RADIOPHARMACEUTICAL PRODUCTION THROUGH THE UTILIZATION OF TRIGA NUCLEAR RESEARCH REACTOR

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ABSTRACT

The techniques in nuclear medicine for diagnostic radiology are grouped under the name of "imaging" and in general need compounds which are labeled with a gamma-ray or positron-emitting radionuclides that are injected in the body of a patient. These compound are various, but undoubtedly the most important one for these practices is the ^{99m}Tc which is a metastable product of the decay of ^{99}Mo. This isotope represents two thirds of all the practices and is produced by means of an industrial process that involves either a nuclear reactor from which we can draw this fission product during its operation, or by means of irradiation by thermal neutrons, driving the neutron flux towards a molybdenum target. There is a third way, by cyclotron that is explained in principle in the paper. Since the main nuclear production units in the world are being phased out, a shortage is foreseen in Italy for the years to come as far as ^{99m}Tc is concerned. ENEA is the research Institute that in Italy has the greatest experience in the nuclear science and operates two research reactors, a TRIGA thermal one, 1 MW_{th} power and a fast one TAPIRO of 5 kW_{th}. The possibility to produce radiopharmaceuticals even if for the local heath care units in central Italy would result in consistent savings for the National Health Service. This paper reports the feasibility studies with the actual plants, includes the results of the preliminary experiences and explores the possible test matrix forwarding the production phase.

1. INTRODUCTION

Radiopharmaceuticals are an advanced field of the nuclear science, their use is mainly in the sector of radiodiagnostics and treatment. The most precise diagnoses of many diseases (e.g. various types of cancer, blood vessels surgery treatments driving) are obtained from PET (Positron Emission Tomography) and through the use of ^{99m}Tc, that includes the 95% of the radiopharmaceuticals ~~amount~~ used in Italy. ^{99m}Tc is a short-lived isotope and a daughter product of the beta-decay of ^{99}Mo.

According to the available information from NEA/OECD ^{99m}Tc is used in more than two-thirds of all diagnostic and medical isotope procedures in the world. There are two basic methods of ^{99}Mo production in nuclear reactors: reaction of ^{235}U fission and reaction of ^{98}Mo neutron capture.

Further to two concomitant events, i.e. the foreseen closing of the Canadian Nuclear reactor (NRU National Research Universal Reactor- Chalk River-Ontario), that covers the 40% of the whole worldwide production and the interruption of the authorization iter of the Canadian reactor Maples-1 that should have compensated the loss of production of the NRU, a worldwide shortage of this fundamental radiopharmaceutical for the diagnostic nuclear-medicine is going to happen.

ENEA, (The Italian National Agency for New Technologies, Energy and Sustainable Economic Development) in the Research Centre Casaccia, near Rome, operates a TRIGA nuclear thermal reactor and TAPIRO a fast reactor that also could be involved in the radiopharmaceutical production in the future. TRIGA, because of its specifications might be suitable for a regional production of the mentioned radiopharmaceutical.

Furthermore the optimization of the technological process for the production will be developed. ENEA has 12 research centres, each one with its own knowledge and peculiarities. A significant coordination task will be undertaken to assign the relevant process phases. Our coordinated activities are with Faenza for the high pressure sintering process and Brindisi for the materials and for a future production of tablets ready for irradiation.

2. METHODS OF PRODUCTION OF MOLY 99

Actually three main production methods of the ^{99m}Mo (precursor of ^{99m}Tc) are operational:

- Nuclear fission (^{99m}Mo as a product of the fission reaction).

The single fission reaction of ^{235}U that occurs in the operation of the nuclear reactors, generally leads to one fragment with a mass number in the range of 85 to 105 and the other fragment with a mass number in the range of 130 to 150 and may produce about 100 nuclides representing 20 different elements [2], with half-lives from 0,1 to 60 days [3]. Fission also leads at the end to the thermal energy production about 200 MeV. This relatively long half-life allows, for those which are of interest of the nuclear medicine, the extraction from the vessel and the further processing for the preparation of the radiopharmacist. In this case, on the contrary some heavy drawbacks are to be taken into account, i.e. the high activity, the necessity to have the complex separation process, and the final disposal of the wastes, to be previously treated and conditioned. These complications in the process are leading to a shortage of ^{99}Mo production through this mode estimated around 30% per year (IAEA 2010).

