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Analysis of molybdenum-99 production at the WWR-K research reactor

A. Gurin[1,3] · Ye. Chakrova[1] · I. Matveyeva[3] · P. Riss[2] · D. Sairanbayev[1] · Z. Medvedeva[1] · Ye. Kulakova[1]

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Abstract
This article describes the preparation of ^{99}Mo isotope using the direct nuclear reaction ^{98}Mo(n,γ)^{99}Mo by neutrons of the WWR-K reactor using molybdenum (VI) oxide of natural and enriched composition, according to the isotope ^{98}Mo (98.66%) as a target. The possibility of using enriched ^{98}Mo oxide to produce ^{99}Mo was considered. The estimation of the maximum specific activity of ^{99}Mo was obtained in a comparative manner under the same irradiation conditions at the reactor.

Keywords Medical isotope production · Production of ^{99}Mo · WWR-K research reactor

Introduction

In recent years, there has been an intensive pace of development in the nuclear medicine and radiopharmaceuticals industry. The development of numerous methods of instrumental diagnostics not only does not reduce the demand for radionuclide diagnostics, but indeed contributes to its growth. This is because new methods are being introduced into clinical practice, and new research protocols are being developed using new radiopharmaceuticals. New generations of equipment appear every year.

One of the main methods of diagnosing oncological diseases at an early stage is diagnosis using radioactive isotopes. This approach is used to determine localization; conduct differential diagnostics between malignant and benign formations; assess the activity of tumour cells as a response to the therapeutic effects of drugs or radiopharmaceuticals, or after radiation therapy; and to assess the functional state of organs and physiological systems, and the number of diagnostic procedures. ^{99m}Tc is the main isotope used in the most common radionuclide diagnostic methods (more than 80%), which are single-photon emission computed tomography (SPECT) and planar scintigraphy [1]. The main source of the ^{99m}Tc isotope is the parent isotope, ^{99}Mo. ^{99}Mo decomposes into technetium-99 m within 66 h, as a result of which half of the activity is lost, and the activity of technetium-99 m decreases within 6 h, so the production of ^{99}Mo/^{99m}Tc generators is carried out continuously, one after the other, every two weeks [2].

Due to the fact that the ^{99m}Tc radionuclide has optimal nuclear physical properties—low energy of gamma radiation Ey = 140 keV, high yield of 89.1% and a short half-life of 6.01 h comparable to the duration of the study ^{99m}Tc isotope is the most promising and widespread gamma-emitting radionuclide for radionuclide diagnostics of oncological diseases worldwide [3]. Figure 1 shows a scheme for the production and decay of ^{99}Mo in ^{99m}Tc. Reactor methods are used to obtain the ^{99m}Tc isotope of high specific activity, and cyclotron methods are also being developed, but the main ways of producing the ^{99}Mo isotope are fission—that is, fission of uranium by the reaction of ^{235}U(n,f)^{99}Mo with an operating time of ^{99}Mo, practically, without a carrier, and 'activation' through the reaction of ^{98}Mo(n,γ)^{99}Mo (Fig. 2). Both methods relate to the reactor method of producing the ^{99}Mo isotope [4–6]. For a flux density up to 10^{14} n cm^{-2} s^{-1}, it is considered possible to obtain three levels of ^{99}Mo specific activity: by reaction (n,γ), in the case of a natural target of about 1 Ci ^{99}Mo/g Mo, enriched by the ^{98}Mo isotope of the target 4–10 Ci ^{99}Mo/g Mo, and in the case of reaction (n,f), 10,000–30,000 Ci ^{99}Mo/g Mo. However, not every

✉ A. Gurin
gurin.andrey@inp.kz

1 RSE Institute of Nuclear Physics, Ministry of Energy of the Republic of Kazakhstan, Ibragimov Str. 1, 050032 Almaty, Kazakhstan

2 University of Mainz, Mainz, Germany

3 Al-Farabi Kazakh National University, 71 Al-Farabi Ave., 050040 Almaty, Kazakhstan

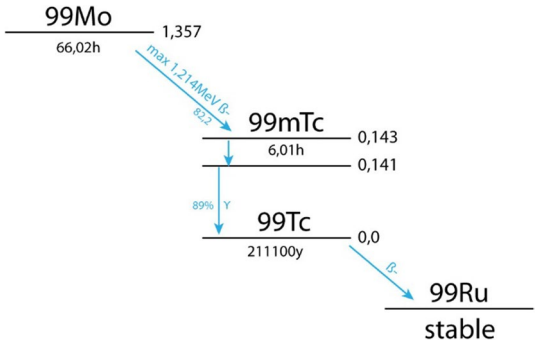

Fig. 1 ^{99}Mo and ^{99m}Tc decay scheme

organization can allow the production of ^{99}Mo using the fission method [7, 8].

