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Research Article

Evaluation of ^{99}Mo and ^{99m}Tc Productions Based on a High-Performance Cyclotron

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Following preliminary feasibility studies which started at Legnaro National Laboratories (LNL) in 2011, the Italian National Institute for Nuclear Physics (INFN) research activities are underway aiming at the alternative, accelerator-driven, ^{99}Mo / ^{99m}Tc production routes. One of the most promising approaches is to use ^{100}Mo-enriched (i.e., >99%) molybdenum metallic targets, bombarded with high-beam-current, high-energy proton cyclotrons. In order to get a comprehensive map of radionuclides expected, a detailed theoretical investigation has been carried out using the TALYS-TENDL 2012 excitation functions extended up to (p,6n), (p,p5n), and (p,2p4n) levels. A series of quality parameters have thus been calculated both at the end of beam (EOB) and at longer times. Results point out that accelerator-^{99}Mo is of limited interest for a possible massive production because of the quite low specific activity with respect to reactor-^{99}Mo. Accelerator-^{99m}Tc quality parameters (i.e., radionuclidic purity (RNP), isotopic purity (IP), and specific activities) calculated are instead quite close to the generator-Tc. Calculations at 15, 20, and 25 MeV have thus been performed to assess the best operative irradiation condition for ^{99m}Tc production while minimizing both the short-lived and long-lived Tc contaminant radionuclides. Although present in minimum quantities, Tc contaminants may indeed have an impact either on the pharmaceutical labeling procedures or on contributing to patient radiation dose during the diagnostic procedures.

1. Introduction

Nearly 80% of the radioisotopes used in nuclear medicine are currently produced by nuclear reactors. Among them, ^{99m}Tc (6.01 h half-life), a decay product of ^{99}Mo (65.94 h half-life), is the most important and widely used one. However, such a vital radionuclide is mainly supplied by two production facilities only, which cover about 65% of the ^{99}Mo world demand: the research reactor NRU at Chalk River, Ontario (Canada), and the HFR reactor at Petten (The Netherlands). The current ^{99}Mo mass production is indeed based upon the isotope separation from fission products by using the highly enriched uranium, weapons-grade (HEU-WG) material (^{235}U enrichment > 80%). Such a production is therefore subject to the strict international regulations and control actions against the proliferation of nuclear weapons. Both reactors have experienced in recent years (2009-2010) some long-scheduled/unscheduled shutdowns, which caused a temporary shortage of ^{99}Mo/^{99m}Tc radionuclides on the international market in 2010. Such an event has thus pushed new ideas about alternative arrangements, all based on accelerators, as well as making use of nonstrategic materials.

Since the early 1970s, ^{99m}Tc production through accelerator systems was demonstrated feasible, as proposed first by Beaver and Hupf [1], mainly by the ^{100}Mo(p,xn) reaction route. However, both excitation functions and production yields, due to the different Tc isotopes and isomeric states generated, still need to be made clearer. That is because of an unexpected spread in results, obtained over the past 40 years in different experimental campaigns. Results provided in the last 20 years, using nonstandard experimental procedures, and reported in different works [2–13] may give an idea about that and explain why further experimental investigations are demanded.

Moreover, labelling efficiency and biodistribution studies of some interesting radiopharmaceuticals have been recently carried out, using both cyclotron- and generator-produced ^{99m}Tc, as reported by Urbano et al. [14], Guérin et al. [15], and Targholizadeh et al. [16]. Such encouraging results have driven the first study aimed at the assessment of irradiation conditions for accelerator-based Tc production, as discussed by Celler et al. [17]. Based on the excitation functions from theoretical nuclear models, both the ^{99m}Tc production yields and a reduced map for other radioactive and long-lived generated isotopes (considering some simplified assumptions and constraints) have been determined.

In the framework of the (Laboratory of Radionuclides for Medicine) (LARAMED) project, funded by the Istituto Nazionale di Fisica Nucleare (INFN), a possible future supply of a set of radioisotopes in Italy, aimed at both research and medical application purposes, has been taken into account. This project derives from the installation at LNL in the near future of a high-performance cyclotron (proton output energy tunable in the range 35–70 MeV, maximum beam current 500 μA).

Taking into account the wide range of irradiation conditions which will be provided by such an accelerator, a theoretical assessment study has been preliminary carried out for both ^{99}Mo and ^{99m}Tc productions. Assuming a ^{100}Mo-enriched molybdenum metallic target, as currently available on the isotopes and pure materials market, a beam power areal density of 500 W/cm^2 and a beam current up to 500 μA, a series of parameters have been calculated for.

(i) *Optimal Molybdenum Layer Thickness.* Two basic configurations have been taken into account; in option 1, the incident beam energy down to the threshold for the reaction is considered, thus avoiding the useless heating due to the Bragg peak (i.e., thick target configuration). In option 2, a recommended thickness based on the estimation of yield distribution versus beam penetration depth is instead analyzed. In such a way, an optimized radionuclide production (i.e., avoiding the drop-off region because of cross section lowering) is achieved, with the minimum required thickness for the isotope-enriched material (not inherently thick target configuration).

(ii) *Different Proton Energies.* Taking advantage from the cyclotron directly tunable beam output energy, the reference cases at 40 and 70 MeV have been taken into account for ^{99}Mo production. ^{99m}Tc direct production at 15, 20, and 25 MeV has instead been investigated, in order to limit the amount of contaminant isotopes. Supposing, as reference, an energy degrader device made of 3.67 mm carbon layer, beam energy may be shifted from 35 MeV (i.e., the minimum cyclotron output energy) down to 20 MeV. In such a case, an approximate Gaussian energy spread ($\pm 3\sigma$) of about $\pm$1.25 MeV occurs. However, 90% of beam current (i.e., 450 μA) is within an energy window of just $\pm$550 KeV which, through a Wien filter (if necessary), may be driven towards the target station at the accelerator beam exit.

(iii) *Different Irradiation Times.* 12 h, 24 h, and full saturation ($T_{\text{irr}} \sim 21$ d) for ^{99}Mo production, while several short irradiation times up to one half-life (i.e., 1 h, 2 h, 3 h, and 6 h) have been taken into consideration in case of ^{99m}Tc production. Irradiation times longer than $t_{1/2}$ are not convenient from the point of view of either the product final cost or the accumulation of useless longer-lived isotopes.

The isotopic composition of the enriched metallic molybdenum material, taken as reference in this study, is the one provided by the ISOFLEX company [18]: ^{100}Mo (99.05%), ^{98}Mo (0.54%), ^{97}Mo (0.07%), ^{96}Mo (0.11%), ^{95}Mo (0.10%), ^{94}Mo (0.05%), and ^{92}Mo (0.08%). The reaction yields for each Mo isotope have been estimated from the theoretical excitation functions leading to nuclei both in isomeric and ground states. For all nuclides, either directly produced following different reaction routes or generated as a decay product in any of the decay chains, the cumulative yields have been calculated.

Considering the direct ^{99m}Tc production, particular attention must indeed be paid to Tc contaminant radionuclides by reaction routes opened up by all Mo isotopes because of the same chemical species. Although present in rather low quantities, their contributions (except ^{100}Mo) are however not negligible in the overall yield estimation of accelerator-produced Tc. Optimal irradiation conditions (i.e., energy intervals, beam current, and irradiation time) are therefore needed in order to minimize their production. Finally, the long-lived ^{97g}Tc, ^{98}Tc, and ^{99g}Tc, having large cross sections and mean lives longer than 10^5 years, need to be produced in as low quantities as possible, having a direct impact on the specific activity of the final product and thus on the labelling procedures of the radiopharmaceutical preparation. Care has also to be taken of the productions of shorter-lived Tc isotopes (mainly ^{96}Tc) because of their contribution to extra radiation dose. However, such an issue is strictly related to the isotopic material composition made available by the supplier, rather than an optimal combination of irradiation time-beam energy parameters.

2. ^{99}Mo and ^{99m}Tc Production Routes

The ^{99}Mo mass production using the commercial proton-driven accelerators currently available, or next to be put into operation (as the one which will be installed at LNL), is known to be hardly achieved through neutron reaction routes, that is, using either the spallation reactions on heavy target systems or the relatively low energy beams driven by high intensity accelerators on light targets, as argued by Froment et al. [19] and Abbas et al. [20]. The radiative capture reaction (n,γ) on ^{98}Mo-enriched samples would provide ^{99}Mo production with good purity level. However, the resulting specific activities estimated and experimented are too low for a feasible massive production, even if 90% of neutrons are slowed down in the ^{98}Mo resonance energy interval (1–100 eV) [19, 20]. Moreover, exploiting the other possible (n,2n) inelastic scattering reaction on ^{100}Mo-enriched

samples, the limited neutron flux makes the expected ^{99}Mo production level poor. Some works are under way, as reported by Nagai and Hatsukawa [21] and Minato [22], although the approach followed to work out the low ^{99}Mo specific activity is to get the ^{99m}Tc through a thermal-induced sublimation of technetium from the irradiated molybdenum bulk targets.

