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Nuclear Medicine without Nuclear Reactors or Uranium Enrichment

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Summary

All commonly used medical radioisotopes can be produced without using nuclear reactors or enriching uranium, or can be replaced with other isotopes that can be produced without a fission reaction, or by alternative technologies.

Reactors not using natural uranium fuel require uranium enrichment, therefore justifying enrichment facilities that can be used for the production of weapons-usable highly enriched uranium (HEU). All reactors also produce weapons-usable plutonium as a byproduct of normal operation, although those using natural uranium fuel produce the most.

These reactors and enrichment facilities are not necessary for medical isotope production. Particle accelerators currently produce many medical isotopes. This report shows that all commonly used medical isotopes currently produced in reactors can be produced in accelerators, or replaced with accelerator-produced isotopes or alternative technologies. None of the accelerator options discussed herein would involve significant proliferation risk.

The extensive literature on production alternatives for the world's most widely used medical isotope, technetium-99m, makes possible an analysis of the cost and security aspects of these alternatives. While there is a good deal of uncertainty associated with cost data, since commercial accelerator production of Mo-99/Tc-99m has not yet commenced, the data suggest that accelerator production has the potential to be cheaper than reactor production, and at the very least will not prove prohibitively expensive.

For commonly used isotopes other than technetium-99m, a detailed cost estimate for accelerator production is beyond the scope of this paper. Nevertheless, it is clear that such alternatives are feasible. It seems unlikely that in the aggregate these alternatives would be prohibitively expensive. More R&D would support a full transition to commercial supply of isotopes other than Tc-99m using accelerator-based processes. Targeted investments in R&D for commercial production of the other isotopes, through contracts by NIH or DOE, could have substantial impact on the commercial availability of accelerator-produced medical isotopes, both in the US and abroad.

Introduction

Medical radioisotopes have been used for decades for both diagnostic and therapeutic purposes. For diagnostic use, a radioactive isotope is attached to a bio-active molecule that allows the radiologist to map out disease or body function using radiation detectors located outside of the patient's body. This powerful technique enables physicians to look for numerous types of disease in a non-invasive manner. Applications include heart disease, cancer identification, and bone fractures. For therapeutic use, radioisotopes provide radiation therapy to either malignant or benign tumors and provide curative or palliative therapy. Radiation therapy is a powerful technique that preferentially destroys cancer cells at a higher rate than healthy, non-cancerous cells. Therapeutic isotopes are often used for cancers of the prostate, the breast, the head, the neck, and the thyroid. Therapeutic isotopes can also be used to provide palliative relief for painful metastatic bone cancer.

Historically, medical isotopes were supplied by separation out of spent uranium fuel, or by exposure of target materials, in some cases including highly enriched uranium, to the neutron flux in a nuclear reactor. In the past, this approach was convenient: medical isotope manufacturers could easily "piggy-back" on the existing capital investment of a nuclear reactor and focus on the isotope chemistry itself. In addition, alternatives to reactor production, including electron or ion accelerators, or spallation neutron sources were expensive. However, the advent of very short-lived positron emitting diagnostic isotopes has created a market for hospital-based ion accelerators, and thus accelerator technology is far less expensive and more capable than in the past. Accelerator technology is now a viable alternative for medical isotope production [95, 97].

For a new source of supply of medical isotopes, accelerators offer several advantages over nuclear reactors. Accelerators present far less of a safety risk to operators or the public nearby. They generate minimal high-level nuclear waste and only modest quantities of low-level waste as a byproduct of medical isotope production. They also require substantially less capital investment than a typical reactor. Most pertinently for this report, accelerators that could be used for medical isotope production present minimal proliferation risk – they do not use any uranium, enriched or otherwise, and, except for very large and dedicated accelerator/reactor combinations called accelerator-driven systems, they are incapable of creating bomb-scale quantities of plutonium. The advantages of accelerator production have come to be recognized by isotope suppliers in the US and Canada. After the Mo-99 supply shortage in 2009, commercial operators in both countries have plans to grow capacity by building accelerators, not reactors.

In this report, we have analyzed the accelerator based production mechanisms in detail for the most commonly used therapeutic and diagnostic isotopes as listed by the medical literature and the IAEA. We find that all of these isotopes can be created, on medical need scales, by accelerators using charged particle reactions, photonuclear reactions or small-scale spallation neutron sources. None of these approaches presents a proliferation risk. In addition, we have prepared a first-order cost estimate for the non-reactor based production of Tc-99m, the most commonly used medical isotope. Accelerator production mechanisms of less commonly used isotopes are also discussed.

Proliferation Risk of Reactor-Based Medical Isotope Production

Construction and operation of nuclear reactors can pose a serious international security risk. Understanding why this is the case requires an understanding of how nuclear power and nuclear weapons work.

Uranium found in nature is a mix of two isotopes, U-238 and U-235. U-235 is the isotope useful for both nuclear weapons and nuclear power, as it is fissile – if hit by a neutron, it breaks apart (fissions) into lighter elements (fission products), releasing energy and more neutrons in the process. These neutrons can cause other U-235 atoms to fission, creating a sustained chain reaction if a "critical mass" of U-235 is available. Such chain reactions are the basis of both nuclear power and nuclear weapons. U-238 is not fissile[1] itself, but it is fertile – it can absorb a neutron to form fissile plutonium-239, which also can be used for both nuclear power and weapons.

U-235 makes up less than 1% of natural uranium. Most nuclear reactors, and all uranium-based nuclear weapons, require uranium with a higher fraction of U-235 in order to sustain a chain reaction (some reactors can use natural uranium). This material is produced in a process called enrichment, wherein undesired U-238 is removed in a "tails" stream, leaving a "product" with a higher fraction of U-235. Uranium is categorized internationally by the fraction of U-235 in the material, as shown in Table 1.

Type of Uranium	U-235 fraction
Depleted Uranium (DU)	<0.711%
Natural Uranium (NU)	0.711%
Low Enriched Uranium (LEU)	0.711 < 20%
Highly Enriched Uranium (HEU)	20%-100%

Table 1. Uranium categories.

Uranium-based weapons require HEU. They almost always use uranium enriched above 90%, sometimes referred to as weapon grade [1], although they can be made of less enriched material.

Most reactors require enriched fuel. For power reactors, this is usually LEU with about 3-5% U-235. Research reactors used for isotope production generally use higher enrichments, often 19.75% LEU, or even HEU. Additionally, production of some medical isotopes, such as Mo-99, use enriched uranium targets, which are often enriched above 90%.

Non-trivial quantities of reactor fuel or target material enriched to weapon grade are obviously a security risk, as this material is directly usable in nuclear weapons. However, it is sometimes forgotten that lower enrichment levels also pose a security risk, as they can be used to justify possession of non-trivial enrichment capacity. The same centrifuges used to produce 3.5% LEU for power reactors can be used to produce 90% HEU for bombs. And the higher the enrichment level for fuel, the less work it takes to enrich it further to weapons-usable material. This is why

[1] U-238 is fissionable, in that neutrons of high enough energy can cause it to fission, releasing energy. However, the neutrons released by U-238 fission are of too low energy to trigger further U-238 fissions.

there has been so much international concern about Iran's production of 19.75% LEU – it is not weapons-usable, but it takes relatively little work to enrich it to weapons grade. It should therefore be stressed that the security issues associated with medical isotope production are not confined to HEU alone.

Additionally, all uranium-fueled reactors produce fissile plutonium as a byproduct of normal operation.[2] Reactors with natural uranium fuel are particularly efficient at plutonium production, largely negating the nonproliferation advantage of not involving enrichment facilities. Iran's IR-40 reactor, which it claims is meant for medical isotope production, would use natural uranium fuel and would be capable of producing roughly 10 kg of plutonium annually – more than enough for a bomb [2].

In view of the serious national and international security concerns that Iran's uranium enrichment program and plans for nuclear reactors have raised, this paper considers ways of providing medical radioisotopes without the use of nuclear reactors or uranium enrichment.

Proliferation Risk of Accelerator Based Isotope Production

Since the dawn of the nuclear age, physicists have recognized that particle accelerators can be used to fabricate Pu-239 [3]. In fact, for several decades, numerous countries pursued an accelerator-based Pu-239 production program. Despite advances in accelerator technology, the costs of creating large quantities of Pu-239 with an accelerator remain prohibitive. Nevertheless, small quantities of Pu-239 could be created by modifying particle accelerators that are initially intended for medical use, whether for isotope production or direct particle therapy. However, except in the case of the possible production of Pu-239 by large specially engineered accelerator/reactor combination called accelerator-driven systems, accelerator-produced quantities of Pu-239 are too small to present a proliferation risk.

Pu-239 is created when U-238 captures a neutron. Although most easily made in a reactor, neutrons for U-238 capture can also be created with an accelerator, either through a charged-particle type reaction or a spallation-type reaction. Accelerator-produced neutrons are typically very energetic. In order to be captured by U-238, the neutrons must be suitably moderated. Efficient clandestine moderation is difficult because it requires material with low absorption cross sections, typically heavy water, deuterated plastic or reactor-grade graphite, i.e. carbon with a very low boron content. These materials are controlled and difficult to obtain. In addition, neutrons will be lost to absorption on other materials in the reactor. Nevertheless, one can place an upper bound on accelerator production of Pu-239 by assuming that all neutrons created by the accelerator are captured by U-238. With this assumption, the neutron flux required to fabricate 10 kg of Pu-239 is easy to calculate. 10 kg of Pu-239 contains 2.5×10^{25} atoms of Pu. To fabricate 10 kg in a year, with a machine that has an 80% up time, one needs a flux of approximately 10^{18} neutrons per second.

[2] Plutonium that is less than about 94% Pu-239 by mass has sometimes been referred to as reactor grade, as long irradiations in power reactors breeds more of the heavy isotopes beyond Pu-239. Reactor-grade plutonium is generally considered less desirable for use in weapons, as these heavier plutonium isotopes add radioactivity that requires shielding and heat dissipation, and neutrons from spontaneous fission that can cause the chain reaction to start prematurely. Nevertheless, reactor-grade plutonium can be used in nuclear weapons [89].

Pu-239 can also be created by directly bombarding a U-238 target with an energetic proton beam, eliminating the need for efficient neutron moderation [98]. A 20 ton depleted uranium target, bombarded with 150 MeV protons at a power of 240 kW (representing a current of 1.6 mA), could provide 10 kg of Pu-239 in 80 machine-years.

Accelerator neutron production can be greatly increased by engineering a sub-critical assembly of natural uranium around the accelerator beam target, i.e., an accelerator-driven neutron source or accelerator-reactor combination. The exact multiplication factor depends on the geometric details of the uranium and moderator. A DOE study determined that a simple, natural uranium and light-water moderated sub-critical assembly could amplify the neutron output of an accelerator neutron source by a factor between 8 and 40 [4]. The report estimates that the U-238 capture rate would be between 3 and 16 times greater than the accelerator-only neutron production rate. For the purposes of analysis here, we assume that a subcritical assembly could amplify the Pu-239 production rate by a factor of 20. Thus, using a sub-critical assembly, one needs a neutron flux of 5×10^{16} n/sec to create 10 kg of Pu-239 per year.

There are several barriers to the clandestine use of a sub-critical assembly. First, diversion of uranium for such a purpose would almost certainly violate the host country's NPT obligations and violate IAEA safeguards. Under IAEA agreement IFCIRC/153 part 37(b), a state is obligated to have inventory control on a total quantity of natural uranium greater than 10 tons in the state [5]. An eight cubic foot sub-critical assembly of natural uranium, capable of multiplying neutron capture by a factor of 13, requires 250 tons of natural uranium. Thus, in order to construct such an assembly a proliferator would have to divert from inventory 25 times the IAEA inventory exemption of natural uranium. In addition, according the IAEA Safeguards Manual SMI3.1.2, a state is obliged to provide the IAEA with design information about any facility that will contain nuclear material, preferably prior to the introduction of this material. An analysis of how the IAEA would be involved with an accelerator-driven system in Belgium is presented in IAEA report IAEA-CN-184/308 [6].

More importantly, a sub-critical assembly would involve substantial engineering and site modification that may be easily discovered. A sub-critical assembly must be cooled, and the radiation output (including gammas, neutrons, and radioactive gases) would be quite different than that from a facility dedicated to medical use. The ability of a determined actor to clandestinely redirect a medical facility to Pu-239 production using a sub-critical assembly would depend on the exact type of facility, the geography, and the technical sophistication of the actor but would likely be very difficult.

