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EVALUATION OF THE PRODUCTION CAPABILITIES OF ^{18}F, ^{11}C, ^{13}N AND ^{15}O PET ISOTOPES AT THE PET-CYCLOTRON-RADIOCHEMISTRY SITE OF MESSINA UNIVERSITY

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ABSTRACT. The production of ^{18}F, ^{11}C, ^{13}N, and ^{15}O positron emitting radionuclides for PET imaging is usually accomplished in Nuclear Medicine Departments through direct nuclear reactions induced by protons accelerated by compact medical cyclotrons on liquid or gaseous targets. Messina University has funded the construction of a PET-cyclotron-radiochemistry plant at the Messina University Hospital, equipped with a 11 MeV self-shielded cyclotron. We estimated the expected production yields of these nuclides, accounting for target thickness, production of other radioactive nuclides, and time effects on the irradiated target purity. To this aim, both TALYS code (v. 1.8) and an analytical approach based on EXFOR experimental data were used. The general agreement between the two approaches, and with the available literature data, allows to assess the expected yields at the End of Bombardment, and relative target purities, to be used for further radiopharmaceutical preparation steps.

1. Introduction

PET imaging is a powerful tool for diagnosis of cancer and monitoring tumor response to therapy. The most used positron emitters are ^{18}F, ^{11}C, ^{13}N, ^{15}O which can be produced with low energy cyclotrons providing yields of medical interest (IAEA 2008, 2009).

The University of Messina has promoted the construction of a PET-cyclotron-radiochemistry plant at the University Hospital *Gaetano Martino* in the framework of the research project entitled *"A model of integrated molecular diagnostics and targeted non-pharmacologic therapy in breast tumours and neuro-oncology"*, funded by the National grant CIPE No. 45602 (PON 2007/2013), under the scientific responsibility of prof. F. Tomasello. The site was equipped by a self-shielded cyclotron (Siemens AG, Germany) accelerating 11 MeV H^- ions on liquid or gaseous targets, to obtain ^{18}F or ^{11}C positron emitting radionuclides to be labeled with different molecules in a radiochemistry laboratory equipped with four hot cells and related syntesis modules. A quality control laboratory and an automatic fractionation system for the preparation of single doses complete the

TABLE 1. Main features of the Siemens Eclipse HP cyclotron

Final energy	11 MeV
Accel. particles	H-
Hill Angle	56 degrees
Hill Gap	1.5 cm
Valley Gap	40 cm (nominal)
Valley/Hill gap	27:1
Pole Diameter	90 cm
Extraction radius	40 cm (11 MeV)
Peak Hill Field	1.9 Tesla
Excitation	51000 Ampere turns
Ion gyro freq.	18 MHz
Cavity res. Freq.	72 MHz
Nom. dee Volt.	30 kV peak
E. gain per turn	140 keV

radiochemistry section of the plant. A state-of-the-art PET-CT tomograph (Philips, The Netherlands) was installed in the diagnostic section.

In this paper we will discuss the evaluation of the yield of the four abovementioned positron emitters that can be achieved with the 11 MeV cyclotron hosted at the PET-cyclotron-radiochemistry site of Messina University. Theoretical evaluations were performed estimating target thickness, production of other radioactive nuclides, time effects on the irradiated target purity. Radioisotope estimated yields were compared with the IAEA (2001) values and a good agreement was observed.

2. Materials and methods

We considered the possibility of producing the following PET radionuclides: ^{18}F, ^{13}N, ^{11}C, ^{15}O by using the 11 MeV cyclotron facility at the University Hospital of Messina. The main features of the Siemens Eclipse HP cyclotron are listed in Table 1. The self-shielded cyclotron is equipped with the dual-beam option, allowing to split the total beam current for the simultaneous irradiation of two targets. Each beam window is equipped with a remotely operable carousel. Each carousel can host up to four targets.