On the other hand, the ^{235}U(n,f) ^{99}Mo fission reactions, that is, the subcritical version of the standard reactor-based route using accelerator-driven neutron multiplier systems, have also to be considered as long-term solutions because of the lack of information on production yields and economics, as discussed in NEA report [23]. For such reasons, only the proton-induced reactions ^{100}Mo(p,pn) ^{99}Mo and ^{10}Mo(p,2n) ^{99m}Tc are taken into account in the present study, being the best short-term solution to the possible future massive supply. The current cyclotrons have indeed the required beam current to ensure a high production level of these vital isotopes.

2.1. ^{99}Mo Production Route: The (p,pn) Reaction on ^{100}Mo. ^{99}Mo production may derive from two reaction routes: the main (p,pn) reaction and as a decay product of ^{99m}Nb ($t_{1/2} \simeq$ 15 s) and ^{99g}Nb ($t_{1/2} \simeq$ 2.5 m), due to the additional (p,2p) reaction, when operating at proton beam energies above 10 MeV. Figure 1 shows a collection of the ^{100}Mo(p,pn) ^{99}Mo experimental excitation functions measured in the last two decades.

As can be observed, results are consistent up to ≈ 25 MeV, while at higher proton energies an unusual spread (i.e., uncertainty band) up to 100 mb (including error bars extension) may be noted among results obtained in different experimental campaigns. Moreover, even considering 100% of ^{100}Mo-enriched samples, additional reaction routes for the production of different Tc, Mo, and Nb isotopes (including Zr in case of a real ≥99% ^{100}Mo-enriched material) are already opened at proton energies higher than 10–15 MeV. The theoretical excitation functions available from the TENDL 2012 library [24] about the other Mo and Nb isotopes, yielded by other open reaction routes on ^{100}Mo, are shown in Figures 2 and 3, up to the (p,p5n) and (p,2p4n) levels, respectively. When available, experimental measurements are plotted as a benchmark.

Although predictions about the excitation functions for some reaction routes still need to be experimentally validated in the entire energy range, we are aware that a production of these nuclides is indeed energetically feasible. Nb and Tc isotopes expected to be yielded by open reaction routes on ^{100}Mo isotope only, are listed in Table 1 as reference, including decay modes. Similar considerations have been performed for the remaining Mo isotopes included in the enriched molybdenum material as well, in order to determine the whole list of nuclides (both stable and radioactive) generated by open reaction routes. The long-lived radioisotopes created, like ^{95}Nb and ^{96}Nb, ^{95m}Tc, ^{96g}Tc, ^{97}Tc, ^{98}Tc, and ^{99g}Tc, are however not considered to be a concern in the following chemical processing aimed at the preparation of

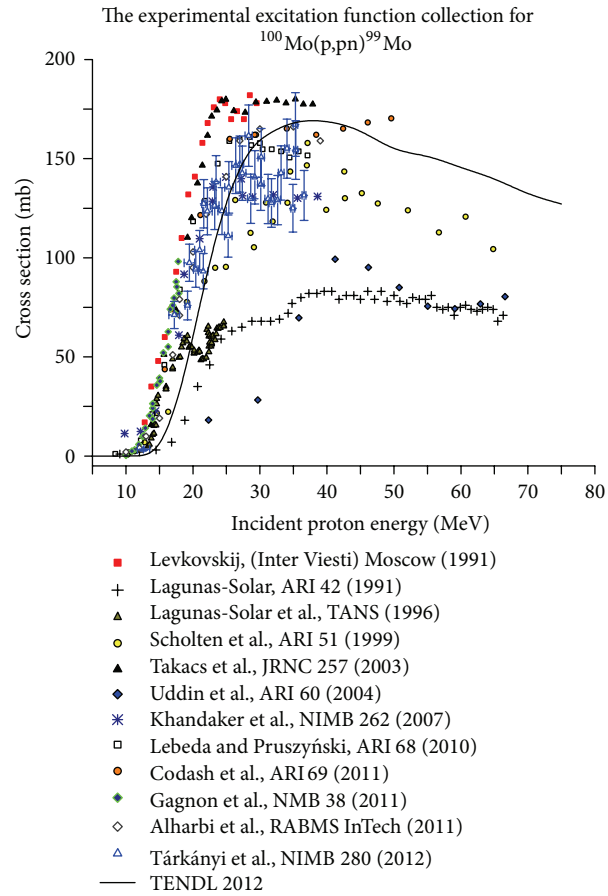

Figure 1: The collection of ^{100}Mo(p,pn)^{99}Mo excitation functions experimentally measured in the last two decades. Error bars are shown for the most recent measurement only performed by Tárkányi (2012) [13]. The most recent theoretical excitation function by the TENDL 2012 library is also shown [24].

^{99}Mo/^{99m}Tc generator. The Nb, Tc, and even Rb elements may indeed be easily chemically separated from Mo for later reuse.

2.2. ^{99m}Tc Production Route: The (p,2n) Reaction on ^{100}Mo. The excitation function ^{100}Mo(p,2n)^{99m}Tc has been repeatedly measured over the past 40 years in different experimental campaigns (part of them shown in Figure 4), proving that within the energy range from 5 up to 70 MeV a single peak is present, centered around 15 MeV and estimated to be about 300 mb by Levkovskij [1] twenty years ago. The measurements repeated later by Scholten [4], Takacs et al. [5], and Khandaker et al. [7] have reduced such a value to about 200 mb. More recent evaluations point out higher peak values, about 250 mb, as reported by Lebeda and Pruszyński [9] and Tárkányi [13], later increased up to 300 mb by Gagnon et al. [12]. Even higher cross section peak values (i.e. >350 mb), originally measured by Lagunas-Solar et al. [11], more recently repeated by Challan et al. [8] are now considered not credible. Analyzing the different works performed, many reasons may be addressed to meet such an unusual spread observed, without a clear trend (i.e., different experimental

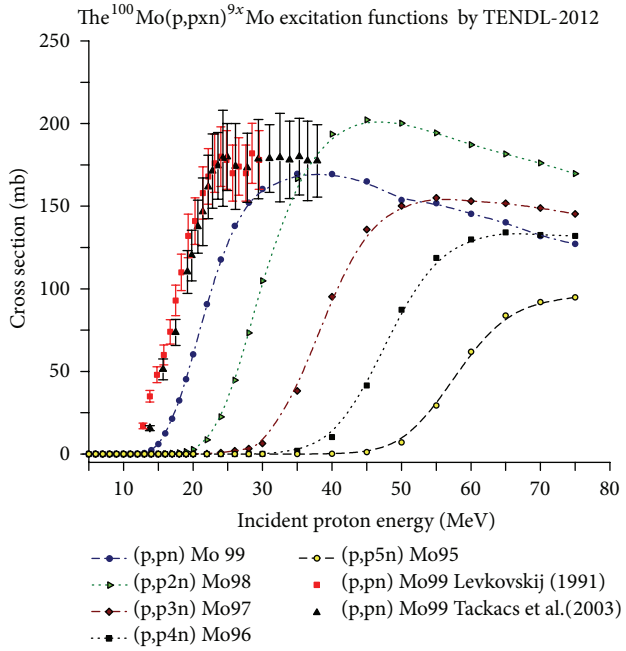

FIGURE 2: The collection of ^{100}Mo(p,pxn)^{9x}Mo theoretical excitation functions from the TENDL 2012 library [24] up to the (p,p5n) level. The experimental measurements of ^{99}Mo by Levkovskij [2] and Takacs et al. [5] only are included for comparison.

TABLE 1: Niobium and technetium isotopes expected to be produced by the ^{100}Mo(p,x) reactions.

Reaction	Product	Decay	$t_{1/2}$	Daughter
p,α2n	^{95}Nb	β^-	34.99 d	^{95}Mo (stable)
p,αn	^{96}Nb	β^-	23.35 h	^{96}Mo (stable)
p,α	^{97}Nb	β^-	72.1 m	^{97}Mo (stable)
p,2pn	^{98}Nb	β^-	2.9 s	^{98}Mo (stable)
p,2p	^{99}Nb	β^-	15 s	^{99}Mo
	^{99m}Nb	β^-	2.6 m	^{99}Mo (96.2%)
		IT		^{99g}Nb (3.8%)
p,6n	^{95m}Tc	EC	61 d	^{95}Mo (96.1%) (stable)
		IT		^{95g}Tc (3.9%)
	^{95g}Tc	EC	20 h	^{95}Mo (stable)
p,5n	^{96m}Tc	EC	51.5 m	^{96}Mo (2.0%) (stable)
		IT		^{96g}Tc (98.0%)
	^{96g}Tc	EC	4.28 d	^{96}Mo (stable)
p,4n	^{97g}Tc	EC	$4.2 \cdot 10^6$ y	^{97}Mo (stable)
	^{97m}Tc	IT	91 d	^{97g}Tc (96.1%)
		EC		^{97}Mo (3.9%) (stable)
p,3n	^{98}Tc	β^-	$4.2 \cdot 10^6$ y	^{98}Ru (stable)
p,2n	^{99m}Tc	IT	6.01 h	^{99g}Tc (99.9963%)
		β^-		^{99}Ru (0.0037%) (stable)
	^{99g}Tc	β^-	$2.1 \cdot 10^5$ y	^{99}Ru (stable)
p,n	^{100}Tc	β^-	15.46 s	^{100}Ru (99.9982%) (stable)
		EC		^{100}Mo (0.0018%) (stable)

set-ups, target material purity, contaminant levels, isotopic compositions, and *ad hoc* procedures followed during sample