In the US, medical accelerators are commonly used to provide electron therapy, x-ray therapy, and proton or other ion therapy [95]. Accelerators are also used to create isotopes for both imaging and therapy. Infrequently, accelerators are used to provide neutron therapy. The best way to make medical isotopes using medical accelerator technology is likely to use commercially available 30 MeV medical cyclotrons. These machines, already used in hospitals worldwide to create short-lived diagnostic medical isotopes, can create longer lived species through charged-particle reactions by bombarding suitable targets with protons, deuterons or alpha particles, or by creating neutrons that are in turn captured or drive a n,p reaction. To make

Pu-239, these machines would be used in the neutron-creation mode. At 30 MeV, the greatest neutron yield is created by bombarding beryllium targets with deuteron ions (protons have a 25% smaller yield) [7, 8]. In these targets, neutrons are created by both a p,n reaction and also by spallation. The neutron yield is approximately 0.03 neutrons/deuteron. These machines can operate at a current of up to 2 mA, generating a flux of 3.7×10^{14} n/sec. The creation of 10 kg of Pu-239 would require at least 3,000 machine-years.

As we show later in this report, many such 30 MeV cyclotrons would be required to meet a country's total medical isotope need. For short-lived isotopes, a distributed production scheme may be very cost-effective as it minimizes the time between production and patient treatment. For longer-lived therapeutic isotopes, a single dedicated accelerator facility that provides a large neutron flux may be prudent [94, 101]. Such a facility would be similar to the spallation neutron source (SNS) at Oak Ridge National Laboratory but with vastly lower neutron fluxes. For example, a 150 MeV machine operating at 240 kW (1.6 mA) could create 10^{16} n/s and would likely meet a small country's need for neutrons for medical isotopes. Such a machine would require at least 100 machine-years to make 10 kg of Pu-239.

Other medical accelerators could be re-engineered to create Pu-239, although at very low rates. Electron accelerators are unfeasible. A 10 MeV electron accelerator, used for whole body skin irradiation, typically operates at 100 μA currents [9]. If such an electron beam was directed at a uranium target, a neutron flux of 2.5×10^{9} n/sec would be created, requiring 400 million machine-years. A dedicated 4 MeV ion accelerator neutron source could create a flux of 1.5×10^{14} n/sec, which would require at least 7,000 machine-years to fabricate 10 kg of Pu-239 [10, 11, 35]. 250 MeV ion accelerators used for proton therapy are not suitable for neutron production. Their low current, typically 10 nA, would create 3×10^{11} neutrons/sec and would require 3 million machine-years to fabricate 10 kg of Pu-239 [12]. Neutron generators for commercial use are also available and could, in principle, be used for production of very small quantities of Pu-239 and are thus a useful point of comparison. These generators typically use either a D-D or D-T fusion reaction. Thermo-scientific sells a neutron generator, the D-711, that can create a flux of 10^{10} n/sec and would require 100 million machine-years to fabricate 10 kg of Pu-239.

Machine/Accelerator	Neutron flux (n/sec)	Minimum Machine-Years to produce 10 kg Pu-239	Minimum Machine Years with sub-critical assembly to produce 10 kg Pu-239.
Dedicated U-238 target (150 MeV, 240 kW)	N/A	80	N/A
Dedicated spallation source (150 MeV, 240 kW)	1×10^{16}	100	5
30 MeV, 2 mA cyclotron	3.7×10^{14}	3,000	150
4 MeV neutron therapy	1.5×10^{14}	7,000	3,500
250 MeV proton therapy	3×10^{11}	3 million	150,000
Thermo Scientific D-711	10^{10}	100 million	5 million

Table 2. Proliferation potential of accelerator-based isotope production technologies.

For comparison, a typical 1000 MWe PWR produces about 330 kg of plutonium per year – or 10 kg per 0.03 machine years [13].

Commonly Used Medical Isotope Overview

Typically, diagnostic isotopes have a short half-life and emit x-rays with an energy greater than 100 keV either directly or through positron annihilation. These x-rays are easy to identify outside of the body and give minimal radiation dose to the patient. Each diagnostic scan typically involves a small quantity of the radio-isotope. Table 3 lists the commonly used diagnostic medical isotopes. Almost all diagnostic isotopes are presently created with cyclotrons [96]. Tc-99m, which emits a 140 keV gamma ray is the most commonly used diagnostic isotope and is the only diagnostic isotope produced in a reactor. It is also typically made using a HEU target. We have not included reactor produced Xe-133 because it can be functionally replaced by Xe-127 which is diagnostically superior.

Two types of diagnostic scans use medical radioisotopes. In a Single Photon Emission Computed Tomography (SPECT) scan, a x-ray emitting radioisotope is introduced into the patient, by injection, ingestion, or inhalation. The high-energy x-rays are captured by gamma cameras which provide a three-dimensional image. In Positron Emission Tomography (PET) scans, a positron emitting isotope is introduced into the patient. Annihilation of the positron with electrons in the patient create characteristic 511 keV gamma-rays which are subsequently captured by gamma cameras.

Isotope	Medical Use	Half-life	Typical Production Method
Tc-99m	SPECT	6 hr	reactor
I-123	SPECT	13.2 hr	cyclotron
Ga-67	SPECT	78.3 hr	cyclotron
Th-201	SPECT	73.1 hr	cyclotron
In-111	SPECT	2.8 d	cyclotron
Xe-127	SPECT	36 d	cyclotron
Co-57	SPECT	272 d	cyclotron
C-11	PET	20 min	cyclotron
N-13	PET	10 min	cyclotron
O-15	PET	2 min	cyclotron
F-18	PET	110 min	cyclotron
Ga-68	PET	68 min	Ge-68 via cyclotron
Ru-82	PET	1.3 min	Sr-82 via cyclotron

Table 3. Medical isotopes commonly used for diagnostic imaging [14].

Therapeutic isotopes can have a long or short half-life. These isotopes are either injected, ingested or implanted into a patient and typically emit low-energy or short-penetrating radiation so that the therapy is targeted to the diseased tissue. Quantities used for each treatment are typically much greater than those used for diagnostic scans. Table 4 summarizes the commonly

used therapeutic isotopes. Except for Pd-103, all the commonly used isotopes for therapy are created in reactors.

Isotope	Medical Use	Half-life	Typical Production Mechanism
P-32	Cystic Brain Tumors	14 d	Reactor
Sr-89	Metastatic Bone Cancer	50 d	Reactor
Y-90	Liver Cancer	2.7 d	Reactor
Pd-103	Prostate Cancer	17 d	Cyclotron
I-125	Prostate Cancer	60 d	Reactor
I-131	Thyroid Disease/Cancer	8 d	Reactor
Sm-153	Metastatic Bone Cancer	1.9 d	Reactor
Re-186	Metastatic Bone Cancer	3.7 d	Reactor
Re-188	Metastatic Bone Cancer	17 h	Reactor
Ir-192	High Dose Rate Brachytherapy (Breast, Head, Neck, Lung Cancer).	74 d	Reactor

Table 4. Medical isotopes commonly used for therapy [15].

Alternative Production Mechanisms to Reactor-Made, Commonly Used Medical Isotopes

Here we present alternatives for producing the most common medical isotopes without using uranium or nuclear reactors. We have analyzed each reactor-made isotope listed in Tables 3 and 4. For most isotopes we have identified possible production reactions using either a 10^{14} n / cm^2 / sec neutron flux, provided by either a 30 MeV cyclotron or a dedicated spallation neutron source[3], or a charged particle reaction assuming a beam current of 500 μA. For Mo-99, we have also considered a photo-nuclear reaction process. For each reaction, we estimate the annual production rate, assuming an 80% up-time.

These estimates should be viewed as preliminary. In particular, for neutron targets, we did not consider neutron transport through the targets, nor did we consider loss of neutron flux due to the requirements of moderation. For charged-particle targets, we did not consider the details of target design. For some targets, the resultant yield from thick targets is published. For others, we have estimated the yield from published cross sections and assume that all reactions occur within the range of the charged particle in the target. Except for Mo-99/Tc-99m, no consideration was made for isotope loss due to radiochemistry processing. Only a cursory analysis was applied to the specific activity requirements. In some cases, the specific activity may be a limiting factor.

For those isotopes where demand figures are not readily available, we estimate the annual demand for each isotope by assuming that a reasonable (10-30%) fraction of the indicated disease (see Table 5) is treated with radiotherapy. Other diseases have not been considered. We use US demand as a proxy for worldwide demand. Typical demand in a 100 million person country is calculated by dividing US demand by a factor of three. This is likely a very

[3] An average thermal neutron flux of 10^{14} n/cm^2/sec is now routinely achieved at the Swiss Spallation Neutron Source [99].

conservative over-estimate for most isotopes. For example, the US consumes more than half of all Mo-99 produced worldwide. The demand estimates in table 5 do not take into account losses due to decay during transport and other logistical steps, which may be important for short-half life isotopes.

Isotope	Activity per Procedure	Maximum US Treatments per year	Maximum US Demand (Ci)	Demand in a 10^8 person country (Ci)	Annual production in a 10^{14} n/cm^2/sec flux (Ci)	Annual production in a 500 μA target (Ci)
Mo-99 /Tc-99m	15-30 mCi (Tc-99m)	20,000,000	1,500,000 (Mo-99)	480,000 (Mo-99)	N/A—See text	35,000 (Tc-99m)
Ir-192	10 Ci	400,000	14,000	4459	300	100
I-131	30 - 200 mCi	200,000	11,000	3503	3400	500
Re-188	90 mCi	100,000	9,000	3,000	N/A	1,000
Sm-153	70 mCi	100,000	7,000	2,300	8,000	100
Re-186	40 mCi	100,000	4,000	1,300	7,000	2,100
Y-90	140 mCi	10,000	1,300	414	7,000	2,800
I-125	50 mCi	10,000	500	170	1600	122
Sr-89	4 mCi	100,000	400	130	400	N/A
P-32	0.5 mCi	<10,000	<5	<3	15	1800

Table 5. Estimated accelerator based capability to produce medical isotopes that are presently made with reactors. Tc-99m can be most efficiently made through a photo-nuclear reaction. Two targets could make 130,000 Ci of Mo-99/ year [21].

Molybdenum-99/Technetium-99m

Technetium-99m is the world's most widely used medical radioisotope – it is used in 80% of nuclear medicine procedures, about 30 million procedures annually [16]. At present, most Tc-99m is provided by a Mo-99 "generator" which decays via beta emission into Tc-99m with a half-life of 66 hrs. Mo-99 is typically created as a product of U-235 fission in enriched U-235 targets exposed to a neutron flux. Annual global demand for Mo-99 is approximately 500,000 "6-day" Ci, which corresponds to about 2.3 million Ci. It decays to stable Tc-99g (ground) with a half life of 6 hours, emitting a 140 keV gamma ray. This energy range is very well suited to gamma cameras, making Tc-99m a workhorse radiotracer isotope [17]. Tc-99m is injected into the patient as part of a SPECT scan. The isotope is incorporated into many different chemical compounds for different imaging procedures, each tailored to concentrate the radioisotope in different types of tissue. These compounds are prepared in "kits" shipped to hospitals, which contain all the necessary chemicals for formulating the desired radiopharmaceutical (see Table 6).

Mo-99 is a product of the fission of uranium-235. It is generally produced by irradiating dedicated uranium targets (usually HEU, but sometimes LEU) in a research reactor. These dedicated targets are designed to be dissolved quickly, allowing chemical processing of the

Mo-99 also to be carried out quickly – Mo-99's 66 hour half life puts a premium on speed throughout the process. In 2009, roughly 40-50 kg of HEU [17], most of it enriched to more than 90% [18], was consumed in targets annually on a global basis – enough to make at least one nuclear weapon.[4]

Progress has been made in shifting to LEU production, spurred on by a recent $10/dose US subsidy of non-HEU production through Medicare payments [19]. Progress reported at Argonne National Laboratory's 2013 Mo-99 topical meeting in Chicago was substantial – all current international producers are on track to convert to Low Enriched Uranium (LEU) for both targets and reactor fuel by 2015, and all new international producers outside of Russia are using LEU from the outset.