- Neutronic activation in nuclear reactors through the reaction ^{98}Mo(n,γ)^{99m}Mo.

As it is well known, neutrons, under particular physical conditions, can be efficiently “captured” by the nucleus of a target atom. The neutron flux in a nuclear reactor is intense; in our TRIGA RC-1 research reactor we measured a thermal flux of $2.7*10^{13}$ n/(cm^2*s) in the central channel of the core in which we want to accommodate the container with the feedstock.

This is a well-known process but it can gain consideration due to the actual shortage of ^{99m}Tc.

An way is to provide ^{98}Mo to be irradiated that is commercially available on the market at an enrichment that is even more than 98.4%. Obviously the cost per gram is high but it can be useful to set the whole chemical process of final separation.

Natural molybdenum can be used taking account of the percentage of ^{98}Mo (which is 24.13 %) and its cross section for the thermal neutrons (0.025 eV) is 0.136 barn.

The outcome of recent studies is that the resonance integral (i.e. the cumulative cross section, related to the capture of neutrons with energies between the keV and the 100 keV) of is about 7.2 barn (see fig.), 50 times greater than the thermal one. This indicates that the neutron spectrum of the “irradiation device” can considerably affect the efficiency of the indicated reaction and then production.

Due to the several decades operation of the TAPIRO fast reactor in the Casaccia research centre, that is an ENEA designed fast machine, the possibility of production of ^{99}Mo, exploiting the fast portion of the neutron spectrum will be also investigated.

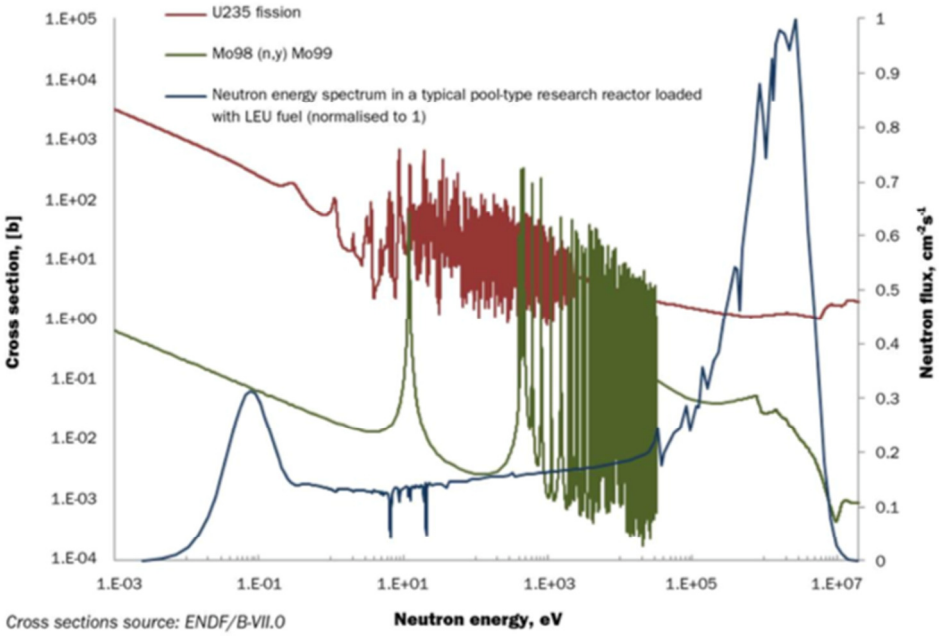


Fig.1 Cross section spectrum of ^{235}U, ^{98}Mo

- Neutronic activation through acceleration machines.

In a cyclotron a magnetic field accelerates in a spiral shape traiectory and in an impulsive mode particles that are driven by two semicircular hollow electrodes called “Dees”. In the gap between the two poles an ion source is fitted to generate charged particles. A high frequency alternating current (AC) voltage generated by a high-frequency oscillator (typically 30 kV, 25-30 MHz) is applied across the dees.
Biomedical cyclotrons have typically a magnetic field of 1.5 Tesla and a “Dee” diameter of 76 cm.

