EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Proposal to the ISOLDE and Neutron Time-of-Flight Committee

Measurement of the ^{176}Yb(n,γ) cross-section at EAR1 and its application to nuclear medicine

[12/05/2021]

F. García-Infantes[1,2], J. Praena[1,2], V. Vlachoulis[1], I. Porras[2], F. Arias de Saavedra[2],
H. Amar Es-sghir[2], N. Colonna[3], M. Mastromarco[3] and C. Massimi[4,5]
for the n_TOF collaboration

[1] European Organization for Nuclear Research (CERN), Geneva, Switzerland
[2] Departamento de Física Atómica, Molecular y Nuclear, Universidad de Granada, Granada, Spain
[3] Istituto Nazionale di Fisica Nucleare, Sezione di Bari, Bari, Italy
[4] Istituto Nazionale di Fisica Nucleare, Sezione di Bologna, Bologna, Italy
[5] Dipartimento di Fisica e Astronomia, Università di Bologna, Bologna, Italy

Spokesperson(s): Javier Praena (jpraena@ugr.es)
Francisco García-Infantes (francisco.garcia.infantes@cern.ch)
Technical coordinator: Oliver Aberle (Oliver.Aberle@cern.ch)

Abstract

Several international agencies recommend the study of new routes and new facilities for producing radioisotopes with application to nuclear medicine as a complementary option to the conventional ones based on nuclear reactors or dedicated cyclotrons. CERN's MEDICIS facility is an excellent example. ^{177}Lu is a versatile radioisotope used for therapy and diagnosis (theranostics) of cancer with good success in neuroendocrine tumours that is being studied to be applied to a wider range of tumours. ^{177}Lu is produced in few nuclear reactors mainly by the neutron capture on ^{176}Lu. However, it could be produced at high-intensity accelerator-based neutron facilities as IFMIF-DONES by means of the route ^{176}Yb(n,γ). This route provides higher specific activity than the conventional one. The energy of the neutrons in accelerator-based neutron facilities is higher than in thermal reactors. Thus, experimental data on the ^{176}Yb(n,γ) cross-section in the eV and keV region are mandatory to calculate accurately the production of ^{177}Lu. At present, there are not experimental data available from thermal to 3 keV of the ^{176}Yb(n,γ) cross-section. In addition, the resonances have not been resolved which are expected in the range from 3 to 50 keV. We propose to carry out an experiment providing data for the first time from thermal to the resolved resonance region and resolving the important resonances foreseen in the ^{176}Yb(n,γ) cross-section. These data will be used in future evaluations of the ^{176}Yb(n,γ) cross-section.

Requested protons: $1.5 \cdot 10^{18}$ protons
Experimental Area: EAR1

1. INTRODUCTION AND SCIENTIFIC MOTIVATIONS

Nuclear medicine has proven to be a much needed medical specialty in order to diagnose and treat several diseases, among them, cardiovascular diseases and cancer, the first and the second causes of mortality worldwide, respectively [1]. Diagnosis represents 90% of the procedures in nuclear medicine [2]. It is mainly performed with two techniques SPECT (Single photon emission computed tomography) and PET (Positron emission tomography). The SPECT is used in more than 80% of the nuclear medicine procedures in the world, and the most used radioisotope is the ^{99}Mo/^{99m}Tc which is produced in nuclear reactors [2]. For this reason, the "world technetium crisis" in 2002 was a first alarm to find out new procedures and facilities to produce radioisotopes for nuclear medicine with the idea to decrease the dependency on few nuclear reactors worldwide [3]. Regarding PET, it has been successful in many types of diagnosis and the ^{18}F-fluorodeoxyglucose is the most used carrier. Besides the exceptional results provided by this carrier, it has been widely reported that causes false positives and false negatives because it is not a cancer-specific agent [4]. Better properties of other radiopharmaceuticals based on ^{11}C (20 min) in many cancers have been reported [5] as well as for cardiovascular diseases with ^{13}N (10 min) and ^{15}O (2 min). The half-life of ^{11}C, ^{13}N and ^{15}O do not allow their transport as in the case of ^{18}F (110 min) reducing their use.

