ESTIMATION OF THE PRODUCTION COSTS OF ^{67}Ga, ^{201}Tl, ^{123}I AND ^{111}In MEDICALLY IMPORTANT RADIOISOTOPES BY A CYCLOTRON FACILITY TO BE INSTALLED AT ANKARA NUCLEAR RESEARCH AND TRAINING CENTRE IN TURKEY

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ABSTRACT

A cyclotron with the proton beam current of 100 μA and a variable proton energy range of 15 – 30 MeV is planned to install at ANRTC to produce the medically important radioisotopes ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In, imported for the need of Turkey. In this work, the annually production rates 170 Ci for ^{67}Ga, 303 Ci for ^{201}Tl, 283 Ci for ^{123}I and 325 Ci for ^{111}In have been calculated theoretically. Also the production costs have been estimated to be 2.7 $/mCi for ^{67}Ga, 2.9 $/mCi for ^{201}Tl, 3.3 $/mCi for ^{123}I and 0.6 $/mCi for ^{111}In levelized ten years' facility amortization. It has been seen that the calculated production costs for these radioisotopes will be less than their import prices.

1. NTRODUCTION

The radioisotopes as radiopharmaceuticals or non-invasive agents have been applied in human health studies and they are able to provide information about organ function and detect abnormalities at very early stage. Today, nuclear medicine techniques are used in a broad range of medical specialities, such as oncology, endocrinology, cardiology, neurology and nephrology. Some medically important radioisotopes produced by means of cyclotrons such as ^{67}Ga($T_{1/2}$=78.3 h), ^{201}Tl($T_{1/2}$=72.9 h), ^{123}I($T_{1/2}$=13.3 h), and ^{111}In($T_{1/2}$=67.3 h) have found wide applications in diagnostic nuclear medicine. Since these radioisotopes have some nuclear properties such as reasonable low half-life, almost single photon emission and its low energy, they are suitable for SPECT(Single Photon Emission Computed Tomography) studies for diagnostic(1,2). Therefore, extensive studies on the production of medically used isotopes such as ^{67}Ga, ^{201}Tl , ^{123}I, and ^{111}In by using cyclotrons have been performed over the years(3) and now they are commercially available to provide health centers' demand. Further, it is known that hundreds of millicuries from the radioisotopes mentioned above are annually imported in Turkey. The main purpose of the calculations presented here is to give the information related to production limits of ^{67}Ga, ^{201}Tl, ^{123}I, and ^{111}In radioisotopes at a cyclotron facility to be installed at ANRTC in Turkey. In addition, it

is to estimate the production costs of ^{67}Ga, ^{201}Tl, ^{123}I, and ^{111}In by means of a 30 MeV-proton cyclotron. The production costs estimated from certain assumptions for these isotopes are compared with their import prices to emphasize whether such a cyclotron facility will be economical in view of providing currently domestic use of some radioisotopes or not

2. PHYSICAL BASIS OF RADIOISOTOPE PRODUCTION

It is well known that radioisotope production is based on nuclear reactions in the general form *X(a,b)Y*, where *X* is target material, *a* is incident particle, *Y* is product nucleus or radioisotope and *b* is outgoing particle. Such a reaction mainly depends on types of particle and target material, the particle energy and reaction cross section. The reaction cross section is a function of incident particle energy called excitation function. The reaction can occur when a incident particle energy, E_a is much higher than the reaction threshold energy($E_a > E_{th}$). If incident particle is a charged particle, its energy must also exceed the coulomb barrier. The relation between the threshold energy in laboratory system, E_{th} and Q-value in center of mass is given by following form:

$$E_{th} = |-Q| \cdot \left(1 + \frac{m_a}{M_X}\right) \qquad (1)$$

where m_a and M_x are incident particle mass and target mass, respectively. Reaction Q-value is calculated as follows:

$$Q = [((M_X + m_a) - (M_Y + m_b)] \cdot c^2 \qquad (2)$$

and Coulomb energy between the incident charged particle and target nucleus is:

