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Příprava ^{99m}Tc na cyklotronu jako reálná alternativa generátoru ^{99}Mo/^{99m}Tc a možné řešení krize výroby ^{99}Mo v jaderných reaktorech

Cyclotron production of ^{99m}Tc as an alternative to the ^{99}Mo/^{99m}Tc generator and a viable solution to the ^{99}Mo production crisis in nuclear reactors

Summary

The decay and chemical properties of ^{99m}Tc (6.01 h) make it very suitable for production of the many diagnostic radiopharmaceuticals used for imaging via Single Photon Emission Computed Tomography (SPECT) or planar scintigraphy. It is by far the most widespread medical radionuclide used in more than 80 % of all nuclear medicine procedures worldwide.

One of the reasons for the large number of ^{99m}Tc radiopharmaceuticals developed is ready availability through eluting radionuclidic generators ^{99}Mo/^{99m}Tc. The half-life of its mother nuclide, ^{99}Mo (65.95 h), allows for its transport far away from the site of manufacture. Currently, 95–98 % of the production of high specific activity ^{99}Mo by nuclear fission of highly enriched ^{235}U is performed in 5 reactors: High Flux Reactor (Petten, Netherlands), BR2 (Mol, Belgium), Osiris (Saclay, France), NRU (Chalk River, Canada) and Safari-1 (Pelindaba, South Africa). All of them range in age from 45 to 54 years and it is in not certain that any of them will be in operation after 2015–2016. The recent supply shortage of ^{99}Mo/^{99m}Tc generators due to the long-lasting and unexpected shutdowns of several of these reactors revealed the serious drawbacks of this production route of ^{99m}Tc.

There are several alternative ways to resolve this crisis, such as more widespread use of smaller reactors for ^{235}U fission, production of low specific activity ^{99}Mo by ^{98}Mo(n,γ) reaction or by of photon-induced reactions ^{100}Mo(γ,n) and ^{238}U(γ,f). Among them, proton- and deuteron-induced reactions on ^{100}Mo and ^{98}Mo represent another promising approach.

We have, therefore, re-measured in detail the excitation functions of the ^{nat}Mo(p,x) and ^{nat}Mo(d,x) reactions resulting in ^{99m}Tc and ^{99}Mo. Attention was paid to careful data processing, in particular to interference corrections. The measured cross-sections for production of both ^{99}Mo and ^{99m}Tc by protons could be converted to isotopic cross-sections of ^{100}Mo(p,x)^{99}Mo and ^{100}Mo(p,2n)^{99m}Tc reactions. Thick target yields of the latter reaction would allow for production of ca 1.7 TBq of ^{99m}Tc in 6 h irradiation with a 500 μA beam—this amount corresponds to the daily consumption of the Czech Republic or any large metropolitan area, even taking into account a further 6 h necessary for target processing, ^{99m}Tc separation and purification, quality control and transport.

A further step we undertook was the experimental determination of the radionuclidic impurities content in the irradiated targets as a function of the isotopic composition of the highly enriched ^{100}Mo. It was revealed that for the best commercially available enrichment of ^{100}Mo, the overall content of other technetium radioisotopes in ^{99m}Tc is below the level of 0.1 % (the expected Pharmacopoeia limit) at the time of administration.

Souhrn

Díky svým rozpadovým a chemickým vlastnostem je radionuklid ^{99m}Tc (6.01 h) vhodný k přípravě řady diagnostických radiofarmak užívaných k zobrazení metodou emisní jednofotonové počítačové tomografie (SPECT) či planární scintigrafie. Je proto zdaleka nejrozšířenějším radionuklidem v nukleární medicíně, kterého se užívá v celosvětovém měřítku ve více než 80 % aplikací.

Jedním z důvodů velkého počtu existujících radiofarmak na bázi ^{99m}Tc je jeho snadná dostupnost elucí radionuklidového generátoru ^{99}Mo/^{99m}Tc. Poločas rozpadu jeho mateřského nuklidu, ^{99}Mo (65.95 h), umožňuje dopravovat generátor na velké vzdálenosti od místa výroby. Příprava ^{99}Mo o vysoké hmotnostní aktivitě štěpením vysoce obohaceného ^{235}U probíhá z 95–98 % pouze v pěti reaktorech: High Flux Reactor (Petten, Netherlands), BR2 (Mol, Belgium), Osiris (Saclay, France), NRU (Chalk River, Canada) a Safari-1 (Pelindaba, South Africa). Tyto reaktory jsou v provozu již 45–54 let a není vyloučeno, že v letech 2015–2016 budou již zavřeny. Nedávné výpadky dodávek generátorů ^{99}Mo/^{99m}Tc z důvodu dlouhodobých a náhlých odstávek několika těchto reaktorů upozornily na vážná rizika této přípravy ^{99m}Tc.

Existuje několik alternativních přístupů k řešení této krize, jako je např. užití menších reaktorů ke štěpení ^{235}U, příprava ^{99}Mo o nízké hmotnostní aktivitě reakcí ^{98}Mo(n,γ) či studium přípravy ^{99}Mo fotojadernými reakcemi ^{100}Mo(γ,n) a ^{238}U(γ,f). Další slibnou cestou jsou reakce protonů a deuteronů na ^{100}Mo a ^{98}Mo, jimiž lze připravit ^{99}Mo nebo přímo ^{99m}Tc.

V naší práci jsme se proto věnovali detailnímu přeměření excitačních funkcí jaderných reakcí ^{nat}Mo(p,x) a ^{nat}Mo(d,x), které vedou ke vzniku ^{99}Mo a ^{99m}Tc. Zvláštní pozornost jsme věnovali zpracování dat, zejména korekci interferencí. Stanovené účinné průřezy pro vznik ^{99}Mo i ^{99m}Tc reakcemi protonů lze konvertovat na izotopové účinné průřezy reakcí ^{100}Mo(p,x)^{99}Mo a ^{100}Mo(p,2n)^{99m}Tc. Výtěžky druhé reakce v tlustém terči by umožnily připravit cca 1.7 TBq ^{99m}Tc šestihodinovým ozařováním ^{100}Mo 500μA svazkem – tj. množství odpovídající denní spotřebě České republiky či velké světové metropole, a to včetně předpokládaného šestihodinového zpoždění nezbytného k zpracování terče, separaci a purifikaci ^{99m}Tc, kontrole kvality a dopravě.

Provedli jsme též experimentální stanovení obsahu radionuklidových nečistot v ozářených terčích jako funkci izotopového složení vysoce obohaceného ^{100}Mo. Ukázalo se, že pro dosud nejvyšší komerčně dostupné obohacení ^{100}Mo bude celkový obsah ostatních radioizotopů technecia v ^{99m}Tc < 0,1 % v okamžiku aplikace. Přitom lze očekávat, že úroveň 0,1 % bude lékopisným požadavkem na obsah radionuklidových nečistot v cyklotronovém ^{99m}Tc.

