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The Production of Medical Isotopes without Nuclear Reactors or Uranium Enrichment

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This article examines the current capability of accelerator technology, which is rapidly improving, to produce medical isotopes. A detailed analysis of 12 medical isotopes that are in active diagnostic and therapeutic use and typically made in nuclear reactors shows that accelerator-based technologies, such as linear accelerators, cyclotrons, and spallation neutron sources, could meet medical demand for these isotopes, without the use of enriched uranium and with low proliferation risk. The feasibility of accelerator-based production of an additional 70 isotopes that have a potential medical use is also discussed.

A simple estimate suggests that accelerators can produce isotopes at a cost comparable to reactors. This article includes four case studies that illustrate the recent choices that emerging market countries have made when expanding domestic medical isotope production. Technical, commercial, and regulatory steps for commercialization are also described. The article concludes with policy suggestions that would increase the adoption of accelerator-based medical isotope production.

INTRODUCTION

Modern medicine uses radioisotopes, also known as medical isotopes, for diagnostic and therapeutic purposes. For some isotopes, the production method is chosen so that it occurs in the same facility where the isotope is utilized due to the isotope's very short half-life. For others, the selected production method is chosen for cost effectiveness or convenience. For example, exposure of targets to the neutron flux in a research reactor is particularly attractive and convenient because manufacturers can "piggy-back" on the ex-

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isting reactor and develop expertise that pertains to the isotope chemistry itself.

Accelerators offer several advantages over nuclear reactors for medical isotope production.[1] Accelerators present far less of a safety risk to operators and the general public. They generate minimal high-level nuclear waste and only modest quantities of low-level waste.

Accelerator-based technology also typically spreads isotope production over a greater number of facilities, minimizing supply disruptions due to single point failures. For example, a global shortage of technetium-99m (Tc-99m) occurred in 2007 and from 2009 to 2010 when Canada's NRU reactor at Chalk River shut down unexpectedly.[2] Furthermore, accelerators present minimal proliferation risk. They do not use any uranium, enriched or otherwise, and, except for the hybrid case of very large and dedicated accelerator/reactor combinations called accelerator-driven systems, which are not necessary for isotope production, they are incapable of creating weapon-scale quantities of plutonium in less than 20 years. Isotope suppliers in the United States and Canada recognize the advantages of accelerator production and operators in both countries have plans to increase their production capacity by building accelerators.[3]

Accelerator-based technology that does not use uranium also has another security advantage: it does not produce radioxenon that mimics the signature of a nuclear explosion. Radionuclide monitoring is one of the four main detection strategies used by the International Monitoring System (IMS) of the Preparatory Commission for the Comprehensive Nuclear-Test-Ban Treaty Organization (CTBTO).[4] Accelerator-based technologies that do not use uranium will reduce atmospheric levels of radioxenon, increase the sensitivity of IMS radioxenon detectors, and make it easier to detect covert nuclear explosions.[5] Recognizing the importance of radioxenon emissions from medical isotope production, in February 2015, China, France, the Russian Federation, the United Kingdom, and the United States issued a joint statement (as the P5) that "all States should engage with producers in their regions to assess the amount of emissions and to reduce where it is possible their negative impact on the environment through minimization of emissions from fission-based medical isotope production."

The feasibility of accelerator-based medical isotopes production is improving rapidly. Accelerators currently produce 29 medical isotopes. The accelerators themselves are far less expensive than in the past and their capability has improved due to the increased use of very short-lived positron emitting diagnostic isotopes and the resulting new market for hospital-based ion accelerators.[6] In addition, new radiochemistry techniques can extract radioisotopes from targets with the low specific activity typical of accelerators.[7]

OVERVIEW OF WORLDWIDE MEDICAL ISOTOPE PRODUCTION

Motivated by non-proliferation concerns, increased medical isotope demand, supply shortages, and research reactor retirements, the global infrastructure for medical isotope production is changing rapidly. This section briefly discusses the status of medical isotope production, the influence of expected changes due to non-proliferation and supply concerns, and four case studies of emerging market countries that are building domestic isotope production infrastructure.

Current Medical Isotope Production Infrastructure

The majority of medical isotope production infrastructure consists of research reactors and associated processing facilities dedicated to producing molybdenum-99 (Mo-99), a parent isotope of technetium-99m (Tc-99m). Tc-99m is used in 30 to 40 million imaging scans annually and represents 80 percent of all nuclear medicine procedures.[8] As only one of many medical isotopes, restricting the discussion to Mo-99 does not give a complete picture of medical isotope production. For example, many medical isotopes are created with hospital-based cyclotrons. Nevertheless, reactor based Mo-99 production facilities are often used to create other isotopes, such as iodine-131 (I-131). Mo-99 facilities set a scale for worldwide reactor-based production.

