USING THE ^{100}MO PHOTONEUTRON REACTION TO MEET CANADA'S REQUIREMENT FOR ^{99m}TC

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SUMMARY

Drawing on work carried out at the Idaho National Laboratory in the 1990s, we show that a single national facility operating two 35 MeV, 100 kW electron accelerators to produce ^{99}Mo using the ^{100}Mo photoneutron reaction could supply all of Canada's requirements for ^{99m}Tc. Suitable industrial-grade accelerators are available from Mevex Corporation, and NorthStar Medical Radioisotopes has developed a ^{99m}Tc separator for low-specific activity material. An economic analysis indicates that the production cost of ^{99m}Tc would be less than the present market price. Using the NRC 35 MeV linac, we have tested all the steps in the process. Attractive features of the (γ, n) approach include: no use of uranium of any kind; simple chemistry for target dissolution; no significant radioactive waste; less than 24 hours between end-of-bombardment and the shipping of ^{99}Mo solution to nuclear pharmacies; and no significant change to the operation of nuclear medicine departments and pharmacies.

The most widely used isotope for medical imaging is ^{99m}Tc. In Canada alone, it is used for about 5500 scans per day. Most ^{99m}Tc, which has a half-life of about 6 hours, is derived from the decay of the parent isotope, ^{99}Mo. Because the half-life of ^{99}Mo is about 66 hours, the time scale during which ^{99m}Tc can be stored and shipped is extended by an order of magnitude compared to the direct production of ^{99m}Tc.

Until recently, the NRU reactor at Chalk River was a major producer of the world's supply of ^{99}Mo. The unexpected, and ill-defined, maintenance requirements of the NRU have led to a world-wide shortage of ^{99}Mo and the current isotope crisis.

Natural Resources Canada (NRCan), in response to the crisis, formed an Expert Review Panel to review Expressions of Interest (EoI) on ways to solve the isotope crisis. The National Research Council (NRC), with three collaborators, submitted an EoI which proposed the use of electron accelerators to produce ^{99}Mo using the ^{100}Mo photoneutron reaction.

Our proposal drew heavily on work carried out at the Idaho National Laboratory in the mid 1990s, where they had proposed the same approach [1]. They examined in detail how a single accelerator could supply the needs of the state of Florida, which has a population about half that of Canada, and showed that the economics were competitive with ^{99}Mo produced by reactors. The viability of the Idaho model was re-examined several years later by Nelson *et al* [2].

Using the NRC 35 MeV electron accelerator, we have demonstrated all the steps in the production process. We have also considered the economics of the process and conclude that a single national facility could produce all of Canada's requirements for ^{99}Mo and at a cost below that presently paid by nuclear medicine departments.

We will review the main features of our proposal, including the science underlying it, the key enabling technologies that are available, the economics of the process and work that we have done at NRC to confirm expected yields.

BASIC REQUIREMENTS

In order to define the technical requirements for a facility to produce ^{99}Mo, we must have estimates of the required production rates. From published work [3] one can determine that Canada requires at least 420 "six-day curies" of ^{99}Mo per week. The concept of the six-day curie is illustrated in Figure 1 and is intended to allow for delays in processing reactor-produced ^{99}Mo and building the ^{99m}Tc generators. If we were to assume the same model applies to accelerator-produced ^{99}Mo the end-of-bombardment (EoB) production rate must be at least 360 Ci/day.

An alternative estimate can be obtained by considering the demand for ^{99m}Tc. There are about 5500 scans per day in Canada, and each scan requires on average 20 mCi of ^{99m}Tc, giving a daily national requirement of 110 Ci.

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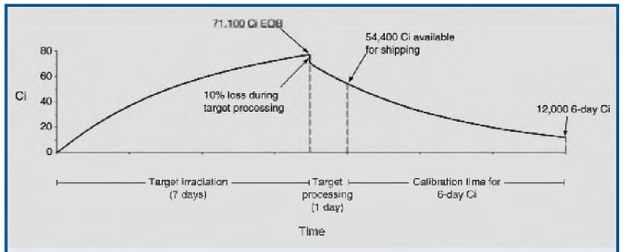

Fig. 1 ^{99}Mo production is specified in terms of the six-day curie. This means the end-of-bombardment target activity must be a factor of about 6 greater than the activity of the material supplied to the customer. (Taken from the US NRC study on "Medical Isotope Production without Highly Enriched Uranium".)