The main producers of ^{99}Mo implementing these chains are high-tech companies in Australia, Canada, Belgium, Holland, France and South Africa. This makes up 95% of the global market; only 5% is regional production. The release of such drugs is carried out under the status of 'for clinical trials', but this is already a fully fledged production, with an entire infrastructure that ensures compliance with the requirements of good manufacturing practice (GMP), which are key in the production of medicines.

The main form of delivery of ^{99}Mo to the consumer is via a ^{99}Mo/ ^{99m}Tc generator; the requirements for its quality are determined by its application. After elution of the ^{99}Mo/^{99m}Tc-generator, an independent radiopharmaceutical is obtained in the form of sodium pertechnetate, which in turn is the basis for numerous radiopharmaceuticals used in SPECT diagnostics. More than 20 'cold' kits for labelling technetium-99 m are known and additional clinical trials with newly developed kits are currently underway (PSMA, etc.).

However, despite the prospects for using radiopharmaceuticals based on ^{99m}Tc, the constant growth in the volume of demand for ^{99}Mo in the Republic of Kazakhstan requires changes to the current production scheme.

This article presents the results of the development of a technological process for the production of the ^{99}Mo isotope at the WWR-K reactor from an enriched and natural target of molybdenum (VI) oxide.

It should also be noted that the Institute of Nuclear Physics (INP), using the research nuclear reactor WWR-K, has been producing molybdenum-99 by activation method from molybdenum (VI) oxide of natural composition for more than 20 years, and produces technetium-99 generators based on it, providing them to centers of nuclear medicine in Kazakhstan. About 120 generators are produced annually. Currently, the INP plans to conclude an agreement for 64 additional generators under the IAEA program to provide the Republic of Kyrgyzstan. Currently, several more nuclear medicine centers are being put into operation in our Republic and one is at the planning stage, which will have an impact on the growing demand for generators.

Theory

The cross-section of the ^{98}Mo(n,γ)^{99}Mo reaction on thermal neutrons is small and amounts to 0.13 barn, although at the same time, for epithermal neutrons (with an energy above 0.4 eV), the cross-section increases to 11.6 barn. So, the optimal choice of the irradiation site in the reactor core can significantly increase the activation of ^{98}Mo. The practically effective cross-section is about 0.5 barn; in some reactors it is possible to realize up to 0.8 barn of effective cross-section.