The aim of the present work is to explore the possibility to obtain ^{99m}Tc from ^{98}Mo activation, using the TRIGA Mark II reactor of ENEA Agency located in the Research Centre Casaccia Rome Italy .

On the basis of the reported data on the RC-1 Safety Report and recent studies in the specific sectorial scientific literature, data were extracted to make a preliminary theoretical evaluation of the capacity production.

TRIGA REACTOR

TRIGA is a thermal pool reactor, with the core located inside a graphite cylindrical reflector, on the bottom of an aluminium vessel. Such a vessel is filled up with demineralized water which has also the function of moderator, cooling agent and biological shield. The fuel consists of cylindrical elements in a Zr, H e U enriched at 19,9% in ^{235}U ternary alloy. Consequently, moderation is not relying to the cooling water only, but to the zirconium hydride of the alloy too, responsible of the high negative prompt temperature coefficient.

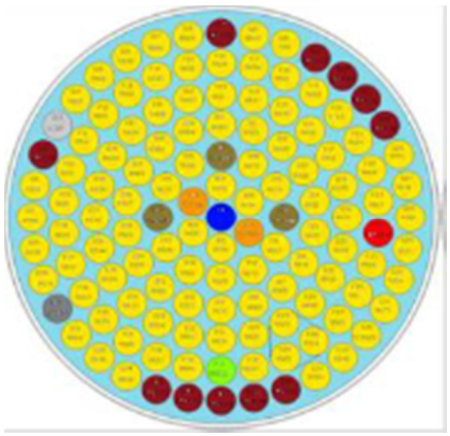
The removal of the core-produced thermal power is achieved by means of the water natural circulation. The water in the pool, to which the power is delivered, is kept at constant temperature by a cooling loop, equipped with heat exchangers and cooling towers.

The main reactor specifications are the following:

- Maximum power: 1 MW

- Neutron flux max: 2,7 10^{13} n/cm^2·sec @ 1 MW
- Cooling by light water in natural circulation
- Irradiation facilities:

  1 central channel
  40 positions in a revolving tray
  1 thermal column
  1 beam of coincided neutrons.
  5 horizontal channels for the neutrons extraction.



EXPERIMENTAL FACILITY	THERMAL FLUX n/(cm^2·s)	R_{Cd}[1]	SHAPE	DIMENSIONS (mm) UNLESS DIFFERENTLY SPECIFIED
A - Radial Channel	4.8 · 10^{12} (*)	~ 2.2	CYLINDER	Ø INT. = 152
B - Radial Channel	4.3 · 10^{10} (*)	~ 3	CYLINDER	Ø INT. = 152
C - Radial Channel	4.3 · 10^{10} (*)	~ 3	CYLINDER	Ø INT. = 152
D – Tangential Channel	5.4 · 10^{10} (*)	10.4	CYLINDER	Ø INT. = 152
Piercing Tangential Channel	1.1 · 10^{6} (**)	1.8	CYLINDER	Ø INT. = 180
Thermal Column Horizontal Channel	2.2 · 10^{6} (**)	3.8	CYLINDER	Ø INT. = 40
Thermal Column Vertical Channel (with plug of graphite)	1.9 · 10^{10}	4.3	SQUARE	SIDE = 100
Thermal Column Vertical Channel (without cap of graphite)	4.2 · 10^{9}	~ 4	SQUARE	SIDE = 100
Central thimble	2.68 · 10^{13}	1.7	CYLINDER "S" SHAPED	Ø INT. = 34.04
Thermalizing Column	1.3 · 10^{8} (**)	> 100	PARALLELEPIPED	608 x 608 x 1[illegible]
Rotary Specimen Rack	2.0 · 10^{12}	2.7	CYLINDER "S" SHAPED	Ø INT. = 32
Removable grid cavity	1.25 · 10^{13}	2.2	TRIANGULAR PRISM	L = 75~ h = 650
RABBIT (Pneumatic transfer tube)	5.1 · 10^{12}	2.0	CYLINDER	Ø INT.. = 14 Ø INT. TUBE = 27
Loop for irradiation of liquids	~5.0 · 10^{12}		CYLINDER	V ~ 150 ml