Klíčová slova
^{99m}Tc, ^{99}Mo, radionuklidový generátor ^{99}Mo/^{99m}Tc, radiofarmaka, SPECT, excitační funkce, příprava radionuklidů, cyklotron, radionuklidová čistota

Key words
^{99m}Tc, ^{99}Mo, radionuclidic generator ^{99}Mo/^{99m}Tc, radiopharmaceuticals, SPECT, excitation functions, production of radionuclides, cyclotron, radionuclidic purity

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1 Introduction

Isomer ^{99m}Tc (6.01 h) is the most widespread medical radionuclide used in more than 80 % of all nuclear medicine procedures worldwide. Currently, there are 18 diagnostic radiopharmaceuticals based on ^{99m}Tc described in the European Pharmacopoeia [1]. They are used for imaging of brain, myocardial perfusion, thyroid, lungs, hepatobiliary and renal systems, bones and tumours [2–4].

The reasons for such a versatility are: a) optimal decay properties of ^{99m}Tc (it decays from 99.9963 % by isomeric transition emitting single γ line with energy of 140.51 keV and intensity of 89 % suitable for imaging with SPECT and planar scintigraphy [5]); b) easy availability through eluting radionuclidic generators ^{99}Mo/^{99m}Tc with 0.15M NaCl in form of pertechnate $^{99m}TcO_4^-$; c) half-life of its mother nuclide, ^{99}Mo, is 65.95 h, and thus allows for its transport far away from the site of manufacture; d) versatile chemistry of this transition metal with several oxidation states and coordination possibilities opens way for labelling of various compounds by complexing of ^{99m}Tc with ligands attached to the carrier by appropriate functional groups [2,3,4]; e) low radiation burden of the patients and almost no radioactive waste, since ^{99m}Tc decays to its ground state ^{99}Tc with half-life of 2.111×10^5 years [5].

Instant availability of ^{99m}Tc at the departments of nuclear medicine resulted in development of kits for production of ^{99m}Tc based radiopharmaceuticals. The kits are sterile and apyrogenic precursors of radiopharmaceuticals prepared by lyophilization and stored in sealed glass vials under nitrogen. They contain a reducing agent, usually stannous chloride, and some additives stabilizing the labelled compound (antioxidants, buffers, catalysts, accelerators, solubilizing agents, fillers) [2]. The kits can be stored for a long time and used for producing of radiopharmaceuticals by simple mixing with generator eluate.

1.1 Production of ^{99m}Tc – current status and its crisis

Radionuclide ^{99m}Tc is now routinely obtained solely from generator ^{99}Mo/^{99m}Tc. The generator is produced predominantly from ^{99}Mo formed by fission of highly enriched ^{235}U. This production route results namely in high specific activity of ^{99}Mo that can be then easily absorbed as molybdate on acidic aluminium oxide of small volume [2,3]. It is highly desirable in order to get the eluate of such activity concentration that is suitable for achieving high labelling efficiency. Moreover, the eluate must comply with all the requirements of Pharmacopoeia, in particular radionuclidic and radiochemical purity, sterility and apyrogenity [1]. Another advantage is high fission yield of the ^{235}U(n,f)^{99}Mo reaction equal to 6.17 %. On the other hand, processing of the irradiated ^{235}U targets is rather complicated and demanding task that results in large amount of long-lived radioactive waste. It is, therefore, highly centralized (see below).

Currently, 95–98 % of high specific activity fission ^{99}Mo is produced in only five reactors and the production is controlled by just four companies. The largest

producer, the Canadian company MDS Nordion provides ca 40 % of the world consumption of ^{99}Mo—the ^{235}U targets are irradiated at the National Research Universal (NRU) reactor at the Chalk River Site in Ontario and processed in Kanata. The second largest producer is Covidien (formerly Mallincrodt) that covers ca 25 % of ^{99}Mo. Covidien irradiates the targets mainly at the High Flux Reactor (HFR) reactor at Petten, Netherlands, and also at the BR2 reactor at Mol, Belgium, as backup. The targets are processed close to the HFR reactor in Petten. Next ca 20 % of ^{99}Mo is provided by the Institut National des Radioéléments (IRE), Belgium that irradiates its targets also at HFR, Petten, at the BR2 and at the reactor Osiris at Saclay in France – targets are then processed in Fleurus, Belgium. Last ca 10 % of ^{99}Mo is produced by the Nuclear Technology Products Radioisotopes (NTP Radioisotopes) at the SAFARI-1 reactor at Pelindaba, South Africa, where the targets are also processed. All these reactors employ ^{235}U enriched to 93 %, except of Safari-1 that uses lower enrichment of 36–45 % [6].

The above mentioned reactors range in age from 45 to 54 years and it is not certain that any of them will be in operation after 2015–2016. The recent supply shortage of ^{99}Mo/^{99m}Tc generators due to long-lasting and unexpected shutdowns of several of these reactors revealed the serious hazards of this production route [6]. Second only to the expiring lifetime of the reactors is the hidden subsidy in the ^{99}Mo price. Namely, none of the producers have ever invested money in the construction, operation and decommissioning of any of the reactors. All of them were constructed as state research centres, and large-scale production of ^{99}Mo is only a side effect of their operation. Construction of new reactors solely for ^{99}Mo production is financially unacceptable.

1.2 Possible solutions of the ^{99}Mo supply crisis

There are several alternatives to solve the above described crisis [6]. The first one seems to be natural—the use of existing smaller research reactors for irradiation of the so far employed highly enriched ^{235}U (HEU) targets. Irradiation of the HEU targets brings at least two problems: a) handling of HEU is limited to countries that conform to the directives of the International Atomic Energy Agency (IAEA); b) such decentralized irradiation of HEU makes the distribution and return of the irradiated HEU rather expensive. There are several research reactors that might participate in that approach (e.g. MURR in the U.S.A., ETRR-2 in Egypt, RP-10 in Peru, RECH-1 in Chile, MARIA in Poland, TRIGA II in Romania, HANARO in South Korea).

Another approach is close to the previous one: building of new large high-flux reactors to replace the old ones, like the JULES HOROWITZ reactor in France (expected to go into operation in 2014) and the PALLAS reactor in the Netherlands (expected to go into operation in 2016), both potentially used by Covidien and IRE. Such projects, in particular PALLAS, will face by no means negligible resistance of the public due to the Fukushima accident and the generally swelling anti-nuclear movement. Even when leaving any emotional arguments aside,

one has to admit that both the suggested ways do retain the problems with handling and processing of the irradiated HEU, including long-lived waste.

The use of low enriched ^{235}U (LEU) does not differ much from the two previously described solutions; moreover, a new separation and purification processes would require the approval of the competent authorities and conversion of HEU to LEU targets would result in considerable investments.