In order to evaluate the theoretical yields for the above radionuclides both TALYS code (v. 1.8) (Koning *et al.* 2005) and an analytical approach based on *Experimental Nuclear Reaction Data (EXFOR)* (2017) were used. TALYS is a code implementing nuclear reaction models to compute excitation functions for many light particle-induced nuclear reactions. It is also used to build up the TALYS-based Evaluated Nuclear Data Library (TENDL) cross section data libraries (Koning and Rochman 2012). In the *medical isotope production* modality, it computes the production yields in homogenous, thick targets for all the reaction channels energetically allowed also for particles with a composite energy spectrum (Amato *et al.* 2016a,b).

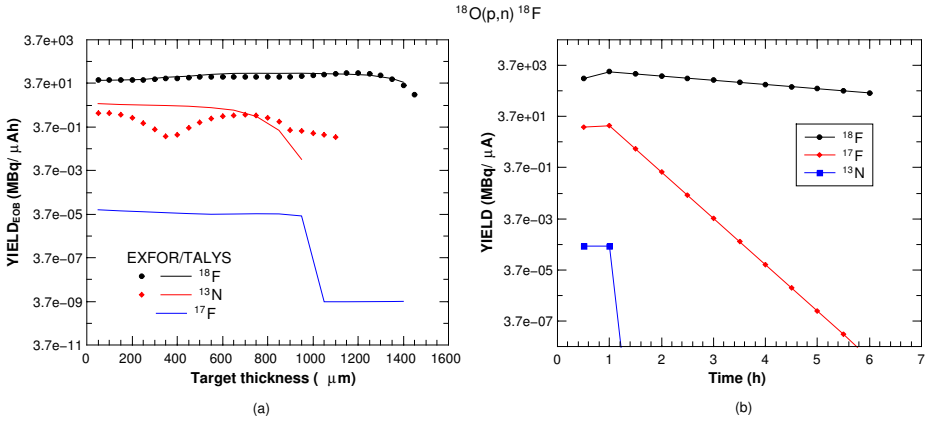

FIGURE 1. ^{18}F Yield vs. (a) thickness and (b) time (EOB set at 1 h)

With the analytical approach, yields (Y) at end of bombardment (EOB) were estimated by means of the following formula:

$$Y_{\mathrm{EOB}} = \frac{\mathcal{N}_A I}{A_T}\left(1-e^{-\lambda t}\right)\int_{E_{th}}^{E_{beam}} \frac{\sigma_T(E)}{S_T(E)}dE \qquad (1)$$

where $\mathcal{N}_A$ is Avogadro's number; I, the proton beam current; A_T, the atomic weight of the target material; λ, the decay constant of the produced isotope; E_{th}, the threshold energy for the reaction channel; E_{beam}, the proton beam energy; $\sigma_T(E)$, the total cross section for the considered reaction channel; $S_T(E)$, the stopping power.

The $S_T(E)$ was computed for each of the four nuclides by carrying out "Monte Carlo N Particle eXtended" (MCNPX) (Pelowitz 2005) simulations of 11 MeV protons interacting with $[^{18}O]H_2O$, H_2O, $[^{14}N]N_2$ and $[^{15}N]N_2$ targets, respectively. $\sigma_T(E)$ was obtained fitting the EXFOR experimental cross section data for the considered reaction channels. Nuclide yields were estimated as a function of target thickness, irradiation and cooling time. The evaluated nuclide yields were then compared with the ones provided by TALYS code. For each nuclear reaction leading to the selected PET radionuclide, contaminant nuclides coming from competing reaction channels were evaluated. The effective radiopharmaceutical yields were also taken into account by a comparison between available data from literature.

3. Results and discussion

3.1. Fluorine-18. For ^{18}F yield evaluation, the ^{18}O(p,n)^{18}F reaction was considered, induced by 11 MeV protons impinging on a 97% enriched $[^{18}O]H_2O$ target. A thick target was employed to estimate the ^{18}F production as a function of the target thickness. As Fig. 1(a) shows, the end-of-production for ^{18}F is reached at 1500 μm, where the proton energy becomes lower than 3.65 MeV, the threshold energy for the above reaction. A fair agreement between TALYS output and EXFOR-based analytical approach was found for ^{18}F.