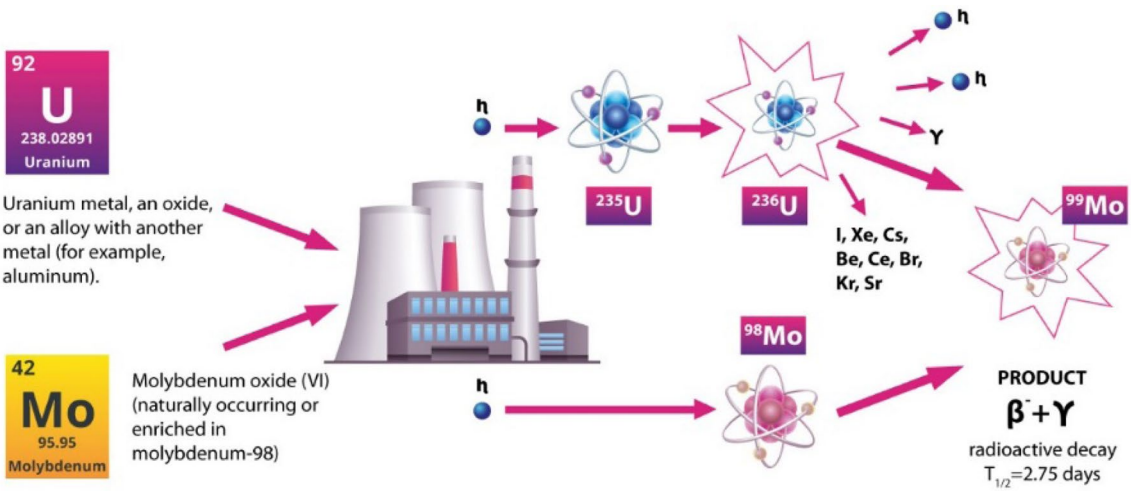

Fig. 2 Schemes for obtaining ^{99}Mo

As a result, when irradiated with molybdenum in a stream with a density of 10^{15} n cm^{-2} s^{-1} for 5 days, the specific activity can reach 14.5 Ci/g for a natural target, and for an enriched one about 60 Ci/g. The characteristic values of γ for the irradiation channels of research thermal reactors (except for high-current ones) are $\gamma = 0 \div 0.1$. Thus, at a flux density of 10^{14} n cm^{-2} s^{-1}, a specific activity of about 1 Ci/g is achieved in a target made of natural molybdenum trioxide, and in an enriched one up to 10 Ci/g. Some studies show the possibility of obtaining ^{99}Mo from a natural target with a specific activity of more than 2.5 Ci/g, with an average effective reaction cross-section of about 0.7 bar.

The assembly of the target involves loading a sealed quartz ampoule into an aluminum capsule and combining a plug and an aluminum capsule. After assembly, it is placed in the reactor channel to complete the training program.

Materials and methods

The ^{99}Mo isotope was obtained from molybdenum (VI) oxide of natural (24%) and enriched (98.9%) composition. All chemical reagents and solvents used corresponded to the chemically pure class and were supplied by well-known manufacturers. The purity of the radionuclide ^{99}Mo was determined using gamma spectrometry with a high-purity germanium detector (Ortec). The ^{152}Eu source (OSGI) was used to calibrate the detector for energy and efficiency. A NaI (Tl) ionization chamber was used for measuring total radioactivity (CAPINTEC, INC., CRC.-2PR, USA).

The WWR-K is a light, water-tank-type thermal reactor with a nominal power rating of 6 MW. Demineralized water serves as the moderator and coolant. Demineralized water and beryllium serve as the side reflectors. Core cooling was performed at a regular coolant flow rate of ~ 600 m^3/h. The enrichment of uranium-235 in the reactor fuel was 19.7%. The reactor was commissioned in 1967 and in 2016 was converted so it could use low-enriched fuel. Currently, the WWR-K reactor has been operating at 6 MW thermal power with the LEU core.

The reactor is intended for a variety of studies in the fields of fission and fusion materials science, radioisotope production, topaz coloration, doping of silicon, and neutron imaging.

Experimental

The technological process was based on the activation method for producing ^{99}Mo by irradiating starting material containing ^{98}Mo with neutrons from a nuclear reactor.

Natural molybdenum (VI) oxide (24%) enriched in the ^{98}Mo isotope (98.6%) was used as a starting material.

At the first stage of production, the starting material was packed into quartz ampoules.

A quartz ampoule for packaging molybdenum (VI) oxide and subsequent irradiation was manufactured in the laboratory according to developed drawings. The quartz ampoule was sealed by boiling it in distilled water for 10 min.

Test production of the ^{99}Mo isotope was carried out in a series of parallel experiments. The main differences in the experiments were associated with the irradiation of various targets by isotopic composition with a flux of thermal neutrons at the WWR-K reactor, in order to study the issue of obtaining the maximum value of specific activity and optimizing the process of transition to an enriched target Fig. 3.

Results and discussion

The irradiation device was designed for irradiation in the WWR-K reactor and could be installed at any irradiation position. The calculations considered an irradiation position located at the periphery of the reactor core.

Calculated by MCNP6 code the energy distribution of neutrons in the corresponding irradiation position shown in Fig. 4. was used for 98Mo(n,γ)99Mo reaction rate calculations [9–11].