Accelerator driven subscritical systems (ADS) consisting of a proton accelerator coupled to a subcritical fast core could be also used in principle for HEU or LEU fission. The ADS suffer from possible long-term unavailability. Namely, the project MYRRHA (Multi-purpose hybrid Research Reactor for High-tech Applications) that is now under preparation at Mol, Belgium, should be operational beyond 2018, but its priorities do not seem to allow its use for the commercial production of radionuclides.

The first approach avoiding fission is the production of low specific activity ^{99}Mo by ^{98}Mo(n,γ) reaction. In that case, low specific activity would result in overlarge alumina columns. Direct elution of such columns would result in too low an activity concentration of ^{99m}Tc in the eluate, and, therefore, in inefficient labellings. This can be solved by central processing of the eluate by extraction of sodium pertechnate and its re-dissolving in a significantly smaller volume of saline. It would lead to the distribution of ^{99m}Tc instead of generators ^{99}Mo/^{99m}Tc. In the high-flux reactors such specific activities of ^{99}Mo could be reached that using another column matrix of high capacity for molybdate, like e.g. zirconium molybdate gel, might enable again direct distribution of the ^{99}Mo/^{99m}Tc generators.

Recently, neutron spallation sources were also proposed for the activation of ^{nat}Mo or ^{98}Mo by the ^{98}Mo(n,γ) reaction. A major disadvantage of this method seems to be too low yield under realistic production conditions.

Production of ^{99}Mo by photon-induced reactions ^{100}Mo(γ,n) and ^{238}U(γ,f) suffers from extremely low cross-sections of photonuclear reactions. Furthermore, a high number of powerful electron accelerators would be necessary for the production of significant amounts of ^{99}Mo.

The last possibility is cyclotron production of ^{99}Mo or ^{99m}Tc. Direct production of ^{99m}Tc by the ^{100}Mo(p,2n) reaction was proposed by Beaver and Hupf already in 1971 [7], but for almost four decades it was considered to be a mere curiosity. The first systematic measurement of the excitation functions of protons on molybdenum was performed by Levkovski in 1991 [8], followed by the three systematic measurements of Scholten et al. [9], Takács et al. [10] and Khandaker et al. [11]. However, the published data in these articles are rather scattered. This might be caused by several interferences in determining the activity of ^{99m}Tc born in the ^{100}Mo(p,2n) reaction. Moreover, none of the works [8–11] describes in detail the corrections for these intereferences.

Cross-sections of deuteron-induced reactions on molybdenum were studied systematically since the seventies in the works of Řanda and Svoboda [12,13],

Zarubin et al. [14] and Sonck et al. [15]. The data presented by the works [12–15] are again scattered and interference correction descriptions are missing, too.

Proper estimating of the ^{99m}Tc or ^{99}Mo cyclotron production feasibility requires, beside yields evaluation, other aspects, like: a) attainable radionuclidic purity; b) separation from the target (efficiency, time consumption, automation); c) radiochemical purity; d) sterility and apyrogenity ensurance; e) production costs.

Our experimental work was, therefore, focused on the following tasks:

- Detailed re-measurement of the excitation functions of the ^{nat}Mo(p,2n)^{99m}Tc, ^{nat}Mo(p,x)^{99}Mo, ^{nat}Mo(d,x)^{99m}Tc and ^{nat}Mo(d,x)^{99}Mo reactions, conversion of the elemental to isotopic cross-sections in the case of ^{100}Mp(p,2n)^{99m}Tc and ^{100}Mo(p,x)^{99}Mo reactions, precise description of the corrections used for determinining ^{99m}Tc activity and calculation of the thick target yields.
- Determination of the radionuclidic impurities content in ^{99m}Tc produced in the ^{100}Mo(p,2n) reaction as a function of isotopic composition of the enriched ^{100}Mo and proton beam energy.

2 Experimental

All the irradiations were performed on the external beamline of the cyclotron U-120M at the Nuclear Physics Institute AS CR, Řež. All the radionuclides' activites were determined with use of γ spectrometer equipped with HPGe detector GMX45Plus (Ortec, USA), calibrated carefully for energy and efficiency by a set of standards supplied by the Czech Institute of Metrology, Prague (^{241}Am, ^{133}Ba, ^{60}Co, ^{137}Cs and ^{152}Eu).

TABLE 1 Half-lives, main γ lines' energies and intensities of the relevant radionuclides. Intensity of 140.51 keV γ line in ^{99}Mo itself is only 4.52 %; the value of 89.6 % refers to the overall intensity of the 140.51 keV γ line in ^{99}Mo decay in transient equilibrium with ^{99m}Tc [17].

RN	$T_{1/2}$	E_γ (keV)	I_γ (%)	RN	$T_{1/2}$	E_γ (keV)	I_γ (%)
^{93}Tc	2.75 h	1 362.94	66.2	^{99m}Tc	6.0082 h	140.51	88.5
^{94}Tc	4.883 h	702.67	99.6	^{99}Mo	65.95 h	140.51	89.6
^{94m}Tc	52.0 min	1 868.68	5.7			181.07	5.99
^{95}Tc	20.00 h	765.79	93.8			739.50	12.13
^{95m}Tc	61 d	835.15	26.6	^{96}Nb	23.35 h	568.87	58.0
^{96}Tc	4.28 d	778.22	99.76	^{97}Nb	72.1 min	657.94	98.23
		812.54	82	^{90}Nb	14.60 h	141.18	66.8
^{97m}Tc	91.0 d	96.5	98			1129.22	92.7

Half-lives, energies and intensities of the measured radionuclides are reviewed in TABLE 1. They were taken preferably from [5]. If the data were missing in [5], we adopted the values from [16] and for ^{99m}Tc and ^{99}Mo from [17].

2.1 Cross-section measurement

For measurement of the excitation functions, we used the stacked foil technique. We irradiated 3 stacks of foils for cross-section measurement of the ^{nat}Mo(p,x) reactions and 2 stacks for ^{nat}Mo(d,x) reactions. The stacks consisted of ^{nat}Mo foils of 20.0 or 11.0 μm thicknesses, interleaved with monitor foils for precise determination of the beam current (^{nat}Cu for protons, ^{nat}Ti and ^{27}Al for deuterons). Recommended cross-sections for the monitoring reactions were adopted from [18]. The stacks were irradiated with protons or deuterons for 1 h having kept the beam current at ca 1 μA. Then, the stacks were dismounted and measured immediately on the γ spectrometer at various distances sample-detector and in different cooling times in order to optimize conditions for measurement of a particular radionuclide.

Cross-sections were calculated according to well-known activation formula:

$$\sigma = \frac{\mathrm{A}ze}{d\rho \mathrm{N_A} I(1 - e^{-\lambda t_b})} \frac{P\lambda t_r}{I_\gamma \eta t_m (1 - e^{-\lambda t_r})} e^{\lambda t_c} \qquad (1),$$

where σ is the cross-section for a given radionuclide in the foil centre [cm^2], A is the atomic weight of the foil metal [g/mol], z is the beam particle charge (for protons z = 1), e is the electron charge (1.602177×10^{-19} C), d is the foil thickness [cm], ρ is the density of the foil metal [g/cm^3], N_A is Avogadro's number (6.022137×10^{23} mol^{-1}), I is the beam current [A], λ is the decay constant of the radionuclide [h^{-1}], t_b is the irradiation (bombardment) time [h], P is net peak area of the γ line used for the activity calculation, I_γ is the its intensity (cf. TABLE 1), η is the detection efficiency, t_m is measurement time (live time) [s], t_r is real time of measurement [h] and t_c is cooling time elapsed between the end of bombardment (EOB) and the start of the measurement [h].