$$E_C = 1.44 \frac{z \cdot Z}{(R_a + R_X)} \qquad (3)$$

where, Coulomb energy E_C is given in MeV; z and Z are the atomic numbers of incident particle and target, respectively. The radius of nucleus is $R = 1.3A^{\frac{1}{3}}\ [\text{fm}]$, in which A is atomic mass number. The literature survey has shown that a large number of nuclear reactions have been investigated for production of medically used radioisotopes by cyclotrons(1-3). However, the present calculations are focused on ^{67}Ga, ^{201}Tl , ^{123}I, and ^{111}In radioisotopes used in mainly SPECT studies. Thus, using highly enriched targets at a small cyclotron with a proton beam energy of less than 30 MeV, the nuclear reaction processes for the estimation of the production rates of ^{67}Ga, ^{201}Tl , ^{123}I, and ^{111}In given in Table 1 has been proved to be more suitable and commonly used in practice. Some nuclear data for the chosen nuclear reactions in Table 1 are about the reaction threshold energy, an optimum bombarding energy range, the mean cross section over energy range of interest, target isotope with natural abundance, target material enrichment used in calculation and physico-chemical form of target

material. The activity calculations for production of the radioisotopes concerned are based on the experimental cross sections which are mainly retrieved via Internet from EXFOR library of OECD-Nuclear Energy Agency(3). The excitation functions for the nuclear reactions chosen for production of ^{67}Ga, ^{201}Tl , ^{123}I, and ^{111}In are plotted by using EXFOR experimental cross sections, excluding the cross sections for above 30 MeV protons. The excitation functions are shown in Fig. 1 to Fig.4. The cross section data used in the excitation functions are not smoothed or fitted. However, the mean cross section value for each reaction process over the optimum proton bombarding energy range is calculated as follows:

$$\overline{\sigma} = \frac{\sum_i \sigma_i E_i}{\sum_i E_i} \qquad (4)$$

where, $\overline{\sigma}$ is the energy averaged cross section over proton bombarding energy range for each type nuclear reaction, σ_i is any measured cross section corresponding to i-th measured proton energy, E_i in the optimum energy range of the excitation function. For the production of isotopes ^{67}Ga, ^{123}I, and ^{111}In by a cyclotron with proton beam, the preferable reactions are ^{68}Zn(p,2n), ^{124}Te(p,2n) and ^{112}Cd(p,2n), respectively. In these reactions, the highly enriched target materials are desirable in order to obtain high yield and to avoid interference activities arisen from other stable isotopes of the target element used. These targets may be metallic plated on Cu or the oxide form molten on Pt such as $^{124}TeO_2$. Then, the activity produced can be calculated by the following formula:

$$A = R \cdot \left(1 - e^{-\frac{0.693}{T_{1/2}} \cdot T_i} \right) \cdot e^{-\frac{0.693}{T_{1/2}} \cdot T_w} \qquad (5)$$

where A is activity, $T_{1/2}$ is half-life of radioisotope, T_i is irradiation time, T_w is cooling(or waiting) time after the end of bombardment and R is reaction rate described as follows:

$$R = \phi \cdot \sigma \cdot n = \left(\frac{I_p}{e} \right) \cdot \sigma \cdot m \cdot C \cdot \frac{N_{Av}}{W} \cdot h$$

where, ϕ is particle flux impinging on the target(particles/cm^2.s) , I_p : proton current (Ampere), e:unit electronic charge(1.6x10^{-19} Amp.s), σ: reaction cross section(barn), m: mass of target element, C: concentration of target element, N_{Av}: Avogadro's number(6.022x10^{23} /mole), W: atomic weight(g/mole), h: abundance of target isotope(or enrichment used).