Mo-99 is typically created as a fission product of low-enriched uranium (LEU) or highly enriched uranium (HEU) targets that are exposed to a thermal neutron flux in a research reactor. Mo-99 processors remove the Mo-99 from the targets and place the Mo-99 in "generators." The generators are shipped to hospitals and clinics worldwide. Inside the generators, the Mo-99 decays with a 66-hour half-life into Tc-99m for clinical use. Annual worldwide demand for Mo-99 is estimated to be approximately 500,000 six-day curies (Ci), which is a measure of the activity of the material six days after the end of processing.[9] Given the 66-hour half-life of Mo-99, one six-day Ci corresponds to 4.5 Ci, so that the total worldwide demand for Mo-99 is about 2.3×10^6 Ci at the end of processing. Mo-99 demand is expected to grow a half a percent annually in mature markets (North America, Europe, Japan and South Korea) and five percent in emerging markets.[10]

Present Mo-99 demand is met by nine research reactors, with a collective capacity of 940,000 six-day Ci or 4.3×10^6 Ci at the end of processing, and six processors, with a collective capacity of 832,000 six-day Ci or 3.8×10^6 Ci at the end of processing.[11] Two of the reactors and one of the processors are expected to shut down by 2016, representing a loss of 250,000 and 187,200 six-day Ci production and processing capacity, respectively.

Changes Due to Non-Proliferation Concerns

The proliferation risk of fabricating medical isotopes using HEU targets has long been recognized, and alternatives have been sought for decades. For example, as early as the 1970s, U.S. and Soviet governments launched programs to encourage the substitution of HEU with LEU in both reactors and targets.[12] The U.S. government has pursued the elimination of HEU targets by limiting access to HEU, providing technical support for producers to switch to LEU targets, and funded the development of non-reactor-based alternatives, such as accelerators. Efforts to facilitate a switch to LEU targets have continued over the last 20 years. In 1992, the Schumer Amendment to the U.S. Atomic Energy Act required non-U.S. medical isotope producers to pursue a switch to LEU targets as a condition of receiving HEU material. This requirement was relaxed by the 2005 Burr Amendment, which exempted producers in Canada and Europe from the Schumer Amendment. However, an even more stringent U.S. policy was implemented in the 2013 American Medical Isotope Production Act, which bans the export of HEU for medical isotope production after 2020.[13]

The U.S. National Nuclear Security Administration's (NNSA) Global Threat Reduction Initiative helps medical isotope producers comply with these requirements by providing technical assistance for switching to LEU targets.[14] In one example, the NNSA assisted South Africa's NTP Radioisotopes commence LEU-based Mo-99 production and achieve FDA clearance for its Mo-99.[15] As a further incentive, the United States also provides a $10 per dose incentive to physicians who purchase LEU produced Mo-99.[16] The NNSA has also provided funds for the development of production alternatives. For example, the NNSA provided approximately $15 million to help NorthStar Medical Radioisotopes (NorthStar) develop both an accelerator-based and reactor-based Mo-99 production technology that does not use uranium.[17]

These efforts are partly responsible for the decline in HEU based medical isotope production. Many producers are in the process of actively switching to LEU and all new producers, with the exception of Russia,[18] plan to use LEU. NTP Radioisotopes presently uses LEU targets for 50 percent of its Mo-99 production and is expected to use 100 percent LEU by the end of 2014.[19] IRE, a European producer, is scheduled to begin commercial production in February 2016.[20] Mallinckrodt, a Dutch producer, is expected to convert by 2017.[21] ANSTO supplies LEU-produced Mo-99 now and is building a new processing facility that should be operational in 2016.[22] Two producers that currently use HEU, NRU in Canada and OSIRIS in France, are expected to cease Mo-99 production in 2016.[23] NorthStar intends to begin production using non-uranium targets after FDA approval is granted, likely sometime in 2015.[24]

Changes Due to Supply Shortages

Although the existing Mo-99 production facilities could meet current demand, most reactors and processors do not operate at full capacity. Unexpected disruptions in supply are common because most of the reactors are over 40 years old. For example, in 2009, the NRU reactor in Chalk River, Canada, shut down due to a heavy water leak. At the same time, the HFR reactor in Petten, Netherlands, shut down for a scheduled, month-long maintenance inspection. The combined loss of production represented 60 percent of the total worldwide Mo-99 production at the time.[25]

In response to these shortages, twelve new reactors and eleven new processors are planned to be operating by 2020.[26] Notably, three new suppliers are expected to enter the market by the end of 2015: two Russian producers using HEU targets and one U.S. producer, NorthStar, using molybdenum targets. The Russian producers will have a combined capacity of 65,000 six-day Ci or 300,000 Ci at the end of processing, while the U.S. supplier will have a capacity of 39,000 six-day Ci or 180,000 Ci at the end of processing.