The overall cross-section uncertainty was calculated as a square root of sum of squares of the following sources of uncertainty that linearly contribute to the calculation of the cross-section:

- beam current measurement ca 10 %
- net peak area mostly < 3 %
- detection efficiency 3–4 %
- gamma lines intensities < 3%
- overall mostly ca 12 %

We have mentioned the interferences in the ^{99m}Tc measurement. They are due to several contributions to the net peak area of its single γ line with energy of

140.51 keV. Beside the signal of the ^{99m}Tc born directly in the nuclear reaction, there are the following contributions: a) signal from ^{99m}Tc born from co-produced ^{99}Mo during and after the irradiation; b) signal from the 140.51 keV γ line of the ^{99}Mo itself (cf. TABLE 1); c) signal from ^{90}Nb born in activation of ^{nat}Mo and emitting γ line of the close energy of 141.18 keV (cf. TABLE 1).

The first interference can be solved analytically. Briefly, the activity of a daughter radionuclide at the EOB is given by the following formula:

$$A_2^{EOB} = \frac{f\left(1 - \frac{\lambda_2}{\lambda_2 - \lambda_1} e^{-\lambda_1 t_b} + \frac{\lambda_1}{\lambda_2 - \lambda_1} e^{-\lambda_2 t_b}\right)}{1 - e^{-\lambda_1 t_b}} A_1^{EOB} \qquad (2),$$

where A_2^{EOB} is the activity of a daughter radionuclide at the EOB [Bq], A_1^{EOB} is the activity of a parent radionuclide at the EOB [Bq], f is the probability of transition of parent to daughter radionuclide (0.876 for ^{99}Mo→^{99m}Tc), λ_1 is the decay constant of a parent radionuclide [h^{-1}], λ_2 is the decay constant of a daughter radionuclide [h^{-1}] and t_b is time of irradiation (bombardment) [h].

Activity of a daughter radionuclide after the EOB is governed by the following equation:

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} f A_1^{EOB}\left(e^{-\lambda_1 t_c} - e^{-\lambda_2 t_c}\right) + A_2^{EOB} e^{-\lambda_2 t_c} \qquad (3),$$

where t_c is the cooling time.

The net peak area of the impacted γ line must be then decreased for the number of counts corresponding to the mean activity $\bar{A}_2$ of a daughter radionuclide born indirectly from its parent during real time of the measurement t_r derived from the equation (3):

$$\bar{A}_2 = \frac{\lambda_2 f A_1^0}{(\lambda_2 - \lambda_1) t_r}\left(\frac{1 - e^{-\lambda_1 t_r}}{\lambda_1} - \frac{1 - e^{-\lambda_2 t_r}}{\lambda_2}\right) + \frac{A_2^0}{\lambda_2 t_r}\left(1 - e^{-\lambda_2 t_r}\right) \qquad (4),$$

where A_1^0 and A_2^0 are the activities of a parent and a daughter radionuclides at the start of the measurement. Activity A_2^0 is then obtained from the equation (3).

We should note that the activity of the parent nuclide can be in this case assessed via some of its interference-free γ-lines (cf. TABLE 1).

The other two interferences can be easily calculated as number of counts corresponding under the condition of measurement to the mean activity $\bar{A}$ of the interfering radionuclide during real time of the measurement t_r:

$$\overline{A} = A^{EOB} e^{-\lambda t_c} \frac{1 - e^{-\lambda t_r}}{\lambda t_r} \quad (5).$$

The elemental cross-sections of the $^{nat}Mo(p,x)^{99m}Tc$ and $^{nat}Mo(p,x)^{99}Mo$ could be converted to isotopic cross-sections just by dividing them by the isotopic abundance of ^{100}Mo in ^{nat}Mo. It is thanks to the fact that they are born solely in the proton reactions on ^{100}Mo. We used the value of the ^{100}Mo abundance in ^{nat}Mo (9.63 %) taken from [16]. However, recently there was published an update of the isotopic compositions of the elements [19] that gives the value of 9.82 %. The isotopic cross-sections we calculated are, therefore, slightly overestimated (for 2 %).

The thick target yields were calculated by integrating the measured cross-sections fitted as polynomials (n = 5 or 6) from the entrance energy to the threshold using stopping power of the given ion in the target material [20].

For details of the experimental setup and data evaluation, see our original articles on systematic measurements of the cross-sections of the proton- [21] and deuteron-induced [22] reactions.

2.2 Thick target yields measurement

Direct production of ^{99m}Tc via the $^{100}Mo(p,2n)$ reaction seems to be the most promising means of its cyclotron production (see below). That is why we decided to proceed to detailed assessment of the radionuclidic impurities in ^{99m}Tc produced via that reaction as as a function of isotopic composition of the highly enriched ^{100}Mo and of the beam energy.

For that purpose, we irradiated thick targets from highly enriched ^{95}Mo, ^{96}Mo, ^{97}Mo and ^{98}Mo at 10, 16, 18, 20, 22 and 24 MeV with beam currents of 0.4–1.0 μA for 5 min. Each target was preceded by 12.1 μm thick Ti monitor. After the irradiation, each target and monitor was measured at different distances sample-detector and at various cooling times in order to optimize conditions for measurement of a particular radionuclide. The thick target yields for ^{94}Tc, ^{94m}Tc, ^{95}Tc, ^{95m}Tc, $^{96m+g}Tc$, and ^{97m}Tc were calculated from the measured activities of these radionuclides. Then, the thick target yields were used to model the effect of isotopic composition of a highly enriched ^{100}Mo target on the radionuclidic purity of produced ^{99m}Tc as function of energy. Finally, targets from highly enriched (99%) ^{100}Mo were irradiated at 24 MeV and their radionuclidic composition was measured and compared with the calculated forecast to validate it. Details of the experiment are given in [23,24].