However, of these isotopes, ^{201}Tl production method is more special case in which the nuclear reactions involved are as follows:

$$^{203}\mathrm{Tl} + \mathrm{p} \rightarrow {}^{201}\mathrm{Pb} + 3\mathrm{n}$$

$$^{201}Pb \xrightarrow{EC(T_{1/2}=9.33h)} {}^{201}Tl \xrightarrow{EC(T_{1/2}=72.9h)} {}^{201}Hg$$

The decay equations for above illustrated two reactions can be written as follows:

$$\frac{dN_{Pb}}{dt} = R - \lambda_1 \cdot N_{Pb}$$
$$\frac{dN_{Tl}}{dt} = \lambda_2 \cdot N_{Tl} - \lambda_1 \cdot N_{Pb} \qquad (6)$$

where, N_{Pb} is the number of ^{201}Pb nuclei and N_{Tl} is the number of ^{201}Tl nuclei. λ_1 and λ_2 are decay constants for ^{201}Pb and ^{201}Tl , respectively. Solving the set of equations in Eq.6 according to boundary conditions(irradiation and target cooling times), a simple expression for production of ^{201}Tl can be written as:

$$A_{Tl} = R \cdot S \cdot D \cdot G \qquad (7)$$

Where, A_{Tl} is ^{201}Tl activity, R is reaction rate,

S is the saturation factor and equals to (1- exp (- 0.693 T_i/T_1)) with T_i = irradiation time in hours, T_1 = half-life of ^{201}Pb = 9.33 h,

D is the decay factor equals to exp(-0.693T_d/T_1) with T_d = the end of first chemistry process(EOC1) in hours,

G is growing factor:

$$G = \left(\frac{T_1}{T_1 - T_2}\right) \cdot \left(e^{-\frac{0.693}{T_2} \cdot T_g} - e^{-\frac{0.693}{T_1} \cdot T_g} \right)$$

with T_2 = half-life of ^{201}Tl = 72.9 hr.

T_g is the growing period which equals to time difference between end of the first chemistry process (EOC1) and start of the second chemistry process (SOC2).

In ^{201}Tl production, optimum value of activity growing factor is calculated to be 0.0946 for T_g = 32 hours and the acceptable limits for irradiation time Ti are 0.5 T_1<T_i<2.5 T_1.

In addition, considering single target per batch and single irradiation mode, the known sample mass for each target isotope of interest given in EXFOR Experimental Data Evaluation studies is used in the calculations(3). Alternatively, sample thickness can be determined from stopping power formula ($S_p = -\frac{1}{\rho}\frac{dE}{dx}$), where S_p is stopping power, ρ is density of target, dE/dx is the specific energy loss(4). For the target isotope enrichment, the available targets with maximum

enrichment shown in the electronic catalog of Oak Ridge National Laboratory(ORNL) are taken into account(5). The weekly irradiation time schedule is given in Annex 1 for the radioisotope production, its maintenance and research experiments to be carried out at a cyclotron. The irradiation times and waiting times of targets for mode of single target irradiation weekly to produce of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In are given in Table 2. The production rates of ^{67}Ga, ^{123}I, and ^{111}In are calculated from Eq.5 and production rate of ^{201}Tl is calculated from Eq.7. Finally, the production rates of the isotopes concerned are estimated to be 170 Ci/year for ^{67}Ga, 303 Ci/year for ^{201}Tl , 283 Ci/year for ^{123}I and 325 Ci/year for ^{111}In. Total uncertainties of the present calculated activities for these isotopes are estimated to be in the range of about ±10-15%. The uncertainty sources are essentially due to total errors in experimental cross sections taken from the literature data.

3. COST ESTIMATION

The unit costs of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In estimated according to operating costs of the planned cyclotron facility including targetry, chemical laboratory, electric consumption, water supply, transportation, personel wages, etc. given in Table 3. Investment cost of such a cyclotron facility(machine+ construction+ equipment) is assumed to be $7x10^6$ US$. With respect to 1, 3, 5, 7 and 10 years of amortization for this facility, the unit cost for each isotope is calculated by dividing the operating cost plus paying back money for the intended amortization's period to the activity produced in a year for each isotope. Total operating cost per year has had been shared to the irradiation time of each isotope used in the operation period of cyclotron. The estimated costs of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In and other import prices are given Table 4.