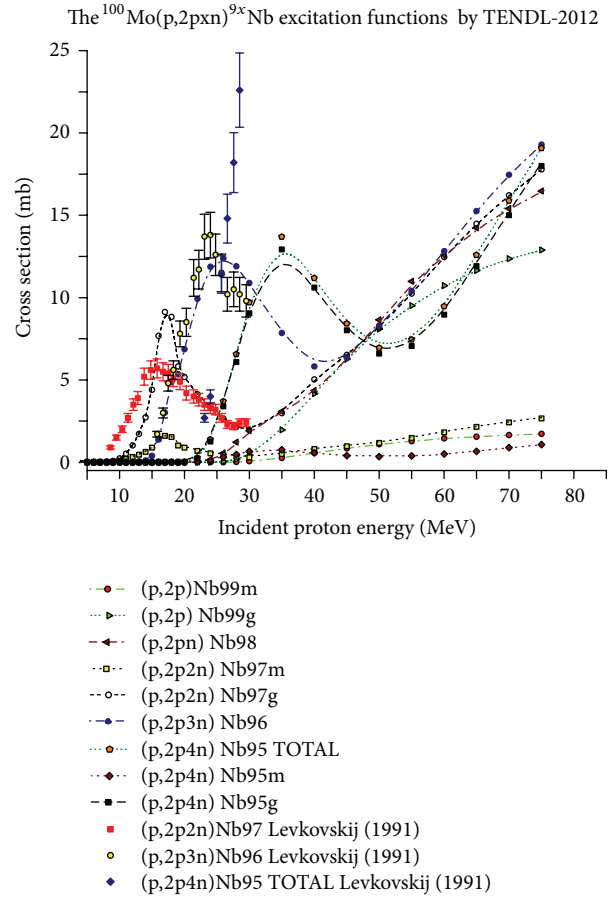

FIGURE 3: The collection of ^{100}Mo(p,2pxn) ^{9x}Nb theoretical excitation functions from the TENDL 2012 library [24] up to the (p,2p4n) level. The available experimental measurements by Levkovskij [2] for $^{95m+g}$Nb, ^{96}Nb, and ^{97}Nb nuclides are included for comparison.

irradiations and detection methods). Moreover, different correction methods are applied in calculating the ^{99m}Tc activity, as deduced by the 140 keV photon peak emissions through gamma spectrometry measurements.

Considering such a production route, particular care has indeed to be taken of the Tc contaminants (see in Table 1 those yielded by ^{100}Mo) since they would remain in the final Tc product. In order to minimize them, irradiation energies at 15, 20, and 25 MeV only have been investigated in this work. In Figure 5, the theoretical excitation functions from the TENDL 2012 library [24], concerning the ^{100}Mo(p,X) reaction routes for additional Tc isotopes production, both in ground and isomeric states, are plotted up to the (p,6n) level. The experimental excitation functions measured for ^{99m}Tc by Takacs et al. [5] and for ^{100}Tc by Skakun [25] are shown for comparison as well. In Figure 5, one can notice that only the long-lived contaminants ^{99g}Tc, ^{98}Tc, and ^{97g}Tc will be produced by ^{100}Mo isotope up to 25 MeV.

Figure 5 also shows the first experimental evaluation of the ^{100}Mo(p,2n) ^{99g}Tc excitation function, performed in the energy range 8–18 MeV and reported by Gagnon et al. [12], from which a general agreement may be found with the

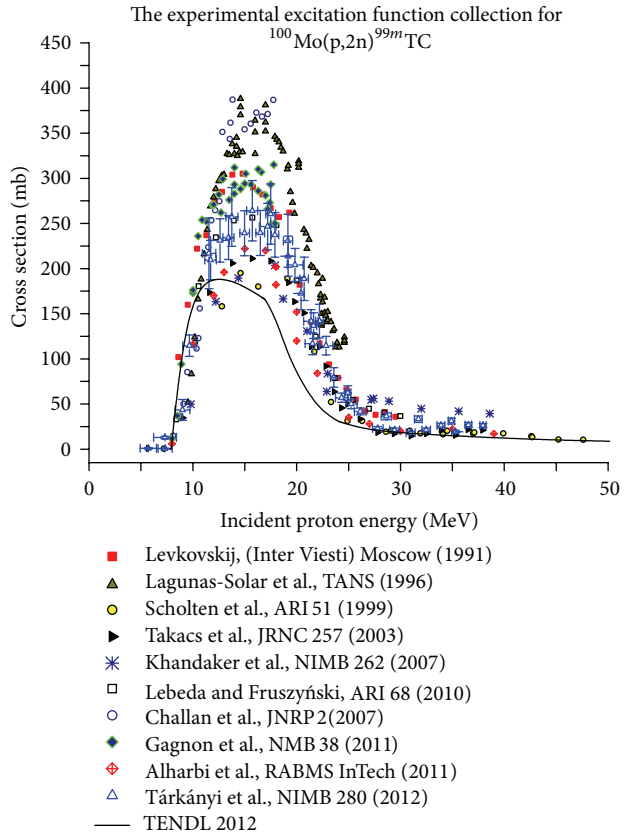

FIGURE 4: The collection of ^{100}Mo(p,2n)^{99m}Tc excitation functions experimentally measured in the last two decades. Error bars are shown for the most recent measurement only performed by Tárkányi (2012) [13]. The most recent theoretical excitation function by the TENDL 2012 library is also shown [24].

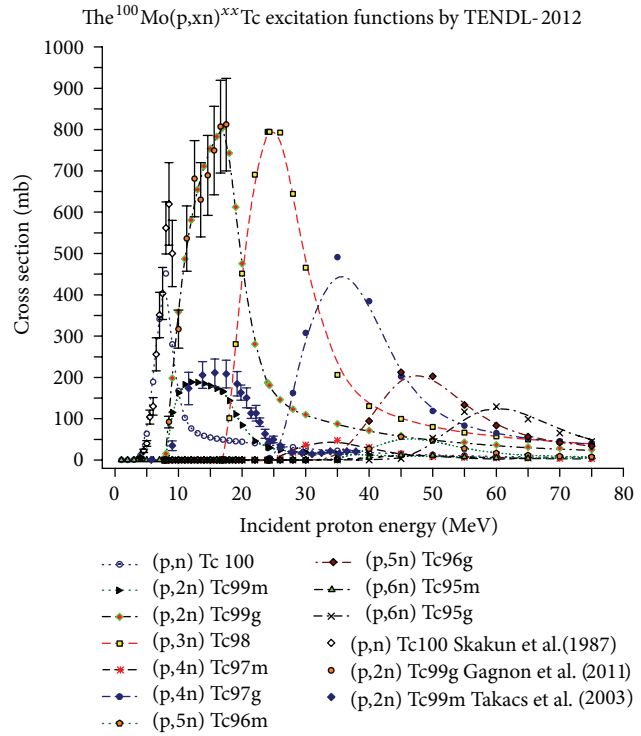

FIGURE 5: The collection of ^{100}Mo(p,pxn)^{xx}Tc theoretical excitation functions from the TENDL 2012 library [24] up to the (p,6n) level. The experimental measurements for ^{99g}Tc (Gagnon et al. [12]), ^{100g}Tc (Skakun et al. [25]), and ^{99m}Tc (Takacs et al. [5]) productions are included for comparison.

theoretical one. Being the largest Tc contaminant produced, further studies and experimental campaigns are however requested, mainly to validate the ^{99g}Tc excitation function in the entire energy range of interest.

Moreover, an additional issue to be assessed is the necessary reuse of the ^{100}Mo-enriched material (quite expensive) in case of direct ^{99m}Tc production. The Mo isotopic composition of the original enriched target material is indeed expected to be modified, if multiple reuse is planned due to economic reasons. In this regard, a preliminary investigation has been carried out on irradiated ^{100}Mo-enriched metal samples, but considering only one recycling stage, as reported by Gagnon et al. [26]. Such a test basically demonstrated the feasibility of molybdenum recovery from the chemical point of view but is however not able to provide a final answer to such a question. The issue about how many times the molybdenum material recovered might be reused, before an impact on the accelerator produced Tc quality becomes critical, still needs to be defined.