Figure 2 shows how a supply of ^{99}Mo can be milked on a 24-hour schedule to recover ^{99m}Tc, and thus the need for new ^{99}Mo should correspond to the loss over a 24 hour period, or about 31 Ci per day. The time from EoB to delivery of ^{99}Mo should be less than 24 hours, leading to a production requirement of about 40 Ci per day. This estimate is a factor of nine smaller than our earlier estimate and is largely because of the losses illustrated in Figure 1. In what follows, we assume the need to produce 360 Ci per day, but we believe the required production rate of a properly designed accelerator facility will be considerably less.

The giant dipole resonance in the (γ, n) reaction was discovered more than 60 years ago. For medium to heavy nuclei the cross section peaks between 10 and 20 MeV and has a width of several MeV. Photo-induced reactions in the molybdenum isotopes were first studied by Gellie and Lokan [4] and the maximum of the cross section for ^{100}Mo was observed at about 15 MeV.

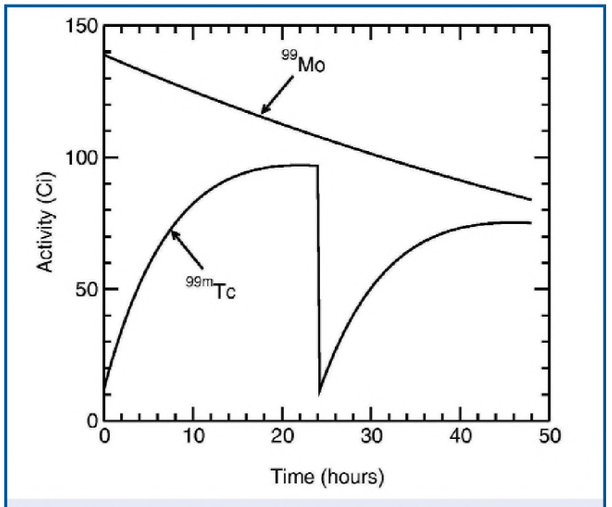

Fig. 2 A solution containing ^{99}Mo can be milked on a 24 hour cycle to recover the ^{99m}Tc activity. The branching ratio for the decay of ^{99}Mo to ^{99m}Tc is about 0.88 and an elution efficiency of 0.9 has been assumed.

^{100}Mo is technically not a stable nuclide, but its half-life of almost 10^{19} years means that, for practical purposes, in can be considered stable. It forms about 9.7 % of the isotopic composition of naturally-occurring molybdenum. Isotopic enrichment facilities, such as those operated in the Netherlands by Urenco, can produce molybdenum enriched to greater than 95 % in ^{100}Mo. Recent work on double beta decay [5] has used more than 1 kg of molybdenum enriched to 98 % in ^{100}Mo.

The bremsstrahlung process, whereby a high-energy electron is scattered by an atomic nucleus, can be used to produce a beam of high-energy photons [6]. The photon spectrum is continuous, with the fluence rate increasing smoothly from zero as the photon energy decreases below the kinetic energy of the incident electron. This means that the energy of the incident electron beam must be significantly higher than the energy of the peak of the photoneutron cross section. There is a trade-off between electron energy and beam power but an electron energy between 30 and 50 MeV is likely optimum [1,3].

Bennett *et al* [1] used Monte Carlo calculations that were tested against measured ^{99}Mo yields to determine the optimum target geometry. They concluded that a cylindrical target, 1 cm in diameter and 2 cm long would be a satisfactory compromise. Their calculations showed that such a target, irradiated for 24 hours by a 14 kW, 40 MeV beam, would yield 25 Ci of ^{99}Mo. This result is consistent with calculations carried out by Diamond and summarized in the TRIUMF task force report [3]. Using the above estimates, two 100 kW machines could produce 360 Ci of ^{99}Mo per day.