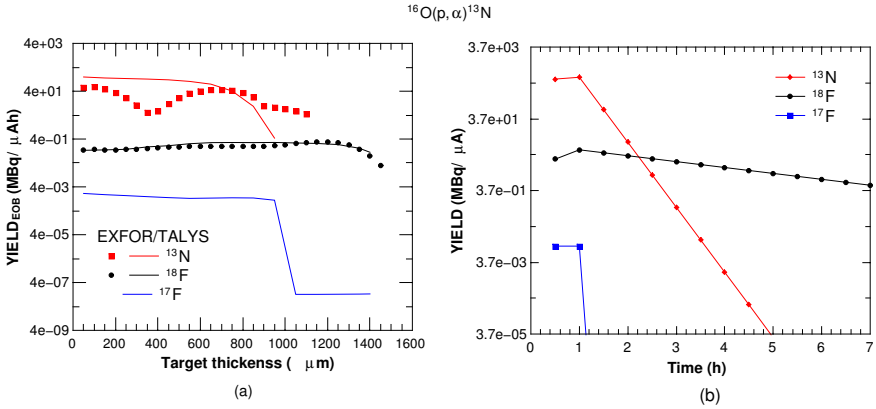

FIGURE 2. ^{13}N Yield vs. (a) thickness and (b) time (EOB set at 1 h)

For 1500 μm target, yields of 2.4E03 and 2.06E03 MBq/μA at EOB of 1 hour were estimated from TALYS code and EXFOR approaches, respectively. Fig. 1(a) reports also the contaminant product yields coming from the ^{16}O(p,α)^{13}N ($E_{threshold} = 5.55$ MeV) and ^{16}O(p,γ)^{17}F competing channels. ^{13}N yield is about two orders of magnitude lower than the ^{18}F one; nevertheless, due to its short half-life (9.96 min), ^{13}N quickly decreases after EOB. For example, after a cooling time of 2 h, yield lowers to about six orders of magnitude less than the ^{18}F one, as shown in Fig. 1(b), where the EOB was set to 1 h. A partial disagreement can be observed in this case because of the existing discrepancies between TENDL-evaluated cross-section and the one obtained from EXFOR experimental data. Negligible concentration of ^{17}F is expected; an estimation was possible only with TALYS code, not being available experimental data in the EXFOR database for the ^{18}O(p,γ)^{17}F reaction; moreover, due to its fast decay ($T_{1/2} = 64.49$ s), it is not relevant as radioactive impurity.

3.2. Nitrogen-13. For ^{13}N yield evaluation, we studied the ^{16}O(p,α)^{13}N reaction, induced by 11 MeV protons impinging on a H_2O target. Yield was estimated as a function of the target thickness, as shown in Fig. 2(a). The end-of-production for ^{13}N is reached at about 1100 μm, where the proton energy lowers to 5.55 MeV, the threshold energy of the ^{16}O(p,α)^{13}N reaction. ^{18}F is produced as a contaminant by proton induced reaction on ^{18}O which occurs with its natural abundance in the H_2O target. It is important to note that for a target thickness larger than 1100 μm the Y(^{18}F) / Y(^{13}N) ratio increases, leading to a larger contamination of the irradiated target by ^{18}F. Moreover, setting a long cooling time the yield of ^{13}N would become comparable to the one of ^{18}F as Fig. 2(b) shows where the EOB was set to 1 h.

Concerning the ^{17}F production, TALYS estimates a yield of about $3.7E-03$ MBq/μA at EOB of 1 h and for a target thickness of 1000 μm. The same considerations hold as before on its fast decay.

