# Alternative production methods to face global molybdenum-99 supply shortage


## Abstract

The sleeping giant of molybdenum-99 ($^{99}$Mo) production is grinding to a halt and the world is wondering how this happened. Fewer than 10 reactors in the world are capable of producing radio nuclides for medicine; approximately 50% of the world's supply of raw material comes from National Research Universal (NRU) reactor in Canada. Many of these reactors, like the NRU, are old and aging. No one of these reactors, and probably not even all of them in combination, can replace the production of NRU. As the healthcare industry faces an aging population and the demand for diagnostic services using $^{99m}$Tc continues to rise, the need for a consistent, reliable supply of $^{99}$Mo has become increasingly important, so alternative methods to produce $^{99}$Mo or even directly $^{99m}$Tc had to be considered to avoid a supply shortage in the coming years. This need guides to the production of $^{99}$Mo by replacing the Highly Enriched Uranium (HEU) target in a nuclear reactor with Low Enriched Uranium (LEU) and furthermore to the use of accelerators for manufacturing $^{99}$Mo or for directly producing $^{99m}$Tc.


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## Introduction

Molybdenum-99 ($^{99}$Mo) is an isotope of the element molybdenum, a metal discovered in the 18th century and is produced using highly enriched uranium (HEU) targets. Brookhaven reactor pioneered research using subatomic particles as tools to investigate the structure of matter. The Brookhaven High Flux Beam Reactor first achieved a self-sustaining chain reaction on October 31, 1965. For over 30 years, this reactor was one of the two premier beam reactors in the world, the other being the Institut Laue-Langevin reactor in Grenoble, France [1].

Nowadays $^{99}$Mo is produced in only six nuclear reactors in the world: High flux reactor (HFR) in The Netherlands, National Research Universal (NRU) in Canada**,** Belgium reactor (BR2), Safari1 in Africa, Osiris in France and Maria in Poland, two of which are considering to have highly uncertain production [2-3]. The location and the percent of the global market produced by each are as follows: Canada (33%), The Netherlands (32%), South Africa (15%), Belgium (6%) and France (6%) with others supplying the remaining 8%, mostly for national or regional consumption, as it is shown in Figure 1. The average age of these reactors is 47 years [4]. Concern is now mounting about the age, safety and reliability of these reactor operations following a series of well publicised technical problems and unscheduled plant shutdowns. New reactors are urgently needed to prevent future shortages of $^{99}$Mo, and hence technetium-99m ($^{99m}$Tc).

On 17 February 2010, Covidien and the Institute of Atomic Energy in Poland have agreed to augment the global supply of $^{99}$Mo by adding the Poland's Maria Research Reactor to the company's supply chain. The reactor, located approximately 30km southeast of Warsaw, first operated from 1975 until 1985 when it was taken off-line for a complete redesign and resumed normal operations in 1993. Maria is considered to be a relatively new reactor, with an operating life extending beyond 2020. The U.S. Food and Drug Administration (FDA) and Health Canada have approved (11 March 2010) the use of the Maria Research Reactor in Poland as a site to irradiate HEU targets for $^{99}$Mo production [5-6].

The raw material, which is produced in a nuclear reactor, is then transferred to a processing facility where it is purified through a multi-step process. The finished raw of $^{99}$Mo is sent to generator manufacturers to introduce them in medical markets (Fig.1) for use of its decay product $^{99m}$Tc in medical applications. In 1959 the U.S. Brookhaven National Laboratory (BNL) started to develop a generator to produce $^{99m}$Tc from the reactor fissionable product $^{99}$Mo, which has a much longer half-life. The first $^{99m}$Tc radiotracers were developed at the University of Chicago in 1964. Between 1963 and 1966, the interest in $^{99m}$Tc

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grew as its numerous applications, as a radiotracer and diagnostic tool, were described in publications. By 1966, BNL was unable to cope with the demand for $^{99}Mo/^{99m}Tc$ generators and withdrew from production and distribution, in favour of commercial generators. The first commercial generator was produced by Nuclear Consultants, Inc. of St. Louis, later taken over by Mallinckrodt (Covidien), and Union Carbide Nuclear Corporation, New York [7].