3. Materials and Methods

3.1. Decay Chain Calculations. When molybdenum targets are irradiated, some of the reaction routes lead to the production of different radioactive isotopes, thus resulting in different radioactive decay chains. Since the same radionuclide may be created through a number of production-decay routes, all of them must be accounted for when estimating the final number of atoms and activity (relative to radioactive ones) available inside the target. The total number of any atom species present at time t, $N(t)$, and the activity $A(t)$ may be obtained by summing up values from the contributing chains. The general production-decay scheme of a single radioactive chain is therefore the following:

$$
\begin{aligned}
&p+^{xx}\mathrm{Mo} \xrightarrow{R_1} N_1 \xrightarrow{\lambda_1} N_2 \xrightarrow{\lambda_2} \cdots \\
&p+^{xx}\mathrm{Mo} \xrightarrow{R_2} N_2 \xrightarrow{\lambda_2} N_3 \xrightarrow{\lambda_3} \cdots \\
&\vdots \\
&p+^{xx}\mathrm{Mo} \xrightarrow{R_k} N_k \xrightarrow{\lambda_k} N_{k+1} \xrightarrow{\lambda_{k+1}} \cdots \\
&\vdots \\
&p+^{xx}\mathrm{Mo} \xrightarrow{R_{n-1}} N_{n-1} \xrightarrow{\lambda_{n-1}} N_n \\
&p+^{xx}\mathrm{Mo} \xrightarrow{R_n} N_n,
\end{aligned}
\tag{1}
$$

where N_k are the number of radioactive products of a given chain, λ_k is the corresponding decay constants, N_n is the number of the last (stable) nuclide, and R_k is the yield rate for the formation of the first nuclide of each chain directly produced. Since the (p,X) cross sections are relatively low (hundred mb as order of magnitude), only nuclear reactions on target nuclei were considered in calculations. Any secondary reaction that may occur at each level of the newly produced isotopes has been ignored. Likewise, the change in the number of target nuclei during the irradiation process has been considered negligible (i.e., R_k are time constants).

For each decay chain, the variation in the number of nuclei versus time is described by the general set of differential equations. In case of more than one decay mode of a given radionuclide, every branch of the chain has been considered as a different, independent chain according to the branching ratio f_k. Consider

$$\begin{aligned}
\frac{dN_1}{dt} &= R_1 - \lambda_1 N_1, \\
\frac{dN_2}{dt} &= R_2 + f_1\lambda_1 N_1 - \lambda_2 N_2, \\
&\vdots \\
\frac{dN_k}{dt} &= R_k + f_{k-1}\lambda_{k-1} N_{k-1} - \lambda_k N_k, \\
&\vdots \\
\frac{dN_n}{dt} &= R_n + f_{n-1}\lambda_{n-1} N_{n-1}
\end{aligned} \tag{2}$$

with boundary conditions for each equation given by

$$N_k(t=0) = N_k^0. \tag{3}$$

Such initial conditions are the most general possible, since at starting irradiation time $t = 0$, a certain amount N_k^0 of each (radioactive) nuclide species might be present inside the target material (i.e., in case of multiple reuse of target material). During calculation runs, however, all initial amounts for radioactive species have been set to zero, since only stable molybdenum isotopes were supposed to be included inside the target material, and a unique irradiation run was considered.

In the first one of (2), N_1 is the number of nuclei of a given species yielded as a result of the nuclear reaction. If such a nuclide species is radioactive, the number of nuclei available at any time t is thus a balance between the production rate R_1 and the radioactive decay with constant λ_1. The solution for N_1 can be easily obtained by multiplying both sides of the equation by $e^{\lambda_1 t}$ and then integrating the following

$$\begin{aligned}
\int_{N_1^0}^{N_1(t)e^{\lambda_1 t}} d\left(N_1\left(t'\right)e^{\lambda_1 t'}\right) &= \int_0^t R_1 e^{\lambda_1 t'} dt', \\
N_1(t)\,e^{\lambda_1 t} - N_1^0 &= \frac{R_1}{\lambda_1}\left[e^{\lambda_1 t} - 1\right]
\end{aligned} \tag{4}$$

which leads to

$$N_1(t) = N_1^0 e^{-\lambda_1 t} + \frac{R_1}{\lambda_1}\left[1 - e^{-\lambda_1 t}\right]. \tag{5}$$

On the other hand, if the N_1 nuclei are stable, then $N_1(t)$ increases linearly with time and is given by

$$N_1(t) = N_1^0 + R_1 t. \tag{6}$$

Likewise, the remaining equations may be analytically solved by direct integration, once the solution for the previous nuclide of the chain has been determined. Consider the following for the generic N_k and N_n nuclides.

$$\begin{aligned}
&\int_{N_k^0}^{N_k(t)e^{\lambda_k t}} d\left(N_k\left(t'\right)e^{\lambda_k t'}\right) \\
&\quad = \int_0^t \left(R_k e^{\lambda_k t'} + f_{k-1}\lambda_{k-1} N_{k-1}\left(t'\right)e^{\lambda_k t'}\right) dt', \\
&\int_{N_n^0}^{N_n(t)} d\left(N_n\left(t'\right)\right) \\
&\quad = \int_0^t \left(R_n + f_{n-1}\lambda_{n-1} N_{n-1}\left(t'\right)\right) dt'.
\end{aligned} \tag{7}$$

After analyzing both stable and unstable solutions for decay chains as long as 6 elements, two general and compact solutions have been obtained, which represent the number of nuclei of, respectively, the unstable N_k and the stable N_n elements of a given decay chains. Consider

$$\begin{aligned}
N_k(t) = \sum_{i=1}^{k} \Bigg\{ & N_i^0 \cdot \prod_{l=i}^{k-1}(f_l\lambda_l) \cdot \sum_{j=i}^{k} \left[\frac{e^{-\lambda_j t}}{\prod_{\substack{m=i \\ m\neq j}}^{k}\left(\lambda_m - \lambda_j\right)} \right] \\
& + \frac{R_i}{\lambda_k}\prod_{l=i}^{k-1}(f_l) \\
& \cdot \left[1 - \sum_{j=i}^{k} \left[e^{-\lambda_j t} \cdot \prod_{\substack{m=i \\ m\neq j}}^{k}\left(\lambda_m - \lambda_j\right) \right] \right] \Bigg\}, \\
N_n(t) = \sum_{i=1}^{n} \Bigg\{ & N_i^0 \cdot \prod_{l=i}^{n-1}(f_l) \\
& \cdot \left[1 - \sum_{j=i}^{n-1} \left[e^{-\lambda_j t} \cdot \prod_{\substack{m=i \\ m\neq j}}^{n-1}\left(\frac{\lambda_m}{\lambda_m - \lambda_j}\right) \right] \right] \\
& + R_i \prod_{l=i}^{n-1}(f_l) \\
& \cdot \left[t - \sum_{j=i}^{n-1} \left[\frac{\left(1 - e^{-\lambda_j t}\right)}{\lambda_j} \cdot \prod_{\substack{m=i \\ m\neq j}}^{n-1}\left(\frac{\lambda_m}{\lambda_m - \lambda_j}\right) \right] \right] \Bigg\}.
\end{aligned} \tag{8}$$

The estimation of every nuclide produced by any decay chain has been thus calculated at any given irradiation time. For each decay chain, the nuclide number $N_k(t)$ and the related radioactivity $A_k(t)$ have been calculated, adding up the different contributions to a given nuclide species. Once the irradiation time is over (t = EOB), the nuclide yields by nuclear reactions stop, while the decays still continue. All R_k for each decay chain are therefore set to zero, and the same set of equations may be solved to calculate both the nuclide number and activity change against the decay time t_D = EOB + t.

3.2. The Estimations of ^{99}Mo and ^{99m}Tc Yields Expected inside Irradiated Samples. As a starting approach, the ^{99}Mo production level expected at EOB on ^{100}Mo-enriched molybdenum metallic targets has been estimated at 40 MeV and 70 MeV proton energies, while for the direct ^{99m}Tc production 15, 20, and 25 MeV have been instead considered. In both cases, the maximum of 500 μA beam current has been assumed as a reference. Yields expected at different beam currents anyway may be easily inferred through simple scaling calculations.

For the thick-target configuration, the required thickness for the molybdenum material has to be primarily assessed both at the minimum and the maximum proton energies, in order to limit the amount of ^{100}Mo and, consequently, the material cost. This can be done assuming, as a starting step, that the proton beam hits the molybdenum sample in normal direction and using tabulated data on stopping power values and projected ranges calculated by SRIM 2012 code [27] or taken by the PSTAR database of the National Institute for Standards and Technology (NIST) website (NIST-STAR database [28]). The estimated metallic molybdenum thickness to fully stop 70 MeV protons turns out to be about 7.1 mm, while 2.6 mm is instead needed when using 40 MeV protons. When the incident energy optimized for ^{99m}Tc production is instead considered 0.48 mm, 0.78 mm, and 1.1 mm are enough to fully stop 15, 20, and 25 MeV proton beams, respectively.

Such penetration thicknesses for protons are actually needed also in other irradiation conditions (tilted targets). The proton energy loss per unit path, as well as the corresponding energy drop off versus penetration depth, has been calculated. Since the sample thickness T_0 required to fully stop the beam is much lower than the maximum linear size (radius) of the target material in the hypotheses of cylindrical configuration, an analytical calculation approach, based on a slab geometry model, may be used in such a case with good approximation (see Figure 6).