Kit Name	Imaging Procedure
Technetium Tc-99m Medronate (MDP)	Bone Scan
Technetium Tc-99m Albumin Aggregated (MAA)	Lung Perfusion
Technetium Tc-99m Pentetate (DTPA)	Kidney Scan and Function
Technetium Tc-99m Sulfur Colloid	Liver Scan
	Sentinel Lymph Node Localization
Technetium Tc-99m Sestamibi	Cardiac Perfusion
Technetium Tc-99m Exametazime	Brain Perfusion
Technetium Tc-99m Mebrofenin	Gall Bladder Function
Technetium Tc-99m Etidronate	Bone Scan
Technetium Tc-99m Disofenin	Gall Bladder Function
Technetium Tc-99m Succimer (DMSA)	Kidney Scan and Function
Technetium Tc-99m Tetrofosmin	Cardiac Perfusion
Technetium Tc-99m Bicisate	Brain Perfusion
Technetium Tc-99m Red Blood Cell	Blood Pool Imaging
Technetium Tc-99m Sodium Pertechnetate	Thyroid, Salivary Gland, Meckel's Scan
Technetium Tc-99m Lidofenin	Gall Bladder Function
Technetium Tc-99m Mertiatide (MAG3)	Kidney Scan and Function
Technetium Tc-99m Oxidronate (HDP)	Bone Scan

NOTE: MAA = methacrylic acid, MDP = methylene diphosphonate, DTPA = diethylene triamine pentaacetic acid, DMSA = dimercaptosuccinic acid, MAG3 = mercapto acetyl triglycine, HDP = hydroxymethylene diphosphonate.

Table 6. A list of Tc-99m procedures [17].

Production alternatives

Mo-99 can be produced by means other than uranium targets. Mo-99 can be created by a photonuclear reaction on Mo-100 or Tc-99m can be created directly by proton bombardment of Mo-100. These methods can likely produce Tc-99m at a lower cost than reactors using HEU targets.

Photo-Nuclear Method

The photo-nuclear method uses an electron beam impinging on a metal target to produce bremsstrahlung gamma rays, which in turn hit a molybdenum target, producing Mo-99 by

[4] The IAEA defines a "Significant Quantity" as "the approximate amount of nuclear material for which the possibility of manufacturing a nuclear explosive device cannot be excluded," For U-235, this consists of any mass of HEU containing more than 25 kilos of U-235 [20].

causing Mo-100 to expel a neutron. This method can use either natural molybdenum targets (which contain 9.6% Mo-100), or targets enriched in Mo-100. The latter is substantially less expensive, as the molybdenum production in a given target is more than ten times greater. According to a report from the IAEA, a photonuclear production facility that operates a 50 MeV electron beam at 100 kW on two enriched 100-Mo targets could produce 1.3×10^5 Ci / year of Mo-99 [21]. NorthStar Medical Radioisotopes, LLC plans to build a facility in Wisconsin with 16 linacs (14 of which would generally be operational, irradiating targets in pairs), which will be capable of meeting at least half of US demand annually [88]. This facility will operate on a commercial basis, and the company believes it can turn a profit despite competition from reactor producers, who are supported by subsidies.

The best data available suggest that the overall cost per patient dose of Tc-99m[5] would be about $5.35 with enriched targets, or about $43.40 with natural molybdenum targets. Meeting current global demand would cost $160 million or $1.3 billion for enriched and natural targets, respectively. These figures should be treated with a good deal of caution, and are essentially zero-order estimates. Efforts have been made to quantify the costs associated with the process, however data are approximate, as commercial-scale accelerator production has not yet commenced.

Nonetheless, it appears reasonable to say that Mo-99 production with enriched Mo-100 targets is unlikely to be much more expensive than reactor produced Mo-99, which costs about $15.15 per dose, or about $460 million to meet current global demand.[6] Using natural molybdenum targets is likely to be substantially more expensive than reactor production of Mo-99, but even this cost may not be prohibitive. If the estimates above are correct, the additional cost per dose is still only about one eighth of the overall procedure cost – $340 in 2010 [16].

p,2n reaction

The charged particle method would produce Tc-99m directly by hitting Mo-100 with a proton, and causing the nucleus to expel two neutrons. Molybdenum enriched in Mo-100 is required – the use of natural molybdenum not only decreases yield but contaminates the product.[7] Production could be carried out either in a dedicated technetium-producing cyclotron, or in one also used to produce isotopes for PET scans. The latter option offers some efficiency advantages: PET cyclotrons are usually idle during night hours because PET isotopes have such short half lives that the vast majority of material produced overnight would decay before the start of the working day. Technetium's relatively long half life (6 hours) would allow it to be economically produced during otherwise idle hours. One expects a production rate of 35,000 Ci per year with an 18 MeV proton beam at 500 μA [22].

[5] Calculation described in detail in Appendix A.
[6] Calculation described in detail in Appendix A. Note that this is the overall production cost – the sale price is lower, due to subsidies.
[7] Nuclear reactions with other molybdenum isotopes produce other technetium isotopes which are useless for imaging, but substantially increase the patient's absorbed radiation dose, so that [22] concluded that "contaminants produced in the proton-induced reaction on the natural molybdenum target will preclude its use in nuclear medicine."

This approach has drawn some industrial interest in Canada. Major cyclotron manufacturer Advanced Cyclotron Systems Inc. (ASCI) of British Columbia has shown particular interest in this process. It has partnered with the University of Alberta and the Centre Hospitalier Universitaire de Sherbrooke (CHUS) by supplying TR 19 cyclotrons to produce small quantities of Tc-99m for proof-of-concept imaging studies. In October 2012 it introduced the TR 24 cyclotron, the first designed with commercial production of Tc-99m in mind, and delivered the first unit to CHUS [23]. This 24 MeV 500 μA cyclotron is a dual-use PET/SPECT isotope producer, capable of producing Tc-99m, as well as the PET isotopes C-11, N-13, O-15, F-18, I-124, Cu-64, and Ge-68 and other SPECT isotopes including I-123, In-111, Ga-67 and Co-57 [24, 25].

A dedicated cyclotron could produce one dose of Tc-99m for about $18.25; while production on a multipurpose PET machine during night hours would cost about $11.50 per dose[8] (see Table 7). Cost data here must also be considered highly uncertain, even more than for the photo-neutron process. Not only has commercial cyclotron production not commenced, the supply chain is substantially different than that of reactor-produced molybdenum, adding further uncertainty. However, it seems that production on multipurpose machines is unlikely to be prohibitively more expensive than reactor production.

	Cost per dose:	Potential market share:	Total Cost (millions):
Reactor	$15.15	100%	$462
Photo-Nuclear (enriched targets)	$5.35	100%	$161
Photo-Nuclear (natural targets)	$43.40	100%	$1,302
Dedicated Cyclotron	$18.25	50%	$272
Multipurpose Cyclotron	$11.50	25%	$86

Table 7. Estimated Tc-99m production costs for different production methods.

Potential proliferation impact

The potential proliferation risk associated with accelerator technetium production is minimal. While accelerators could be turned into neutron sources, which could in turn be used to irradiate U-238 to breed plutonium, and centrifuges used to enrich Mo-100 for targets could conceivably be turned to enriching uranium, this would result in very tiny global production capability, particularly compared with research or power reactors.[9]

The proliferation capability of 30 MeV accelerators has been described above. A photo-nuclear Mo-100 facility could be clandestinely redirected to fabricate Pu-239, but, would be very inefficient. At 50 MeV, the neutron yield on a uranium target is 0.024 neutrons per electron so that a 100 kW facility could generate a neutron flux of 3×10^{14} neutrons per sec. This technology would require 3000 machine-years to fabricate 10 kg of Pu-239. Producing enough fissile material for a weapon with a single state's technetium infrastructure would take centuries, and

[8] Cost calculation detailed in Appendix A. Some sources have reported lower figures, e.g. $7.80-$8.10 per dose for multipurpose cyclotrons in [86].
[9] Appendix B has detailed calculations of the proliferation capability associated with this infrastructure.

would involve activities that could not be plausibly explained as part of medical isotope production. Even in the absence of formal safeguards on these facilities, such long-term illicit operation would be likely detected.

Both the photo-nuclear and cyclotron methods would also spread isotope production around to a larger number of facilities than the current system of a small number of reactors. This avoids the single points of failure inherent in the current system, wherein problems at a single facility can cause global supply shortages, such as those that occurred when Canada's NRU reactor went offline unexpectedly in 2007 and 2009-2010 [18].

Alternatives to Tc-99m use in medicine

Positron Emission Tomography (PET) scans can substitute for Tc-99m procedures in some applications. 27% of respondents in a 2011 OECD Nuclear Energy Agency survey expected 25% or more of Tc-99m medical procedures to be displaced by alternative technologies by 2030 [26].

Most of this displacement is expected to come from PET scans. These use shorter-lived cyclotron-produced[10] isotopes (see Table 8) that decay via positron emission, producing gammas with higher energies than those emitted by Tc-99m. These are often diagnostically superior to SPECT scans, and for some procedures, deposit in the patient a lower radiation dose than a Tc-99m scan. They are, however, significantly more expensive. PET scans cost $983 per procedure,[11] or almost three times as expensive as the average SPECT procedure ($340). Furthermore, the short half-life of PET isotopes means that they must either be produced on site or from a nearby external supplier. This limits growth in the use of PET to densely populated areas representing markets large enough to justify cyclotron construction.

This suggests that PET is unlikely to completely supplant SPECT in the near term. Nevertheless, growth in the number of PET procedures has the potential to reduce demand for Tc-99m and other SPECT isotopes.

Isotope	Half-life	Energy (MeV)
Fluorine-18	109.7 min	0.635
Carbon-11	20.4 min	0.96
Nitrogen-13	9.96 min	1.19
Oxygen-15	2.07 min	1.72

Table 8. A list of the most common PET isotopes.

Iridium-192

Ir-192 is used for high-dose rate brachytherapy as part of an "after-loader." In this treatment methodology, catheters are placed in the patient that go through the tumor or tumor bed. The radioactive source is then automatically positioned in the tumor by a machine, the so-called

[10] Since PET isotopes decay by positron emission, they are "proton-rich," and therefore are more easily produced via proton activation (in cyclotrons) than neutron activation (in reactors).
[11] Taken from Medicare reimbursement rates reported in [90], and adjusted to 2010 dollars.

after-loader, that positions the sources within the catheter. Common indications include prostate, breast, head, neck and soft tissue sarcomas. Each after-loader contains one Ir-192 source with an activity of 10 Ci. There are approximately 350 after loaders in the US, and each Ir-192 source is replaced four times per year, so that there is a total US need of 14,000 Ci per year [27].

Ir-192 sources are typically fabricated by exposing natural iridium wire to a neutron flux [47]. Each after-loader source is typically a cylinder with a diameter of 0.034 cm and a length of 0.25 cm. Ir-191 has an absorption cross section of 954 barns and represents 37% of natural iridium. If exposed to a neutron flux of 10^{14} n/cm^2/sec, a natural iridium after-loader source will be exposed to a neutron rate of 8.5×10^{11} neutron/sec. It will likely absorb almost all of these neutrons so that Ir-192 will be generated at a rate of approximately 2.5 micro-Ci per sec. (This estimate ignores the small contribution of Ir-193 capture). Considering the half-life, exposure for 120 days would be required to activate such a cylinder to 10 Ci. However, the sources are so small that each such machine could likely irradiate 100 sources per cm^2 per 120 days giving a total annual yield of 300 Ir-192 sources.

Ir-192 can also be produced with an accelerator via the Os-192(d,n)Ir-192 reaction. Tarkayi estimate a production rate on an enriched osmium target of 0.013 Ci/hr at 500 μA, so that 10 Ci could be produced in 30 days [28]. Assuming an 80% uptime, that corresponds to an annual production rate of 100 Ci per osmium target.

Iodine-131

I-131 is used to treat both thyroid cancer and benign hyperthyroid disease. Treatment for thyroid cancer typically requires 200 mCi, while treatment for benign disease typically requires 30 mCi [29]. I-131 treatment is not prescribed for every case of thyroid disease, however, an estimate of the incident of both cancer and hyperthyroidism can place an upper bound on I-131 demand. In the US, thyroid cancer presents in about 45,000 patients per year [30]. Hyperthyroidism presents with an incidence of 0.04% of women and 0.01% of men per year so that in the US one expects 75,000 cases per year [75]. Thus, one would expect a maximum US demand of 11,000 Ci of I-131 per year.