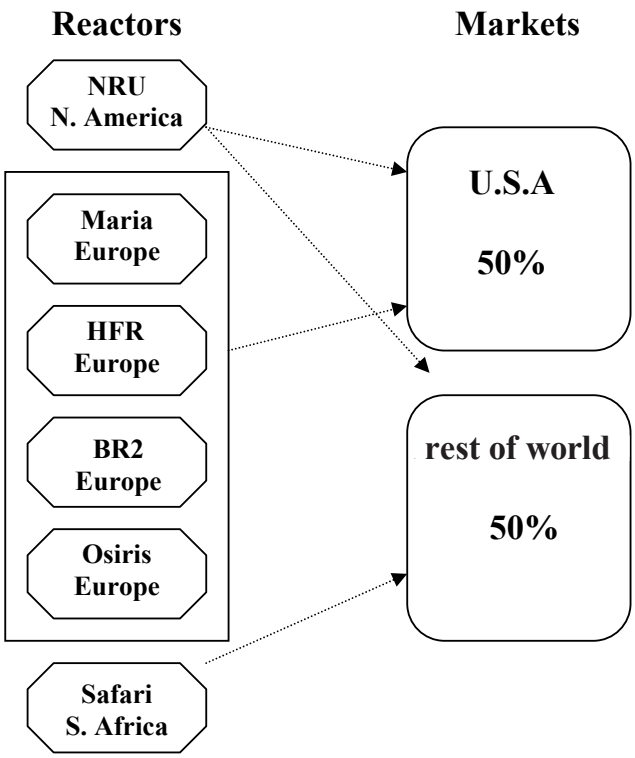


**Figure 1.** Current $^{99}Mo$ suppliers in 2010.

## Uranium ($_{92}U$)

*Natural uranium* found in the Earth's crust consists almost entirely of $^{238}U$; only about 0.7% is $^{235}U$. *Uranium-238* ($^{238}U$) is the most common isotope of uranium found in nature. It is not fissile, but is a fertile material: it can capture a slow neutron and after two beta decays becomes fissile plutonium-239. $^{238}U$ is fissionable by fast neutrons, but cannot support a chain reaction because inelastic scattering reduces neutron energy. It has a half-life of $4.468X10^9$ years, or 4.468 billion years radiates alpha-particles and decays into $^{234}U$, which has a half-life of 245,500 years. The relation between $^{238}U$ and $^{234}U$ gives an indication of the age of sediments that are between 100,000 years and 1,200,000 years in age.

*Highly enriching uranium* (HEU) includes enough $^{235}U$ to maintain a chain reaction. $^{235}U$ nucleus can release energy by splitting into smaller fragments, which then hit and split other $^{235}U$ atoms, and so on. When the $^{235}U$ component is enriched to 90% or more the atoms abide fission in the controlled conditions of a nuclear reactor. HEU is also used in fast neutron reactors, whose cores require about 20% or more of fissile material. Significant quantities of HEU are used in the production of medical isotopes and molybdenum-99 for technetium-99m generators. Highly enriched uranium is a critical component for both civil nuclear power generation and military nuclear weapons. The International Atomic Energy Agency (IAEA) attempts to monitor and control enriched uranium supplies and processes in its efforts to ensure nuclear power generation safety.

*Low enriched uranium* (LEU) is considered to be enhanced with less than 20% of $^{235}U$. Uranium enriched to three to five per cent, for example, is used to fuel reactors that generate electricity. Fresh LEU used in research reactors is usually enriched 12% to 19.75% $^{235}U$.