4. CONCLUSION

It is known that the total annually imported isotope activities are 3.6 Ci for ^{67}Ga, 32.1 Ci for ^{201}Tl, 0.463 for Ci ^{123}I and 0.269 Ci for ^{111}In and total money paid is 532.231 $ per year(6). When a compact cyclotron having single particle (only proton), variable beam energy range of 15 to 30 MeV and proton beam current of 100 μA is installed at ANRTC in Turkey, the annually total isotope production capacities will be 170 Ci for ^{67}Ga, 303 Ci for ^{201}Tl, 283 Ci for ^{123}I and 325 Ci for ^{111}In. The unit production costs have been determined to be 2.7 $/mCi for ^{67}Ga, 2.9 $/mCi for ^{201}Tl, 3.3 $/mCi for ^{123}I and 0.6 $/mCi ^{111}I for 10 years facility amortization. It is obvious that the production costs for these isotopes are cheaper than their importing prices.

In conclusion, such a cyclotron facility seems to be an economical facility in view of providing currently domestic use of some radioisotopes. In addition, such a cyclotron will be used in beneficial research activities related to charged particle physics at medium energies and also neutrons produced from reactions will be able to be used in various research fields.

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Table 1. Some nuclear data for the calculation of the cyclotron production rates of ^{67}Ga, ^{201}Tl, ^{123}I ve ^{111}In using highly enriched target materials

Radio-isotope	Half life $T_{1/2}$ (h)	Reaction process used	Threshold Energy (MeV)	Energy Range[a] (MeV)	Cross Section[b] (mb)	Target Material[c,d]		
						Isotope	Natural Abundance %	Enrichment used %
^{67}Ga	78.3	$^{68}Zn(p,2n)$	12.16	22→12.8	562.5	^{68}Zn	18.8	99.71
^{201}Tl	72.9	$^{203}Tl(p,3n)^{201}Pb\rightarrow$	17.49	30→20	914.6	^{203}Tl	29.5	96.54
^{123}I	13.3	$^{124}Te(p,2n)$	11.53	26→23	1061.8	^{124}Te	4.8	96.70
^{111}In	67.3	$^{112}Cd(p,2n)$	11.14	23→17	932.7	^{112}Cd	24.1	98.27

a) An optimum bombarding energy range depending on cross section behavior is chosen to obtain maximum target yield.

b) OECD NEA Data Bank EXFOR-experimental cross sections are used in calculation (**3**). In addition, the uncertainties of cross sections are given within ±5-10%.

c) Highly enriched targets are practically preferred in order to minimise impurities arising from other isotopes of target and to obtain higher activities.

d) Enrichment percentages for ^{68}Zn, ^{203}Tl, ^{112}Cd and $^{124}TeO_2$ are taken the electronic catalog of Oak Ridge National Labaratory(ORNL)(**5**).

Table 2. Optimum irradiation and waiting times related to production of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In for single target irradiations as weekly

Radioisotope	Irradiation time(h)	Waiting time(h)
^{67}Ga	4	12
	6	12
	7	12
	9	12
	15	12
^{201}Tl	7	3+ 32
	10	4+32
	10	4+32
	11	4,5+32
	12	5+32
	13	5+32
^{123}I	6	8
	6	8
	6	8
	6	8
^{111}In	16	18

Table 3. The operating costs of a cyclotron facility for the calculation of unit costs of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In .