After irradiation, the metal targets must be dissolved so that the ^{99m}Tc, which is continually being formed from the decay of ^{99}Mo, can be extracted. Molybdenum can be dissolved in nitric acid or hydrogen peroxide to form MoO_3. A wide range of techniques have been developed to separate the technetium from the molybdenum oxide. The Idaho group developed a sublimation process that takes advantage of the difference in vapour pressures between the technetium and molybdenum oxides. However, most techniques use columns that selectively bind either the technetium or molybdenum while in solution.

KEY TECHNOLOGIES

Electron Linear Accelerators

Industrial electron linear accelerators delivering 50 kW of beam power at 10 MeV are in routine use for radiation processing. Typically, these machines do not operate at energies greater than 10 MeV to avoid activating the product. The beam current required to deliver 50 kW at 35 MeV is less by a factor of 3.5 than that required at 10 MeV. Thus, current injection and transport is not a limitation to achieving 100 kW at 35 MeV. Furthermore, the energy of a linear accelerator can be increased by adding identical accelerating sections, perhaps the most famous example being the Stanford linear accelerator.

Mevex Corporation (http://www.mevex.com/) has extensive experience building high-power, industrial grade, linear accel-

Fig. 3 A Mevex 25 MeV, 25 kW electron accelerator. The machine uses two identical accelerating sections, each fed by an S-band klystron.

erators. Figure 3 shows a 25 MeV, 25 kW machine recently installed in Germany. Adding two additional accelerating sections and associated modulators will produce a 35 MeV, 100 kW electron beam. The overall length of the machine will be about 3 m and will require about 650 kW of electrical power.

Isotope Enrichment

The availability of molybdenum highly enriched with ^{100}Mo gives a ten-fold increase in yield over what could be achieved with naturally occurring molybdenum. There are at least two facilities that can produce large quantities of ^{100}Mo using gas centrifuges. The amount of material required for a national facility is largely determined by the frequency at which one recycles target material. Assuming the spent solutions are allowed to decay for 40 days, an inventory of about 1200 g of ^{100}Mo would be required. Even at the present cost of 2 k$/g, the purchase price of an adequate supply of ^{100}Mo is much less than the cost of the accelerators. Furthermore, one supplier has indicated that the cost will drop significantly once production rates are increased and orders for ^{100}Mo approach the kg range.

^{99m}Tc Separators

The operation, characteristics and advantages of the NorthStar automated radionuclide separation (ARSII) are discussed in detail in a recent paper [7]. In the most common technetium generator, the Mo is retained on an alumina column and the technetium washed off. Although this approach works well if the specific activity of the ^{99}Mo is high, as is the case for ^{99}Mo obtained as a fission product, it is not practical for ^{99}Mo produced by the photoneutron reaction, where the specific activity is two orders of magnitude smaller. The ARSII reverses the approach of the conventional generator and uses a column that selectively retains the technetium as the parent solution passes over it. Thus, the technetium can be extracted from a relatively large volume of parent solution. Once the column is cleared of the parent solution, a separate saline rinse of the column removes the technetium as sodium pertechnetate, meeting the same specifications as the solution obtained from a conventional generator.

The ARSII, shown in Figure 4, is designed with a view to obtaining regulatory approval and is already in clinical trials for the separation of other daughter-parent isotopes. Although the chemistry involved is quite different than that of a conventional generator and the device is technically more complicated, it should not lead to any significant changes in the operation of nuclear pharmacies. Whereas the conventional generator is shipped to the pharmacy the ARSII would be permanently installed and only the solution containing the ^{99}Mo would be transported.

Fig. 4 The Automated Radionuclide Separator (ARSII) developed by NorthStar. The parent solution, in a lead container, is connected to the unit on the left and the product is delivered on the right. A typical run takes about 60 minutes and is fully automated.

ECONOMICS

We estimate that two 100 kW electron accelerators could easily meet Canadian requirements for ^{99}Mo. The capital costs for a single national facility are estimated to be about 35 M$ and are dominated by the cost of the accelerators. The variable costs are dominated by the cost of capital but utilities, maintenance and staff salaries are also significant contributions. We estimate the variable costs to be about 10 M$ per year, and lead to a production cost of ^{99m}Tc well below the current price of about 100 ¢/mCi to the end user. A single scan requires about 20 mCi of ^{99m}Tc so the cost of the isotope is a small part of the total cost of a scan, which is estimated to be about $200.