Four Case Studies of New Medical Isotope Production Infrastructure

Because of the recent Mo-99 supply interruptions, increased demand, and a need to replace aging research reactors, many emerging market countries are pursuing new domestic production.[27] This section includes case studies of four emerging markets that are presently building or are considering building domestic infrastructure: Brazil, Argentina, Indonesia, and Armenia. Two of these countries are pursuing research reactors, one is considering both reactors and accelerators, and one is pursuing cyclotron-based production alone. Although collectively these four countries represent a small fraction of the total worldwide market, they illustrate that countries are actively building new production infrastructure, and that accelerator-based technology can play a role in meeting new demand for medical isotopes.

Brazil

Presently, Brazil imports Mo-99, I-131, chromium-51 (Cr-51), indium-111 (In-111), yttrium-90 (Y-90) and lutetium-177 (Lu-177). Brazil produces I-131 and samarium-153 (Sm-153) with a research reactor and iodine-123 (I-123), gallium-67 (Ga-67), and thallium-201 (Tl-201) with cyclotrons. Partially in response to the global Mo-99 shortage and the growing domestic demand for medical isotopes, Brazil has decided to build a 30 MW research reactor. The reactor is projected to create Mo-99, I-131, Cr-51, Sm-153, Lu-177, holmium-166 (Ho-166), Y-90, tungsten-188 (W-188), phosphorus-32 (P-32), iodine-125 (I-125), iridium-192 (Ir-192), Co-60, mercury-203 (Hg-203), and bromine-82

(Br-82). Mo-99 production is projected to be approximately 200,000 Ci per year.[28] The reactor is intended to support nuclear fuel and material research and to provide neutron beams for scientific and applied research. The project is expected to cost $500 million, and operation is scheduled to begin in 2018.[29]

Argentina

Motivated primarily by increasing domestic and regional demands for medical isotopes, Argentina has recently decided to build a 30 MW LEU research reactor to replace a reactor that has been in operation for over 40 years. This new reactor will create Mo-99, Lu-177, Ir-192 and other isotopes, such as bismuth-213 (Bi-213). Mo-99 production is expected to be approximately 500,000 Ci per year[30] and is scheduled to begin in 2018.[31]

Indonesia

Indonesia has a long history of producing medical isotopes domestically.[32] To replace an aging research reactor, meet increasing domestic demand and create an export market, Indonesia recently announced plans to build a new 30 MW LEU reactor. The reactor is expected to cost $100 million, be completed by the end of 2016, and produce approximately 47,000 Ci per year (primarily Mo-99), a threefold increase over Indonesia's current production capacity.[33] In addition, Indonesia has announced a memorandum of understanding with a U.S. based company, SHINE Medical Technologies, to develop local accelerator-based Mo-99 production.[34] The Indonesian State-owned Enterprise Minister has publicly suggested that a SHINE facility may be built instead of the 30 MW reactor.[35]

Armenia

Armenia imports all Mo-99 consumed for medical use. At present, there is demand for 5,000 doses per year but Armenia is only able to import 1,000 doses per year. Armenia has experience with its own nuclear power reactor, the Metsamor Nuclear Power Plant. Nevertheless, with guidance from the IAEA, the country intends to produce Tc-99m using an 18 MeV cyclotron at the Yerevan Physics Institute.[36]

ACCELERATOR TECHNOLOGY ALTERNATIVES FOR MEDICAL ISOTOPE PRODUCTION

This section discusses the capabilities of three accelerator-based technologies to produce medical isotopes without uranium enrichment: linear accelerators, cyclotrons, and spallation neutron sources. See online supplement for a de-

tailed discussion applying these technologies to specific isotopes.[37] Accelerators can also be used to create neutrons that in turn drive fission reactions in LEU targets for fission-produced isotopes, such as Mo-99. This process is being developed by SHINE but is not discussed here because it is based on LEU. [38]

Photo-Nuclear Reactions with a Linear Accelerator

In a photonuclear reaction, a high-energy photon absorbed by a nucleus expels one or several nucleons, thereby transmuting a stable isotope into a radioisotope. The photons can be created by impinging a high powered electron beam from a linear accelerator onto a high-Z target thereby generating bremsstrahlung photons. For sufficiently high-Z isotopes, the stable isotope can also be the bremsstrahlung target. Such a scheme for the production of Mo-99 was first proposed by Idaho National Laboratory in the 1990s and has been demonstrated at the Canadian National Research Council (CNRC). Others have suggested photonuclear production of I-123.[39] Because the photonuclear method does not use LEU or HEU targets, it does not require HEU or LEU processors, which are both bottlenecks in Mo-99 supply and eliminates a source of radioxenon.