In the 1970s, recognizing the risks of nuclear proliferation and terrorism associated with civilian use of HEU, both the U.S. and Soviet governments launched programs to facilitate the substitution of HEU by non-weapon-usable LEU, containing less than 20% $^{235}U$, for use HEU in civilian research-reactor fuel and in radionuclide production targets. This program is now international [8, 9].

Molybdenum-99 ($^{99}Mo$) and some important medical isotopes can be produced either in a HEU or a LEU reactor.

## Molybdenum ($_{42}Mo$)

Molybdenum is a Group 6 chemical element with atomic number 42. The name comes from Ancient Greek μόλυβδος *molybdos*, meaning *lead*, since its ores were confused with lead ores. The free element is a silvery metal. It readily forms hard, stable carbides, and for this reason it is often used in high-strength steel alloys. Molybdenum does not occur as the free metal in nature, but rather in various oxidation states in minerals.

Molybdenite is the principal ore from which molybdenum is now extracted and was previously known as molybdenite which was often implemented as it were graphite. Even when molybdena was distinguishable from graphite, it was still confused with a common lead ore, called galena. In 1754, Molybdenite examination results showed that it did not contain lead. Molybdenum was differentiated as a new entity from minerals salts of other metals in 1778. The metal was first isolated in 1781.

There are 35 known isotopes of molybdenum ranging in atomic mass from 83 to 117, as well as four metastable nuclear isomers. Of the seven naturally occurring isotopes, only molybdenum-92 ($^{92}Mo$) and molybdenum-100 ($^{100}Mo$) are unstable and decay into isotopes of niobium, technetium and ruthenium. Molybdenum-98 ($^{98}Mo$) is the most abundant comprising 24.14% of all Mo.

The production of $^{99}Mo$ by neutron irradiation of targets of HEU or of LEU in a nuclear reactor is organized in terms of three processes. Fabrication of uranium targets, irradiation of targets in a nuclear reactor and dissolution of the uranium target, recovery and purification of $^{99}Mo$. The $^{99}Mo$ is a parent radioisotope to the short-lived gamma-emitting daughter radioisotope $^{99m}Tc$, the nuclear isomer which $^{99m}Tc$ is used in nuclear medicine imaging [10-11].

### *$^{99}Mo$ in medical applications*

Technetium-99m is the most widely utilized radionuclide in the world for molecular and nuclear diagnostic imaging tests. At over 18.5 million doses, $^{99m}Tc$ accounts for 82% of all diagnostic radiopharmaceutical injections each year. This isotope has a half-life of about 6 h and emits 140keV photons as it decays to $^{99}Tc$, a radioactive isotope with about 214,000 years half-life. Technetium-99m is a critical component of many medical imaging tests, referring to almost all organs of the human body. When a $^{99}Mo/^{99m}Tc$- pertechnetate ($^{99m}TcO^-_4$) generator is eluted to obtain $^{99m}Tc$ , a very small amount

of $^{99}$Mo is released too. The generator can no longer be used when the amount of $^{99}$Mo in the eluted solution exceeds a certain level.

As the healthcare industry faces an aging population and the demand for diagnostic services continues to rise, the need for a consistent, reliable supply of $^{99}$Mo has become increasingly important [12]. Because of its relatively short half-life (66h), $^{99}$Mo cannot be stockpiled for use. It must be made on a weekly or more frequent basis to ensure continuous availability. The processes for producing $^{99}$Mo/$^{99m}$Tc generators as well as for delivering them to customers are tightly scheduled and highly time dependent.

*The shortage of $^{99}$Mo availability in the world today*

Chronically, $^{99}$Mo shortages come and go, as it is shown in Table 1 [13]. However, the acute and worsening shortage moving into the first quarter of 2010 has not only impacted patient access to care, but has some countries wondering about the future of nuclear medicine [2].