Neutron-physical calculations for the irradiation device were carried out with the Monte Carlo method using the MCNP6.2 [12] transport code and the ENDF/B-VII.1 incident-neutron data [13]. The MCNP6 transport code is based on the random simulation of events of the interaction of neutrons and other particles with matter in a material environment. The code makes it possible to calculate various functions representing the convolution of a neutron or photon flux with nuclear physics data [14]. All tallies are normalized to be per starting particle which are normalized to be per fission neutron generation. The F4 tally (track length estimate of cell flux) was utilized for the flux analysis. Neutron energy levels can also be specified with the E4 tally energy card. The flux results are normalized to

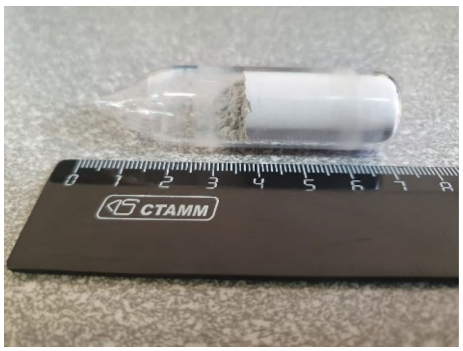

Fig. 3 Ampoule used in the production of ^{99}Mo/^{99m}Tc—generator

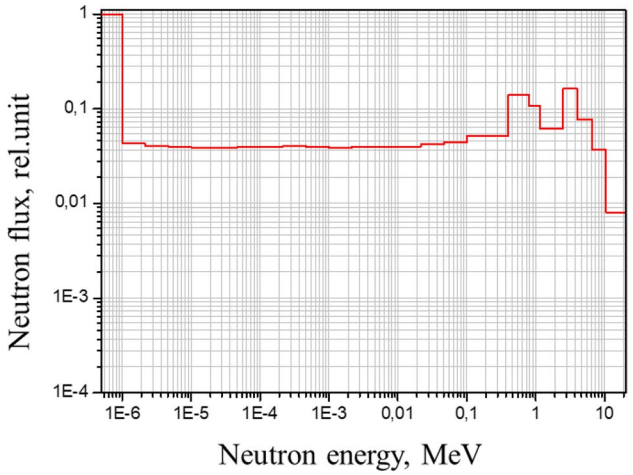

Fig. 4 Energy spectrum of neutrons in the considered irradiation position of the WWR-K reactor

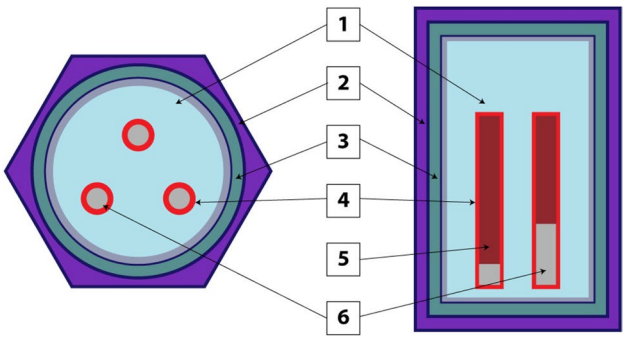

Fig. 5 Horizontal (**a**) and vertical sections (**b**) of the device: (1)—water, (2)—aluminium displacer, (3)—irradiation tube, (4)—quartz flask, (5)—air, (6)—molybdenum samples

6 MW and factor $5.12*10^{17}$ is used. Each input file included 500 cycles made of 20 inactive and 480 active cycles with 2,400,000 histories per cycle. As close the Monte Carlo model describes the real situation the calculations accuracy will be better. The most accurate results were obtained using a detailed heterogeneous model. This approach was used to describe the core of the WWR-K reactor. The simulation considered the actual composition of the reactor core, the fuel burnup in the fuel assembly, and the poisoning of the beryllium neutron reflector. The statistical error of the calculations did not exceed 5% Fig. 5.

The irradiation of the target with molybdenum-99 was carried out in the WWR-K reactor for 60 min. Channels of the core periphery were used to irradiate the ^{98}Mo isotope; under these conditions, the thermal neutron flux density of targets with ^{98}Mo was ensured at a level of $9.0•10^{13}$ n cm^{-2} s^{-1}.