I-131 is typically created by neutron capture on Te-130, creating Te-131 which subsequently beta-decays to I-131 with a 25 min half-life [47]. Exposing a full mole of unenriched TeO2 (i.e. 34% Te-130) to a neutron flux of 10^{14} neutrons/sec will create 3,400 Ci of I-131 per year. I-131 can also be produced via charged particle reactions. In fact, the first production was accomplished with the Berekely Cyclotron in the late 1930's. An accelerator production facility would use the reaction Te-130(d,p)Te-131 which subsequently decays to I-131 and the Te-130(d,n)I-131 reaction, which has a cross section ten times smaller [31]. An enriched target would be necessary to prevent contamination with other Iodine isotopes [32]. At a beam current of 500 μA, one would expect an annual production rate per target of 500 Ci / year.

Rhenium-188

Re-188 is used for palliative care of metastatic bone disease, i.e., cancer that has metastasized into a patient's skeletal system [33]. In the US, approximately 280,000 patients are thought to

need care for metastatic bone disease [34]. Only a fraction of these patients are likely to be prescribed radio-therapy for bone pain, and of those, only another fraction will choose Re-188. Here we assume that the bone pain therapy market will be equally divided between the four available isotopes. Thus, if 100,000 patients are treated with radio-therapy, only 25,000 would choose Re-188. A typical patient can be treated up to four times per year so that at a maximum one would expect 100,000 annual Re-188 treatments. The average prescription dose is 90 mCi so that one expects a maximum US demand of 9,000 Ci/year.

Re-188 is typically provided by a W-188 generator that is created by neutron capture in a reactor. Re-188 can also be produced via the d,p reaction on Re-187. A 12 MeV, 500 μA deuteron beam will create 1,000 Ci/year [31].

Samarium-153

Sm-153 is also used for palliative bone therapy [53]. The typical prescription dose is 1 mCi /kg so that the average 70 kg patient needs 70 mCi, up to 4 times per year [93]. If 25,000 patients per year were treated with Sm-153, the total US demand would be 7,000 Ci.

Sm-153 can be produced via neutron capture on enriched Sm-152 oxide or via an alpha, n reaction on enriched Nd-150. The neutron absorption cross section is very large so that a Sm-153 target will likely absorb all impinging neutrons and could in principle create 1,000 Ci/day when exposed to a 10^{14} n/sec flux. However, the specific activity requirement for this product is very high, at 10^4 Ci/g. Seven days exposure is typically required to reach 10^4 Ci/g [36]. A 20 mg target could provide 8,000 Ci/year. Production via Nd-150(alpha,n)Sm-153 could produce 100 Ci/year [37, 38]. Given the different chemistries of the target and Sm-153, the specific activity of Sm is likely not a limiting factor in this process.

Re-186

Re-186 is also used for bone-pain palliative care [33]. The average prescription does is 40 mCi so that if 25,000 patients per year were treated with Re-186 one expects a maximum US demand of 4,000 Ci/year.

Re-186 can be produced in a neutron flux via neutron capture on enriched Re-185. In a flux of 10^{14} n/sec, one expects to produce 24 Ci/day in a 0.1 g target, which corresponds to 7,000 Ci/year [47]. Re-186 can also be produced via proton bombardment on W-186. Experimental measurements suggest that one can create 2,100 Ci/year by bombarding a 20 MeV 500 μA deuteron beam on an enriched W-186 target [39, 40, 49].

Y-90

Y-90 is most commonly used as a form of palliative care for unresectable liver cancer [41]. 30,000 patients per year present with liver cancer in the US [42], but only a fraction of those are likely to use Y-90 therapy. The typically dose is approximately 0.14 Ci [43]. If 10,000 patients per year choose Y-90 therapy, the maximum annual US demand is 1,300 Ci/year.

Historically, Y-90 has been produced as a decay product of Sr-90, which itself is a fission product from uranium targets. However, Y-90 can be created by neutron capture on Y-89, with a cross section of 1.3 barns. Exposing a 5 g target to 10^{14} n/sec would create 7,000 Ci/year, more than enough to meet US demand. Y-90 can also be created via the d,p reaction on Y-89 [44]. The d, p reaction for a 20 MeV beam at 500 μA will create 2,800 Ci/year. However, this process would also create Sr and Zr isotopes; clever chemistry would be required to separate the Y-90.

Iodine-125

I-125 is used as the therapeutic isotope in low-dose rate brachytherapy devices. Most I-125 is used to treat prostate cancer. Each I-125 prostate cancer treatment requires on average 50 mCi [45]. In the US, about 200,000 men develop prostate cancer per year and 10,000 of them will be treated with I-125 therapy [46]. The US demand for I-125 brachytherapy is thus about 500 Ci per year.

I-125 is typically made by neutron capture on Xe-124 that subsequently decays to I-125. A neutron flux of 10^{14} neutrons/cm^2/sec can create 46 Ci per year at 80% uptime with natural Xenon or 1,600 Ci/year with enriched Xe-124 [47]. I-125 can also be produced by the reaction ^{125}Te(p, n)^{125}I, at an estimated rate of 122 Ci/year with a 30 MeV cyclotron at 500 μA [48].

Sr-89

Sr-89 is also used for palliative care of metastatic bone disease [33]. A typical treatment requires 4 mCi and can be delivered up to four times a year. If 25,000 patients were treated with Sr-89 four times per year than the total US demand would be approximately 400 Ci.

Sr-89 can be made by neutron capture on Sr-88. For this treatment modality, specific activity is likely critical to achieve therapeutic effect. Metastron, the commercial version of Sr-98, has a specific activity of 0.16 Ci/g. To reach this activity with neutron capture on a mole of natural Sr would require 10 days of exposure to a 10^{14} n/cm^2/sec flux. This exposure time would create 14 Ci of Sr-89 so that 400 Ci could be produced per year assuming an 80% uptime. Production via a d,p reaction on Y-89 using a 500 micro-Amp, 20 MeV beam will be 1000 times slower than the neutron capture reaction and thus unfeasible for commercial use [44].

P-32

In the past, P-32 was used for types of ovarian cancer, blood disease and metastatic bone cancer. Today, it is mostly a niche isotope used for a certain type of cystic brain tumor called cystic craniopharyngiomas [50]. Each treatment requires on average 0.5 mCi of P-32 [51]. A total of 20,000 patients present with brain cancer in the US per year. Only a very small fraction of these patients will likely need P-32 therapy. 10,000 per year is a very conservative upper bound.

P-32 is typically made by exposing natural sulfur containing 95% S-32 to a fast neutron flux. A 10^{14} n/cm^2/sec fast flux impinging on a 250 g target will make 15 Ci / year. Although early supplies of P-32 were created with the Berkley cyclotron [52], a charged particle reaction for P-

32 production has not been investigated for a very long time. A d,2p reaction on S-32 could create 1,800 Ci/year [44].

Alternative Production Mechanisms to Reactor-Made, Infrequently Used Medical Isotopes

Actinium-225

Actinium-225 is an alpha emitter with a 10 day half life. It is used for targeted alpha therapy (TAT). A decay product, bismuth-213, is also a therapeutic alpha emitter. The dominant production method is indirect, involving neutron activation of thorium-232, producing U-233. The decay chain of U-233 produces Ac-225 (via two alpha decays and one beta). U-233 is a weapons-usable fissile isotope with a bare-sphere critical mass of about 15 kg, as opposed to 10 kg for Pu-239 and about 47 kg for U-235 [54].

Ac-225 can be produced in cyclotrons or linacs, both with a Ra-226 target. Proton cyclotrons would make use of the reaction Ra-226 (p,2n). Linacs would use brehmsstrahlung gammas to produce Ra-225 via the reaction Ra-226 (γ,n), which would decay to Ac-225 with a 15 day half life. Both of these reactions not only avoid fission but also production of the fissile U-233.

Americium-241

Americium-241 is an alpha emitter with a 432 year half life. It has some medical use in cardiovascular imaging and osteoporosis detection [55], though its main use is in well logging for hydrocarbon exploration, where it serves as a neutron source when alloyed with beryllium [56]. Am-241 is itself fissile, with a critical mass of roughly 60 kg though its use in weapons has never been seriously pursued [57].

It is produced by the decay of Pu-241 (with a half life of 14 years), which in turn is produced in reactors by three successive neutron captures on U-238 – a process that involves production of fissile Pu-239. It can also be produced more directly by bombarding U-238 with alpha particles, yielding Pu-241 via (α,n) reactions, which decays to Am-241 [58], though this would involve some co-production of Pu-239 as well with free neutrons. However, the viability of this approach for large-scale production is unknown, and it would still produce Pu-241 – a fissile isotope with a 13 kilogram critical mass [54].

Global production of americium totals a few kilograms per year [58]. However, only a small minority of this production is for medical uses, and Am-241 is not considered a key therapeutic or diagnostic isotope.

Californium-252

Californium-252 decays by alpha emission (97% of the time) and spontaneous fission (3%) with a half life of 2.6 years. The spontaneous fission decay mode makes Cf-252 attractive for medical and industrial purposes, as it gives off 3.75 neutrons per fission [59], making it a very intense neutron source. This makes it particularly useful for neutron brachytherapy, where radioactive

sources are placed adjacent to the area to be treated (either internally or externally). However, external neutron brachytherapy is not commonly prescribed.

Production overview and alternatives

Cf-252 is produced by successive neutron capture starting with U-238, which must absorb 14 neutrons without fissioning to yield Cf-252 [56]. This is generally performed in stages – instead of U-238 capturing 14 neutrons in one target, U-238 will be irradiated to produce Plutonium and Americium, which will be processed and irradiated to produce curium, which is irradiated to produce californium. Cf-252 is itself fissile, with a very low bare sphere critical mass of about 6 kg [54]. Producing Cf-252 from U-238 involves the production of many intermediate isotopes, and substantial losses to fission – producing a single atom of Cf-252 requires breeding at least 300 atoms of Pu-239 (see Fig. 1).

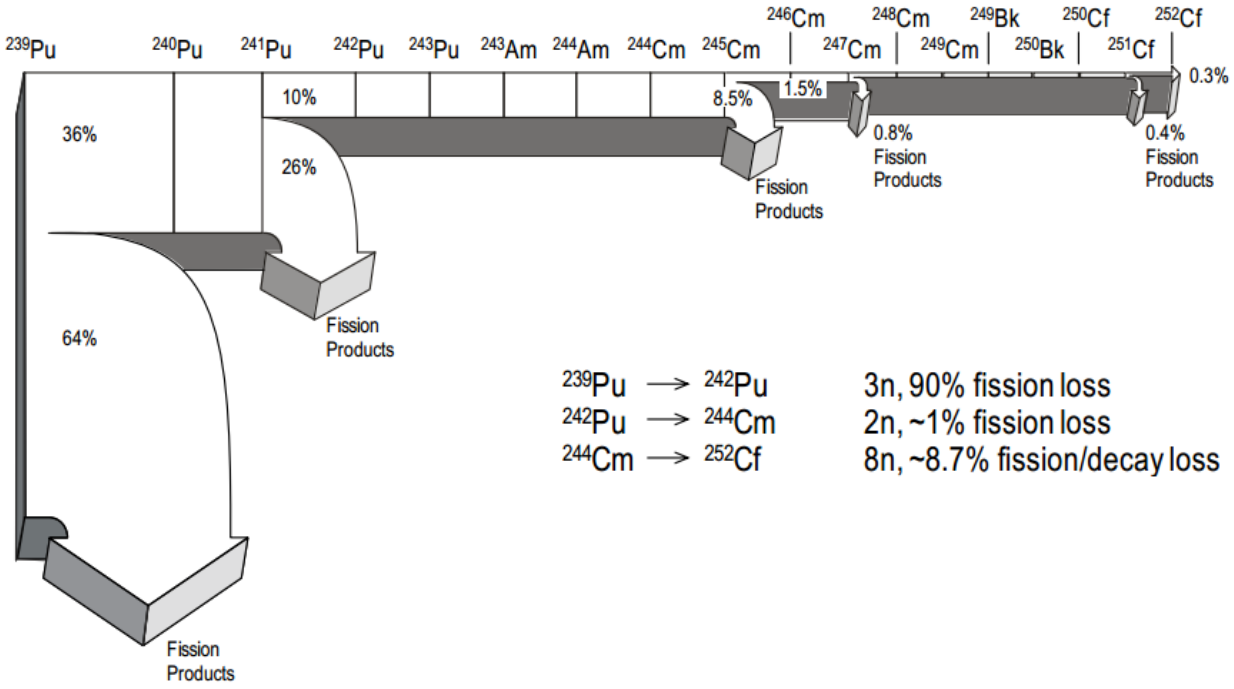

Figure 1. A diagram of californium production [60].