In the past, photonuclear production of Mo-99 has not been feasible because photonuclear Mo-99 has a much lower specific activity than HEU-produced Mo-99. However, a new Tc-99m generator technology has been commercialized that enables low specific activity Mo-99 to be used to produce high quality Tc-99m solutions.[40] In a traditional Tc-99m generator, Mo-99 is adsorbed onto an alumina column, and Tc-99m is eluted by passing a solution over the column. In the new technology, a Mo-99-containing solution is passed over a column, which selectively absorbs Tc-99m. The Tc-99m is then eluted from this column by a second saline rinse. In contrast to traditional Mo-99/Tc-99m generators that can only be used once, this new technology is reusable, may offer an increased Tc-99m yield, and should be quicker to prepare because the Mo-99 is not adsorbed on a column prior to generator shipment. The expected shorter preparation time and increased yield may increase the number of Tc-99m doses that can be delivered per Ci of Mo-99. NorthStar has recently submitted its commercial version, called the "TechneGen," to the FDA for approval, and commercial photonuclear production of Mo-99 is being pursued by NorthStar in the United States.[41]

Charged-Particle Reactions with a Cyclotron

In a charged-particle reaction, an ion, such as a proton, deuteron, triton or alpha, with energy in the tens of MeV range, is absorbed by a stable isotope, which in turn emits one or many nucleons and thereby transmutes a stable iso-

tope into a radioisotope.[42] Although conventionally used for the production of proton-rich radioisotopes, in principle, charged-particle reactions can be used to create other radioisotopes. Indeed, prior to the advent of nuclear reactors, radioisotopes for medicine were produced exclusively via charged-particle reactions. For example, P-32 produced by the Berkeley cyclotron was used at least as early as 1938 to treat leukemia.[43]

Most positron emission tomography (PET) isotopes are currently produced via a charged-particle reaction with small scale cyclotrons located in hospital basements. At least 350 of these machines are now in operation worldwide.[44] Because of the demand for these accelerators, they are readily available from many manufacturers with energies between 14 and 70 MeV and currents between 300 and 1200 μA.[45] Interest in cyclotron-based production is not confined to North America and Europe. Scientists at the Atomic Energy Organization of Iran have produced small quantities of Tc-99m with cyclotrons, synthesized several Tc-99m radiochemical kits, and carried out test studies on animal subjects.[46]

Neutron Capture with a Spallation Neutron Source

Radioisotopes are also transmuted from stable isotopes by absorbing a thermal neutron. Although such neutrons are most commonly created in reactors, they can also be created using a particle accelerator in a spallation neutron source (SNS). In this machine, high-energy protons with energies between 100 and 1000 MeV impinge on a high Z target, such as mercury or tungsten, fragmenting the high-Z nucleus and liberating many neutrons.[47] These neutrons in turn can be moderated, i.e., slowed, to thermal velocities and used to produce radioisotopes.[48]

Modern spallation neutron sources can achieve very high thermal neutron fluxes that can match or exceed the peak flux from a nuclear reactor. For example, the Swiss Spallation Neutron Source (SINQ) is a continuous neutron source that achieves a time-averaged thermal flux near the spallation target of 10^{14} n/cm^2/sec.[49] The Spallation Neutron Source at Oak Ridge National Laboratory is a pulsed neutron source that can provide a peak thermal neutron flux of approximately 10^{16} n/cm^2/sec and an average flux of 10^{14} n/cm^2/sec.[50] The Chinese Spallation Neutron Source is also a pulsed source that will have a peak flux of 10^{16} n/cm^2/sec.[51]

Constructing and operating even a small spallation source suitable for medical isotopes would be a significant undertaking. However, the technology is well established; the SINQ source has been operational since 1998.[52] Note that building a spallation source is likely to require more technical sophistication than building a reactor and thus bring more technical prestige to a country looking to create neutrons for medical isotope production.

OVERVIEW OF RADIOISOTOPES IN MEDICINE

A systematic survey of the medical literature was undertaken to identify radioisotopes that are currently used, have been used, or have the potential to be used in medicine. Eighty-two radioisotopes were identified and categorized as diagnostic or therapeutic, in active use, less commonly used, or other. In this section, an example medical use, typical production method, and accelerator-based alternative are listed for each isotope. Tc-99m is discussed here in detail. Production and medical use for other isotopes are described in the online supplement.