Determination of the number of nuclei (activities) of the ^{99}Mo isotope accumulated during irradiation was carried out using gamma lines (181.1 keV, 366.4 keV, 739.5 keV and 777.9 keV) of irradiated samples of natural isotopic composition and enriched in the ^{98}Mo isotope (Fig. 6). Gamma spectra were measured using a semiconductor detector made of highly pure germanium, starting immediately after the end of irradiation (short-lived isotopes), and long-term measurements were carried out over a month (long-lived isotopes).

Recalculation of the experimental values of the number of produced nuclei of active ^{99}Mo isotopes in activity showed that the maximum that can be obtained is about 1 GBq/g with irradiation for 1 h; in the case of a target of natural composition that is enriched during irradiation with neutrons in the peripheral WWR-K channel, as the irradiation time increases, the difference will increase. Table 1 shows the experimental data, theoretical data of Mo-99 activity obtained by (1) which consider only thermal flux density and production cross-Sect. 0.13 barns, and MCNP calculations data. According to the data, the calculated MCNP data are in very good agreement with practical for enriched and natural targets, respectively (Table 1, Fig. 7).

$$\lambda N_{99}(t) = (1 - exp^{-\lambda t})N_{98}\sigma_{th}\Phi_{th} \quad (1)$$

The yield of ^{99}Mo and the specific activity of ^{99}Mo at the end of irradiation (EOB) are given. The ^{99}Mo yield values are given per 1 g of molybdenum and per neutron flux density of $9.0•10^{13}$ n cm^{-2} s^{-1}.

As a result of the irradiation of natural molybdenum, the isotopes ^{93}Mo and ^{101}Mo are simultaneously produced. In addition, isotopes such as ^{187} W ($\leq$0.01%), ^{60} Co ($(2 \div 6)\cdot10^{-6}$%) and ^{134} Cs ($(0{,}6 \div 2)\cdot10^{-5}$%) can be formed. This problem is partially solved by prolonged cooling of samples after irradiation in the case of short-lived isotopes or using highly enriched molybdenum with a minimum amount of impurities. Long-lived isotopes, as studies have shown, are contained at a low level and, during the production of the generator, are in the structure of a molybdenum-zirconium gel, when passing through which the saline solution, these impurities are not washed out, in addition, each generator is equipped with a filter made of active aluminum oxide, which is also a barrier to impurities of many metals. Thus, with a 5 day irradiation of 10 g of a natural target (500–600 GBq from saturation yield), one can expect more than 99% radiochemical purity of ^{99m}Tc.

Conclusions

Molybdenum-99, from which the technetium-99 m isotope is formed as a result of radioactive decay, is the most popular and promising radioisotope for radionuclide diagnostics.