In the last decades more than 3000 radioactive isotopes have been discovered and detected in different nuclear physics facilities. Many of them could have properties that make them useful for nuclear medicine and potentially they could have better properties for diagnosis and therapy than the conventional ones, as mentioned before for PET. In this framework, several international agencies and committees recommend the study of new routes for producing radioisotopes with application to nuclear medicine [2,3,6,7]. This has been specially pushed in the last years with the development and the availability of high-intensity accelerators and new installations because they allow to study the production of emergent or new radioisotopes. In addition, these new installations can provide several radioisotopes quantities at regional level. CERN's MEDICIS Isolde facility is an excellent example [8]. Therefore, these facilities can provide a complementary production of radioisotopes to the present production at nuclear reactors or dedicated cyclotrons.

Besides the charged-particle facilities also accelerator-based neutron sources are being considered for radioisotope production. IFMIF-DONES (International Fusion Material Irradiation Facility - Demonstration Neutron Source) is one of the possible facilities to be used for this. It is an ESFRI (European Strategy Forum on Research Infrastructures), and the European city host is Granada (Spain) [9]. Its main objective is the irradiation of materials for fusion reactor technology. IFMIF-DONES has already considered the production of radioisotopes as one the main complementary applications of the facility [10]. Indeed, the design of the building has already foreseen an experimental hall for such applications. ^{177}Lu is one of the radioisotopes under consideration for its production due to its outstanding characteristics for both, diagnosis (by SPECT) and radiotherapy.

^{177}Lu ($t_{1/2} \approx 6.65$ d) is one the of most important emergent radioisotopes. It is used for theranostics (therapy and diagnosis), with good success in gastroenteropancreatic neuroendocrine tumours [11]. Currently, ^{177}Lu is under study for several other tumours with good results [12]. At present, ^{177}Lu is only produced in nuclear reactors through two production routes:

- The direct route, ^{176}Lu(n,γ)^{177,177m}Lu.
- The indirect route, ^{176}Yb(n,γ)^{177}Yb ($t_{1/2} \approx 1.9$ h) $\rightarrow ^{177}$Lu + ^{177m}Lu [13].

At present, the production is made in nuclear reactors and the most used production route is the direct route, ^{176}Lu(n,γ). Although the cross-section of the direct route is higher, several advantages in the indirect route have been pointed out:

i) The specific activity is four times higher [13]. About 100% of the theoretical specific activity can be achieved [14,15].

ii) The contaminants that remain in the final quantity of the material are much lower.

iii) The undesirable ^{177m}Lu ($t_{1/2}\approx$160 d) is produced in the direct route, 0.05%, whereas in the indirect route is less than 10^{-5} % [16]. ^{177m}Lu creates important problems, the urine of the patient must be treated as radioactive waste, and the patient receives an undesirable dose.

These properties have a direct impact on the quality of the diagnosis and the therapy. The higher specific activity allows a much better tumour uptake; thus, the dose deliver to tumour for the same activity is much higher in case of the indirect route, and in addition, the quality of imaging of the tumour is much better [14,15]. In this proposal, we will measure the ^{176}Yb(n,γ)^{177}Yb cross-section which is a fundamental quantity for the production of ^{177}Lu by the indirect route.

2. STATUS OF THE ^{176}Yb(n,γ)^{177}Yb CROSS-SECTION DATA

The available experimental data for the ^{176}Yb(n,γ)^{177}Yb cross-section are shown in Figure 1 taken from EXFOR database [17]. At thermal energies, there are few experiments for which the most recent ones agree within 9% [18,19,20,21,22]. Above thermal energy there are several important facts that recommend a high-resolution measurement. The most relevant are:

i) There are no data from thermal to 3 keV.

ii) There are no resolved resonances in the ^{176}Yb(n,γ) cross-section. However, resonances have been detected in transmission experiments [23,24].