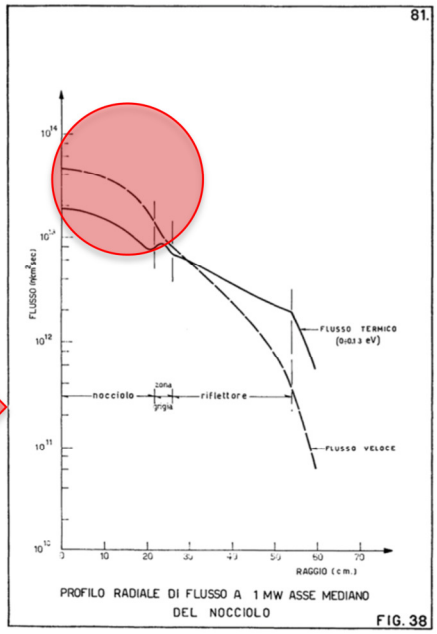


Fig. 2 Characteristics of TRIGA RC-1 reactor

At first an evaluation of the feasibility of production of ^{99}Mo through this process was undertaken by means of the capture reaction ^{98}Mo(n,γ)^{99}Mo through the irradiation of ^{98}Mo enriched metallic molybdenum targets. The above mentioned TRIGA characteristics and the specialized literature in this field were considered and then the following starting hypothesis were set.

1. Irradiation in the central channel having a 3 cm dia; it is believed possible the utilization of a peripheral channel also;
2. The maximum value of the neutron flux is kept in the central channel of the reactor; the only thermal portion was considered $1.7*10^{13}$ n/(cm^2*s), but it is possible to foresee the harnessing of the epithermal and fast components of the neutron spectrum of ^{98}Mo, that result in a corrective term of the cross-section;
3. The cross-section for the thermal neutrons (0.025 eV) of the capture reaction was assumed σ=0.136 barn;
4. Considering also the contribution of the epithermal and fast portion of the neutron flux ^{98}~~Mo~~ spectrum it is evaluated to assume an "effective" cross section that keeps into account the contribution of the resonance region. This contribution is assessed from the literature around the 68% in the case of molybdenum enriched in 98 and about 78% for the natural isotopic composition molybdenum. Experiences in analogous facilities (TRIGA in Wien) evaluate σ around 0.4-0.5 barn, to arrive, in the case of the IRT-T reactor of the Nuclear Physics Institute @Tomsk to values around 0.7 barn. Prudentially and waiting for an experimental campaign for the actual preliminary calculations a σ = 0.25 barn is assumed (conventionally estimated twice the thermal one).
5. 120 hours irradiation time that correspond to two half-lives of ^{99}Mo ($T_{1/2}$= 66 hours);
6. Target: enriched in ^{98}Mo metallic sample (density 10.28 g/cm^3).

The advantages of this method is that the technology is not complicate, final chemical separation of the irradiated material is a well-known methodology and no ~~high level~~ wastes are produced.

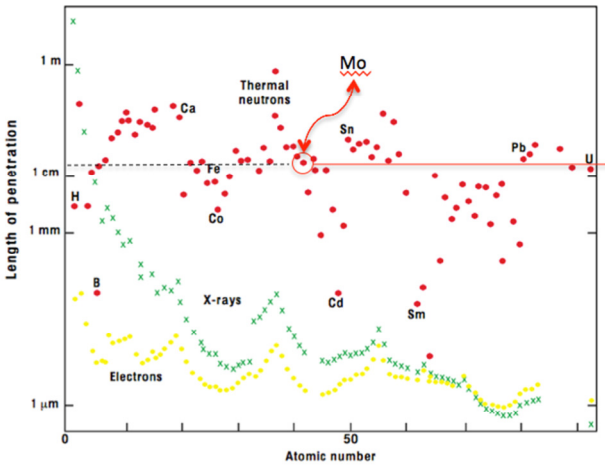
On the basis of these hypothesis the data shown in tab.1 were obtained; they were positively compared with the extrapolation of the data obtained experimentally using ^{98}Mo in natural isotopic composition and lower irradiation periods.