However, the overall production of Cf-252 is small enough to make these quantities manageable from a proliferation standpoint. Global production was only about 275 mg in 2008 [56]. Starting with U-238 targets, breeding this amount of californium would involve the production of on the order of 100 g of Pu-239 annually. Furthermore, only a very small minority of this production could be justified for medical demand. Therefore, while production in spallation neutron sources would involve breeding plutonium, the quantities would be minimal. Plutonium production could be avoided altogether by using targets of americium-241, produced by alpha bombardment of U-238 as described above. This would also decrease the losses to fission in the process, as well as the required neutron flux [60].

Alternative technologies

For neutron therapy, Cf-252 can be replaced by small accelerator neutron sources, which can be placed near a tumor just as isotope brachytherapy sources would be. This method provides advantages in customizing neutron energy to the needs of the particular procedure [61].

Cesium-131

Cesium-131 decays by electron capture with a 9.7 day half life. It is primarily produced by neutron activation of barium-131, and is used for brachytherapy [71]. It can be produced in cyclotrons by proton activation of Xe-131 [72].

Cesium-137

Cesium-137 is a beta and gamma emitter with a half life of 30.2 years. Historically, it was used as a source of high-energy x-rays for both external x-ray therapy and internal high-dose-rate brachytherapy. However, the large x-ray energies and the security hassle of handling large quantities of Cs-137 disfavor the use of this isotope for medical applications. Most Cs-137 medical sources have been replaced by Ir-192 or electron accelerator x-ray sources.
Large sources are still used for equipment sterilization [62], and for food irradiation. The use of Cs-137, particularly in larger sources like those used in food irradiation, has become a security issue in the United States, aside from any concerns relating to the fuel cycle, due to the possibility that a cesium source could be used for radiological dispersal devices, so-called "dirty bombs." While such concerns have been articulated about many long-lived isotopes, cesium is of particular concern because it is usually in the chemical form of cesium chloride, which is soluble in water and easily dispersible [63].

Alternative technologies

Electron accelerators can also serve as medical sterilizers, either operating as gamma sources, or by using their electron beams directly.

Chromium-51

Chromium-51 is a gamma emitter with a 28 day half life used to label red blood cells and quantify gastro-intestinal protein loss. Cyclotron-produced indium-111 may be a more efficient blood labeler [73, 74]. I-111's 2.8 day half life allows it to be produced by idle cyclotrons during night hours with minimal overnight decay loss.

Cobalt-60

Cobalt-60 is a gamma emitter with a 5.27 year half life. It has been used for external beam radiotherapy, brachytherapy, equipment sterilization and food irradiation. As with Cs-137, there are concerns that larger sources might be used in radiological dispersal devices. Although in the past Co-60 was commonly used for radio-surgery (the GammaKnife), modern stereotactic radio-surgery devices, such as the CyberKnife, use 6 MeV electron accelerators to create

bremstraulung x-rays. Brachytherapy Co-60 sources have been replaced by Ir-192. Electron accelerator gamma sources may also be cost-competitive in food irradiation.

Copper-64

Copper-64 is a positron emitter with a half life of 12.7 hours, used in PET. Although it is usually produced in reactors by neutron activation of Cu-63 [47], it can be produced in cyclotrons by multiple reactions, most commonly proton activation of nickel-64 via a (p,n) reaction [69]. The energy range is such that Cu-64 can be produced in PET/SPECT cyclotrons, and the half life is long enough that it can be produced during night hours without too much loss to decay.

Europium-155

Europium-155 is a beta emitter with a 4.73 year half life, used for osteoporosis detection. Though a fission product, it is most often produced by neutron activation of samarium-154 [64], which could be carried out with accelerator-produced neutrons.

Iodine-132

Iodine-132 is a little-used radioiodine isotope, formed by the decay of the fission product tellurium-132. It undergoes beta and gamma decay with a half life of 2.3 hours. It can be produced by alpha bombardment of natural tellurium [32].

Lutetium-177

Lutetium-177 is a beta and gamma emitter with a 6.7 day half life. It is used for simultaneous imaging and therapy of tumors. It is produced by neutron activation of natural or enriched lutetium-176 targets. Deuteron bombardment of ytterbium-176 targets can produce high specific activity Lu-177. This has the additional advantage of avoiding the undesirable contaminant Lu-177m, which increases patient dose without contributing to imaging resolution [76].

Manganese-54

Manganese-54 decays by electron capture with a half life of 312 days, and is used as a radiotracer [77]. Although it is often produced in reactors by neutron activation of iron-54 via an (n,p) reaction, production by deuteron bombardment of chromium-53 via a (d,n) reaction is an established alternative [64].

Niobium-95

Niobium-95 undergoes beta decay with a 35 day half life, and has some applications in imaging [55]. Although a fission product, it can be produced by neutron activation of zirconium-94, producing Zr-95 which decays to Nb-95 [64].

Ruthenium-106

Ruthenium-106 is a beta emitter with a 374 day half life, used to provide high-energy (3.54 MeV) beta particles for brachytherapy. It is usually applied in surface plaques, which irradiate tissue close to the surface of the skin. Ru-106 is rarely used. Surface brachytherapy is now most commonly performed with either high-dose rate Ir-192 sources [102] or electronic x-ray sources.

Selenium-75

Selenium-75 decays by electron capture with a 120 day half life. It is used in the form of seleno-methionine to study the production of digestive enzymes. It can be produced by irradiating natural bromine with protons in the 60 MeV range [78].

Tellurium-129m

Tellurium-129m is a beta and gamma emitter with a 33.6 day half life. Although a fission product, it can be produced by neutron activation of Te-128 [66], which could be carried out with accelerator neutrons, albeit with a lower specific activity.

Xenon-133

Xenon-133 is a beta and gamma emitter with a 5.25 day half life used for pulmonary ventilation studies. Its international medical role has diminished and it is no longer used in the United States. Xe-133 can be replaced with Xe-127, which offers superior resolution, reduced patient dose, and a longer shelf life (36.4 days) [67]. Xe-127 is produced in cyclotrons by activating natural iodine with 10-20 MeV protons [69]. As with I-123, this energy range is compatible with PET/Tc cyclotrons, which can produce long-lived Xe-127 during night hours when they would otherwise be idle.

Ytterbium-169

Yb-169 decays by electron capture with a 32 day half life. It is used for cerebrospinal fluid studies in the brain. It can be produced in a cyclotron by activating natural thulium with 30 MeV protons [92]. This could be done in a PET/Tc-99m cyclotron during night hours.

Yttrium-91

Y-91 is a beta emitter with a 58.5 day half life, used in brachytherapy. Although a fission product, creation by a n,p reaction on Zr-91 is a feasible alternative [70].

Additional Isotopes that could be created via neutron capture at a small-scale spallation neutron source

All isotopes currently produced in reactors by neutron activation of non-fissile, non-fertile targets can be produced without fission or fissionable targets by irradiating targets with neutrons

from small-scale spallation neutron sources. Spallation sources can produce these isotopes with a specific activity equal to or greater than that of reactor production, as they have the ability to match or exceed the neutron flux densities of reactor sources. Isotopes with modest medical use that can be created through neutron capture are listed in Table 9.

Arsenic-73	Gold-198	Potassium-42	Tellurium-123m
Calcium-45	Holmium-166	Radium-223	Tellurium-125m
Carbon-14	Holmium-166m	Radium-224	Terbium-160
Chlorine-36	Iron-59	Samarium-145	Thorium-227
Cobalt-58	Nickel-63	Scandium-46	Thulium-170
Copper-63	Osmium-191	Scandium-47	Tin-113
Copper-67	Osmium-194	Silver-111	Tin-117m
Dysprosium-165	Palladium-109	Sodium-24	
Erbium-169	Phosphorous-33	Sulphur-35	
Gadolinium-153	Platinum-195m	Tantalum-182	

Table 9. A list of other isotopes that have potential medical use and that can be created with a small spallation neutron source.

Conclusion and Discussion

Accelerators can supplant reactors entirely in nuclear medicine. For technetium-99m, switching to accelerator production may reduce costs – at the very worst, it will not significantly increase them compared to procedure costs. And the necessary accelerator infrastructure, if diverted to fissile material production, would be able to produce only very small quantities of weapons-usable fissile material.

Furthermore, this infrastructure would be spread out globally, so that in any one state only a fraction of the total amount of fissile material could be produced. This suggests, as discussed, that the proliferation risk of accelerators is very small when compared to the uranium enrichment and plutonium production inherent in operating reactors for medical isotope production.

Quantification of the costs of infrastructure needed to produce or replace isotopes other than Mo-99/Tc-99m is beyond the scope of this report. The financial costs and proliferation risks of producing these other isotopes may exceed those associated with Tc-99m, despite the fact that the latter is used in a majority of medical isotope procedures. Nevertheless, it is clear that accelerator alternatives are possible, and it seems likely that their implementation would have a significant security benefit. The fissile material production capability of these accelerators would be less than that of the reactors they replace. Fissile material production could only occur as a result of dedicated activities that could not be explained away as part of normal medical isotope production (namely, uranium enrichment and neutron bombardment of uranium), as opposed to the uranium enrichment and continuous plutonium production associated with normal reactor operations.

The question of how these accelerator options might be implemented is an important one. A detailed discussion of the topic is outside the scope of this paper, but a few observations can be made.

First, global implementation of accelerator production would undermine a potential proliferator's justification for reactors. Accelerator options implemented on a global scale would obviate the use of nuclear medicine as a justification for proliferation-sensitive infrastructure.

Second, subsidies have often impacted the economics of reactor produced radioisotopes. Regardless of the role of subsidies, capital costs will have to be incurred to build the required accelerator infrastructure. However, it should be noted that the same issue applies to reactor production, as many current isotope-producing reactors are very old.

A final suggestion can be made with respect to technology development of accelerator-based isotope production facilities. The US federal government has a strong track record of promoting and funding the development of commercial-scale production facilities of medical isotopes. For example, NorthStar's development of the photo-nuclear Mo-99 production process was funded under contract from the NNSA [91]. For all commonly used medical isotopes, the analysis performed here has demonstrated that accelerator-based production is feasible. More R&D would support a full transition commercial supply of isotopes other than Tc-99m using accelerator-based processes. Targeted investments in R&D for commercial production of such isotopes, through contracts by NIH or DOE could have substantial impact on the commercial availability of accelerator-produced medical isotopes, both in the US and abroad.

Appendix A – Cost calculations for technetium

Reactors

Mo-99 and Tc-99m production is often measured in "six-day curies," which equals the activity of Mo-99 scaled to source strength after six days of decay in transit. Global demand is approximately 500,000 six-day curies annually amounting to 30 million doses [79]. This suggests a six-day curie can provide about 60 doses. The production cost per six-day curie is at least $910 for a research reactor [16], implying a cost per dose of about $15.15. Note that this refers to the cost of production and includes capital costs, not the sale price, which is typically lower due to subsidy.

Photo-Nuclear Process via Linacs

Quantifying the costs of the linear accelerator process requires some comparison of the linac and reactor supply chains. In the current reactor production scheme, reactor-origin Mo-99 is distributed in disposable "technetium generators." These are alumina columns with adsorbed molybdate, where technetium in the form of pertechnate is periodically removed by application of saline solution, a process referred to as "elution," or, less formally, "milking." This is performed either at hospitals themselves, or at distributor facilities known as radiopharmacies, which ship prepared medical products to hospitals (see Fig. 2).