Target Material*	**Expenses($/yil)**
• ^{68}Zn isotope 99.71% enrichment (0.6 g/week x 52 week x 5390 $/g)	**168,168**
• ^{203}Tl isotope 96.54% enrichment (3.6 g/week x 52 week x 2400 $/g)	**449,280**
• ^{124}Te isotope 96.70% enrichment (0.4712 TeO_2 g/week x 52 week x 30760 $/g)	**753,694**
• ^{112}Cd isotope 98.27% enrichment (0.6 g/week x 52 week x 2900 $/g)	**90,480**
Electric Consumption** (100 kW x 24 h/day x 332 day x 0.1 $/kWh)	**74,880**
Water supply+ Transportation+ Cooling	**12,400**
For chemicals	**50,000**
Maintanence cost of machine and other equipment	**50,000**
Personel Wages (10 person x 12 month x 1000 $/person x month)	**120,000**

* ORNL target prices are used.

** Power input is considered to be 100 kW, which is estimated from a typical cyclotron's magnets, ion source and RF systems power requirements.

1kWh electrical energy price in Turkey is assumed to be 10 cent.

Table 4. The calculated unit costs of ^{67}Ga, ^{201}Tl, ^{123}I and ^{111}In isotopes and their 2000 year's importing prices.

Amortization Period	1 - year	3 - year	5 - year	7 - year	10 - year	In 2000 Year Import Price* ($/mCi)
Radioisotope	Radioisotope Unit Cost ($/mCi)					
^{67}Ga	13,2	5,4	3,8	3,2	2,7	15,4
^{201}Tl	12,0	5,3	3,9	3,4	2,9	12,1
^{123}I	7,0	4,2	3,7	3,5	3,3	44,1
^{111}In	2,8	1,2	0,9	0,7	0,6	99,4

*:The price data for these isotopes are provided officially from the Turkish Atomic Energy Authority. Unit importing cost for each isotope is calculated by using total pay for the activity imported into Turkey in first four months of 2000's year (**6**).

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6. Official information provided by TAEK-RGSD's letter dated 09.05.2000 and number B.02.1.TAE.0.11.00.01-10500-249.

ANNEX-1

Time Schedule for Radioisotope Production, Research Experiments and **Maintenance as weekly**

Day/Hour	00:00	02:00	04:00	06:00	08:00	10:00	12:00	14:00	16:00	18:00	20:00	22:00	00:00
Sunday	→ ^{123}I 2 h		^{201}Tl 10 h					**AD 1h**	^{67}Ga 7 h			^{123}I → 4 h	
Monday	→ ^{123}I 2 h		^{201}Tl 12 h						^{67}Ga 6 h			^{123}I → 4 h	
Tuesday	→ ^{123}I 2 h		^{111}In 16 h								**AD 2h**	^{123}I → 4 h	
Wednesday	→ ^{123}I 2 h		^{201}Tl 13 h							^{67}Ga 9 h		→	
Thursday	→ ^{67}Ga 4 h			Maintenance 15 h							^{201}Tl 5 h	→	
Friday	→ ^{201}Tl 5 h				**AD 3 h**	^{201}Tl 7 h			**AD 3 h**		^{201}Tl 6 h	→	
Saturday	→ ^{201}Tl 5 h				^{67}Ga 15 h							^{123}I → 4 h	

NOTES: 1-Irradiation times assigned radioisotope production: 63 h for ^{201}Tl, 24 h for ^{123}I , 41 h for ^{67}Ga, 16 h for ^{111}In.

2-Time assigned research experiments: AD : 9 h

3-Maintenance period: 15 h .

Fig.1. Zn-68(p,2n)Ga-67 Excitation Function (EXFOR : Experimental Data)