Programmed production and deliveries of $^{99}$Mo could be stopped for any reasons. For example, a planned maintenance of a reactor or an unscheduled shutdown of a reactor because of a strike would be followed by a shortage in $^{99}$Mo production. In June 1997, radiopharmaceutical suppliers were scrambling to find alternate suppliers of $^{99}$Mo after a strike commenced on June 19 at the NRU reactor in Chalk River, Canada. The reactor owned by the Atomic Energy of Canada Limited (AECL) was used by Nordion International in Kanata, Canada. Nordion supplied, then, 60% of $^{99}$Mo in North America for use in the production of $^{99m}$Tc-labelled radiopharmaceuticals. The strike was resolved on June 24 1997 and the reactor was back on line that evening [14].

Similarly any problems related to the transportation of $^{99}$Mo, can lead to a shortage. The Maria Research Reactor in Poland began to produce $^{99}$Mo for a global transportation and a month later, the huge cloud of grit and ash covered much of Northern and Central Europe cancelled all flights of the precious $^{99}$Mo.Airport closures also affected reactors in Belgium and France [15].

The reactors in which $^{99}$Mo is produced, up to now use HEU [16], which is a direct use material for nuclear weapons. It must be taken into account that most of the reactors mentioned above, range in age from 42 and 51 years, and it is considered to be quite difficult, nowadays, an approval be obtained to build a new reactor [17, 18]. One also has to be aware of the amount of time required for $^{99}$Mo to reach to the destination from the production place. For example when one week is needed for $^{99}$Mo to be delivered, its activity becomes one-sixth of the initial value [16, 19].

An interruption at any point in the production, transport or delivery of $^{99}$Mo-$^{99m}$Tc generators could have substantial impacts on patient care. It is necessary to study alternative routes to produce $^{99}$Mo in order to ensure a constant reliable supply of $^{99}$Mo.

*Alternative $^{99}$Mo production processes*

After the continued disruptions in the supply of $^{99m}$Tc and other radioisotopes in the past years, Canada commissioned a group of experts to find ways for a more secure supply of radioisotopes. This "Expert Review Panel on Medical Isotope Production" presented its findings at the end of November 2009. Different methods of isotopes production with accelerators, for the production of $^{99}$Mo or direct production of $^{99m}$Tc, are currently being investigated in Canada [20].

Artificially made radioisotopes, among which those for medical use, are mainly produced by research reactors. Currently more than 80% of the medical radioisotopes are produced by research reactors. The remaining isotopes are made by particle accelerators, mostly with cyclotrons and sometimes with linear accelerators (linacs), or by other methods.

**Table 1.** A selected chronology of events that have affected $^{99}$Mo supply [13]

| | Events which have affected $^{99}$Mo supply 1989 Cintichem Reactor |
|---|---|
| 1989 | Cintichem Reactor, the only domestic supplier of $^{99}$Mo to the USA, is permanently shut down. |
| 1992 | The U.S. Department of Energy (DOE) begins an effort to produce $^{99}$Mo in its reactors. |
| 1999 | DOE ends its efforts to produce $^{99}$Mo after a solicitation of private companies yields no interest. |
| 2001 | $^{99}$Mo shipments to USA by air are halted temporarily after 11$^{th}$ of September terrorist attacks. |
| 2002 | HFR is shut down for 42 days because of reactor operation safety concerns. |
| 2005 | Production of $^{99m}$Tc generators of Mallinckrodt is shut down in the USA on November 18 because of a product recall. Production is not restarted until April 2006. |
| 2006 | NRU reactor is shut down for approximately 6 days because of technical problem. |
| 2007 | NRU reactor is shut down for 24 unplanned days by the regulator to address safety concerns. |
| 2008 | HFR is voluntarily shut down in August 2008 after a corrosion problem in the primary cooling system is discovered and is not scheduled to come back online until February 2009.<br>IRE is shut down in August 2008 after $^{131}$I was unexpectedly vented through a stack. The facility received approval to restart on November 4, 2008. |
| | A scheduled 5-day shutdown of NRU reactor in December 2008 was extended for several additional days. |
| 2009 | NRU is shutdown for repairs in May 2009. |
| 2010 | NRU is shut down up to 18 August 2010<br>HFR is shut down for repairs in February 2010- back to service in September 2010. |