Diagnostic Medical Isotopes

Diagnostic isotopes are typically used in two different types of noninvasive diagnostic procedures: single photon emission computed tomography (SPECT) scans or positron emission tomography (PET) scans.[53] Table 1 lists 15 diagnostic medical isotopes that are in active use worldwide. Table 2 lists 17 isotopes that are less commonly used. In a SPECT scan, an x-ray emitting radioisotope is attached to a suitable molecule and introduced into the patient by injection, ingestion, or inhalation. The molecule then travels through the patient and binds to the tissue of interest. While bound to the tissue, the isotope

Table 1: Diagnostic medical isotopes in active use

Isotope	Example medical use	Half-life	Typical production method	Non-reactor alternatives
Carbon-11	PET	20 min.	Cyclotron	
Cobalt-57	SPECT	272 d.	Cyclotron	
Fluorine-18	PET	110 min.	Cyclotron	
Gallium-67	SPECT	78.3 hr.	Cyclotron	
Gallium-68	PET	68 min.	Germanium-68 via Cyclotron	
Indium-111	SPECT	2.8 d.	Cyclotron	
Iodine-123	SPECT	13.2 hr.	Cyclotron	
Iodine-131	SPECT	8 d.	Reactor (n,γ) or fission	Cyclotron, SNS
Nitrogen-13	PET	10 min.	Cyclotron	
Oxygen-15	PET	2 min.	Cyclotron	
Rubidium-82	PET	1.3 min.	Stronium-82 via Cyclotron	
Technetium-99m	SPECT	6 hr.	Mo-99 via Reactor (fission)	Linear Accelerator, Cyclotron
Thallium-201	SPECT	73.1 hr.	Cyclotron	
Xenon-127	SPECT	36 d.	Cyclotron	
Xenon-133	PET	5.2 d.	Reactor (fission)	Xe-127 or Tc-99m aerosols

Table 2: Other diagnostic medical isotopes that are less commonly used

Isotope	Example medical use	Half-life	Typical production method	Non-reactor alternatives
Americium-241	SPECT	432 yr.	Pu-241 via Reactor	Cyclotron, Tc-99m, I-127
Bromine-76	PET	16.2 hr.	Cyclotron	
Cobalt-55	PET	17 hr.	Cyclotron	
Copper-60	PET	23.7 m.	Cyclotron	
Copper-64	PET	12.7 hr.	Cyclotron	
Gadolinium-153	SPECT calibration	240 d.	Reactor (n,γ)	SNS
Gallium-66	PET	9.5 hr.	Cyclotron	
Iodine-124	PET	4.2 d.	Cyclotron	
Iodine-132	SPECT	2.3 hr.	Reactor (fission)	Iodine-123, Cyclotron
Iron-59	Blood disorders	44 d.	Reactor (n,γ)	SNS
Osmium-191 / Iridium-191m	SPECT	15 d. / 5 s.	Reactor (n,γ)	SNS
Technicium-94m	PET	52 m.	Cyclotron	
Tellurium-123m	SPECT	119 d.	Reactor (n,γ)	SNS
Tin-113 / Indium-113m	SPECT	115 d. / 99 m.	Reactor (n,γ)	SNS
Yittrium-86	PET	14.7 hr.	Cyclotron	
Ytterbium-169	SPECT	32 d.	Reactor (n,γ)	Cyclotron
Zirconium-89	PET	78 hr.	Cyclotron	

decays, and the emitted x-rays are imaged by photon cameras located outside of the patient. These images enable a health-care provider to evaluate organ function or locate disease with external photon detectors. Applications include diagnosing heart disease, cancer, and bone fractures.

Tc-99m is the most commonly used SPECT isotope, and the most commonly used radioisotope in medicine. Tc-99m decays to stable Tc-99g with a half-life of six hours, emitting a 140 keV gamma ray, which is very well suited to SPECT cameras.[54] Tc-99m can be incorporated into different chemical compounds that target different types of tissues. These compounds are prepared in "kits" that contain all the necessary chemicals for formulating the desired radiopharmaceutical in a clinical setting. At least 17 different compounds are in common use.[55]

A PET scan operates in a manner similar to a SPECT scan except that the isotope emits a positron instead of an x-ray. The emitted positrons annihilate electrons in the patient and create 511 MeV gamma-rays that are subsequently imaged by gamma cameras located outside of the patient. Because of momentum conservation, these gamma-rays travel away from the patient directly opposite to each other, enabling coincidence detection techniques.