For accurate determining the yields, the net peak area of a particular γ-line used for the calculation of a particular radionuclide activity was corrected for its mean attenuation in the target. The correction was achieved by integrating the product of relative profile of the activity in the target and attenuation. For that purpose, mass attenuation coefficients were adopted from [25] and relative pro-

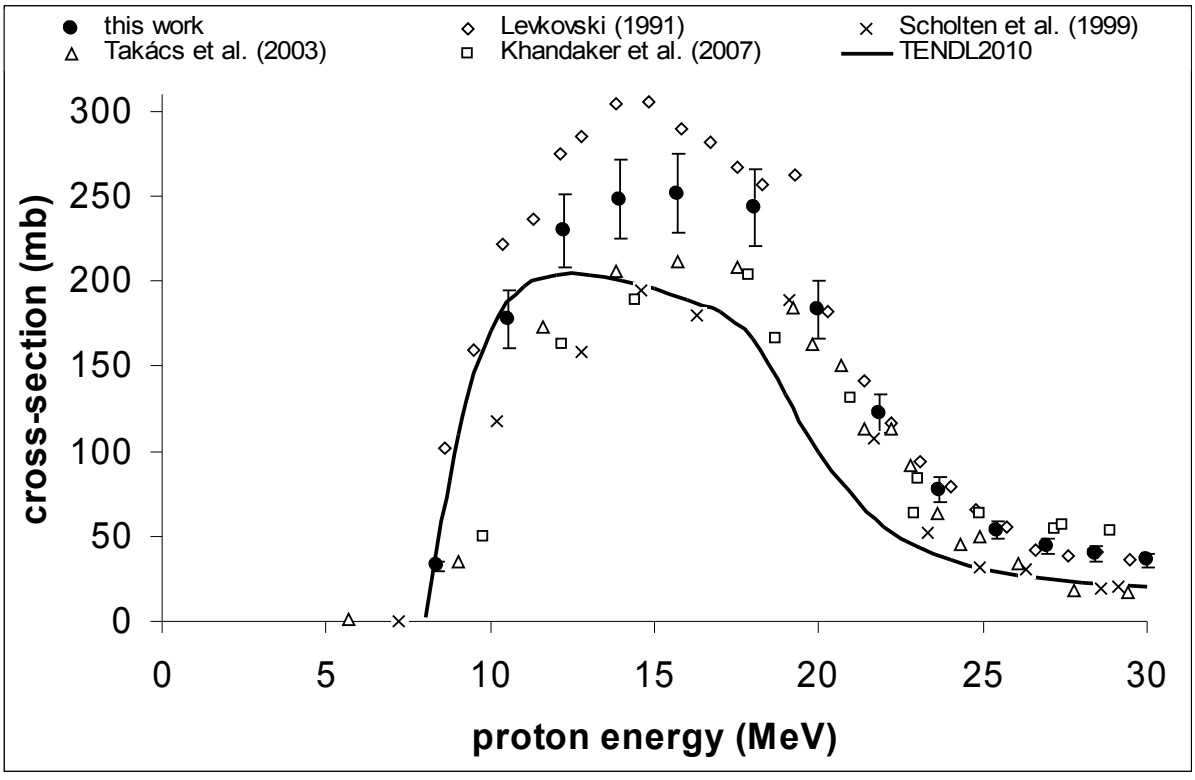
file of the activity was obtained from the forecast of the excitation functions in TENDL-2010 library [26] and the stopping power of protons in the targets taken from program SRIM [20].

3 Results and Discussion

3.1 Excitation functions

Experimentally determined cross-sections of the reactions ^{100}Mo(p,2n)^{99m}Tc and ^{100}Mo(p,x)^{99}Mo in the context of previously published data are displayed on FIG. 1 and FIG. 2. For the ^{100}Mo(p,2n)^{99m}Tc reaction, our cross-section values [21] are for ca 25 % higher around the maximum than those published in [9–11], in contrast to the work [8] that gives for ca 20 % higher cross-sections. Our data are also systematically higher than the forecast of the model code TALYS as adopted from the TENDL-2010 library [26] for E_p > 10 MeV.

FIG. 1 Experimental cross-sections for the ^{100}Mo(p,2n)^{99m}Tc reaction in comparison with previously published data and prediction of TENDL-2010



In the case of the ^{100}Mo(p,x)^{99}Mo reaction, our data [21] show fair agreement with the works [8,10,11] only for E_p < 18 MeV, while for higher energies the works [8,10] give higher and the works [9,11] lower values. In particular the work [9] differs significantly from our data. Prediction of the TENDL-2010 library is for E_p < 22 MeV systematically lower, but for E_p > 22 MeV it is in good agreement with our data. The TENDL-2010 forecast takes into account only the direct formation of ^{99}Mo via the ^{100}Mo(p,pn)^{99}Mo reaction.

FIG. 2 Experimental cross-sections for the ^{100}Mo(p,x)^{99}Mo reactions in comparison with previously published data and prediction of TENDL-2010