*Production of $^{99}$Mo from LEU*

Production $^{99}$Mo can be completed by nuclear reactors using LEU targets instead of HEU targets that are commonly used. A big advantage of using LEU targets is the reduction of nuclear proliferation concerns. A drawback of producing $^{99}$Mo from LEU targets is that they contain, by definition, less than 20% of fissile $^{235}$U and as a consequent the produced $^{99}$Mo has a very low specific activity, about five times lower compared to that produced from HEU [21, 22].

Nevertheless, Open Pool Australian Light water reactor (OPAL), a LEU reactor, a modern, powerful and effective neutron source, is a 20 MW open pool design using Low-Enriched fuel (less than 20% enriched). $^{99}$Mo is made by irradiating a foil target of uranium, causing fission, and separating the $^{99}$Mo from other fission products in a hot cell. The targets are 2.2% enriched uranium silicide. OPAL is the first research reactor in the world to use only LEU as a target for neutron irradiation in the production of $^{99}$Mo. [3].

Fission $^{99}$Mo from LEU targets is being produced in Argentina, at the Ezeiza Atomic Centre, since 2002.NTP Radioisotopes, a subsidiary of South African Nuclear Energy Corporation (NESCA), delivered to the United States the first batch of $^{99}$Mo produced with LEU. The operators also completed conversion of targets and radiochemical processes to LEU and obtained final approval from medical regulators [23-25].

On December 6th, 2010, the National Nuclear Security Administration (NNSA) and the South Africa Nuclear Energy Corporation (NESCA) announced that the first shipment of the medical isotope $^{99}$Mo, produced with LEU and approved for patient use, has arrived in the United States. Lantheus Medical Imaging,in Massachusetts, was the first company in North America that received the first quantity of LEU-produced $^{99}$Mo approved for medical use[24].

*Production of $^{99}$Mo by neutron activation, $^{98}$Mo (n, γ) $^{99}$Mo reaction*

The production of $^{99}$Mo by neutron activation of enriched $^{98}$Mo targets in a reactor is considered to be an attractive alternative to the HEU $^{99}$Mo production [26]. A disadvantage of this method is that the specific activity of $^{99}$Mo produced by this procedure is low because of the small neutron capture cross section at the thermal neutron energy 0.14barn (1barn is equal to$10^{-24}$ cm$^2$) [27-28]. Another reason why the $^{99}$Mo produced by this process has a very low specific activity is that most of the molybdenum (Mo) in the product is $^{98}$Mo [29-30]. Nuclear reactors with a thermal neutron with flux$10^{12}$n/(cm$^2$/s) are considered to be useful for the production of $^{99}$Mo [31]. It has to be taken into account that highly radioactive waste in the production of $^{99}$Mo by $^{98}$Mo (n, γ) $^{99}$Mo reaction has the minimal levels (Table 2).

*Neutron capture $^{99}$Mo production versus fission- produced $^{99}$Mo*

The ability to produce large amounts of $^{99}$Mo from the direct reaction route would depend upon the availability of a high flux reactor that could compensate for the lower cross section. For example, typical fluxes from the National Research Universal (NRU) reactor are around 1.5X1014 neutrons per cm$^2$ per second while the High Flux Isotope Reactor (HFIR) at Oak Ridge has a flux of 1015 neutrons per cm$^2$ per second, more than enough to be competitive in producing large amounts of $^{99}$Mo via the (n, γ) approach [32].Others showed that the specific activity for fission-produced $^{99}$Mo is two to four orders of magnitude higher than that from the neutron capture process [33].