RESULTS FROM NRC

The NRC 35 MeV, 2 kW electron accelerator is well suited for testing the photoneutron production of ^{99}Mo. Although the Idaho study was comprehensive, their work was based largely on calculated yields so independent tests of the production rates are important. Another important goal is to test the operation and separation efficiency of the ARSII. While the NRC linac cannot produce clinically relevant quantities, it can produce enough material for a robust test of all the steps from irradiation through to the elution of ^{99m}Tc solution which, in principle, is ready to be injected into a patient. Although we have purchased small quantities of molybdenum enriched in ^{100}Mo all our tests to date have been with natural molybdenum.

For one test, we measured and calculated production rates as well as the radial distribution of activity within the target. Two molybdenum disks, each 2 cm in diameter and separated by 1.8 cm were irradiated as shown in Figure 5. The total activity of each disk was measured using a Ge detector with a known efficiency. The activity as function of position on each disk was also determined by mounting the molybdenum disk behind a 1 mm lead collimator and measuring the count rate as the disk position was changed.

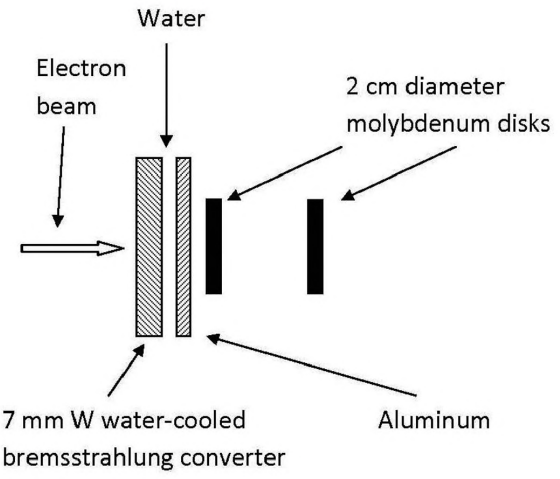

Fig. 5 Irradiation geometry. The electron beam energy was 35 MeV and the average beam current 40 μA. Each molybdenum disk was 1 mm thick and they were separated by 1.8 cm. The figure is not to scale.

The Monte Carlo calculations were carried out using the MCNP5 code and the (γ, n) cross section for ^{100}Mo was taken from the work of Beil *et al* [8]. The electron beam was simulated as a pencil beam having a radius of 2.5 mm.

The measured and calculated yields are given in Table 1. There is an indication that the calculated yields are about 25 % larger than the measured values, although results with smaller uncertainties are needed for a definitive conclusion. The measured and calculated profiles for the upstream disk are shown in Figure 6. The results are plotted as activity per unit radial distance, to give an indication of the relative importance of various parts of the disk to the total activity.

TABLE 1

Comparison of the measured and calculated ^{99}Mo yields for the two disks irradiated as shown in Figure 5. The disks were irradiated for about 1 hour at a beam power of 1.5 kW. More specifically, 0.15 C of charge was stopped in the converter.

	Upstream plate	Downstream plate
Measured (mCi)	0.57 (+/- 10 %)	0.32 (+/- 10 %)
Calculated (mCi)	0.72 (+/- 10 %)	0.38 (+/- 16 %)
Differences	25 %	20 %

Electron scattering in the fully-stopping tungsten converter tends to broaden the angular distribution of the photon beam and the tungsten also attenuates the photons. We have done a model study in which we calculated the induced ^{99}Mo activity as the thickness of the converter was decreased. The yield is largest for a 1 mm tungsten converter, but only by a few percent compared to using no converter at all. Figure 7 shows the activity for the case when the electron beam impinges directly on a cylindrical molybdenum target, 1 cm in diameter and 2 cm long. The beam parameters corresponding to those proposed for the national facility have been used.