The estimation of local yield contribution dY_i, that is, the nuclide species i produced inside the given infinitesimal thickness dt at depth t of the target material, is described by the following equation:

$$dY_i = n_{\mathrm{Mo}} \cdot \sigma_i \left(E_0 - \int_0^t \frac{dE}{dx} dx \right) \cdot \frac{I_0}{Q} \left(\prod e^{-n_{\mathrm{Mo}} \sigma_R (E_0 - \int_0^x (dE/dx')dx')dx} \right)_t \cdot dt, \quad (9)$$

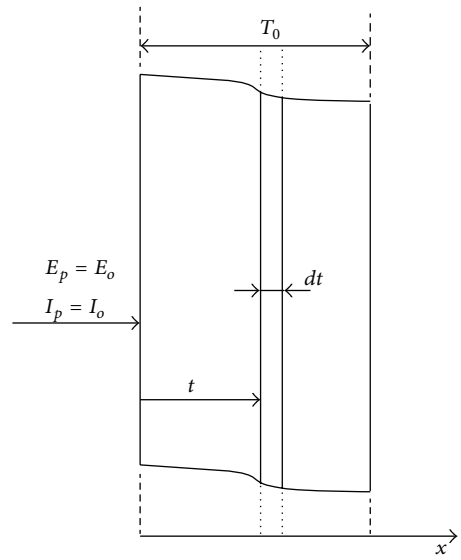

Figure 6: The main parameters in the slab approximation geometry for the calculation of yield distributions inside molybdenum sample thickness.

where n_{Mo} is the atomic density of the enriched molybdenum target material (i.e., $n_{\mathrm{Mo}} = \rho_t f_x (N_A / M_{\mathrm{mol}})$) with ρ_t the target density, f_x the weight fraction of the ^{9x}Mo isotope considered, N_A the Avogadro number, and M_{mol} the molar mass of the target. Then, $\sigma_i(E(t))$ is the ^{9x}Mo(p,x) cross section for the production of the given nuclide species, as a function of the proton energy E at each thickness t (estimated by an iterative calculation process once known the proton stopping power dE/dx and the incident proton energy E_0). The proton beam current I_0 divided by the electric charge unit Q is the n_p number of protons per unit time, hitting the target ($n_p = I_0/Q$).

The product expression within brackets is the fraction of incident protons, available at the generic depth t inside the sample, because of the contribution of the exponential attenuations in any single infinitesimal slab. The removal cross section $\sigma_R(E(t))$ takes into account all the reaction routes that remove protons from the main stream.

The resulting contribution of the exponential, for each infinitesimal thickness inside samples, however turns out to be basically constant and quite close to unity, mainly because of the order of magnitude of the cross section involved (i.e., 10–100 mb). Expression (9) may therefore be simplified to a very good approximation in the next one. The overall nuclide production dY_i, normalized for incident proton, is obtained by integrating (9) over the whole target thickness T_0 and dividing by n_p as follows:

$$\frac{Y_i}{n_p} = n_{\mathrm{Mo}} \cdot \int_0^{T_0} \sigma \left(E_0 - \int_0^t \frac{dE}{dx} dx \right) dt. \quad (10)$$

Equation (10) was used for later calculations of the in-target production of any Mo, Nb, Zr and Tc nuclides. The theoretical excitation functions for the reaction routes of interest, involving up to 6 emitted particles (i.e., protons

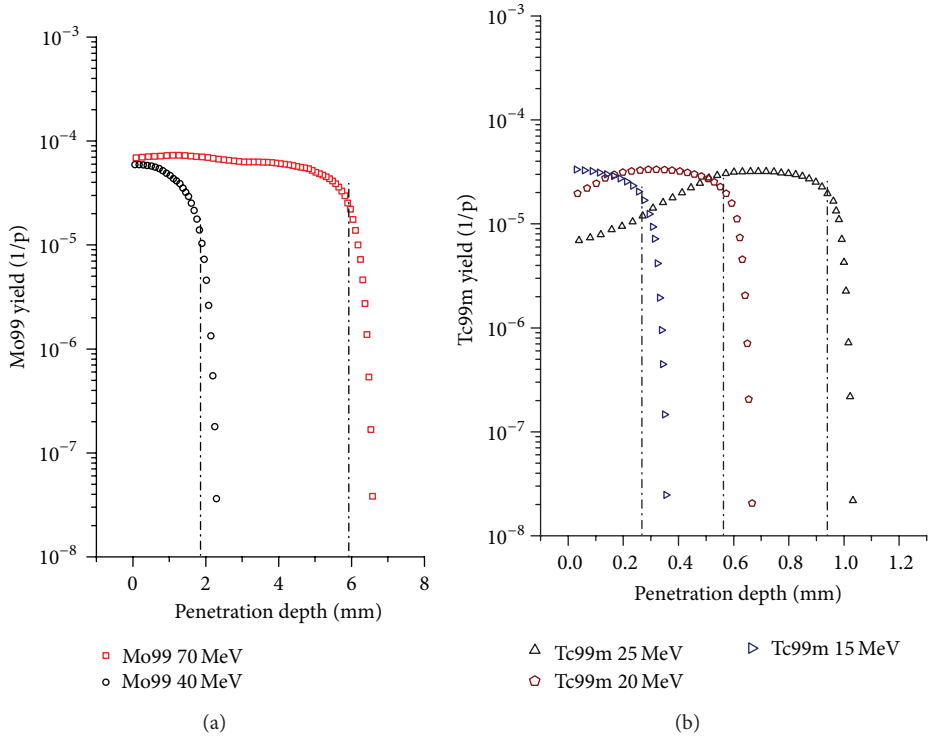

FIGURE 7: The distributions of the nuclide yields, normalized per incident proton, versus penetration depth, calculated inside 99.05% ^{100}Mo-enriched samples: (a) 70 MeV and 40 MeV are considered for ^{99}Mo production; (b) the same plot for 15, 20, and 25 MeV beam, in case of direct ^{99m}Tc production. The eye-guide vertical lines show the recommended sample thicknesses to get an optimized production.

and/or neutrons), have been taken into account as provided by the TENDL 2012 library and available as output by TALYS code. The excitation functions for both isomeric and ground states may therefore be calculated taking into account a complete set of nuclear models developed (i.e., optical model, direct reactions, compound reactions, etc.). Further information may be found in [24].

4. Results and Discussion

^{99}Mo and ^{99m}Tc yields versus sample thicknesses calculated, normalized per incident proton, are plotted in Figure 7 for the energies concerned. As can be noticed, values are within one order of tenth, up to the point where the yield drop off starts down to the corresponding energy threshold for the reaction (i.e., energy exit without the useless heat power deposition corresponding to the Bragg peak). Figure 7 also shows the recommended thicknesses for an optimized production, saving the target material.

In Table 2, the isotope productions expected by both thick and optimized target thicknesses, normalized per incident proton, are reported for the selected proton energies. As can be seen, the accelerator production of ^{99}Mo is interesting at energies larger than 40 MeV, in order to operate in the most useful energy range for the the excitation function (see Figure 2).

As for the direct ^{99m}Tc production, the quality parameters (i.e., the ^{99m}Tc / $^{(99m+g)}$Tc and the ^{99m}Tc/$\sum$ ^{xx}Tc nuclei ratios) have been calculated and listed. Such parameters, which directly relate the ^{99m}Tc production quality expected to the proton beam energy selected, have to be as high as possible. Almost all of the Tc nuclides directly yielded at 15 MeV, caused by ^{99m}Tc and ^{99g}Tc mainly, with a contribution of about 10% from the short-lived ^{100}Tc, are shown in Table 2, in case of the optimized target configuration. At 20 and 25 MeV, significant contributions are instead from other Tc contaminants (i.e., mainly from ^{98}Tc, $^{(97m+g)}$Tc $^{(96m+g)}$Tc, and at lesser extent by $^{(95m+g)}$Tc $^{(99m+g)}$Tc) produced by the reaction routes due to the other Mo target isotopes, which basically cause a decrease of the ^{99m}Tc /$\sum$ ^{xx}Tc ratio. The contribution from Tc nuclides other than $^{(99m+g)}$Tc, compared with ^{99m}Tc, indeed increases to about 17% and 37%, respectively.

On the basis of these considerations, it may be inferred that the best irradiation energy which should be considered for the accelerator ^{99m}Tc production is 15 MeV. However, the ^{99m}Tc production rate is about 2.0 times lower at this energy than expected at 20 MeV. A weighted balance, between the ^{99m}Tc yield ratio and production yield expected, is therefore needed at such an energy range. The production at 25 MeV should instead be avoided because of the low ^{99m}Tc /$\sum$ ^{xx}Tc ratio (basically the half with respect to 15 MeV) which is available just from direct reactions only. It has anyway to be kept in mind that once produced, the compositions of different Tc nuclides are continuously modified by the decay

Table 2: The integral production yields (normalized per incident proton) estimated on ^{100}Mo-enriched sample thicknesses both for ^{99}Mo and ^{99m}Tc productions. Additional production quality parameters for ^{99m}Tc are listed as well.