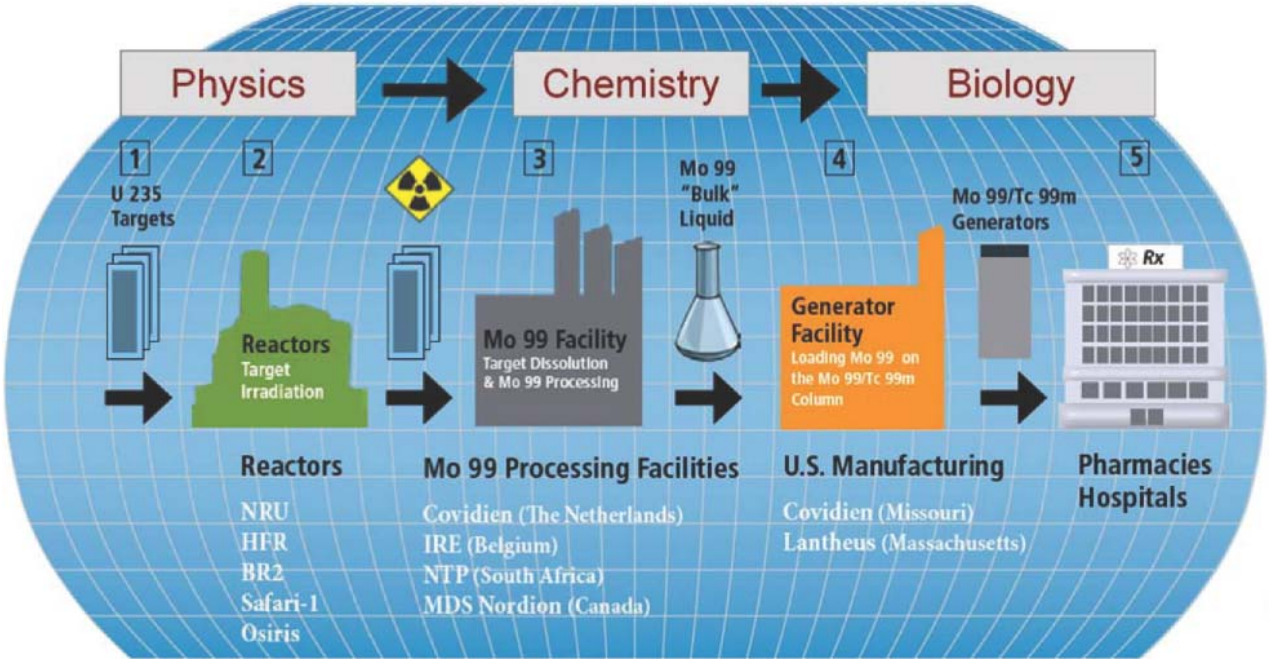

Figure 2. The reactor-based Mo-99 supply chain [80].

Linac-produced Mo-99 has a very low specific activity, as the Mo-99 product cannot be chemically separated from the Mo-100 target. This makes typical technetium generators impractical for linac produced Mo-99. However, a new technetium generator technology has been developed that passes a molybdenum solution over a column which adsorbs any technetium, which is then eluted. This approach allows reusable generators, as opposed to the disposable ones used by the current system. Molybdenum product needs only to be prepared in alkaline solutions rather than adsorbed, which saves generator manufacturing costs and saves the roughly 18 hours needed to manufacture a traditional technetium generator. These generators also have elution efficiencies of over 95%, compared to an industry average of about 80% [88]. These advantages allow about 43% more technetium to be extracted from a six-day Ci of linac Mo-99 than a six-day Ci of reactor origin Mo-99 under the current system. Therefore, one six-day curie of linac Mo-99 should be considered equivalent to about 85 doses as opposed to 60 for a six-day curie of reactor material.

Cost estimates were based on a notional Canadian linac facility described in [81]. This facility would have two 100 kW linacs and on-site processing facilities. It would output two targets each containing 180 Ci of Mo-99 at the end of bombardment (EOB), five days a week. With a processing time of 6 hours, and a processing efficiency of 98%,[12] this translates into 20,700 six-day curies annually. Taking into account the efficiency advantages described above, this single facility, with two linacs, would provide about 1.76 million doses annually, or about 5.9% of current global demand.

[12] Over 98% of the Mo-100 in targets can be recovered [100]. This means that overall molybdenum losses throughout the process are less than two percent. Therefore, Mo-99 losses prior to processing must be less than two percent.

The facility would have capital costs of $20.7 million and annual operations and maintenance costs of $5.73 million, excepting Mo-100 but including shipping. The facility would require an initial supply of 900 g of Mo-100,[13] and at 98% recycling efficiency,[14] additional supplies of 160 g/year would be needed. At $500/g,[15] total costs including Mo-100 would therefore be $21.15 million capital and $5.8 million for operations and maintenance, or $7.17 million total equivalent annual cost.[16] The 17 such facilities required to meet current global demand would cost about $122 million annually

Counting generator costs, estimated as $1.25 per dose [81], this works out to a cost of about $5.35 per dose, or about 35% the cost of reactor production.

If isotopic enrichment on any scale were unavailable, then cyclotron production can be eschewed, and linacs can produce Mo-99 using natural molybdenum targets, albeit at substantial costs in yield and specific activity. This would cut yield and specific activity by a factor of about ten compared to the use of enriched targets.

Using natural molybdenum would have a large impact on the price of the Mo-99 product. Natural molybdenum is only 9.6% Mo-100, so yield would be cut by a factor of 10.4. 177 facilities of the type described in [81], using 354 linacs, would be required. Taking into account savings from not having to enrich molybdenum for targets, and assuming that generator costs per Ci are unaffected by the lower specific activity, this would increase prices by about $38.05, to about $43.40. This is nearly three times the price of reactor origin material, but still only about an eighth of the procedure cost.

p,n Production via Cyclotrons

The cyclotron and reactor supply chains were compared by constructing a model of a typical generator's output. Transit times at each stage of the process were taken from Table 10 (which applies to the current reactor system). When ranges are given, the mean value is assumed.

[13] Targets are 15 g. Recycling turnaround time is stated as 40 days. At five days a week, at most 30 bombardments would be carried out during this time. Hence, an initial supply of 900 g would be required to provide 40 days worth of target material.

[14] A speculative recycling efficiency of 96% is given in [81], however, subsequent research [100] has demonstrated efficiencies of over 98%. The latter figure is therefore used.

[15] Small quantities cost roughly $2000/gram, while kilogram quantities cost about $500/gram [81]. Given that global implementation of accelerator production would drive demand into the kilogram quantities, the latter figure is used.

[16] Assuming 5% interest and a payback time of 30 years for infrastructure.

Process steps	Typical process times (hr)
U-235 target irradiation and cooling	130–168 (5–7 days)
Shipping and processing of target to extract Mo-99	6–28
Mo-99 packaged and shipped	6–12
Tc-99m generator prepared and packaged	12
Tc-99m generator shipped	1–24
Tc-99m generator used by hospital or radiopharmacy	168–336 (7–14 days)

Table 10. Transit times for individual steps of reactor-based Mo-99 production [17].

It was assumed that 21 hours elapse between the end of processing and the end of generator preparation (9 in shipping, 12 in generator preparation). During this time technetium is not accumulating usefully. Another 12 hours elapse in transit between the generator facility and the hospital or radiopharmacy, at which point the generator is eluted immediately. The generator is then eluted at alternate intervals of 6 and 18 hours, or roughly at 8 AM and 2 PM, to provide pertechnate product during working hours. It is disposed of after ten days.

These figures suggest that about 20% of the Mo-99 mass decays en route before generator preparation, and another 5.7% is disposed of after ten days. Of the 74% that decays between generator preparation and disposal, almost half – 37% of the total – is available for elution, the rest decaying to Tc-99g between the elution intervals (particularly the 18 hour overnight interval). Assuming an average elution efficiency of 80% for generators currently on the market,[17] and the fact that 13.5% of Mo-99 decays directly into Tc-99g, about 28% of the mass of Mo-99 available at the end of processing is delivered as Tc-99m output from generators.

This suggests that in order to replace a six-day curie of Mo-99, with a mass of 9.46 μg, a technetium-producing cyclotron must deliver about 2.81 μg of Tc-99m to a hospital. To produce a single dose of 25 mCi (with a mass of about 4.7 ng), a cyclotron must deliver 41 ng (see Table 11 for masses of common units). This provides a base of comparison for calculating the effective production capability of a cyclotron.

Common Quantity of Tc-99m measurement	Mass
1 Ci of Mo-99	2.08 μg
Six-day curie Mo-99	9.46 μg
1 Ci of Tc-99m	189 ng
Dose Tc-99m (25 mCi)	4.73 ng

Table 11. Conversion factors for different quantities of Tc-99m treatment.

[17] [17] gives a range of 70-90% as standard.

The two cyclotron scenarios were considered as follows:

1) A dedicated Tc-99m cyclotron that carries out two six-hour bombardments daily, timed so that processed material will arrive at hospitals and radiopharmacies at the start of the day. The time between end of bombardment (EOB) and product deliveries will be taken as 4 hours, on the assumption that cyclotrons are only supplying large metropolitan areas.[18] Since this is a dedicated facility, technetium prices must include capital costs. Since these would be practical in any reasonably-sized urban area with good transportation infrastructure, their potential market share was assumed to be 50%.

2) A multi-purpose cyclotron that produces Tc-99m in one six-hour bombardment in the early morning. In order to leave time for a two hour F-18 bombardment timed around the start of the day, the bombardment is considered to take place two hours earlier than in the dedicated Tc-99m cyclotron case, increasing the interval between EOB and delivery to six hours. Since technetium production is not interfering with PET production, capital costs are not included in technetium prices. Variable operations and maintenance costs associated with Tc-99m production are considered to be 50% those of the dedicated facility described above, as it is bombarding samples for half as much time. Since these would only be practical in markets where PET demand was already substantial, their potential market share was assumed to be 25%.

The cyclotron in question was assumed to be a 1200 μA, 30 MeV TR 30, as this has a known cost of $12.3 million [82]. 30 MeV is an effective energy range for Tc-99m production, with a yield about 10% higher than at 24 MeV, about 22 Ci/mAh [83], so considering a 30 MeV cyclotron is a reasonable approximation for the use of lower energy machines.

ACSI estimates associated facility costs for a TR 30 facility of $10 million [84]. The on-site processing facilities would have capital costs of $450,000, with annual operating costs of $250,000 [85]. Other operational costs were conservatively estimated at approximately $1 million annually, based on the estimated costs for a 70 MeV, 2 mA cyclotron described in [82].

Target mass is difficult to estimate, and has not been described in the literature for accelerators of this energy and current. It would be subject to many technical considerations, not least of which would be cooling. A rough estimate of molybdenum consumption can be made by comparison with target masses reported for lower energy accelerators. [86] gave a target mass of 1.24 g for a 22 MeV protons being degraded to 10 MeV at 300 μA. Holding the deposited beam power per unit mass constant, a target for a 30 MeV, 1.2 mA proton beam would need to be about 8.3 g. This will serve as a rough estimate.

Recycling of the Mo-100 in targets would have to wait until the target radioactivity had decayed enough to make it safe to handle. 40 days was assumed to be sufficient, meaning that a 40 day

[18]Processing can be carried out in under 90 minutes [86]. Due to the use of even shorter lived PET isotopes, infrastructure exists for shipping product to end users on time scales short enough for this to be feasible.

initial supply would be necessary to allow operations during this period. A recycling efficiency of 90% was taken as typical [86].

Assuming an 80% capacity factor and a processing efficiency of 85% [87], a single dedicated facility could deliver about 6.7 mg – 165,000 doses or 0.55% of current global demand – of Tc-99m to hospitals and radiopharmacies annually, while a single multipurpose facility could deliver 2.7 mg – 65,000 doses or 0.22% of current global demand.

Assuming a hardware lifetime of 30 years, and interest on capital costs of 5%, the annual costs for the dedicated facility come to $3 million, and those for the multipurpose facility to $750,000. Meeting 50% of current demand with dedicated cyclotrons would require 91 machines, costing $272 million annually. Meeting 25% of demand with multipurpose machines would require 115 machines and cost $86 million annually. Cost per dose would be $18.25 and $11.50 for the dedicated and multipurpose facilities, respectively. This suggests a substantial economic advantage to multipurpose facilities.

Appendix B – Fissile material production and technetium infrastructure

All of the methods discussed in this paper for producing Mo-99/Tc-99m need to be evaluated against the risk they pose for proliferation. Molybdenum-enriching centrifuges can be turned to uranium enrichment, and accelerators could be used as neutron sources to irradiate natural or depleted uranium. These risks, however, appear to be minimal.

Molybdenum Enrichment

Most proposed accelerator or neutron activation processes call for the use of enriched molybdenum targets to increase production yield. Currently, Mo-100 enrichment is carried out with centrifuges, primarily by URENCO and at the Krasnoyarsk Electrochemical Plant. Thus a continued need for enriched molybdenum points to a continued availability of some enrichment capacity for medical needs.

However, the material flows are not substantial, particularly since most schemes utilizing enriched material make heavy use of target recycling. The enrichment infrastructure needed to meet global target demand would be too small to produce weapons on any practical time scale.

17 facilities like those described in [81], each employing two linacs, producing Mo-99 in quantities sufficient to meet current global demand would require approximately 2.7 kg of Mo-100 per year. Assuming targets require 99% Mo-100, this would require about 31 SWU per kilogram of product[19] or 84 SWU to meet global demand. Enriching U-235 from 0.711% to 90% requires at least 162 SWU per kilogram,[20] so this infrastructure would be capable of producing about 0.5 kg of HEU annually, or about one significant quantity every 45 years.