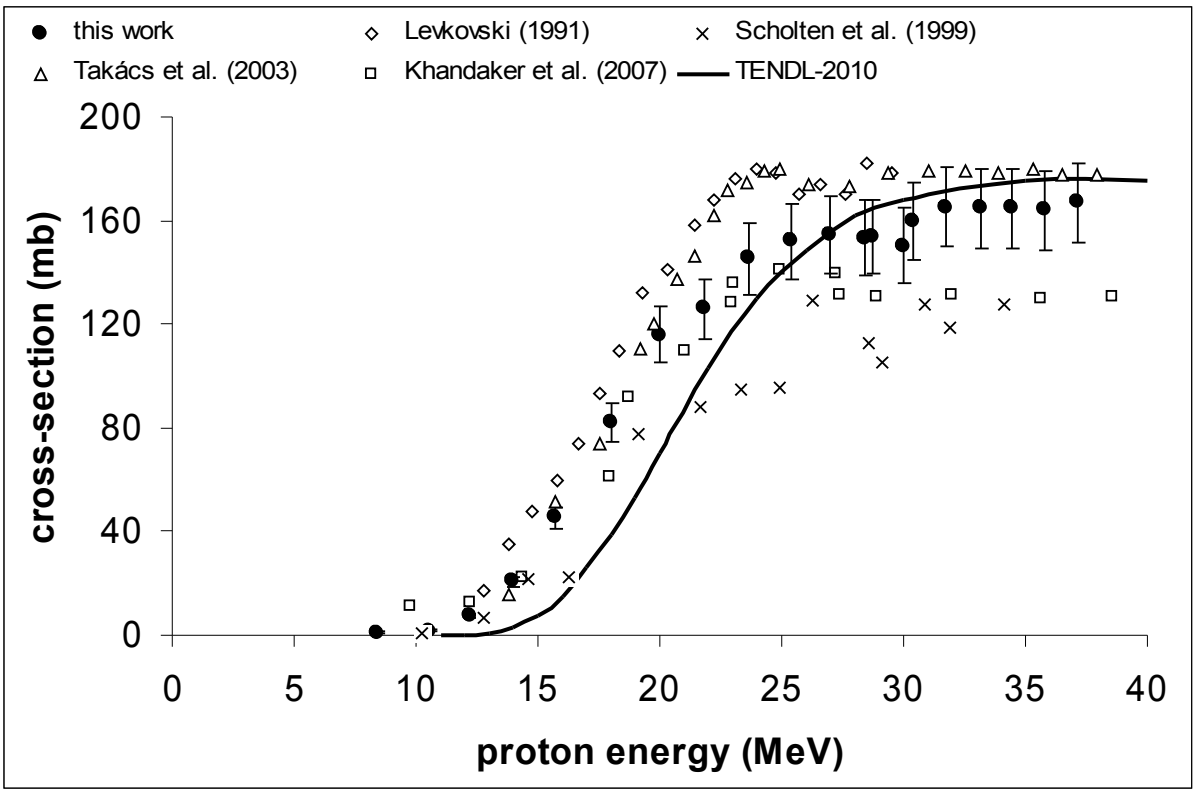
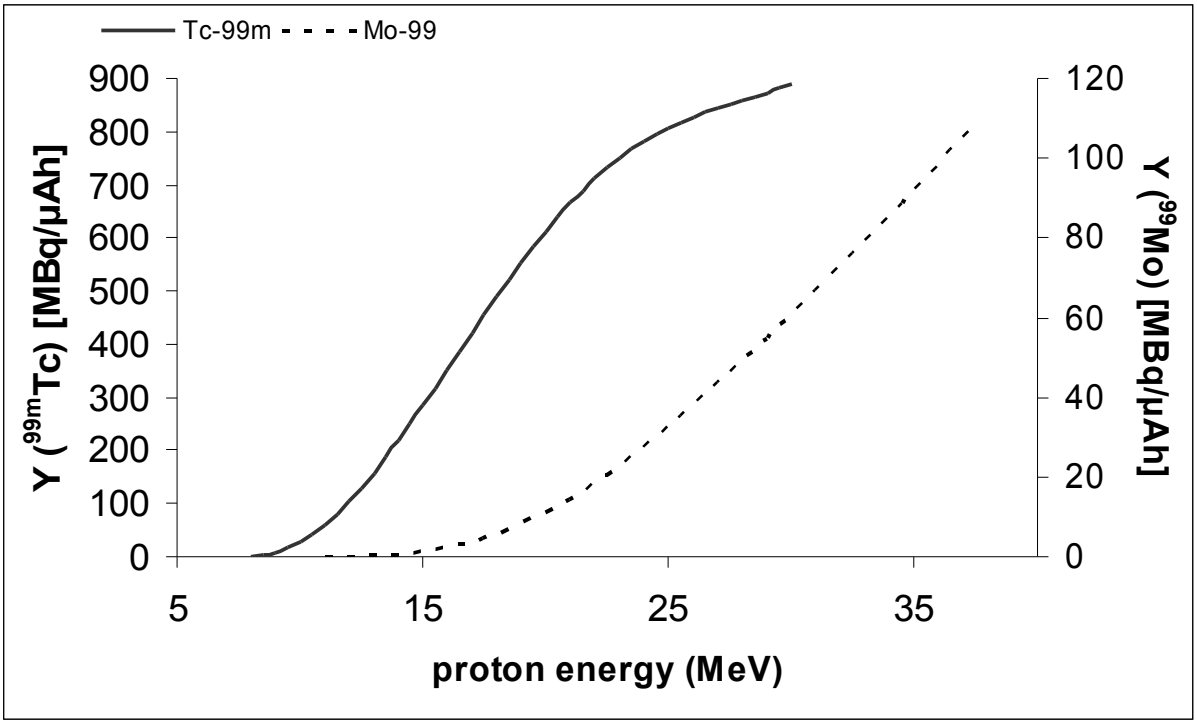


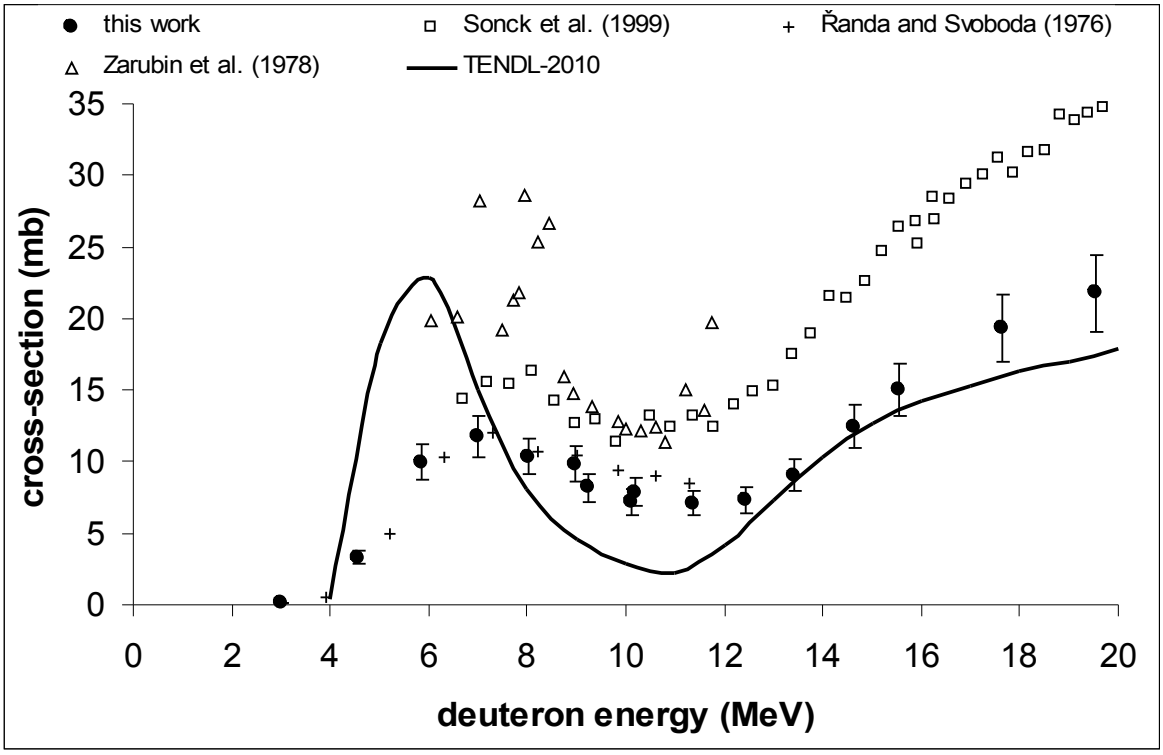
FIG. 3 Physical thick target yields of ^{100}Mo(p,2n)^{99m}Tc and ^{100}Mo(p,x)^{99}Mo reactions calculated from the data displayed on FIGS. 1 and 2



Physical thick target yields for ^{99m}Tc and ^{99}Mo calculated from the measured data are displayed on FIG. 3. Thick target yields of the former reaction would allow for the production of ca 1.7 TBq of ^{99m}Tc in 6 h irradiation with 500 μA beam at 24 MeV. This amount corresponds to the daily consumption of the Czech Republic or any large metropolitan area, even taking into account another 6 h necessary for target processing, ^{99m}Tc separation and purification, quality control and transport. Thick target yields of the latter reaction allow for production of ca 80 GBq of ^{99}Mo under the same conditions as assumed for production of ^{99m}Tc. Increasing the proton energy to 30 MeV (the maximum in commercially available production cyclotrons) would improve the production of ^{99}Mo to 177 GBq. In contrast to cyclotron production of ^{99m}Tc, production of ^{99}Mo via ^{100}Mo(p,x) reactions on highly enriched ^{100}Mo has certain drawbacks, e.g. low specific activity of ^{99}Mo, need to recycle ^{100}Mo from the generators etc. For efficient cyclotron production of ^{99}Mo, new, higher energy machines with E_p = 50 MeV would be necessary to develop and introduce on the market [27].