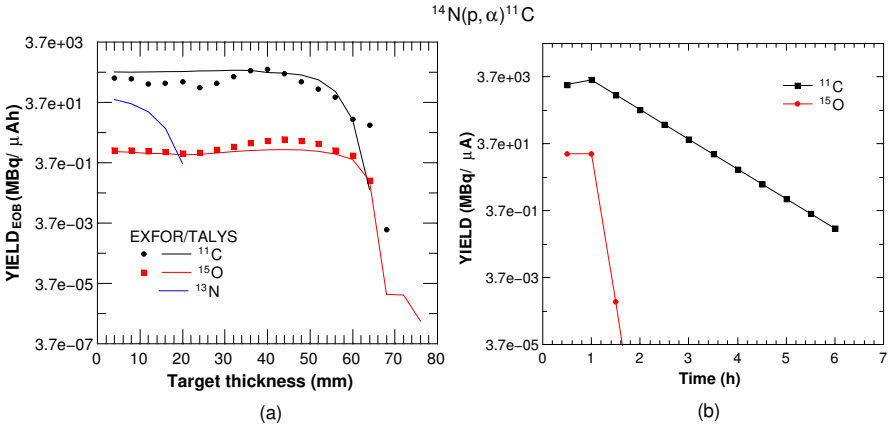

FIGURE 3. ^{11}C Yield vs. (a) thickness and (b) time (EOB set at 1 h)

3.3. Carbon-11. ^{11}C production was estimated considering the ^{14}N(p,α)^{11}C reaction induced on a gaseous [^{14}N]N_2 target at 320-330 psi pressure (Medical Solutions Siemens Healthineers 2011). A yield of the order of $3-4.8$ GBq/μA at EOB of 1 h is expected. In Fig. 3(a) ^{11}C yield is plotted as a function of the depth in the target: beyond 50 mm a negligible contribution to ^{11}C yield is expected. As a matter of fact, the first layers are affected also by production of ^{13}N, due to competing reaction ^{14}N(p,d)^{13}N; nevertheless, such channel is quickly extinguished, both for the high energy threshold ($\sim$ 8.88 MeV) and the short half life of ^{13}N ($t_{1/2} = 9.96$ min).

^{15}O is produced by the competing reaction ^{15}N(p,n)^{15}O induced by protons on ^{15}N present in the target, with its natural abundance of about 4%; ^{15}O yield is about three orders of magnitude lower than the one of ^{11}C and it is produced along all the target thickness. Nevertheless, ^{15}O rapidly decays ($t_{1/2} = 122.24$ s) resulting negligible in the irradiated target, as shown in Fig. 3(b) where the EOB was set to 1 h.

3.4. Oxygen-15. The ^{15}N(p,n)^{15}O reaction was considered for the estimation of ^{15}O production on a gaseous [^{15}N]N_2 target, 96% ^{15}N enriched, at 320-330 psi pressure (Medical Solutions Siemens Healthineers 2011). As already noticed for ^{11}C, also for ^{15}O production the same remarks hold concerning abundances of ^{14}N and ^{15}O, expected that they be exchanged. Estimation of yields of ^{15}O, ^{11}C and ^{13}N are shown in Fig. 4(a). At the EOB of 1 h, a ^{15}O yield of about 2.72 GBq/μA is expected, which is two orders of magnitude larger than ^{11}C yield; however, in one hour it becomes comparable to the yield of ^{11}C.

A comparison between the expected yields at EOB of 1 h of the considered positron emitters is summarized in Table 2, as evaluated by the analytical approach and TALYS, respectively. IAEA estimations for 11 MeV protons are also reported. IAEA evaluations are based on the recommended cross section values tabulated by IAEA (2001) and updated online at the *NDS* (2017) webpage, where the expected activity after 1 h and 1 μA irradiation is reported for different proton energies. A fairly good agreemeent between data obtained in this paper using the analytical approach and the cross sections estimated by fitting the