[19] This assumes that the discarded "tails" are only about 1% Mo-100, or, in other words, that 90% of the Mo-100 is concentrated in the product. If this is relaxed to about 3%, the work needed drops to 22 SWU/kg.

[20] This assumes tails of 0.45% U-235. While consistent with current Iranian practice, it is much more wasteful of UF6 than the 0.2-0.3% used by most international suppliers. At 0.25% tails, enriching one kilogram of 90% U-235 requires about 208 SWU.

Cyclotron Mo-100 demand is more substantial. With targets of 8.3 g, and 90% recycling efficiency, net Mo-100 consumption would be about 475 g/year for a dedicated cyclotron, or 240 g/year for a multipurpose one. 91 dedicated machines meeting 50% of global demand would need about 43 kg annually, while 115 multipurpose machines meeting 25% of demand would require about 27 kg. This would require enrichment infrastructure capable of producing roughly 8 or 5 kg of weapon grade uranium annually, respectively.

However, this would still require global molybdenum enrichment infrastructure to be turned to HEU production for several years to acquire a weapon.

A quick comparison with reactors is illustrative – see Table 12. An average 1000 MWe PWR uses fuel enriched to 3.75%, and consumes 21.5 tons of LEU annually [13]. This would require about 80,000 SWU – enough to produce about 500 kg of 90% HEU annually.[21]

	Potential market share	Dedicated machines needed	Mo-100 needed (kg/year)	HEU that could be produced by required enrichment facilities (kg/year)*
Linac (enriched)	100%	34	2.72	0.5
Linac (natural)	100%	354	0	0
Dedicated Cyclotron	50%	91	43.4	8.2
Multipurpose Cyclotron	25%	0	27.4	5.1
Typical Power Reactor (1000 MWe PWR)	N/A	N/A	0	500

Table 12. HEU production capacity implied by Mo enrichment capability. Natural uranium is assumed as the feed stock.

[21] Assuming both fuel and weapons material have tails of 0.45%, and that bomb material is enriched from natural feed, rather than fuel stockpiles.

References

1. A. Glaser, "On the Proliferation Potential of Uranium Fuel for Research Reactors at Various Enrichment Levels," *Science and Global Security*, **14** 1 (2006), available online at http://scienceandglobalsecurity.org/archive/sgs14glaser.pdf.
2. T. M. Willig, C. Futsaether, H. Kippe, "Converting the Iranian Heavy Water Reactor IR-40 to a More Proliferation-Resistant Reactor," *Science & Global Security* **20** 97 (2012).
3. S. Kemp, "Nuclear Proliferation with Particle Accelerators," *Science and Global Security*, **13**. 183 (2005). Available at http://www.princeton.edu/~rskemp/Kemp%20-%20Nuclear%20Proliferation%20with%20Particle%20Accelerators.pdf
4. D. Riendeau, D. L. Moses, A. P. Olson, "Proliferation Potential of Accelerator-driven Systems: Feasibility Calculations," Oak Ridge National Laboratory, available at http://www.osti.gov/bridge/servlets/purl/12464-s1ZzJe/webviewable/12464.pdf.
5. IAEA, "INFCIRC/153 (Corrected) – The Structure and Content of Agreements Between the Agency and States Required in Connection with the Treaty on the Non-Proliferation of Nuclear Weapons," (International Atomic Energy Agency, Vienna, 1972), available at http://www.iaea.org/Publications/Documents/Infcircs/Others/infcirc153.pdf.
6. R. Carchon, A. Borella, K. van der Meer, "Safeguards for a Gen IV type reactor – Safeguards Approach versus Design Information," (Tech. Rep. CN-184/308, International Atomic Energy Agency, Vienna, 2010), available at http://www.iaea.org/safeguards/Symposium/2010/Documents/PapersRepository/308.pdf.
7. L. L. Lucas and J. W. Root, "(d,n) thick-target yields and total cross sections between 1 and 40 MeV," *J. Appl. Phys.* **43**, 3886 (1972).
8. Yun-Kwei Tai, G. P. Milliburn, Selig N. Kaplan, B. J. Moyer, "Neutron Yields from Thick Targets Bombarded by 18- and 32-Mev Protons," *Phys. Rev.* **109**, 2086–2091 (1958).
9. C. J. Karzmark et al., "Total Skin Electron Therapy: Technique and Dosimetry," (AAPM report 23, American Association of Physicists in Medicine, 1987), available at http://www.aapm.org/pubs/reports/rpt_23.pdf
10. C.-K. Chris Wang and B. R. Moore, "Thick beryllium target as an epithermal neutron source for neutron capture therapy," *Med. Phys.* **21**, 1633 (1994).
11. Ludwiget et al., "An epithermal neutron source for BNCT based on an ESQ-accelerator" (Lawrence Berkeley National Laboratory, 1997) available at http://www.osti.gov/bridge/servlets/purl/554880-pINNLJ/webviewable/554880.pdf.
12. M. Goitein et al., "Treating Cancer with Protons," *Physics Today* **55**, 45 (2002).
13. D. Bodansky, "Nuclear Energy: Principles, Practices, and Prospects," 2nd Ed. (2004), pg. 499.
14. Ziessman, "Nuclear Medicine – The Requisites", 2nd Ed. (2005).
15. IAEA, "Established Radioisotopes" available at http://www-nds.iaea.org/radionuclides/list_estab_nuclides.htm.
16. Nuclear Energy Agency, "The Supply of Medical Radioisotopes: An Economic Study of the Molybdenum-99 Supply Chain," (Organisation for Economic Co-operation and

Development, Paris, 2010) available at http://www.oecd-nea.org/med-radio/reports/MO-99.pdf

17. National Research Council, "Medical Isotope Production Without Highly Enriched Uranium," (The National Academies Press, Washington, D.C., 2009), available at http://www.nap.edu/catalog.php?record_id=12569.
18. "Civilian HEU: Canada," (Nuclear Threat Initiative, http://www.nti.org/analysis/articles/civilian-heu-canada/, retrieved 10 June 2013).
19. D. P. Guarino, "U.S. Proposes Bigger Medicare Payouts to Avoid Bomb-Grade Uranium," Global Security Newswire, 11 July 2012, available at http://www.nti.org/gsn/article/us-proposes-bigger-medicare-payouts-avoid-bomb-grade-uraniu/.
20. IAEA, "IAEA Safeguards Glossary – 2001 Edition," (International Nuclear Verification Series No. 3, International Atomic Energy Agency, Vienna, 2001), available at http://www-pub.iaea.org/MTCD/publications/PDF/nvs-3-cd/PDF/NVS3_prn.pdf.
21. IAEA, "Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m," available at http://www-pub.iaea.org/MTCD/Publications/PDF/Pub1589_web.pdf.
22. A. Celler, X. Hou, F. Benard and T. Ruth, "Theoretical modeling of yields for proton-induced reactions on natural and enriched molybdenum targets," 2011 *Phys. Med. Biol.* **56** 5469 (2011).
23. "World's First Hybrid PET/SPECT Cyclotron Successfully Commissioned at 500μA," Advanced Cyclotron Systems Incorporated (2012), available at http://www.advancedcyclotron.com/news/world%E2%80%99s-first-hybrid-petspect-cyclotron-successfully-commissioned-500ma.
24. "TR 24 Cyclotrons," Advanced Cyclotron Systems Incorporated, http://www.advancedcyclotron.com/cyclotron-solutions/tr24, retrieved 10 June 2013.
25. "CYCLOTEC™ Brings Canada Closer to Solving Medical Isotope Shortage," Advanced Cyclotron Systems Incorporated (2012), available at http://www.advancedcyclotron.com/news/cyclotec%E2%84%A2-brings-canada-closer-solving-medical-isotope-shortage-0.
26. Nuclear Energy Agency, "The Supply of Medical Radioisotopes: An Assessment of Long-term Global Demand for Technetium-99m," (Organization for Economic Co-operation and Development, Paris, 2011) available at http://www.oecd-nea.org/med-radio/reports/long-term-assessment-99mtc.pdf.
27. H. Kubo et. al., "High dose-rate brachytherapy treatment delivery: Report of the AAPM Radiation Therapy Committee Task Group No. 59" Med. Phys. **25,** 375 (1998), available at http://www.aapm.org/pubs/reports/rpt_61.pdf.
28. F. Tarkanyi, "Study of the ^{192}Os(d,2n) reaction for production of the therapeutic radionuclide ^{192}Ir in no-carrier added form," *Applied Radiation Isotopes* **65**, 1215 (2007).
29. "Specific Therapies," (International Atomic Energy Agency, Vienna, retrieved 10 June 2013), available at https://rpop.iaea.org/RPOP/RPoP/Content/InformationFor/HealthProfessionals/3_NuclearMedicine/TherapeuticNuclearMedicine/Therapeutic_nuclear_medicine_-_specific_therapies.htm.

30. C. Sayre, "The Rising Incidence of Thyroid Cancer," New York Times, available at http://www.nytimes.com/ref/health/healthguide/esn-thyroid-cancer-ess.html, retrieved 10 June 2013.
31. S. Mukhammedov, "Application of proton and neutron activation method of analysis for the determination of elements with z > 42" *Soviet Atomic Energy*, **56** 56 (1984).
32. P. P. Dmitriev, M. V. Panarin, Z. P. Dmitrieva, "Yields of 123I, 124I, 125I, 126I, 130I, 131I, and132I upon the irradiation of tellurium by protons, deuterons, and α particles and antimony by α particles," *Soviet Atomic Energy* **49**, 798 (1980), available at http://link.springer.com/article/10.1007%2FBF01120760.
33. Liepe, "Systemic radionuclide therapy in pain palliation," *Am. J. Hosp. Palliat. Care* **22** 457 (2005).
34. Li, "Estimated number of prevalent cases of metastatic bone disease in the US adult population," *Clinical Epidemiology* **4** 87 (2012).
35. G. Randers-Pehrson and D. J. Brenner, "A practical target system for accelerator-based BNCT which may effectively double the dose rate," *Med. Phys.* **25** 894 (1998).
36. J. Tse, "High SpecificActivity [Samarium.-153]EDTA for Imaging of Experimental Tumor Models," *Journal of Nuclear Medicine*, **30** 202 (1989).
37. S. Qaim, "Nuclear data for production of 88Y, 140Nd,153Sm and 169Yb via novel routes," *Radiochimica Acta*, **95** 313 (2007).
38. I. Spahn et al, "New nuclear data for production of 73As, 88Y and 153Sm: important radionuclides for environmental and medical applications," Paper presented at the International Conference on Nuclear Data for Science and Technology 2007, available at http://nd2007.edpsciences.org/articles/ndata/pdf/2007/01/ndata07351.pdf.
39. P. P. Dmitriev, "Yields of Re-181,Re-182-m,Re-182,Re-183,Re-184-m, Re-184 and Re-186 when irradiating tungsten with protons and deuterons, and tantalum with alpha particles," *Soviet Atomic Energy*, **48** 150 (1980).
40. M. E. Moustapha et al., "Preparation of cyclotron-produced 186Re and comparison with reactor-produced 186Re and generator-produced 188Re for the labeling of bombesin," *Nucl. Med. Biol.* **33**(1) 81 (2006).
41. Salem, "Yttrium-90 Microspheres For The Treatment Of Hepatocellular Carcinoma: A Review,"*Int. J. Radiation Oncology Biol. Phys.*, **66**(2), S83–S88 (2006).
42. N. Howlader et al., *SEER Cancer Statistics Review, 1975-2010*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013. Available at http://seer.cancer.gov/statfacts/html/brain.html.
43. W.A. Dezarn et al., "Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies," (AAPM report 23, American Association of Physicists in Medicine, 2011), available at http://www.aapm.org/pubs/reports/rpt_23.pdf.
44. N. Baron and B. L. Cohen, "Activation Cross-Section Survey of Deuteron-Induced Reactions," Physical Review **129**, 2636 (1963).

45. K. Wallner, J. Roy, L. Harrison, "Tumor control and morbidity following transperineal iodine 125 implantation for stage T1/T2 prostatic carcinoma," *Journal of clinical Oncology*, **14** 449, (1996).