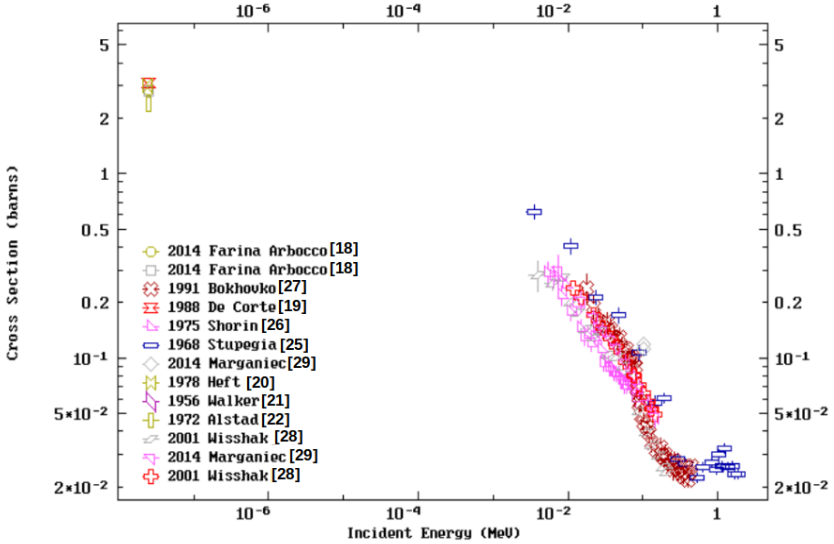

Fig. 1. Experimental data available in EXFOR for the ^{176}Yb(n,γ) cross-section.

Stupegia *et al.* [25] in 1968 reported a cross-section 2 or 3 times larger than all the later measurements. Shorin *et al.* [26] and Bokhovko *et al.* [27] differed by more than 30% in average, and Wisshak *et al.* [28] data are in average between them. However, the resonances were not resolved in the mentioned works. Marganiec *et al.* provided integral values of the cross-section in a *quasi*-stellar field [29]. Regarding evaluations, ENDF/B-VIII.0 [30] and JEFF-3.3 [31] foreseen different upper limits for the resolved resonance region, 5 and 50 keV, respectively. A new measurement at n_TOF will clarify this situation concerning the evaluations and providing data for the first time in different energy ranges. These data will allow a further improvement of the evaluations of the ^{176}Yb(n,γ) cross-section as was required by IAEA [32].

3. EXPERIMENTAL SETUP

We propose to carry out the measurement of the capture cross-section of ^{176}Yb at the n_TOF facility in the EAR1. The γ-rays cascade, with a total energy of around 5.24 MeV emitted after each capture reaction in ^{176}Yb [28], will be detected using a set of four C_6D_6 detectors [33]. The Monte Carlo-based pulse height weighting technique (PWHT) will be used in the analysis [34]. Both, the analysis technique, and the detectors, have been widely used by the n_TOF Collaboration.

Regarding the sample, we will follow the method used by Wisshak *et al.* [28], where the ^{176}Yb sample was prepared from isotopically enriched oxide powder, heating the sample to remove any water contamination. Then, the batch was pulverized in an agate mortar and pressed into granules, after cooling, the sample was prepared by canning the granules in airtight Aluminum cylinders. Trace Science International company delivers $^{176}Yb_2O_3$ in powder with less than 1% contaminants and with an enrichment greater than 96% in ^{176}Yb [35] improving a bit the properties and the enrichment of Wisshak *et al.* [28].

Table 1. Sample enrichment, mass and area density of the $^{176}Yb_2O_3$.

$^{176}Yb_2O_3$	
Enrichment [%]	>96%
Mass [g]	0.5
Area density [at/barn]	$3.857 \cdot 10^{-4}$

Table 1 summarizes the characteristics of our $^{176}Yb_2O_3$ sample. As in previous capture measurements at n_TOF-EAR1, ^{208}Pb, ^{197}Au and natural isotopic samples will be used for the background and normalization measurements.