Experimentally determined cross-sections of the ^{nat}Mo(d,x)^{99m}Tc (^{99}Mo) reactions in the context of previously published data are displayed on FIG. 4 and FIG. 5. In the case of the ^{nat}Mo(d,x)^{99m}Tc reactions, our cross-sections [22] are significantly lower than those published in [14,15], but they correspond well with the work [12]. The forecast adopted from the TENDL-2010 library [26] is calculated from contribution of both ^{98}Mo(d,n) and ^{100}Mo(d,3n) reactions. It differs from our experimental results except of the 13–16MeV region.

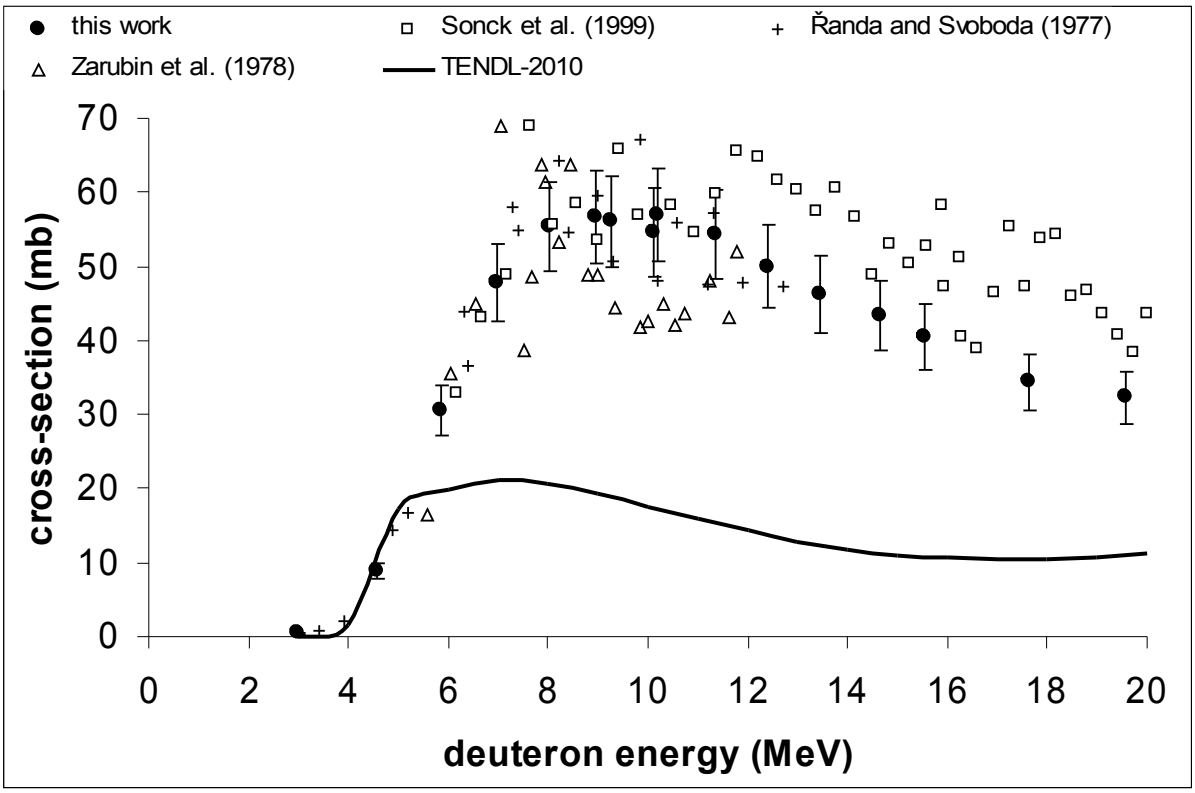
FIG. 4 Experimental cross-sections for the ^{nat}Mo(d,x)^{99m}Tc reactions in comparison with previously published data and prediction of TENDL-2010



The significant disagreement between our results [22] and the results of [14,15] seems to be due to the missing corrections for the contribution of indirectly born ^{99m}Tc from ^{99}Mo/^{99m}Tc that resulted in apparently higher ^{99m}Tc activity at EOB.

The measured cross-sections [22] for the ^{nat}Mo(d,x)^{99}Mo reactions are much lower for E_d > 12 MeV than the results of [15], they agree relatively well with the work [13] and are much less scattered than all the previously reported data [13–15]. The TENDL-2010 prediction starts to differ significantly from our data from E_d = 5 MeV and rapidly falls to ca 3× lower values.

FIG. 5 Experimental cross-sections for the ^{nat}Mo(d,x)^{99}Mo reactions in comparison with previously published data and prediction of TENDL-2010



Although both reactions have potential for routine production of both ^{99m}Tc and ^{99}Mo, they seem to be less favourable in comparison with proton-induced reactions on ^{100}Mo. Namely, reaction ^{98}Mo(d,n)^{99m}Tc has too low cross-sections, while much more promising ^{100}Mo(d,3n)^{99m}Tc reaction would require deuteron energies exceeding 20 MeV, i.e. far beyond the scope of commercially available production cyclotrons. The same is true for production of ^{99}Mo via the ^{98}Mo(d,p) and ^{100}Mo(d,t) reactions (and via decay of $^{99m+g}$Nb). The yields of these reactions resulting in ^{99}Mo are namely lower than those of proton-induced reactions, to say nothing about the problems that remain the same for production of ^{99}Mo from isotopic target material.

3.2 Assessment of radionuclidic impurities

Experimentally determined physical thick target yields for formation of ^{97m}Tc, $^{96m+g}$Tc, ^{95m}Tc, ^{95}Tc, ^{94m}Tc and ^{94}Tc in reactions on $^{95–98}$Mo are displayed in TABLE 2. The missing thick target yields for ^{94}Mo(p,n)^{94m}Tc and ^{94}Mo(p,n)^{94}Tc used in further considerations we calculated from cross-sections in [28].