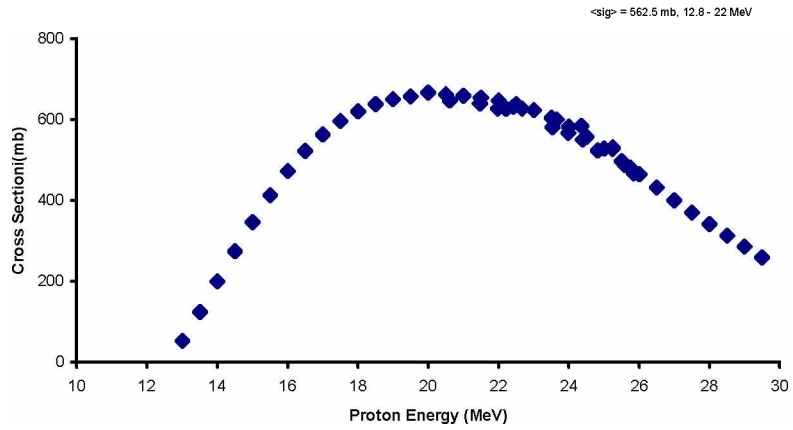

Fig. 2 . Te-124(p,2n)I-123 Excitation Function(EXFOR:Experimental Data)

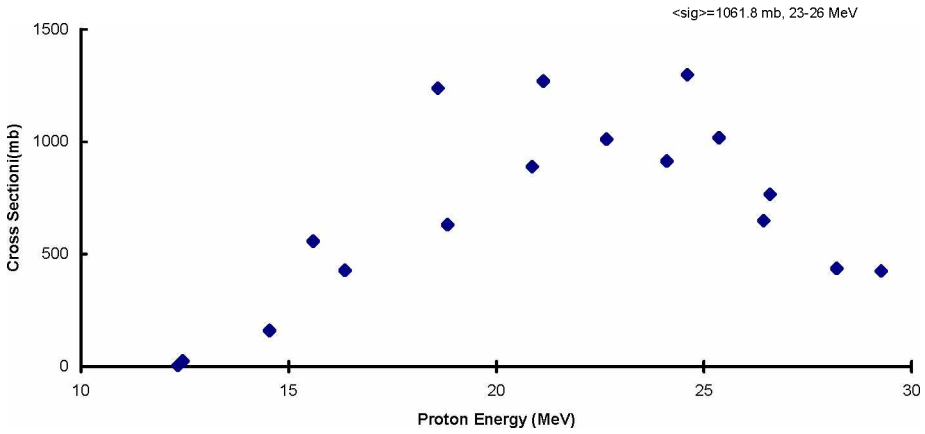

Fig. 3. Tl-203(p,3n)Pb-201 Excitation Function (EXFOR: Experimental Data)

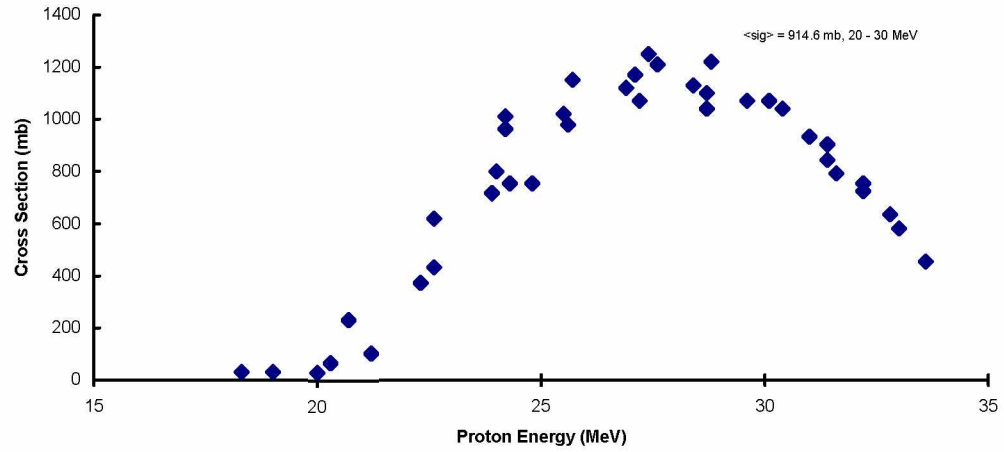

Fig. 4. Cd-112(p,2n)In-111Excitation Function (EXFOR:Experimental Data)