4. COUNTING RATE ESTIMATION

The number of protons required has been estimated by a compromise between the resolution of the resonances, a reasonable statistical uncertainty and reasonable beam time. The calculations have been carried out considering the sample in Table 1 and its Al can, the ENDF/B-VIII.0 cross-section [30], the neutron flux at EAR1 and the efficiency of the setup based on four C_6D_6, as in previous experiments at n_TOF-EAR1, i.e. [36]. The expected total number of counts with 500 bins per neutron energy decade (bpd) are displayed in Figure 2. It has been obtained considering a total of $1 \cdot 10^{18}$ protons on target. Figure 2 shows both, the total expected counts for the ^{176}Yb(n,γ) reaction (blue) and for the ^{176}Yb(n,γ) reaction and the expected background (black), considering the scattering in all elements of the sample and the container.

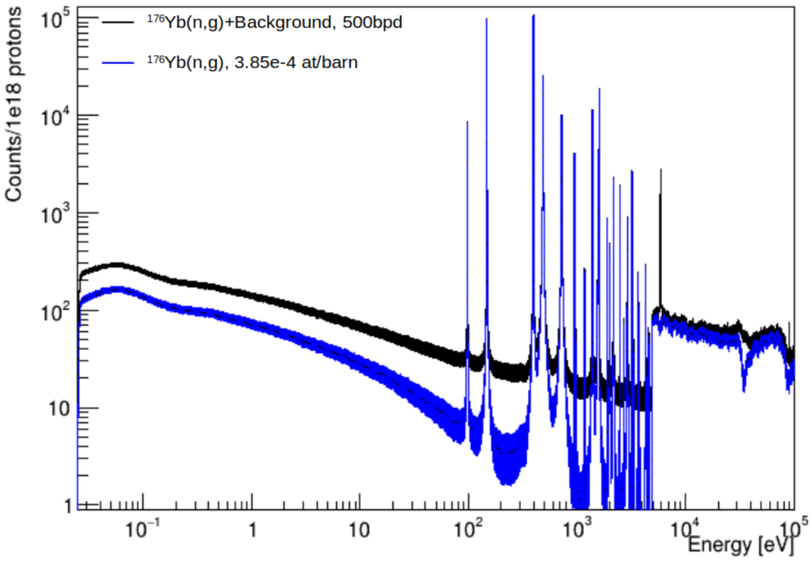

Fig. 2. Expected total number of counts in n_TOF-EAR1 for 500 bpd and $1{\cdot}10^{18}$ protons on target for ^{176}Yb(n,γ) (blue) and for the ^{176}Yb(n,γ) and background (black).

Our experiment aims to:

- To provide data for the first time from thermal to the resonance region.
- To resolve the resonances for the first time.
- To provide data from thermal to 100 keV in a single measurement for the first time.

The data obtained in this experiment will allow an accurate calculation of the production of ^{177}Lu by means of the ^{176}Yb(n,γ) reaction in accelerator-based neutron facilities. This production could be complementary to the present production carried out at nuclear reactors worldwide. In addition, the high-resolution data provided at n_TOF will allow for new and more accurate evaluations of the ^{176}Yb(n,γ) cross-section used for basic science and nuclear technologies.

Summary of requested protons at EAR1: A total of $1.5{\cdot}10^{18}$ protons are requested.

$1{\cdot}10^{18}$ for the ^{176}Yb(n,γ)

$0.4{\cdot}10^{18}$ for background measurements.

$0.1{\cdot}10^{18}$ for ^{197}Au normalization

References:

[1] https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer.

[2] Nuclear Physics European Collaboration Committee: nuclear physics for medicine. ISBN: 978-2-36873-008-9. http://www.nupecc.org/pub/npmed2014.pdf.