These two types of scans have different capabilities. PET scans can offer better image quality, shorter scans, lower radiation dose to the patient, and improved time resolution. SPECT scans often have better specific targeting abilities because the SPECT agents more preferentially bind to the targets of interest and biological processes can be observed in real-time over the course of several hours or days.[56] For some purposes, PET scans can substitute for Tc-99m SPECT scans. In fact, 27 percent of respondents in a 2011 OECD Nuclear Energy Agency survey expected 25 percent or more of Tc-99m scans to be displaced by alternative technologies by 2030.[57] However, PET scans are significantly more expensive. In the United States, PET scans are reimbursed at $1,200 per procedure,[58] which is more than four times the $340 cost of an average SPECT scan. Furthermore, PET isotopes typically have a very short half-life and must be used very near the point of production. This logistical challenge limits the use of PET to densely populated areas that have sufficient demand to justify construction of production facilities.

Therapeutic Medical Isotopes

Therapeutic medical isotopes provide either curative or palliative radiation therapy to treat disease. The radiation emitted by these medical isotopes provides curative or palliative therapy by killing cells. Radioisotopes are often used to treat the prostate, the breast, the head, the neck, the thyroid, and the skeletal system. These isotopes are employed in myriad ways. They can be attached to a molecule that targets diseased tissue, a so-called radiopharmaceutical (I-131 or Sm-153), fabricated into a medical device that is either manually or automatically implanted directly into a tumor as part of so-called "brachytherapy" (I-125, Pd-103 or Ir-192), or incorporated into microspheres that become lodged in tumorous liver tissue when introduced into a patient's blood stream (Y-90). The quantity needed to achieve a therapeutic effect is typically much greater than that needed for diagnostic scans. Table 3 lists 12 therapeutic radioisotopes that are in active use worldwide.[59] Table 4 lists 24 therapeutic radioisotopes that are less commonly used.

Other Medical Isotope Uses

Radioisotopes also have other medical uses. For example, radioisotopes such as Co-60 and Cesium-137 (Cs-137) can provide a source of γ-ray photons that in turn are directed to diseased regions of a patient using appropriate collimators and provide external radiation therapy. γ-ray photons from radioisotopes can also be used to irradiate blood prior to transfusion to inactivate lymphocytes or to sterilize medical devices prior to patient contact

Table 3: Therapeutic medical isotopes in active use

Isotope	Example medical use	Half-life	Typical production method	Non-reactor alternatives
Cesium-137	Brachytherapy	30.97 y.	Reactor (fission)	Ir-192
Iodine-125	Prostate Cancer	60 d.	Reactor (n, γ)	Cyclotron, SNS
Iodine-131	Thyroid Disease/Cancer	8 d.	Reactor (n, γ) or fission	Cyclotron, SNS
Iridium-192	Breast, Neck, Cervical and other Cancers	74 d.	Reactor (n, γ)	Cyclotron, SNS
Palladium-103	Prostate Cancer	17 d.	Cyclotron	
Phosphorus-32	Cystic Brain Tumors	14 d.	Reactor (n,γ)	Cyclotron, SNS
Radium-232	Metastatic Bone Cancer	11.2 d.	Reactor (n, γ)	Cyclotron, SNS
Rhenium-186	Metastatic Bone Cancer	3.7 d.	Reactor (n, γ)	Cyclotron, SNS
Rhenium-188	Metastatic Bone Cancer	17 h.	Reactor (n, γ)	Cyclotron
Samarium-153	Metastatic Bone Cancer	1.9 d.	Reactor (n, γ)	Cyclotron, SNS
Strontium-89	Metastatic Bone Cancer	50 d.	Reactor (n, γ)	SNS
Yttrium-90	Liver Cancer	2.7 d.	Reactor (n, γ) or fission	Cyclotron, SNS

(Table 5). Radioisotopes can also be used to trace different metabolic or other pathways in biomedical research (Table 6).

Alternatives for Radioisotopes that Would be Difficult to Produce with Accelerators

Six of the 82 isotopes identified here would be difficult to produce with accelerator-based technologies: Co-60, Cs-137, californium-252 (Cf-252), I-132, Am-241, and xenon-133 (Xe-133). However, these isotopes are either no longer used, or readily available, and in some cases, superior alternatives exist (see online supplement). Cf-252 is a neutron source that has been replaced by cyclotron-based neutron production. Am-241 has been replaced by other radioisotopes for imaging. I-132 has been replaced by I-131 or I-123. Cs-137 for brachytherapy has been replaced by Ir-192, while Cs-137-based external beam machines have been retired worldwide. Cs-137-based blood-treatment machines can be replaced with accelerator-based alternatives and are likely to be replaced in developed countries due to the security risk of Cs-137.[60] Xe-133 can be replaced by Tc-99m aerosols and xenon-127 (Xe-127), both of which are superior.