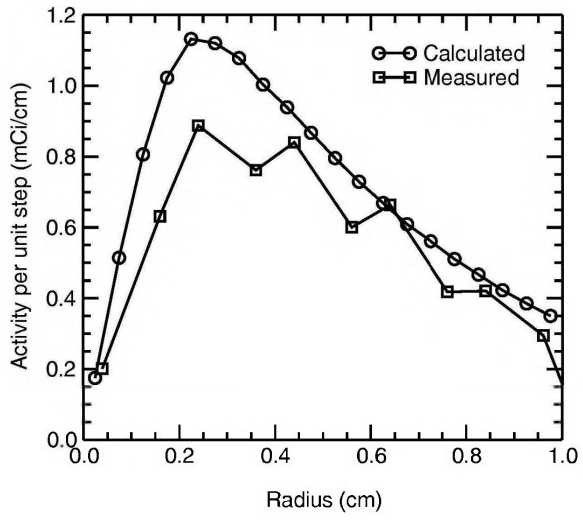

Fig. 6 Measured and calculated profiles of ^{99}Mo activity for the upstream disk, irradiated as shown in Figure 5. The results are shown as activity per unit radial distance to better indicate the contribution of various parts of the disk to the total activity. There is little contribution from the centre of the disk because there is little material there, even though that is where the photon fluence rate is largest.

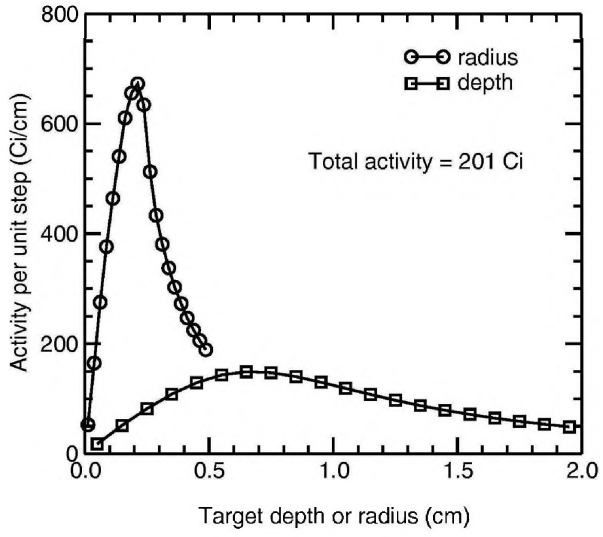

Fig. 7 Calculated activity for a 35 MeV, 100 kW, electron beam impinging on a cylindrical target of ^{100}Mo, 1 cm in diameter and 2 cm long. The simulated irradiation period was 24 hours. The radial profile was calculated for cylindrical rings the length of the target while the depth profile was calculated for radial slices across the target.

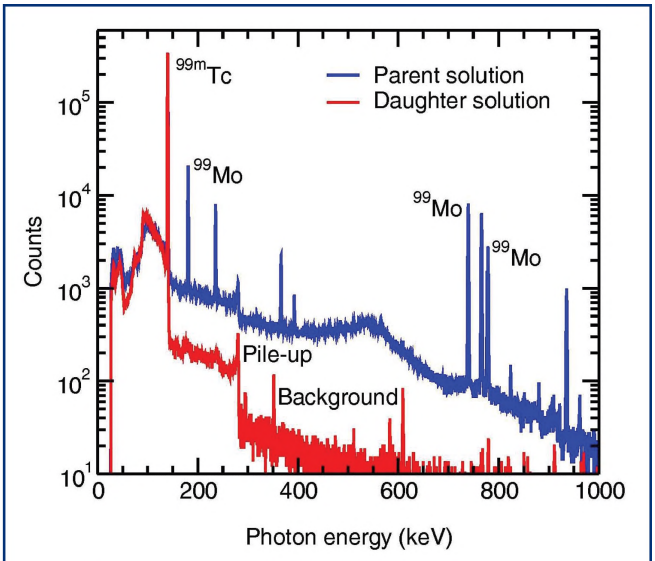

Fig. 8 Gamma-ray spectra of the parent solution (blue) presented to the ARSII separator and of the product solution (red). The edge at 280 keV is due to the pile-up of two ^{99m}Tc lines.