[3] European Nuclear Society, The Medical Isotope Crisis. http://www.euronuclear.org/1-information/news/medical-isotope-crisis.htm.

[4] A. Hoover *et al.,* Rad. & Oncol., 90 1 (2014). https://doi.org/10.1016/j.ijrobp.2014.05.1717.

[5] M. Picchio and P. Castellucci, Theranostics 2012; 2(3): 313–317. https://doi.org/10.7150/thno.4007.

[6] NuPEcc. Long Range Plan 2017 Perspectives in Nuclear Physics. https://www.esf.org/fileadmin/user_upload/esf/Nupecc-LRP2017.pdf.

[7] European Observatory on the supply of medical radioisotopes. https://ec.europa.eu/euratom/observatory_en.html

[8] https://medicis.cern/

[9] http://www.roadmap2018.esfri.eu/projects-and-landmarks/browse-the-catalogue/ifmif-dones/.

[10] J. Praena *et al.*, Radioisotope production at the IFMIF-DONES facility, EPJ Web of Conferences 239, 23001 (2020). https://doi.org/10.1051/epjconf/202023923001.

[11] K. Kim *et al.*, Lu-177-Based Peptide Receptor Radionuclide Therapy for Advanced Neuroendocrine Tumors, Nucl Med Mol Imag., 2018 Jun; 52(3): 208–215. https://doi.org/10.1007/s13139-017-0505-6.

[12] J. Zhang *et al.*, Clin. Nucl. Med., January 2020, Volume 45, Issue 1, p e48-e50. https://doi.org/10.1097/RLU.0000000000002655.

[13] A. Dash *et al.*, Production of ^{177}Lu for targeted radionuclide therapy: available options. Nuc. Med. and mol. 1Ima., 49(2):85–107, 2015. https://pubmed.ncbi.nlm.nih.gov/26085854/.

[14] R. Henkelmann, Thursday, 28 February 2013, Lu-177 production with a focus on radiation in the KBA at FRM II, SAAGAS 24, TUM Garching https://indico.frm2.tum.de/event/0/attachments/4/14/Henkelmann_177Lu_gek.pdf.

[15] E. A. M. Ruigrok *et al.*, Extensive preclinical evaluation of lutetium-177-labeledPSMA-specific tracers for prostate cancer radionuclide therapy, Eur. J. Nucl. Med. Mol. Imaging, 2020 Oct 23. 10.1007/s00259-020-05057-6.

[16] K. M. Ferreira *et al.*, Half-life measurement of the medical radioisotope ^{177}Lu produced from the ^{176}Yb(n,γ) reaction. EPJ Web of Conferences Vol 146, pag 08002, EDP Sciences, 2017. https://doi.org/10.1051/epjconf/201714608002.

[17] V. V. Zerkin and B. Pritychenko, The experimental nuclear reaction data (EXFOR): Extended computer database and Web retrieval system, Nuc. Inst. and Met. in Phy. Res., A 888 (2018) 31-43. https://doi.org/10.1016/j.nima.2018.01.045.

[18] F. Farina Arboccò *et al.*, Experimental determination of k_0, Q_0 factors, effective resonance energies and neutron cross-sections for 37 isotopes of interest in NAA, J. Radioanal. Nucl. Chem., (2014) 302:655–672. http://dx.doi.org/10.1007/s10967-014-3281-0.

[19] F. De Corte and A. Simonits, A compilation of accurately measured 2200 m/s cross-sections for 101 n,gamma reactions of interest in activation analysis; a critical comparison with literature, Conf: Conf. on Nucl. Data For Sci. and Technol., Mito 1988, p.583 (1988), Japan.

[20] R. E. Heft, A consistent set of nuclear-parameter values for absolute instrumental neutron activation, Conf. on Computers in Activ. Anal., Mayaguez 1978, p.495 (1978).

[21] W. H. Walker, The relative abundances and pile neutron capture cross sections of the isotopes of samarium, gadolinium, dysprosium and ytterbium, Thesis: Walker (1956).