In developed countries, Co-60-based external beam machines have been almost entirely replaced by accelerator-based alternatives that provide more pre-

Table 4: Other, less common, therapeutic medical isotopes

Isotope	Therapeutic use	Half-life	Typical production method	Non-reactor alternative
Actinium-225	Radiopharmaceutical	10 d.	Reactor (n, γ) on Th-232	Cyclotron
Astatine-211	Radiopharmaceutical	7.2 hr.	Cyclotron	
Bismuth-213	Radiopharmaceutical	45.6 min.	Actinium-225	
Californium-252	Neutron Therapy	2.6 y.	Reactor (n, γ) on U-238	Cyclotron produced neutrons
Cesium-131	Brachytherapy	9.7 d.	Reactor (n,γ)	Cyclotron
Copper-67	Radiopharmaceutical	61.8 hr.	Cyclotron	
Dysprosium-165	Arthritis	2.3 hr.	Reactor (n,γ)	SNS
Erbium-169	Inflammatory joint disease	9.3 d.	Reactor (n,γ)	SNS
Gold-198	Brachytherapy and radiopharmaceutical	2.7 d.	Reactor (n,γ)	SNS
Holmium-166	Metastatic Bone Cancer	26.8 hr.	Reactor (n,γ)	SNS
Indium-114m	Radiopharmaceutical	49.5 d.	Cyclotron	
Lutetium-177	Neuroendocrine tumors	6.6 d.	Reactor (n,γ)	Cyclotron
Palladium-109	Radiolabeled monoclonal antibody	13.7 hr.	Reactor (n,γ)	SNS
Promethium-149	Radiopharmaceutical	2.2 d.	Reactor (n,γ)	SNS
Rhodium-105	Radiopharmaceutical	35 hr.	Reactor (n,γ)	SNS
Ruthenium-106 /Rhodium-106	Choroidal melanomas	372 d. / 30 s.	Reactor (fission)	SNS, photofission, cyclotron
Samarium-145	Brachytherapy	340 d.	Reactor (n,γ)	SNS
Silver-111	Arthritis	7.5 d.	Reactor (n,γ)	SNS
Tantalum-182	Brachytherapy	115 d.	Reactor (n,γ)	SNS
Terbium-149	Radiopharmaceutical	4.1 hr.	Cyclotron at 1 GeV	
Terbium-161	Radiopharmaceutical	6.9 d.	Reactor (n,γ)	SNS
Thorium-227	Radiopharmaceutical	18.7 d.	Reactor (n,γ)	SNS
Thulium-170	Metastatic Bone Cancer	127 d.	Reactor (n,γ)	SNS
Tin-117m	Metastatic Bone Cancer	13.8 d.	Reactor (n,n')	SNS

Table 5: Radioisotopes for external sources of radiation therapy

Isotope	Example medical use	Half-life	Typical production method	Non-reactor alternative
Cesium-137	Blood irradiators, external beam radiotherapy	30.1 y.	Reactor (fission)	Accelerator x-ray source
Cobalt-60	External beam radiotherapy, medical device sterilization	5.3 y.	Reactor (n,γ)	Accelerator x-ray source

cise treatment without the use of radioactive material.[61] In developing countries, Co-60 based machines are still used, but there is an ongoing debate in those countries as to whether they are actually less expensive to own and operate than modern linear accelerators, given the expense and difficulty of disposing of Co-60 sources.[62] Co-60 is used as the radiation source for medical device sterilizers.[63] Although in the past, it has been difficult to replace these sterilization devices with accelerators, electron accelerator-based solutions are now commercially available and have been deployed in Europe. The cost of these facilities is expected to be comparable to the cost of Co-60 sterilizers.[64]

DETAILED ANALYSIS OF 12 HISTORICALLY REACTOR-PRODUCED, COMMONLY USED, MEDICAL ISOTOPES

Of the 82 isotopes identified as having potential medical use, 12 diagnostic and therapeutic medical isotopes were selected for more in-depth analysis because they are in active use, are typically fabricated with reactors, and provide the