In order to test the performance of the ARSII separator, we have irradiated molybdenum pellets, 1 cm in diameter and 1 mm thick. The pellets were dissolved using 30 % H_2O_2 to form MoO_3, and the oxide was dissolved in 6 M NaOH. The ^{99m}Tc activity of the saline product was measured and compared to that of the parent solution. Separation efficiencies of about 90 % have been observed, consistent with values reported in the literature. Figure 8 compares the spectra of the parent and daughter solutions. Apart from lines related to the natural background, only the 140 keV ^{99m}Tc line is present in the product solution.

IMPLEMENTATION

We envision a single national facility to produce ^{99}Mo for the Canadian market. The facility would be designed to accept two 35 MeV, 100 kW linacs, but would likely begin operations with only one while the market and distribution network was established. Each linac would irradiate a 15 g target of ^{100}Mo for a 24 hour period. The target would be removed and over the next 12 to 24 hours it would be dissolved and aliquoted for shipping in shielded containers designed to connect to the input of the ARSII separator.

At the nuclear pharmacy, the aliquot would be milked once a day for up to 10 days using the ARSII to recover the ^{99m}Tc. The spent aliquot would be stored for several days at the nuclear pharmacy before being returned to the central facility. Because only a few µg of ^{100}Mo are transmuted for each 100 Ci of ^{99}Mo produced, the target material would be recycled.

OUTLOOK

After reviewing all 22 EoIs, the NRCan Expert Panel concluded that "The lowest-risk path to new ^{99}Mo/^{99m}Tc production capacity is to build a new multi-purpose research reactor." With regard to linear accelerator options they stated "… we prefer the technology based on ^{100}Mo transmutation since the projected economies appear better, and it largely avoids nuclear waste management issues".

Potential investors are reviewing the details of our photoneutron approach to determine if a viable business case can be made. They must be satisfied that they have robust access to the key technologies and that they will have fair access to the isotope market.

As part of our EoI, we proposed the construction and operation of a full-scale demonstrator before constructing a national facility. We identified a suitable location on NRC grounds and have estimates for preparing the site and establishing the necessary infrastructure. The demonstrator would be used to test and refine all the steps in producing large-scale quantities of ^{99}Mo. Subject to regulatory approval, it could also be used in the short term to produce clinically relevant quantities of ^{99}Mo. We estimate the time from the beginning of site preparations to the conclusion of the demonstrator phase to be about two years at a cost of 12 M$. Most of the equipment would be available for the national facility and represents about 9 M$ of the cost.

Although our focus has been on the production of ^{99}Mo because of the dominant role of ^{99m}Tc for medical imaging, the photoneutron reaction can be used to produce other isotopes that have applications for imaging or therapy. In particular, ^{123}I

can be produced via the ^{124}Xe(γ, n)^{123}Xe reaction, with ^{123}Xe decaying to ^{123}I with a 2-hour half-life. Xenon gas, enriched in ^{124}Xe, is commercially available and there have been several investigations of the production rate using low-power linacs.

Other than a nuclear reactor, which is at least an order of magnitude more expensive, we believe that the electron accelerator route is the best option for producing large quantities of ^{99}Mo. We are cognizant of the fact that the Idaho proposal in the 1990s seemed equally compelling but was never exploited commercially. A major reason may have been the reluctance of the business community to invest in a process that would be in competition with the Maple reactors. The present climate may be more favourable to a new approach, given the fragile nature of the present, reactor-based, supply chain.

CONCLUSIONS

Several possible solutions to the isotope crisis are under consideration. Most of these propose alternative methods for producing ^{99m}Tc, but some look for ways to lessen the dependence on ^{99m}Tc.

The established advantages of ^{99m}Tc suggest that it will remain an important isotope for medical imaging, assuming a reliable and inexpensive supply is available. We believe that the transmutation of ^{100}Mo using electron accelerators represents the best option for producing ^{99}Mo on a national scale. The process eliminates concerns surrounding the use of uranium, generates almost no waste, can be implemented on a relatively short time scale, produces minimum disruption to the operation of nuclear medicine departments and is economically competitive with reactor-produced ^{99}Mo.

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