46. J. Marder, "A User's Guide to Cancer Treatment," *Science,* **326** (5957), 1184-1186 (2009).

47. IAEA, "Manual for reactor produced radioisotopes," (IAEA-TECDOC-1340, International Atomic Energy Agency, Vienna, 2003), available at http://www-pub.iaea.org/MTCD/publications/PDF/te_1340_web.pdf.

48. Y. T. Petrusenko, "Production Of Medical 123–125I In The Cv-28 Cyclotron Using Tellurium Targets," *Atomic Energy*, **190** 350 (2011).

49. M. E. Fassbender et al., "Proton irradiation parameters and chemical separation procedure for the bulk production of high-specific-activity ^{186g}Re using WO_3 targets," *Radiochimica Acta* **101** 339 (2013).

50. "Radiation Therapy Principles," American Cancer Society (2012), available at http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/radiationtherapyprinciples/radiation-therapy-principles-how-is-radiation-given-radiopharmaceuticals.

51. B. E. Pollack et al., "Phosphorus-32 intracavitary irradiation of cystic craniopharyngiomas: Current technique and long-term results," Int. J. Rad. Oncology **33**, 437 (1995).

52. R. Simoni et al., "The Early Use of Artificial Radioactive Isotopes: Waldo. E. Cohn" *J. Biol. Chem.* **277** e33 (2002).

53. Sartor O, Reid RH, Bushnell DL, et al. "Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain," *Cancer* **109** (3) 637 (2007).

54. E. Greenspan et. al., "Maximum Fuel Utilization in Fast Reactors Without Chemical Reprocessing," (Summary Report, NEUP Project 09-769; University of California, Berkeley, 2012), available at Greenspan et. al., 2012.

55. "List of Nuclear Medicine Radioisotopes," National Isotope Development Center, http://www.isotopes.gov/outreach/med_isotopes.html, retrieved 10 June 2013.

56. "Radiation Source Use and Replacement: Abbreviated Version," (The National Academies Press, Washington, D.C., 2008), http://www.nap.edu/catalog.php?record_id=11976.

57. H. Dias, N. Tancock and A. Clayton, "Critical Mass Calculations for 241Am, 242mAm and 243Am," presented at JAERI conference 2003, available at http://typhoon.jaea.go.jp/icnc2003/Proceeding/paper/6.5_022.pdf.

58. "Toxicological Profile For Americium," (Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, 2004), available at http://www.atsdr.cdc.gov/ToxProfiles/tp156.pdf.

59. E. J. Axton and A. G. Bardell, "Neutron Yield from the Spontaneous Fission of 252Cf," *Metrologia* **21**, 59 (1984).

60. E.D. Collins, C.W. Alexander, D.E. Benker, J.P. Renier, "Analogies of experience in the United States Transuranium Element Production Program with partitioning and transmutation of transuranic actinides in commercial used fuels," Presented at OECD Nuclear Energy Agency 11th Information Exchange Meeting on Actinide and Fission

Product Partitioning and Transmutation, San Francisco, USA 1-4 November 2010, available at http://www.oecd-nea.org/pt/iempt11/poster/VI-4.pdf.

61. H. Song, J.C. Yanch, R.E. Klinkowstein, "Accelerator-based neutron brachytherapy," *Med. Phys.* **29** 15-25, (2002).
62. EPA Facts about Cesium-137," Environmental Protection Agency (2002), available at http://www.epa.gov/superfund/health/contaminants/radiation/pdfs/cesium.pdf
63. J. Medalia, ""Dirty Bombs": Technical Background, Attack Prevention and Response, Issues for Congress," Congressional Research Service Report (2011), available at http://www.fas.org/sgp/crs/nuke/R41890.pdf
64. "Table of Radionuclides," (Monographie BIPM-5, Bureau International des Poids et Mesures, 2004), available at http://www.bipm.org/utils/common/pdf/monographieRI/Monographie_BIPM-5_Tables_Vol2.pdf.
65. A. Flynn, "Isotopes and delivery systems for brachytherapy," in P. J. Hoskin and C. Coyle, "Radiotherapy in Practice: Brachytherapy," Oxford University Press (2005)
66. Yu. Maeda, S. Kitao, M. Seto, Y. F. Hsia, H. Sakai, "Preparation of Mg3 129TeO6 Mössbauer source," *Hyperfine Interactions* **92**, 1167 (1994)
67. H.L. Atkins et. al, "A clinical comparison of Xe-127 and Xe-133 for ventilation studies," *J. Nucl. Med.* **18** 653 (1977).
68. R. Coppola et. al. "A comparison of xenon-133 and xenon-127 for the determination of regional cerebral blood flow measured by dynamic SPECT," *Psychiatry Research* **45** 187 (1992)
69. "Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods," (Technical Reports Series No. 468, International Atomic Energy Agency, Vienna, 2009), available at http://www-pub.iaea.org/MTCD/Publications/PDF/trs468_web.pdf
70. .W. Coleman, thesis, Oregon State University (2004), available at http://ir.library.oregonstate.edu/xmlui/bitstream/handle/1957/30428/ColemanJosephW2004.pdf?sequence=1.
71. Venselaar et al., "Comprehensive Brachytherapy: Physical and Clinical Aspects," (CRC Press, 2012).
72. F. Tarkanyi et. al., "Cross section measurements of the (131)Xe(p,n) reaction for production of the therapeutic radionuclide (131)Cs," *Appl. Radiat. Isot.* **67** 1751 (2009).
73. A. G. Palestine et. al., "Lymphocyte Migration in the Adoptive Transfer of EAU," Invest Ophthalmol Vis Sci. **27**, 611-5 (1986), available at http://www.iovs.org/content/27/4/611.full.pdf.
74. K. Kinuya, S. Matano, H. Nakashima and S. Taki, "Scintigraphic prediction of therapeutic outcomes of splenectomy in patients with thrombocytopenia," *Annals of Nuclear Medicine* **17** 161 (2003).
75. M. P. J. Vanderpump, "The epidemiology of thyroid disease," British Medical Bulletin **99** 39 (2011).

76. S. Manenti, M.L. Bonardi, L. Gini, F. Groppi "Lu-177g produced with high specific activity by deuteron irradiation for metabolic radiotherapy / - In: Program and abstract book of 3. International nuclear chemistry congress : 3. INCC / [a cura di] F. Groppi. - Milano, Italia : Università degli studi di Milano, Dipartimento di fisica, 2011 Sep. - ISBN 978-88-901562-3-6. - pp. 63-63 ((Intervento presentato al 3. convegno International nuclear chemistry congress : INCC tenutosi a Città del Mare (Palermo), Italy nel 2011.
77. B. L. O'Dell and R. A. Sunde, "Handbook of Nutritionally Essential Mineral Elements," CRC Press (1997).
78. M. Fassbender, D.de Villiers, M. Nortier, N. van der Walt, "The natBr(p,x)73,75Se nuclear processes: a convenient route for the production of radioselenium tracers relevant to amino acid labelling," Applied Radiation and Isotopes, **54**, 905 (2001).
79. Nuclear Energy Agency, "A Supply and Demand Update of the Molybdenum-99 Market," (Organisation for Economic Co-operation and Development, Paris, 2012) available at http://www.oecd-nea.org/med-radio/docs/2012-supply-demand.pdf.
80. "Backgrounder -- Medical Isotopes," Science Media Center Canada (15 October 2010) available at http://www.sciencemediacentre.ca/smc/index.php?option=com_content&view=article&id=94%3Aisotopes&catid=1%3Alatest-news&Itemid=49&lang=en.
81. C. Ross, "Using the 100 Mo Photoneutron Reaction to Meet Canada's Requirement for 99mTc," presented at seminar at Centre Hospitalier Universitaire De Sherbrooke, available at http://web.archive.org/web/20110827192344/http:/irs.inms.nrc.ca/publications/presentations/pdf/present-Ross-2010.pdf.
82. "Cost/Benefit Comparison For 45 Mev And 70 MeV Cyclotrons," Jupiter Technical, Security, and Management Solutions (2005), available at http://www.isotopes.gov/outreach/reports/Cyclotron.pdf.
83. F. Tarkanyi et. al., "Investigation of activation cross-sections of proton induced nuclear reactions on natMo up to 40 MeV: New data and evaluation," *Nucl. Instr. Meth. B* **280**, 45-73 (2012).
84. "TR 30 Cyclotrons," Advanced Cyclotron Systems Incorporated, http://www.advancedcyclotron.com/cyclotron-solutions/tr30, retrieved 10 June 2013.
85. Nuclear Energy Agency, "The Supply of Medical Radioisotopes: Review of Potential Molybdenum-99/ Technetium-99m Production Technologies," (Organisation for Economic Co-operation and Development, Paris, 2010), available at http://www.oecd-nea.org/med-radio/reports/Med-Radio-99Mo-Prod-Tech.pdf.
86. P. Schaffer, "Direct Production of 99mTc on Canada's Existing Cyclotron Infrastructure," presentation at 2013 Mo-99 Topical Meeting April 1-4, 2013, Chicago Il, available at http://mo99.ne.anl.gov/2013/pdfs/Mo99%202013%20Web%20Presentations/S8-P2_Benard.pdf.
87. Guerin et al, "Cyclotron Production of 99mTc: An Approach to the Medical Isotope Crisis," The Journal of Nuclear Medicine **51**, 13 (2010), available at http://jnm.snmjournals.org/content/51/4/13N.full.pdf.

88. J. T. Harvey, G. H. Isensee, G. P. Messina, and S. D. Moffatt, "Domestic Production of Mo99," presented at the Mo-99 Topical Meeting, Santa Fe, New Mexico December 4-7, 2011.

89. J. Carson Mark, "Explosive properties of reactor-grade plutonium," Science & Global Security **4** 111 (1993), available at http://scienceandglobalsecurity.org/archive/sgs04mark.pdf.

90. "Reimbursement Information for Positron Emission Tomography (PET)," (Consumer Advisory, GE Healthcare, 2012), available at http://www3.gehealthcare.com/en/Products/~/media/Downloads/us/Product/Reimbursement/Customer-Advisories/GEHealthcare-Customer-Advisory_Position-Emission-Tomography-PET-Reimbursement-Info-2013.pdf.

91. "NNSA Awards Agreement to Establish Non-HEU-Based Production of Molybdenum-99 in US," (Press Release, National Nuclear Security Administration, 15 Nov 2012), available at http://nnsa.energy.gov/mediaroom/pressreleases/mo99111512.

92. H. Nadi et al., "Cyclotron production of 169Yb: a potential radiolanthanide for brachytherapy," *Journal of Radioanalytical and Nuclear Chemistry* **289** 361 (2011).

93. E.B. Silberstein, "Society of Nuclear Medicine Procedure Guideline for Palliative Treatment of Painful Bone Metastases," Available at http://interactive.snm.org/docs/pg_ch25_0403.pdf.

94. IAEA, "Development opportunities for small and medium scale accelerator-driven neutron sources," (IAEA-TECDOC-1439 2004) available at http://www-pub.iaea.org/MTCD/publications/PDF/te_1439_web.pdf.

95. R. Hamm and M. Hamm, "The beam business: Accelerators in industry," *Physics Today*, **64** 46 (2011).

96. M. J. Welch, C. S. Radvanly, eds., "Handbook of Radiopharmaceuticals: Radiochemistry and Applications," Wiley, Hoboken, NJ (2006).

97. US Department of Energy, "Accelerators for America's Future," (US DOE, October 2009), available at http://www.acceleratorsamerica.org/report/index.html.

98. M. Englert, C. Pistner and W. Liebert, "Neutronics calculations for the assessment of proliferation risks associated with spallation neutron sources, " Nucl. Instr. Meth. A. **562** 567 (2006).

99. B. Blau et al., "The Swiss Spallation Neutron Source SINQ at Paul Scherrer Institut" *Neutron News* **20** 5 (2009).

100. P. Tkac, et. al., "ANL Activities in Support of Accelerator Production of 99Mo through the γ/n reaction on 100Mo," presented at 2013 Mo-99 Topical Meeting, April 1-4, 2013, Embassy Suites Chicago Downtown, Chicago, Il, available at http://mo99.ne.anl.gov/2013/pdfs/Mo99%202013%20Web%20Papers/S10-P3_Tkac_Paper.pdf.

101. G. Bauer, "Physics and technology of spallation neutron sources," *Nucl. Instr. Meth. A* **463** 505 (2001).

102. B. Guix, "Treatment of skin carcinomas of the face by high-dose-rate brachytherapy and custom-made surface molds," *Int. J. Radiat. Oncol. Biol. Phys.* **47** 95 (2000).