Proton energy	Target for ^{99}Mo (mm)	Target for ^{99m}Tc (mm)	^{99}Mo/p (adu)	^{99m}Tc/p (adu)	^{99m}Tc/$^{99m+g}$Tc yield ratio	^{99m}Tc/all Tc yield ratio
70 MeV	Optimized 5.93	/	$5.52 \cdot 10^{-3}$	/	/	/
	Thick 6.74	/	$5.67 \cdot 10^{-3}$	/	/	/
40 MeV	Optimized 1.82	/	$1.66 \cdot 10^{-3}$	/	/	/
	Thick 2.47	/	$1.72 \cdot 10^{-3}$	/	/	/
25 MeV	Optimized 0.66	0.94	$2.75 \cdot 10^{-4}$	$6.70 \cdot 10^{-4}$	0.187	0.117
	Thick 1.00	1.04	$2.78 \cdot 10^{-4}$	$7.03 \cdot 10^{-4}$	0.191	0.115
20 MeV	Optimized 0.46	0.57	$5.83 \cdot 10^{-5}$	$5.65 \cdot 10^{-4}$	0.198	0.170
	Thick 0.63	0.65	$5.83 \cdot 10^{-5}$	$5.97 \cdot 10^{-4}$	0.203	0.161
15 MeV	Optimized 0.14	0.26	$1.95 \cdot 10^{-6}$	$2.84 \cdot 10^{-4}$	0.235	0.211
	Thick 0.33	0.35	$1.99 \cdot 10^{-6}$	$3.23 \cdot 10^{-4}$	0.244	0.185

Table 3: The ^{99}Mo production yields expected at EOB for different irradiation conditions, based on 99.05% ^{100}Mo-enriched metallic molybdenum (thick and optimized target configurations), 500 μA proton current, and 500 W/cm^2 mean areal power density on target.

^{99}Mo production	E_P = 70 MeV		E_P = 40 MeV	
Beam power on target (kW)	35		20	
Target configuration	Thick	Optimized	Thick	Optimized
Beam power deposited in target (kW)	31.1	24.1	16.1	10.1
Irradiation time: 12 h				
Integral yield (mCi/μA)	119.5	116.5	34.7	34.5
In-target activity (Ci)	59.7	58.3	17.4	17.3
Specific activity (mCi/g)	119.8	136.5	159.5	205.2
Irradiation time: 24 h				
Integral yield (mCi/μA)	224.8	219.2	65.4	65.1
In-target activity (Ci)	112.4	109.6	32.7	32.6
Specific activity (mCi/g)	225.4	256.9	300.0	386.0
Saturation: ≈21 d				
Integral yield (mCi/μA)	1003.3	978.3	291.9	290.5
In-target activity (Ci)	501.6	489.2	145.9	145.3
Specific activity (mCi/g)	1011.4	1152.3	1345.4	1731.1

chain contributions during the irradiation time, up to the EOB and for times longer, as discussed later in a more detailed way. In other words, the yield ratio numbers listed in Table 2 are the upper values for the isotopic purity (IP) parameter that may be achieved in the theoretical approach concerned.

Table 3 reports the ^{99}Mo in-target yields estimated at EOB for different irradiation conditions, taking into account the contribution from the decay of parent nuclides $^{(99m+g)}$Nb. The proton beam spot size and energy, resulting from the mean areal power density, uniquely defines the size and mass of the requested samples (thick or optimized), thus allowing to estimate the specific activity as well.

Table 4 reports the ^{99m}Tc production yields estimated at EOB at 15 and 20 MeV for the optimized sample configuration at the irradiation times as long as $t_{1/2}$ (1 h, 2 h, 3 h, and 6 h). The ^{99m}Tc specific activity (in isotopic carrier condition) is estimated as well. Moreover, all technetium radionuclides, as well as ^{99m}Tc activity, versus activities of all radioactive species, are calculated. The specific activity, the radionuclidic purity (i.e., $\mathrm{RNP}(t) = A(t)_{^{99m}\mathrm{Tc}} / \sum A(t)_{^{xx}\mathrm{Tc}}$), and the isotopic purity (i.e., $\mathrm{IP}(t) = N(t)_{^{99m}\mathrm{Tc}} / \sum N(t)_{^{xx}\mathrm{Tc}}$) expected at EOB are also listed, taking into account the contributions from all the radioactive chains available.

As may be observed, almost all of the in-target radioactivity produced at EOB is due to Tc radioisotopes (i.e., about 98% at 15 MeV and 95% at 20 MeV, resp.). The ^{99m}Tc radionuclidic purity (RNP) is however relatively low (around 20–30%), even considering the best irradiation combination (e.g., 15 MeV proton beam and the short irradiation times in order to get the highest IP). The reason for that is basically the contribution of the quite short-lived ^{100}Tc, the presence of which may not be avoided. At both energies considered, the ^{100}Tc activity contribution ranges from 5 times larger to values almost equal to that provided by ^{99m}Tc, at increasing irradiation times.

Table 4: The ^{99m}Tc production yields estimated at EOB for different irradiation times at 15 and 20 MeV proton beams on 99.05% ^{100}Mo-enriched metallic molybdenum and optimized target configuration. 500 μA proton current and 500 W/cm^2 mean areal power density are considered on target. A series of production quality parameters are calculated and listed (see body text).

^{99m}Tc production	E_P = 15 MeV			
Beam power on target (kW)	7.5			
Beam power deposited inside Mo sample (kW)	1.41			
Irradiation time	1 h	2 h	3 h	6 h
Integral yield (mCi/μA)	5.32	10.05	14.28	24.38
In-target activity (Ci)	2.66	5.03	7.14	12.2
Specific activity (Ci/g)	$1.16 \cdot 10^6$	$1.10 \cdot 10^6$	$1.04 \cdot 10^6$	$8.86 \cdot 10^5$
Tc/Total activity	0.9877	0.9853	0.9848	0.9861
^{99m}Tc/Total activity	0.1809	0.2929	0.3693	0.4984
^{99m}Tc/$^{99m+g}$Tc	0.2224	0.2103	0.1990	0.1699
Isotopic purity (IP)	0.2200	0.2081	0.1970	0.1682
Radionuclidic purity (RNP)	0.1831	0.2973	0.3750	0.5055
^{99m}Tc production	E_P = 20 MeV			
Beam power on target (kW)	10.0			
Beam power deposited inside Mo sample (kW)	3.95			
Irradiation time	1 h	2 h	3 h	6 h
Integral yield (mCi/μA)	10.35	19.58	27.81	47.56
In-target activity (Ci)	5.17	9.79	13.90	23.78
Specific Activity (Ci/g)	$8.96 \cdot 10^5$	$8.47 \cdot 10^5$	$8.01 \cdot 10^5$	$6.84 \cdot 10^5$
Tc/Total activity	0.9573	0.9488	0.9468	0.9491
^{99m}Tc/Total activity	0.2006	0.3162	0.3926	0.5190
^{99m}Tc/$^{99m+g}$Tc	0.1862	0.1760	0.1665	0.1420
Isotopic purity (IP)	0.1698	0.1606	0.1520	0.1297
Radionuclidic purity (RNP)	0.2095	0.3333	0.4147	0.5468

As a reference, in Table 5, the calculated integral yields (mCi/μA) at 3 and 6 hours irradiation, from all of the Tc radioactive products expected at EOB inside the thin target configuration, are listed at the three bombarding energies of 15, 20, and 25 MeV.

Based on all the calculations performed, the resulting ^{99}Mo activity expected after 24 h irradiation inside sample at EOB is 109.6 Ci, considering an optimized target configuration under 70 MeV beam, while the specific activity is being 256.9 mCi/g. When 40 MeV protons are instead taken into account, 32.6 Ci activity is estimated at EOB, with a specific activity increase to 386.0 mCi/g.

Although these in-target ^{99}Mo activity levels seem to be enough to cover a regional demand, it should be however noted that the resulting specific activities are a factor of 10^4 lower than the one present inside the current Mo/Tc generators, achieving levels of about 10^4 Ci/g. If the current industrial method for Mo/Tc generator manufacturing has to be maintained, the accelerator ^{99}Mo production is therefore not a favourable option of practical interest, considering the high cost of the target material, the very large alumina column needed, and the resulting large elution volumes, as discussed by Morley et al. [29].

