lu-DOTA-AE105 Inhibits Dissemination of Metastatic Prostate Cancer, **Mol. Pharmaceutics**, v. 11, p. 2796–2806, 2014;
- [4] KONDEV, F. G. Nuclear Data Sheets for A = 177, **Nuclear Data Sheets**,v. 98, p. 801–1095, 2003.
- [5] MUGHABGHAB, S. F. **Thermal Neutron Capture Cross Sections Resonance Integrals And G-Factors - INDC(NDS)-440**, Vienna :IAEA, 2003.
- [6] DVORAKOVA, Z.; HENKELMANN, R.; LIN, X.; TÜRLER, A.; GERSTENBERG, H. Production of <sup>177</sup>Lu at the new research reactor FRM-II: Irradiation yield of <sup>176</sup>Lu(n,  $\gamma$ )<sup>177</sup>Lu, **Appl Radiat Isot**,v. 66, p. 147–151, 2008.
- [7] KOPECKY, J. **NGATLAS - Atlas of Neutron Capture Cross Sections**, Vienna :IAEA, 2001. Available at: <<https://www-nds.iaea.org/ngatlas2/>>. Last accessed 15 May 2020.

- [8] KOYAMA, M.; MATSHUSHITA, R. Use of Neutron Spectrum Sensitive Monitors for Instrumental Neutron Activation Analysis, **Bulletin of the Institute for Chemical Research, Kyoto University**, v. 58, p. 235–243, 1980.
- [9] HØGDAHL, O. T. **Neutron absorption in pile neutron activation analysis - Report MMPP-226-1**, Ann Arbor:University of Michigan, 1962.
- [10] WESTCOTT, C. H. **Effective cross section values for well moderated thermal reactor spectra - Report AECL-1101**, Chalk River : Chalk River Laboratory, 1960.
- [11] COURSEY, J. S. ; SCHWAB, D. J. ; TSAI, J. J. ; DRAGOSET, R. A. **Atomic Weights and Isotopic Compositions with Relative Atomic Masses**, NIST, 2015. Available at : <<https://physics.nist.gov/comp>>. Last accessed 15 May 2020.
- [12] HOLDEN, N. E. Temperature dependence of the Westcott g-factor for neutron reactions in activation analysis, **Pure Appl. Chem.**, v. 71, p. 2309–2315, 1999.
- [13] DE CORTE, F.; SIMONITS, A. Recommended nuclear data for use in the k0 standardization of neutron activation analysis, **Atomic Data Nucl. Data Tables**, v. 85, p. 47-67, 2003.
- [14] PILLAI, M.R.A.; CHAKRABORTY, S. ; DAS, T. ; VENKATESH, M. ; RAMAMOORTHY, N. Production logistics of  $^{177}\text{Lu}$  for radionuclide therapy, **Appl Radiat Isot**, v. 59, p. 109–118, 2003.
- [15] CHAKRABORTY, S. ; VIMALNATH, K.V.; LOHAR, S.P. ; SHETTY, P. ; DASH, A. On the practical aspects of large-scale production of  $^{177}\text{Lu}$  for peptide receptor radionuclide therapy using direct neutron activation of  $^{176}\text{Lu}$  in a medium flux research reactor: the Indian experience, **J Radioanal Nucl Chem**, v. 302, p. 233–243, 2014.