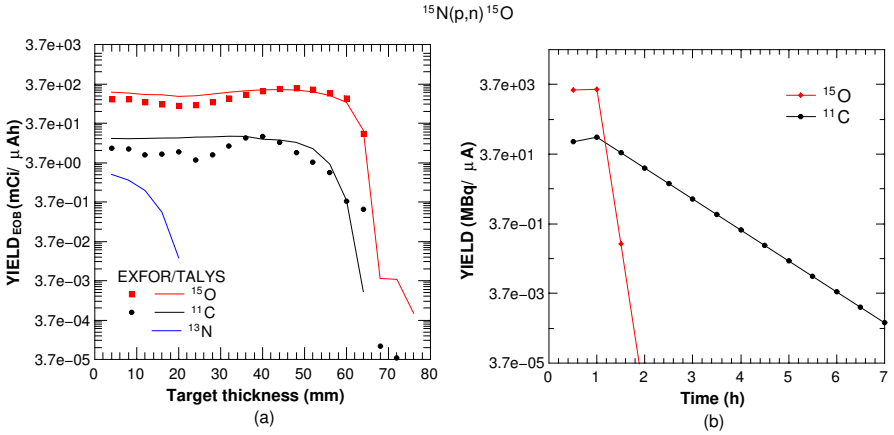

FIGURE 4. ^{15}O Yield vs. (a) thickness and (b) time (EOB set at 1 h)

TABLE 2. Expected yields of ^{18}F, ^{13}N, ^{11}C, and ^{15}O at 1 h EOB

	^{18}F	^{13}N	^{11}C	^{15}O
		GBq/μA		
EXFOR	2.061	0.532	3.020	2.716
TALYS	2.402	1.618	4.884	3.230
IAEA - *NDS* (2017)	2.7	0.57	2.89	2.86
		GBq for $I = 60\,\mu$A		
EXFOR	123.628	31.956	181.213	162.96
TALYS	144.136	97.088	293.040	193.806

experimental data taken from the EXFOR database, and the IAEA estimations can be stated. For ^{13}N, ^{11}C and ^{15}O discrepancies with respect to TALYS calculations arise, mainly due to the differences between TENDL data libraries and experimental data which, in some cases, are significant as shown in Fig. 5.

Finally, it has to be explicitly noticed that data reported in Table 2 refer to theoretical extimations. Our calculations do not take into account some physical/chemical effects occurring during irradiation and/or during the delivery of the irradiated target to the synthesis cells (e.g., changes in the density/thickness of the target material due to thermal effects; adhesion of radioactive ions to the target chamber walls, with consequent reduction in the extracted activity; etc.). All these effects, which are strictly dependent on the experimental setup, can contribute to the reduction of the effective yields with respect to the theoretical estimations.

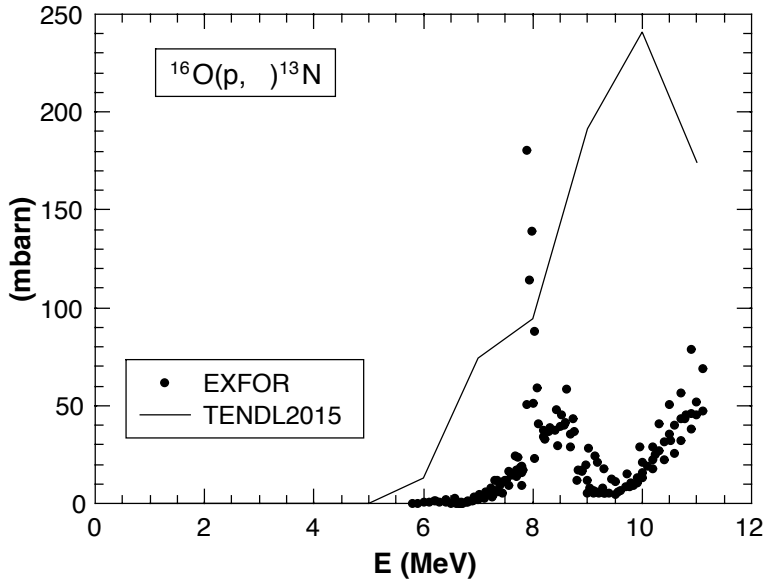

FIGURE 5. Comparison between EXFOR data for the ^{18}O(p,α)^{13}N reaction cross sections and TENDL2015 data

3.5. Radiopharmaceutical yields. After irradiation of the target, and elapsed the proper cooling time, the radiopharmaceutical has to be prepared; a series of chemical and radiopharmaceutical steps have to be accomplished to achieve the final product. The target material is transferred to the radiochemistry section of the laboratory and chemical separation of the radionuclide from the target is carried out. The procedures depend on the physical state of the irradiated target, presence of undesired nuclides, its solubility, recovery of the isotope used for enriching the target, etc. In this meanwhile the radioisotope decays and the effective yield reduces.