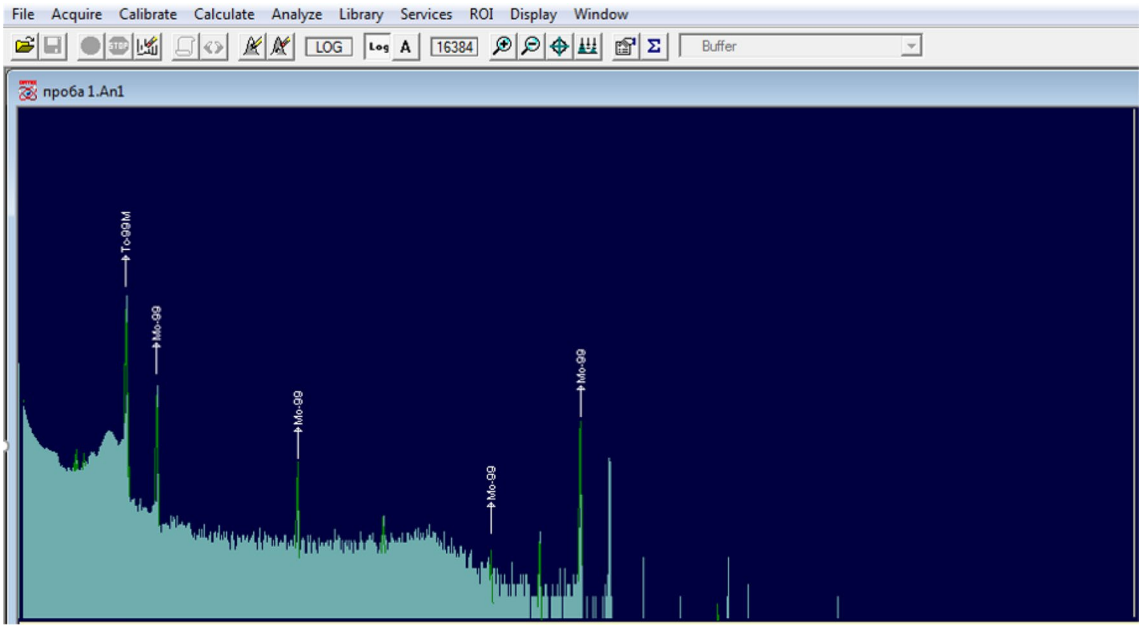

Fig. 6 Gamma-ray spectra of ^{99}Mo

Table 1 Comparative characteristics of experimental data with theoretical ones

	Practical significance		Theoretical calculation (EOB, single-speed approach)	MCNP calculations		C_T/E, C_{MCNP}/E
	Irradiation time [sec]	Cooling time [sec]	Irradiation time [sec]	Irradiation time [sec]	Cooling time [sec]	
Mo-99	3600	20880	3600	3600	20880	
	Activity, [MBq]					
Enriched target	**69 ± 14%**	*65*	*52*	*69 ± 6%*	*65 ± 6%*	*0.80, 1.00*
Target of natural composition	**16 ± 4%**	*15*	*13*	*16 ± 7%*	*15 ± 7%*	*0.87, 1.00*

The data are provided to simplify the reader's understanding of convergence and comparison in the results of the experiment and calculations

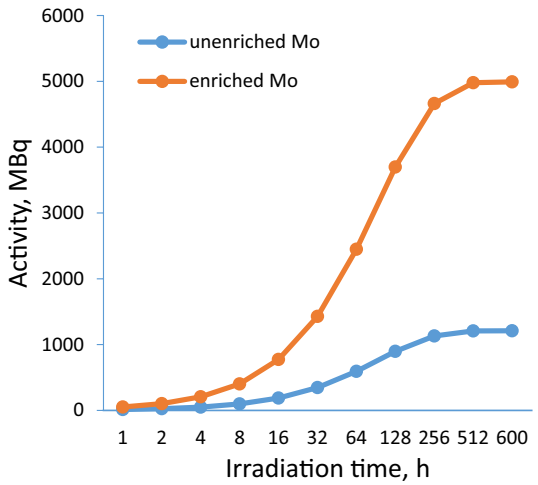

Fig. 7 Theoretical accumulated activity of ^{99}Mo

Molybdenum-99, from which the technetium-99 m isotope is formed as a result of radioactive decay, is the most popular and promising radioisotope for radionuclide diagnostics.

In the Republic of Kazakhstan, only at the WWR-K research reactor is it possible to produce molybdenum-99 using the nuclear activation reaction (n, γ). The reactor has a large number of irradiation positions with different neutron fluxes in it. Based on experimental data, the potential for producing high specific activity from natural and enriched molybdenum (VI) oxide was determined, which is important for the further development of molybdenum production and the possibility of switching to the fragmentation method for its production.

This study has shown the specific activity of ^{99}Mo in the amount of 1 GBq/g when irradiated for an hour, obtained

by irradiation at the WWR-K reactor with a thermal neutron flux of $9.0 \cdot 10^{13}$ n cm^{-2} s^{-1}, while the central channel flux can reach $1.2 \cdot 10^{14}$ n cm^{-2} s^{-1}, allows for a higher specific activity. This specific activity of ^{99}Mo is sufficient to cover the domestic market and neighbouring countries. The activity of the parasitic radioisotopes during this irradiation time is less than 1% of ^{99}Mo activity. Thus, the opportunity for the production of ^{99}Mo at the WWR-K reactor to use in targeted radionuclide diagnostics has been demonstrated.

We have recommendations for increasing the specific activity of ^{99}Mo:

– To consider the specific activity of ^{99}Mo by reaction (n,γ), it is necessary to use a target of enriched composition.
– To consider the possibility of developing a neutron trap with an increase in the neutron flux and the proportion of epithermal neutrons in the integral neutron flux.
- Consider introducing a fragmentation method for producing the ^{99}Mo isotope, but also note that this requires radiochemical separation of nuclides.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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