This causes restrictions in use of neutron capture for $^{99}$Mo production in medical isotope procedures. First, the $^{99m}$Tc generators that use fission-produced $^{99}$Mo would have to be redesigned in order to use neutron capture-produced $^{99}$Mo. A larger $^{99m}$Tc generator column would be needed, the size and weight of its shield would be also increased. In addition all of the current $^{99m}$Tc kits would be reformulated, because a larger volume of liquid would be required to elute $^{99m}$Tc from the column [13, 34].

*Accelerator production of $^{99}$Mo*

Many methods for accelerator production of $^{99}$Mo as well as for direct production of $^{99m}$Tc have been proposed [35-36].

One accelerator-based method essentially mimics the reactor production route, in which the accelerator becomes the source of neutrons, that are used in order to produce fission in a blanket of $^{235}$U surrounding the neutron source. The required fluxes would be difficult to achieve in the necessitated geometry in order this method be competitive with reactor-generated neutrons. Moreover, such an accelerator would be expensive to be built and operate, although it would be less expensive than a new reactor [30].

*Photon induced reaction $^{100}$Mo (γ, n) $^{99}$Mo in accelerator*

An alternative method would be the use of an electron beam to generate high-intensity photons which in turn would be used to initiate a nuclear reaction on enriched Mo such as $^{100}$Mo (γ, n) $^{99}$Mo reaction which creates the desired product [30]. This method faces same problems as discussed above and there are also technical challenges associated with producing a high-energy electron machine with sufficient beam flux to be able to produce sufficient $^{99}$Mo in order to be competitive. As a result, discussions around the design of electron linacs capable of accelerating tens of milliamps of electrons are raised.

Photo-fission of $^{238}$U using natural or depleted uranium targets is another method that can be used for production

**Table 2.** Comparison of the two methods (Fission and Neutron) of $^{99}$Mo production

| $^{235}$U(n , f) $^{99}$Mo | $^{98}$Mo(n , γ) $^{99}$Mo |
|---|---|
| Produces high specific activity $^{99}$Mo | Produces low specific activity $^{99}$Mo |
| Requires enriched $^{235}$U target | Requires highly enriched $^{98}$Mo target |
| Complex chemical processing | Simple chemical processing |
| Requires dedicated processing facility | Requires high flux neutron source |
| High-level radioactive waste | Minimal waste |

*Modified from S. Mirzadeh, Oak Ridge National Laboratory [32]*

of $^{99}$Mo. The issues are the same as have been mentioned for the other photon induced reaction such as $^{100}$Mo (γ, n) $^{99}$Mo reaction. A very high intensity beam is needed in order to overcome the factor of about 1000 times smaller cross section for this reaction versus neutron fission of $^{235}$U, although the fission yields are almost identical (nearly 6%).

Both of these accelerator techniques would require multiple machines since the fluxes of neutrons and photons would not be sufficiently high to be competitive with those of a reactor. Moreover the cost of building and operation of multiple machines would have to be considered.

Despite the reserved attitude regarding the use of linacs, earlier tests with the linac method have shown good results. In 1998, researchers from Ukraine, published their results on $^{99}$Mo production by targeting $^{100}$Mo with an energetic electron beam produced by the linac according to the charged particle reaction $^{100}$Mo (γ, n) $^{99}$Mo. They concluded that the proposed technique has the promise of returning very high profits in a not too distant future [37].

*Direct accelerator production of $^{99m}$Tc by $^{100}$Mo (p, 2n) $^{99m}$Tc reaction*

The direct production of $^{99m}$Tc from the $^{100}$Mo (p, 2n) $^{99m}$Tc reaction is by a cyclotron based on bombarding enriched $^{100}$Mo targets with protons to produce $^{99m}$Tc. This is the only option in which $^{99m}$Tc is produced directly without first generating $^{99}$Mo [20].

It has been reported that the cross section for the direct production of $^{99m}$Tc from enriched $^{100}$Mo would be approximately 629MBq/μAh [3]. Moreover, the yield calculation by $^{100}$Mo (p, 2n) $^{99m}$Tc at proton energies ($E_{p)}$ between 7MeV and 17MeV, using a highly enriched $^{100}$Mo target, gives 300MBq/(μAh) [38].