Tab.1 – Obtainable activity concentrations

Considered neutron spectrum	Cross section ^{98}Mo (n,γ) ^{99}Mo (barn)	Source	Activity Concentrations (End Of Bombardment) in GBq/g
thermal	0.136	ENDF-VI Library	10.1
thermal + epithermal	0.250	First working assumption	18.6
Whole neutron spectrum	0.400	Experimental data	33.0

We have to remark that 0.136 is a value that is validated from the literature, 0.250 is an "ingegneristic" and prudential value, based on the consideration of the characteristics of the ^{98}Mo cross section curve (Fig. 1), 0.400 is a quantity that obtained "a posteriori", based on the first experimental evidence after a test undertaken on the reactor on 20 December 2016. In the central channel two small natural Molybdenum bars and an Au-Al leaf at 11.31% were irradiated for 60 minutes at a power of 1 kW.
The effective σ value has been drawn from these quantities and it matches the values that were found in the TRIGA reactor in Vienna, i.e. σ= 0.4÷0.7 barn. [3]
As far as the mass of ^{98}Mo that can be efficiently irradiated inside the TRIGA core, the evaluation can be made on the basis of the neutron penetration inside the sample. This to estimate the optimum thickness that takes into account the two contributions, i.e. thermal and epithermal one. We can state from the figure 3 below that:

1. The geometry of the central channel and the TRIGA RC-1 neutron axial flux allow to use for the molybdenum samples, a 10 cm height, to keep the target in the maximum flux area, to neglect the border effects on the axial profile of the same;
2. With an available diameter of the central channel of 3 cm we can use a cylindrical container for the sample having a diameter of 2.5 cm, we assume that for every session of 120 hours we can irradiate a mass of metallic molybdenum about 150 g.



Penetration depth of a beam of thermal neutrons (0.18 nm), of X-rays (0.1 nm) or of electrons (0.004 nm) as a function of the atomic number. Note the logarithmic scale along the vertical axis.

Mo at 10.20 g/cm^3

Source neutrons: 1.798 Å = 25.30 meV = 2200 m/s
Source X-rays: 1.542 Å = 8.042 keV

1/e penetration depth (cm)		Scattering length density (10^{-6}/Å^2)		Scattering cross section (1/cm)		X-ray SLD (10^{-6}/Å^2)	
abs	6.297	real	4.299	coh	0.363	real	75.733
abs+incoh	6.197	imag	-0.000	abs	0.159	imag	-4.959
abs+incoh+coh	1.907	incoh	0.361	incoh	0.003		

Neutron transmission is 96.82% for 0.2 cm of sample (after absorption and incoherent scattering).
Transmitted flux is 9.682e+12 n/cm^2/s for a 1e13 n/cm^2/s beam.

Mo at 10.20 g/cm^3

Source neutrons: 0.000 Å = 500000000.00 meV = 9780413 m/s
Source X-rays: 1.542 Å = 8.042 keV

1/e penetration depth (cm)		Scattering length density (10^{-6}/Å^2)		Scattering cross section (1/cm)		X-ray SLD (10^{-6}/Å^2)	
abs	27995.212	real	4.299	coh	0.363	real	75.733
abs+incoh	385.100	imag	-0.000	abs	0.000	imag	-4.959
abs+incoh+coh	2.735	incoh	0.361	incoh	0.003		

Neutron transmission is 99.95% for 0.2 cm of sample (after absorption and incoherent scattering).
Transmitted flux is 9.995e+12 n/cm^2/s for a 1e13 n/cm^2/s beam.

Fig.3

The following values of specific activity (Bq/g) were obtained assuming an irradiation in the central channel with a neutron flux of 2,7 10^{13} n/(cm^2 *s) and an effective microscopic cross section of 0.4 barn.

EOB (End Of Bombardment).

Metallic Mo enriched at 98,4% ^{98}Mo.