When the radioisotope is chemically isolated, the radiopharmaceutical has to be synthesized. Synthesis does not have 100% efficiency and depend on the synthesis modules and procedures employed.

Several data, available in literature, deal with the yields obtained with different modules and procedures, as reported in Table 3 for the most used ^{18}F-, ^{13}N-, ^{11}C-, ^{15}O-labelled radiopharmaceuticals. For example, [^{18}F]-FDG can be produced with yields of $50-60\%$ in about 50 min with radiochemical purity up to 97% using standard procedures (Hamacher *et al.* 1986; Khwaj *et al.* 2014; Toorongian *et al.* 1990; Yu 2006). Nevertheless, the use of most recent synthesizers and innovative methods allows to increase yields to about 70% in 20 min with a radiochemical purity equal to 99.2% (Fang *et al.* 2007; Lemaire *et al.* 2002).

The equipment available at the PET-cyclotron-radiochemistry site of Messina University is capable of producing most of the radiopharmaceuticals cited in Table 3, delivering yields comparable to the ones obtained with the standard procedures.

TABLE 3. Radiopharmaceutical yields (Y), synthesis time (T), radiochemical purity (P) and related references

Radiopharmaceutical	Y (%)	T (min)	P (%)	References
[^{18}F]FDG	$\sim$50	50	$95-97$	(A)
	$\sim$70	20	≥ 99	(B)
[^{18}F]FLT	$38-49$	$50-60$	≥ 97	(C)
[^{18}F]MISO	$30-58.5$	$60-65$	≥ 97	(D)
[^{11}C]Methionine	$41-63$	12	≥ 97	(E)
	≥ 75	12	≥ 99	(F)
[^{11}C]-Acetate	$52-80$	$8-12$	≥ 98	(G)
[^{11}C]-Choline	up to 96.5	$12-25$	≥ 99	(H)
[^{11}C]-PIB	18	38	≥ 97	(I)
	53	40	≥ 99	(J)
[^{13}N]NH_3	$87-91$	10	≥ 99	(K)
[^{15}O]H_20	29	2.5	n.a.	(L)

(A) Yu (2006), Hamacher *et al.* (1986), Toorongian *et al.* (1990), and Khwaj *et al.* (2014)
(B) Fang *et al.* (2007) and Lemaire *et al.* (2002)
(C) Oh *et al.* (2004), Yun *et al.* (2003), and Teng *et al.* (2006)
(D) Chang *et al.* (2007) and Oha *et al.* (2005)
(E) Boschi *et al.* (2009), Cheung and Ho (2009), and Gómez *et al.* (2008)
(F) Gomzina and Kuznetsova (2011) and Pascali *et al.* (1999)
(G) Boschi *et al.* (2009), Cheung and Ho (2009), Le Bars *et al.* (2006), and Roeda *et al.* (2002)
(H) Lodi *et al.* (2012)
(I) Cheung and Ho (2009)
(J) Philippe *et al.* (2011)
(K) Kumar *et al.* (2009)
(L) Powell and O'Neil (2006)

4. Conclusions

In the present work a complete theoretical estimation of the production capabilities of the four main PET isotopes is presented, for which concerns the production site built at the Messina University Hospital, equipped with a Siemens Eclipse HP cyclotron. The agreement between the results obtained by means of the two independent calculation methods allows us to assess the expected yields and to confirm the capability of the plant to produce the isotopes required both for internal use and external distribution of PET radiopharmaceuticals.

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