[22] J. Alstad, L. Hertzenberg and A. C. Pappas, Thermal neutron capture cross section and resonance integral for lanthanide nuclei II, ^{169}Tm,^{168}Yb, ^{174}Yb and ^{176}Yb, Norwegian rep. to the I.N.D.C., No.1, p.1(2) (1972).

[23] S. F. Mughabghab and R. E. Chrie, Neutron Cross Sections and Resonance Parameters of Yb Isotopes, Phy. Rev. C, Volume 174, Number 4, 20 OCTOBER 1968. https://doi.org/10.1103/PhysRev.174.1400.

[24] H. I. Liou et al., Neutron Resonance Spectroscopy. XI. The Separated Isotopes of Yb, Phys. Rev. C 7, 823, 1 February 1973, https://doi.org/10.1103/PhysRevC.7.823.

[25] D. C. Stupegia, M. Schmidt, C. R. Keedy and A. A. Madson, Neutron capture between 5 keV and 3 MeV, Jour: J. of Nucl. En., Vol.22, p.267 (1968), UK. https://doi.org/10.1016/0022-3107(68)90001-4.

[26] V. S. Shorin, V. N. Kononov and E. D. Poletaev, Cross Sections for Radiative Neutron Capture in the Energy Range 5-80keV for Yb Isotopes, Jour: Soviet J. of Nucl. Phy., Volume 20, p.572 (1975), USA.

[27] M. V. Bokhovko, V. N. Kononov *et al.*, Neutron radiation capture cross-section and transmission of fast neutrons for nuclei of rare-earth elements Ta-181 and Os-187, Rept: Fiz. Energ. Inst., Obninsk Rep., No.2169-91 (1991), Russia.

[28] K.Wisshak *et al.*, Stellar Neutron Capture Cross Sections of the Yb Isotopes, Phy. Rev., C 61 6 p.065801 (2000). https://doi.org/10.1103/PhysRevC.61.065801.

[29] J. Marganiec *et al.*, Stellar (n,γ) cross sections of neutron-rich nuclei: Completing the isotope chains of Yb, Os, Pt, and Hg. Phy. Rev. C 90, p.065801 (2014), USA; http://dx.doi.org/10.1103/PhysRevC.90.065801.

[30] D. A. Brown *et al.*, ENDF/B-VIII.0: The 8th Major Release of the Nuclear Reaction Data Library with CIELO-project Cross Sections, New Standards and Thermal Scattering Data, Nucl. Data Sheets, Volume 148, February 2018, Pages 1-142; https://doi.org/10.1016/j.nds.2018.02.001.

[31] A. J. M. Plompen et al., The joint evaluated fission and fusion nuclear data library, JEFF-3.3, Eur. Phys. J. A (2020) 56:181 https://doi.org/10.1140/epja/s10050-020-00141-9.

[32] S.M. Qaim, F. Tárkányi, R. Capote. IAEA Technical report series (2011), Nuclear data for the production of therapeutic radionuclides. https://inis.iaea.org/search/search.aspx?orig_q=RN:43038210.

[33] P. F. Mastinu *et al.*; New C6D6 detectors: reduced neutron sensitivity and improved safety, (The n_TOF Collaboration), CERN-n TOF-PUB-2013-002 (2013).

[34] U. Abbondanno, G. Aerts *et al.*, New experimental validation of the pulse height weighting technique for capture cross-section measurements, Nuclear Instruments and Methods in Physics Research A 521 (2004) 454–467. https://doi.org/10.1016/j.nima.2003.09.066.

[35] https://www.tracesciences.com/

[36] A. Gawlik, C. Lederer-Woods, *et al.*, Measurement of the ^{70}Ge(n,γ) cross section up to 300 keV at the CERN n_TOF facility, Phy. Rev. C 100, 045804 (2019). https://doi.org/10.1103/PhysRevC.100.045804.