- irradiation time 6 h/d (4 d/week): 7 GBq/g
- irradiation time 120 h continuously (5 d/week): 30 GBq/g

Assuming a weekly supply of ^{99m}Tc generators (devices that are supplied and used in the hospitals for the eluition of ^{99m}Tc from the ^{99m}Mo solution), from about 20 GBq, about 4,8 grams of metallic Molybdenum should be irradiated in discontinuous mode, while in continuous mode about 1,1 grams considering a delivery time from the end of the irradiation of about two days.

Further with these theoretical evaluations and an assessment test on the reactor as mentioned above, a test matrix to validate the calculations was set. At first the shape of the sample was designed. Since in the core the reactor channel is cylindrical with a maximum diameter of 3 cm in the axial central region and the container for the sample has a diameter of 2.5 cm, the procurement of the ^{98}Mo was commercially possible only in powder that had to be sintered before the irradiation in the reactor. At the end, taken into account the procured mass of isotopic molybdenum and the variety of the possible tests, we approved a natural or ^{98}Mo tablet of cylindrical shape of an average diameter of 9.2 mm and an height of 1.2 mm resulting in 1 g mass.

The sintering process was performed in our Faenza laboratories, the metallic powder was shaped into a monoassial press and then, to minimize the first monodirectional application of

the pressure, in a hydrostatic press at 200 MPa and subsequently in a vacuum oven at 1760 °C for a two days heating.

Fig. 4 Sinterization process of molybdenum powder

This “conditioning” phase leads to a density of 94% and to an enlargement of the crystalline grain, giving to the tablet the necessary homogeneization and facilitating the neutron penetration.

At a temperature of 2000 °C a 98% of the theoretical density can be achieved.

Under these evaluations and results, a matrix for further field tests forwarding a real small production phase was compiled and will be implemented in the next months (Tab 2).

Irradiation n°	Reactor Power MW	Irradiation duration time h	Tablets number	Location	Material	Scope of the test
1	1	0.5÷1	1	Central thimble	^{98}Mo	Activity assessment
2	1	0.5÷1	1	Central thimble	Natural molybdenum	Activity assessment
3		0.5÷1	3/5	Central thimble[1]	Natural molybdenum	Epithermal flux, cross section assessment vertically
4	1	0.5÷1	Two natural Molybdenum stripes, 0v. 100 g	Central thimble	Natural molybdenum	Absorbed reactivity by molybdenum

Tab.2 Test matrix for the assessment of the activity output after irradiation

3. CONCLUSIONS

- The preliminary tests and the calculations that we recently performed showed the feasibility to obtain a radiopharmaceutical production by irradiating a target of molybdenum, in metallic or isotopic composition,
- This production, on the basis of the TRIGA reactor flux, is envisaged to be industrialized for a local supply; in the area of Casaccia Research Centre the largest health care units of the Rome area are located, it is obvious that the minimization of production and transportation costs would result in massive savings for the ~~SSN (~~National Health Service~~)~~,
- 85 structures of Nuclear Medicine are in operation in the centre of Italy (Toscana, Marche, Umbria, Lazio e Sardegna) representing about the 30% of the national capability; the national turnover for imaging analyses is estimated in 100 M€.
- Whatever the chosen production rhythm will be, it will be economically appealing for ENEA, since it will maximize the use of the plants, foster experienced experts and will characterize the Institute as a reference point in the field for the national community,

The involvement of three ENEA centres each one with its peculiarities and knowledge would result in a strong coordination and possibility to become a main player in this business. The partnership consolidation with other firms for other process activities such UJV (Nuclear Research Institute Řež in the Czech Republic) for the setting of the white rooms (extraction of ^{99}Mo after the irradiation and generators loading), with Permafix for the supply and setting of the generators for the final administration of the radiopharmaceutical scientists would qualify the Institute for further R&D in this sector an high social acceptance that

- The ENEA experts, plants and installations would benefit of high social acceptance that could result in a better environment for the nuclear science, maintaining experience and knowledge in this historical period of generation gap.

[1] Vertically disposed, with a tablet in the centre of the channel and the other two couples at equal distance upon and under the central axis.

4. References

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