A disadvantage of this method is that the final product $^{99m}$Tc, which is the one used in nuclear medicine procedures, is directly produced and has a short half-life (6h). Losses associated with transport and chemical efficiencies for separating the $^{99m}$Tc from the target matrix have to be taken into account [13, 25, 39].

However, this production is decentralized. Cyclotrons are located hospital-based, by which the delivery of pharmaceuticals to patients is easy and secured. In addition the risk of transport accidents or delays is practically zero [20].

*Accelerator production of $^{99}$Mo by proton induction, $^{100}$Mo (p, pn) $^{99}$Mo reaction*

Others have explored the production of $^{99}$Mo from the $^{100}$Mo (p, pn) $^{99}$Mo reaction [29, 40]. Their results indicated a thick target yield (40-45MeV) of 140,7MBq/μAh. The daily production for a similar cyclotron would be about 1850GBq thus about 100 cyclotrons would be required for this approach.

Another approach would be through the spallation (high-energy projectile collides with the target nucleus with enough energy in order a very large array of products be produced) of a target to produce $^{99}$Mo. The production rate of $^{99}$Mo from most reasonable target materials would be at best many orders of magnitude lower than the reactor methods and two orders of magnitude lower than the $^{99}$Mo production by other accelerator reactions [19].

*Accelerator production of $^{99}$Mo by neutron activation, $^{100}$Mo (n, 2n) $^{99}$Mo reaction*

Another way to produce $^{99}$Mo is by the $^{100}$Mo neutron activation by $^{100}$Mo (n, 2n) $^{99}$Mo reaction. In this reaction cross section is large, ~1.5Barn at neutron energies $12 \leq E_n \leq 17$MeV, which is 10-times larger than the thermal-neutron capture cross section of $^{98}$Mo in the production of $^{99}$Mo by neutron activation of enriched $^{98}$Mo targets in a reactor. It must be taken into account that the cross section was measured many times since the first measurement at $E_n$=14.5MeV in 1953, mainly due to interest in the reaction mechanism [38]. The latest data are consistent with the evaluated cross section of ~1.5Barn [26, 41]. The cross section of $^{100}$Mo (n, 2n) $^{99}$Mo reaction is the largest one (except of elastic scattering cross section which is ~2.4Barn), in the neutron-induced reaction of $^{100}$Mo [42]. As a result, any activity, except for $^{99}$Mo reaction, produced by bombarding an enriched $^{100}$Mo target with neutrons is not significant. Thus, radioactive wastes produced during this chemical processing would not be a serious problem. Furthermore, a large amount of a Mo target, ~1 mole of $^{100}$Mo, can be used on contrary to that for proton beam irradiation on $^{100}$Mo.

Hopefully, intense neutrons with energy of 12-17MeV, which are necessary to produce $^{99}$Mo with high specific activity, are already available. Neutrons with ~14MeV are known to be produced by the $^{3}$H (d, n) $^{4}$He reaction with a reaction Q-value of 17.59MeV at deuterium energy ≤300keV. In fact, at Fusion Neutronics Facility (FNS) at Japan Atomic Energy Agency (JAEA), a sample with neutrons of about $10^{12}$ n/(cm$^2$/s) using the $^{4}$He reaction [43] may be irradiated. Similarly, at a facility with the rotating target neutron source (RTNS-II) in USA, 14MeV neutrons with an intensity of a factor times $10^{13}$ n/cm$^2$/s were obtained by $^{3}$H (d, n) $^{4}$He [44]. The estimated specific activity of $^{99}$Mo with neutron intensity available in the present day's technique is about 79GBq/g, and is comparable to that obtained by $^{98}$Mo (n, γ) $^{99}$Mo using a thermal-neutron flux of $10^{14}$ n/(cm$^2$s) [13]. In Table 3 alternative ways of $^{99}$Mo production and the processes reactions are summarized.