TABLE 2 Experimental thick target yields for formation of various Tc isotopes on $^{95–98}$Mo

reaction	physical yield (MBq/μAh)					
energy (MeV)	9.94	16.02	18.00	19.80	22.04	24.11
^{97}Mo(p,n)^{97m}Tc	0.218	0.666	—	—	—	—
^{98}Mo(p,2n)^{97m}Tc	0	0.765	1.17	1.60	1.77	1.80
^{96}Mo(p,n)$^{96m+g}$Tc	17.1	65.9	71.6	73.3	72.8	74.2
^{97}Mo(p,2n)$^{96m+g}$Tc	0.26	48.8	81.0	102	126	136
^{98}Mo(p,3n)$^{96m+g}$Tc	0	0	0	0	1.70	7.37
^{95}Mo(p,n)^{95m}Tc	0.375	1.38	1.45	1.48	1.48	1.47
^{96}Mo(p,2n)^{95m}Tc	0	0.810	1.51	1.93	2.39	2.62
^{97}Mo(p,3n)^{95m}Tc	0	0	0	0	0.037	0.153
^{95}Mo(p,n)^{95}Tc	63.4	259	273	275	276	276
^{96}Mo(p,2n)^{95}Tc		122	240	326	413	493
^{97}Mo(p,3n)^{95}Tc					13.8	47.4
^{95}Mo(p,2n)^{94m}Tc		1 325	2 743	3 930	4 956	5 772
^{95}Mo(p,2n)^{94}Tc		215	481	738	985	1 248

Comparison of the calculation based on the data in TABLE 2 with the experiment determining activities of various radionuclides in highly enriched ^{100}Mo (^{100}Mo 99.03 %, ^{98}Mo 0.54 %, ^{97}Mo 0.08 %, ^{96}Mo 0.11 %, ^{95}Mo 0.09 %, ^{94}Mo 0.07 %, ^{92}Mo 0.08 %) irradiated with 23.8→12.5MeV protons is given in TABLE 3. Maximum difference between the both values was 20 %, well within uncertainties of the experimentally obtained yields in TABLE 2.

TABLE 3 Measured activities A_{EXP} in the two irradiated enriched ^{100}Mo targets in comparison with calculation based on the data in TABLE 2. Targets were irradiated for 5 min with 23.8→12.5 MeV protons of 1.94 and 0.91 μA current.

target no.	RN	^{99m}Tc	^{97m}Tc	^{96mg}Tc	^{95m}Tc	^{95}Tc	^{94}Tc	^{94m}Tc	^{93}Tc
1	A_{EXP} (kBq)	73 200	—	30.6	0.531	106.0	249	—	198
	A_{CALC} (kBq)		1.60	30.3	0.559	108.4	209	1158	—
	ΔA (%)		—	1.0	−5.1	−2.3	19.1	—	—
2	A_{EXP} (kBq)	33 460	—	14.4	0.232	49.0	118	—	93.3
	A_{CALC} (kBq)		0.752	14.2	0.263	51.0	98.2	544	—
	ΔA (%)		—	1.2	−11.7	−3.8	20.1	—	

Finally, we applied the data from TABLE 2 and from works [21,27] to the isotopic composition of the best commercially available enrichment of ^{100}Mo (^{100}Mo 99.54 %, ^{98}Mo 0.41 %, ^{97}Mo 0.0016 %, ^{96}Mo 0.0012 %, ^{95}Mo 0.0076 %, ^{94}Mo 0.0051 % and ^{92}Mo 0.006 %). Results are summarized in TABLE 4.

TABLE 4 The saturated thick target yields for Tc radioisotopes calculated from the data in TABLE 2 for proton beam energy loss 24→10 MeV and the best commercially available enrichment of ^{100}Mo. Relative activities A_{rel} of Tc isotopes were calculated from the saturated thick target yields for 6 h long irradiation time and 6 h cooling time.

RN	^{99m}Tc	^{97m}Tc	$^{96m+g}$Tc	^{95m}Tc	^{95}Tc	^{94m}Tc	^{94}Tc
Y_{sat} (MBq/μA)	6 508	23.3	4.98	0.543	0.660	0.848	0.798
A_{rel} (%)	99.97	0.0027	0.012	0.000094	0.062	0.00043	0.012

The European Pharmacopoeia sets the following limits on the content of radionuclidic impurities in generator-produced ^{99m}Tc at the time of administration: max. 0.1 % of ^{99}Mo and 0.01 % of other radionuclidic impurities. One can, therefore, expect that the requirement on radionuclidic purity of cyclotron-produced ^{99m}Tc would be at the level of 0.1 % at the time of administration. At most, individual limits could be set, in particular for longer-lived Tc radioisotopes. As obvious from TABLE 4, the overall content of other technetium radioisotopes in ^{99m}Tc is far below the level of 0.1 % for the best commercially available enrichment of ^{100}Mo.

The yields given in TABLE 2 cover only radionuclidic purity with respect to the relative content of technetium radioisotopes that cannot be separated from the produced ^{99m}Tc by chemical means, but can be controlled by isotopic composition of the target. Besides that, one has to take into account that significant amounts of ^{99}Mo, ^{97}Nb and ^{96}Nb are co-produced by proton activation of ^{100}Mo itself. Content of these radionuclides must be then reduced in the course of ^{99m}Tc separation from the target far below 0.1 %. It seems, however, to be feasible by optimizing known separation methods.

4 Conclusion

The recent supply crisis of ^{99}Mo/^{99m}Tc generators triggered off the search for alternatives to the production of ^{99}Mo by the fission of highly enriched ^{235}U in high flux research reactors, which are close to decommissioning. One of them is based on proton- and deuteron-induced reactions on ^{100}Mo and ^{98}Mo. A prerequisite for properly estimating the actual potential of cyclotron production of ^{99m}Tc and ^{99}Mo is the availability of reliable cross-sections and yields for the most promising reactions. Previously published data showed rather large scatter, thereby raising doubts whether the authors always applied all the necessary corrections for interferences present in measurement of ^{99m}Tc activity. Another, no

less important prerequisite, is a sound knowledge of the achievable radionuclidic purity of the product and its dependence on the composition of the target matrix and irradiation parameters.

We have, therefore, re-measured carefully the excitation functions of the proton- and deuteron-induced reactions on natural molybdenum and described in detail all the present interferences and the corrections we performed. It was revealed that the reaction ^{100}Mo(p,2n)^{99m}Tc seems to be the most promising from all the heavy-charged-particles-induced reactions, when it comes to the routine manufacturing of ^{99m}Tc or ^{99}Mo. We have also measured thick target yields for the production of various Tc radioisotopes on stable molybdenum nuclides $^{95–98}$Mo by protons. The results allowed us to model the radionuclidic purity of cyclotron-produced ^{99m}Tc as a function of proton beam energy and the isotopic composition of the enriched ^{100}Mo.

All the experimental data given above demonstrate that direct cyclotron production of ^{99m}Tc is a realistic concept that deserves further research and development, in particular in the following fields: high-current targetry, separation methods and quality control. The aim is to provide an efficient tool for replacing reactor-produced ^{99}Mo/^{99m}Tc generators by an elegant cyclotron-based technology supplying high amounts of ^{99m}Tc that meet Pharmacopoeia requirements for an acceptable price, while minimizing radioactive waste.

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