When the ^{99m}Tc direct production is instead taken into account in the range 15–25 MeV, the estimation of the resulting specific activity (see Table 4) is similar to the one provided by the current Mo/Tc generators, which turns out to be about $1.5 \cdot 10^6$ Ci/g at any standard 24 h elution. Table 5 shows that the major contribution to the Tc-produced activity at EOB is from the short-lived ^{100}Tc and the production energy range of which is only partly included in the optimized target configuration. Although the exit proton energy, at the indicated target thicknesses reported in Table 2, turns out to be around 9.6 MeV, its production may not be avoided. Because of the quite short mean life, ^{100}Tc does not play a disturbing role in the final Tc contaminants. Just a few minutes after EOB, the ^{100}Tc activity indeed drops off, transmuting in the stable ^{100}Ru which may be later separated in the chemical process of the target dissolution. The contributions from other main Tc contaminants to the overall Tc activity which, instead, remain in the final Tc solution are, in order of decreasing activity (reference case at 20 MeV protons and 3 hrs irradiation), ^{96m}Tc, ^{94g}Tc, ^{92}Tc, ^{94m}Tc, ^{93g}Tc, ^{95g}Tc, ^{93m}Tc and ^{96g}Tc. On the other hand, the activity contribution from the long-lived ^{99g}Tc, ^{98}Tc, and ^{97g}Tc, which are produced in larger amounts because of the highest values of the excitation functions, is minimal and therefore irrelevant for dosimetry considerations. Nevertheless, their impact on the ^{99m}Tc isotopic purity level is not negligible and may affect the radiochemical quality of the accelerator-Tc labelled pharmaceuticals.

Table 5: The calculated integral yields (mCi/μA) at EOB after 3 and 6 hours irradiations for the expected Tc radioactive species inside the target. 99.05% ^{100}Mo-enriched metallic molybdenum in the optimized target configuration irradiated at 15, 20, and 25 MeV is considered. The whole list of all Mo, Nb, and Zr radioactive yields is not reported here for the sake of brevity.

Product	$t_{1/2}$	3 h irradiation			6 h irradiation		
		15 MeV	20 MeV	25 MeV	15 MeV	20 MeV	25 MeV
^{100}Tc	15.46 s	$2.357E+01$	$3.871E+01$	$5.427E+01$	$2.357E+01$	$3.871E+01$	$5.427E+01$
^{99m}Tc	6.01 h	$1.428E+01$	$2.781E+01$	$3.321E+01$	$2.438E+01$	$4.756E+01$	$5.707E+01$
^{99g}Tc	$2.1 \cdot 10^5$ y	$1.867E-07$	$4.525E-07$	$5.804E-07$	$3.871E-07$	$9.339E-07$	$1.204E-06$
^{98}Tc	$4.2 \cdot 10^6$ y	$3.696E-11$	$2.383E-09$	$1.737E-08$	$7.392E-11$	$4.766E-09$	$3.475E-08$
^{97m}Tc	91 d	$2.122E-04$	$4.792E-04$	$6.994E-04$	$4.241E-04$	$9.580E-04$	$1.398E-03$
^{97g}Tc	$4.2 \cdot 10^6$ y	$4.037E-11$	$1.197E-10$	$2.156E-10$	$8.075E-11$	$2.394E-10$	$4.312E-10$
^{96m}Tc	51.5 m	$8.741E-02$	$1.567E-01$	$4.117E-01$	$9.516E-02$	$1.706E-01$	$4.483E-01$
^{96g}Tc	4.28 d	$3.230E-03$	$6.209E-03$	$2.294E-02$	$7.040E-03$	$1.345E-02$	$4.846E-02$
^{95m}Tc	61 d	$7.551E-05$	$1.849E-04$	$2.806E-04$	$1.509E-04$	$3.696E-04$	$5.607E-04$
^{95g}Tc	20 h	$1.722E-02$	$4.414E-02$	$7.529E-02$	$3.275E-02$	$8.393E-02$	$1.431E-01$
^{94m}Tc	52 min	$2.744E-02$	$6.489E-02$	$9.470E-02$	$2.993E-02$	$7.078E-02$	$1.033E-01$
^{94g}Tc	293 min	$3.409E-02$	$1.094E-01$	$1.951E-01$	$5.637E-02$	$1.809E-01$	$3.225E-01$
^{93m}Tc	43.5 min	$6.191E-04$	$1.525E-02$	$3.005E-02$	$6.543E-04$	$1.612E-02$	$3.176E-02$
^{93g}Tc	2.75 h	$2.318E-03$	$4.935E-02$	$1.218E-01$	$3.476E-03$	$7.426E-02$	$1.824E-01$
^{92}Tc	4.25 min	$5.181E-02$	$1.017E-01$	$1.152E-01$	$5.181E-02$	$1.017E-01$	$1.152E-01$
^{91m}Tc	3.3 min	$0.000E+00$	$0.000E+00$	$2.595E-03$	$0.000E+00$	$0.000E+00$	$2.595E-03$
^{91g}Tc	3.14 min	$0.000E+00$	$9.369E-06$	$1.190E-02$	$0.000E+00$	$9.369E-06$	$1.190E-02$

As recalled, a key parameter to be carefully assessed considering the ^{99m}Tc accelerator production is the ground state ^{99g}Tc, which is useless for the diagnostic procedures. In the report by the european commission [30], a limiting purity of the end product, approximately composed by 25% ^{99m}Tc and 75% ^{99g}Tc (i.e., $^{99m}\text{Tc}/{}^{(99m+g)}\text{Tc}$ ratio equal to 0.25), is reported to interfere with the function of some labelled radiopharmaceuticals, thus reducing the effectiveness of Tc-based scans. Unfortunately, it is not clear in [30] how such an IP level should affect the diagnostic procedures, as neither the radiolabelling processes nor the resulting SPECT images quality are mentioned.

In order to get a reference, when technetium ($^{99g+99m}$Tc), under pertechnetate form (TcO_4^-), is eluted as a sterile solution from a standard Mo/Tc generator after intervals of 24 h, the maximum ^{99m}Tc activity is reached and the corresponding isotopic purity IP turns out to be about 0.26, as may be inferred by the considerations reported by Alfassi et al. [31]. On the other hand, on the basis of our theoretical approach it can be noted that such a ratio is never higher than 0.22 (see Table 4). It has to be reminded that the ^{99m}Tc excitation function from the TENDL 2012 library shows the peak located at the bottom of the uncertainty band from the experimental measurements, as shown in Figure 4. Therefore, it has to be reasonably expected that an IP value similar to Tc generators might be obtained at both short irradiation times and low bombarding energies (i.e., 1-2 hr, 15 MeV).

Once produced, and eventually chemically separated from other radioactive and stable isotopes of other chemical species, the expected evolution of both the isotopic purity (IP) and the radionuclidic purity (RNP) for the accelerator-produced ^{99m}Tc, against the decay time after EOB, is finally shown in the three plots of Figure 8. The sharp increase of RNP, with respect to the ones enlisted in Table 4 up to values higher than 95%, occurs in just a few minutes, mainly because of the quick decay of ^{100}Tc. The decays of other short-lived Tc isotopes lead the RNP increase to values as high as 99% in about 1 hour after EOB, considering the reference case of 3 h irradiation at 20 MeV energy. RNP values above 99% for accelerator-produced Tc are quite important, considering that the same parameter from the generator-produced Tc is about 99.99%. Such a limit is basically approached (i.e., 99.58%) if the irradiations at proton energies as low as 15 MeV are performed, whatever the irradiation time chosen. Moreover, the accelerator produced ^{99m}Tc, having RNP values never higher than 99% and IP ones always lower than 10% 1 h after EOB, clearly points out that irradiations at 25 MeV have to be avoided, even using highly enriched molybdenum material.

Some experimental investigations have been performed in recent times to assess the influence of the IP parameter on radiolabelling procedures, using ^{99m}Tc from standard Mo/Tc eluates at times as long as after 3 days from the previous elution. In a recent study performed by Urbano et al. [14], the ^{99g}Tc and oxidizing impurities amounts present in different eluates were accurately determined and their influence in radiochemical purity determination of different radiopharmaceuticals, for example, ^{99m}Tc-DTPA (diethylenetriaminepenta-acetic acid), ^{99m}Tc-MIBI (methoxyisobutylisonitrile), and ^{99m}Tc-HMPAO (hexamethylpropylene amine oxime), was carefully evaluated. It was found that the radiolabelling procedures of these commercial