**Table 3.** Alternative $^{99}$Mo production processes and their cross sections

| Alternatives | Reaction | Cross section (barn) |
|---|---|---|
| Reactor | $n + {}^{235}U \rightarrow {}^{99}Mo + xx + 2n$ | $586 \times 6\% = 35.16$ |
| | $n + {}^{98}Mo \rightarrow {}^{99}Mo$ | 0.14 |
| Accelerator | $\gamma + {}^{100}Mo \rightarrow {}^{99}Mo + n$ | 0.16 |
| | $\gamma + 2^{38}U \rightarrow {}^{99}Mo + xx + 2n$ | $0.16 \times 6\%$ |
| | $+ {}^{100}Mo \rightarrow {}^{99}mTc + 2n$ | 0.20 |
| | $p + {}^{100}Mo \rightarrow {}^{99}Mo + p + n$ | 0.15 |
| | $n + {}^{100}Mo \rightarrow {}^{99}Mo + 2n$ | 1.5 |

## Discussion

The production of $^{99}$Mo by neutron activation of $^{98}$Mo targets leads to low specific activity of $^{99}$Mo although the level of highly radioactive waste is much lower compared to that from fission-produced $^{99}$Mo. The accelerator production methods of $^{99}$Mo lead to low production rate of $^{99}$Mo and thus there is difficulty in covering the world demand, though there are many advantages of the radioisotopes production with cyclotrons over a nuclear reactor, such as safety, cheaper operating and decommissioning costs.

The contrast between a nuclear reactor and a cyclotron is startling. Reactors are huge complex machines in running 24h a day, surrounded by layer upon layer of security and shutdown systems, and with radioactive waste that will last for millennia. The volume of radioactive waste produced by cyclotrons is significantly less and much less hazardous than the radioactive waste of research reactors and more, there is no nuclear proliferation risk. As cyclotrons are powered by electricity rather than the uranium fission reaction of a nuclear reactor, they generate less than 10% of the waste of research reactors. The decision to develop radioisotopes with the use of cyclotrons seems to be a logical choice. It saves costs and protects the environment. Moreover, cyclotrons guarantee a safe and secure supply and disruptions in the supply of isotopes will be over forever.

The Canadian researchers invented the idea of a National Cyclotron Network to Produce Medical Isotopes show the route to a safe and secure production of radioisotopes. It can serve as a model for other nations. It also shows how quickly the transformation of a reactor-based to an accelerator based production of medical isotopes can take place.

If, for example, the Dutch government should choose now for such a transformation, like the one that the Canadian government does, the cyclotron-based isotopes could easily cover the Dutch domestic demand for medical isotopes in 2016. Cyclotrons in Groningen, Utrecht, Rotterdam and Eindhoven are enough to cover the Dutch domestic demand for $^{99m}$Tc [45].

The replacement of HEU targets in reactors with LEU has as a result the production of $^{99}$Mo with low specific activity and may be not efficient to cover the world demand. In spite of the above controversies, the first $^{99}$Mo/ $^{99m}$Tc generator produced by LEU $^{99}$Mo in South Africa is in market since 6$^{th}$ of December 2010. Moreover, the United States Congress has called for all $^{99}$Mo be supplied by reactors running on LEU, instead of HEU and called for proposals for a LEU-based supply of $^{99}$Mo for the United States market. This supply should reach 111000 six-day GBq per week by mid-2013, a quarter of world demand. Tenders for this closed in June 2010 [25].

The above alternative techniques are facing the challenges of low reaction rates and small target volumes. Consequently, there is a need for new alternative approaches to be explored in comparison to the cost of constructing and commissioning a new reactor facility [46-49].

*In conclusion*, restoring the global supply of $^{99}$Mo, could contribute in patients' vital need for diagnostic and therapeutic benefits, ensuring that the future of $^{99}$Mo supply is crucial.

*All authors declare that they have no conflicts of interest*

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