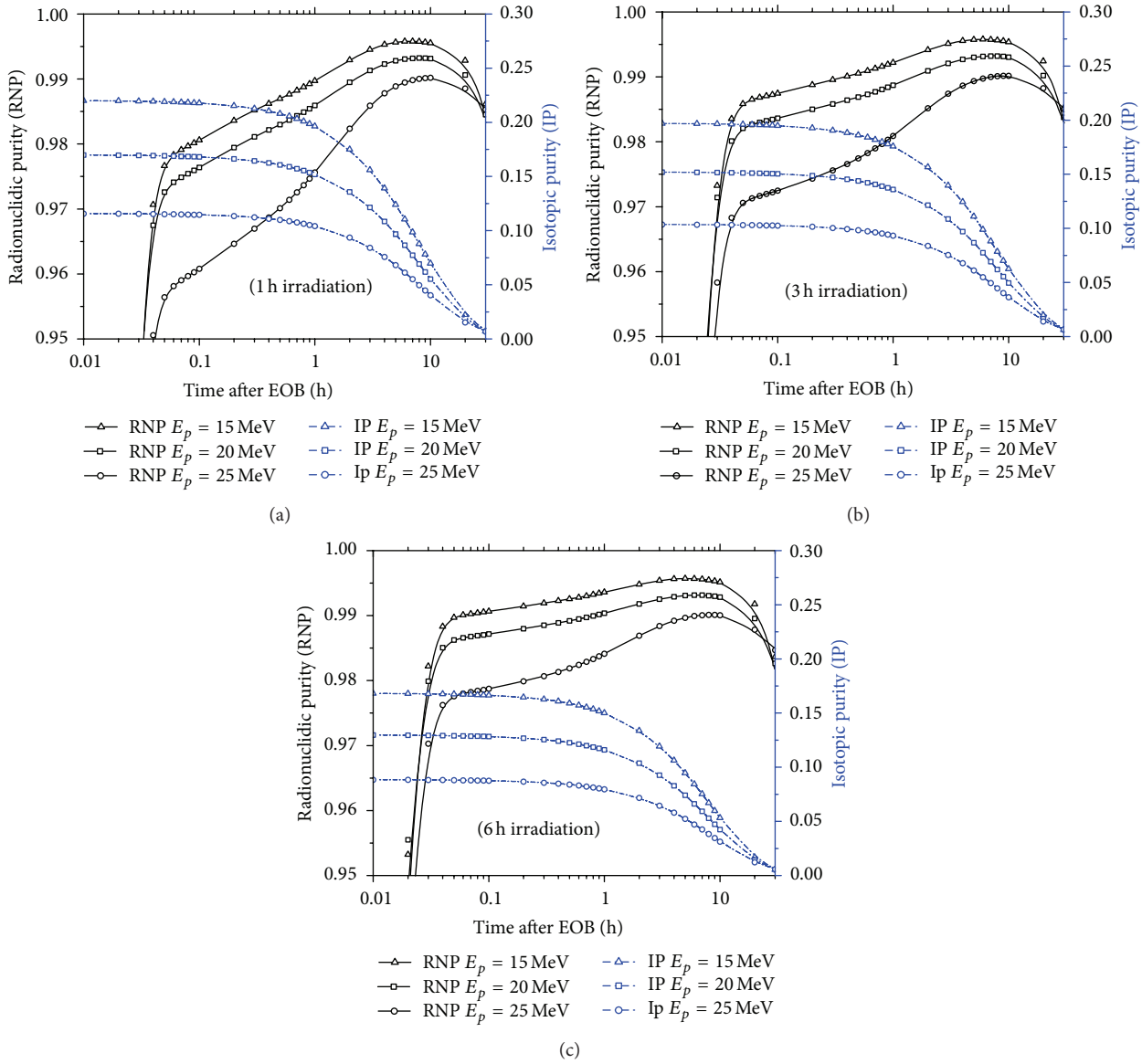

Figure 8: The evolution of ^{99m}Tc isotopic purity (IP) and radionuclidic purity (RNP) expected inside the target (or supposing a quick chemical separation process of accelerator Tc produced) versus the decay time after EOB. 99.05% ^{100}Mo-enriched metallic molybdenum in optimized sample configuration bombarded at 15, 20, and 25 MeV protons and 1, 3, and 6 h irradiation times has been considered.

kits were not affected when using eluates at 72 h and at longer times from the previous one (i.e., solutions with an IP value as low as about 0.08). Moreover, the USP requirements were fulfilled in all the cases considered, even with those radiopharmaceuticals whose stannous contents were low (i.e., MIBI and HMAPO). Such a consideration suggests that, as shown in Figure 8, the useful time-window (1–10 h) after EOB for labelling procedures may be fulfilled by accelerator-produced Tc at energies below 20 MeV and irradiation times within 3 h.

It has to be noted that some interesting imaging *in vivo* tests have also been performed on healthy rats, to get a comparison between the generator-produced against the cyclotron-produced ^{99m}Tc, as reported in a newsline of JNM by Guérin et al. [15]. After short irradiations (1.5–3 h) at 17 MeV using 99.5% ^{100}Mo-enrichment, the resulting labeling, the resulting labelling efficiencies of ^{99m}Tc-MDP and ^{99m}Tc-MIBI were above the USP requirements (>90%), and identical patterns were found for the cyclotron- and the generator-produced ^{99m}Tc radiopharmaceuticals, within normal individual variations between each pair of animals.

Moreover, *in vivo* biodistribution studies in rats were performed, using the cyclotron-produced ^{99m}Tc-BRIDA pharmaceutical, whose radiochemical purity after the technetium labelling procedure was above 97%, finding agreement with the expected time behaviour of the kit in different organs (Targholizadeh et al. [16]). Therefore, it may be concluded that the long-lived isotopes ^{99g}Tc and ^{98}Tc, certainly present

in the radiopharmaceuticals, seem to induce a marginal effect (if any) on the results of the diagnostic procedures. Additional and more accurate investigations are however needed in order to have clearer indications.

It should at last be reminded that the chemical separation process described by Chattopadhyay [32, 33] may be completed very quickly, just within 1 h from EOB, as confirmed by Guérin et al. [15]. In case of a direct ^{99m}Tc accelerator production, it must be assumed that a fully dedicated radiochemical plant for separation and purification processes, up to the final radionuclides in GMP chemical form ready for use, should be available in the same regional area of the production site. In such a way, the already established distribution network for short-lived radionuclides may be exploited.

5. Conclusions

In this work, a comprehensive feasibility study, aimed at the ^{99}Mo / ^{99m}Tc alternative production through high-performance cyclotron-based proton accelerators up to 70 MeV, has been presented. For such a purpose, a wide set of TENDL 2012 theoretical excitation functions have been used, available for the reaction routes on all Mo isotopes present inside ^{100}Mo-enriched molybdenum metallic material, up to (p,6n), (p,p5n), and (p,2p4n) levels. No simplified constraints, about either the magnitude of cross section values for the various isotope productions (both ground or isomeric states) or assumptions about jumps on the different decay chains (based on the short mean life of radionuclide concerned) have been adopted, thus following the most general theoretical approach.

The estimated theoretical yields obtained in this study are, on the whole, consistent with the previous ones performed by Celler et al. [17], based on a different theoretical approach. An agreement with the experimental results reported in the works by Scholten [4], Takacs et al. [5], and Gagnon et al. [12], mainly about the ^{99}Mo and ^{99m}Tc and ^{99g}Tc yields by direct reactions on ^{100}Mo, has been found. For all of the theoretical excitation functions taken into account about the Mo isotopes present inside the target material, a benchmark study has been performed as well in the EXFOR database [34], collecting all of the experimental nuclear reaction data available. A general agreement (although with some deviations) has been found, as may be seen in Figures 2, 3, and 5 for the case of ^{100}Mo isotope, thus confirming the general reliability of the TENDL 2012 theoretical excitation functions.

This study proves that the expected in-target specific activities for the ^{99}Mo production (mainly in the 40–70 MeV energy range), even using the incoming high-performance cyclotron at LNL, are about a factor of 10^4 lower than the one currently available inside the standard Mo/Tc generators. Although the in-target yields estimated for the irradiation parameters investigated may be considered enough, such a route is however not interested as a production way, if maintaining the current standard Mo/Tc generators manufacturing because of the high cost of the target material.

On the contrary, the direct proton-driven ^{99m}Tc production is feasible and quite interesting. Although the in-target yields are improved moving towards beam energies higher than 20 MeV, the production of other Tc contaminants starts increasing to levels that are not negligible. Some impacts may therefore occur on the quality of accelerator-Tc radiopharmaceuticals, as well as on dosimetric aspects. The calculation results clearly show that the energy region of 15–20 MeV is the best operative solution for the accelerator production of ^{99m}Tc. In such a, case the main quality-related parameters, that is, the isotopic purity (IP) as well as the resulting radionuclidic purity (RNP) evolution some hours after EOB, are indeed closer to the generator-produced ^{99m}Tc if short irradiations (i.e., not longer than 3 h) are chosen. Moreover, results also show that the expected specific activity at EOB is similar to the one available from the current Mo/Tc generators, that is, around 10^6 Ci/g for 15–20 MeV proton beam. A good balance between production yields and isotopic/radionuclidic purities concern is therefore likely to be found within such constraints. A series of short irradiations are thus preferable instead of a unique per day, in order to minimize the amount of Tc-contaminants. Moreover, a key parameter is the production of the ground state ^{99g}Tc that has a strong influence on the IP parameter. Although recent studies have shown that labelling procedures performed on some commercial kits were not affected using eluates from the standard Mo/Tc generator at 72 h and longer from the previous one, such a consideration suggests that a time window, ranging from 2 h and up to 10 h after EOB, may be exploited for medical procedures with the accelerator-^{99m}Tc pharmaceuticals. Further studies and experimental campaigns are however requested to validate the ^{100}Mo(p,2n)^{99g}Tc excitation function in the entire energy range and to find out the acceptable IP and RNP limits preferably through imaging *in vivo* tests. These basic aspects will be the subject of future experimental investigations as well as the evaluation of the amount of other technetium isotopes produced (e.g., ^{95,96,97,98}Tc) from the irradiation of available enriched ^{100}Mo targets.

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