Table 6: Radioisotopes for biomedical research

Isotope	Example medical use	Half-life	Typical production method	Non-reactor alternative
Arsenic-73	Tracer	80.3 d.	Cyclotron	
Calcium-45	Tracer for calcium metabolism	163 d.	Reactor (n,γ)	SNS
Chromium-51	Tracer	27.7 d.	Reactor (n,γ)	SNS
Cobalt-58	Vitamin B-12 labeling	70.9 d.	Reactor (n,p)	SNS
Manganese-54	Tracer	312 d.	Reactor (n,p)	Cyclotron
Phosphorous-33	Tracer for research	25.4 d.	Reactor (n,p)	SNS
Platinum-195m	Tracer	4.0 d.	Reactor (n,γ)	SNS
Potassium-42	Tracer	12.3 hr.	Reactor (n,γ)	SNS
Scandium-46	Tracer, blood flow	83.8 hr.	Reactor (n,γ)	SNS
Scandium-47	Tracer, monoclonal antibodies	3.3 d.	Reactor (n,p)	SNS
Selenium-75	Tracer	120 d.	Reactor (n,γ)	Cyclotron
Sodium-24	Tracer	15 hr.	Reactor (n,γ)	SNS
Sulfur-35	Tracer	87 d.	Reactor (n,p)	SNS

most modern standard of care for the diagnosis or treatment of disease. Two actively used isotopes are not included: Xe-133 was excluded because both Xe-127 and Tc-99m aerosols have been shown to be superior alternatives, while Cs-137 was excluded because it has been replaced by Ir-192 for brachytherapy. Of the twelve, Tc-99m and Mo-99 are discussed in detail here; the remaining ten are discussed in detail in the online supplement.

Demand Estimate

Table 7 lists the estimated U.S. demand for the 12 common isotopes. For some isotopes, the rates of consumption are well documented in the public literature. For others, the annual demand was estimated by assuming that a fraction of the indicated disease is treated with isotope-based radiotherapy. U.S. level demand for most isotopes is likely to be a conservative overestimate of worldwide demand because the United States consumes more medical isotopes, on a per capita basis, than any other country.[65] Despite what may be an inflated estimate of demand in other countries, U.S. level demand is discussed in the public literature and can be established with some precision. Further, it represents a conservative upper limit on the proliferation risk of accelerator-based technologies.

Approximately 15×10^6 Tc-99m SPECT procedures are performed in the United States each year. Each procedure utilizes between 15 and 30 mCi of Tc-99m, so that, the total U.S. demand for Tc-99m is about 450,000 Ci.[66] Tc-99m,

Table 7: Estimated U.S. level consumption of reactor-produced medical isotopes

Isotope	Activity per procedure (mCi)	Annual number of procedures	Annual consumption (Ci)	
			Measured at time of treatment	Measured at end of production
Mo-99				1,150,000
Tc-99m	30	15,000,000	450,000	
Ir-192	10,000	400,000		14,000
I-131	30–200	52,000	6,000	
Re-188	90	45,000	4,000	
Sm-153	70	45,000	3,000	
Re-186	40	45,000	2,000	
Y-90	100	10,000	1,000	
I-125	50	10,000	500	
Sr-89	4	45,000	200	
P-32	0.5	<10,000	<5	
Ra-223	0.1	45,000	5	

Note: Only Tc-99m is used clinically; Mo-99 is a precursor. A clinic will have demand for either Tc-99m or Mo-99, depending on the production method, but not both. Ir-192 is used for multiple patients during its useful life so that there is no consumption at the time of treatment.

however, is not distributed in its final form. Instead, Tc-99m "generators" are shipped to hospitals and clinics. The generators consist of alumina columns with adsorbed molybdate (Na_2MoO_4) containing Mo-99. Tc-99m in the form of pertechnetate ($NaTcO_4$) is periodically eluted by application of a saline solution. The United States consumes about half of the Mo-99 produced worldwide, so that U.S. demand for Mo-99 is about 1.15×10^6 Ci.[67]

Quantifying the demand for medical isotopes can be misleading due to the decay of the material. The amount of a medical isotope that must be produced at a reactor or accelerator can be far greater than the amount actually used in treatments, especially for short-lived isotopes, such as Tc-99m. The loss between production and clinical use depends on the logistical details of the supply chain. For short-lived isotopes, such as Mo-99 and Tc-99m, these losses can be substantial. For example, one Ci of Mo-99 could, in principle, create approximately three Ci of Tc-99m if a Mo-99 generator is emptied of Tc-99m once per day over the course of seven days. However, presently in the United States, 1.15×10^6 Ci of Mo-99 provides treatments totaling 0.45×10^6 Ci of Tc-99m. Given the logistical decay losses, only the demand at the end of production for Mo-99 and Ir-192, which are well discussed in the literature, are presented. For all other isotopes, only the demand as measured at the time of treatment is estimated.

Production Capacity of Accelerator-Based Technologies

The ability of each accelerator-based technology to produce each medical isotope was estimated (see Table 8 and online supplement).[68] Estimates based on measured yields are likely to be accurate to within 10−20 percent due to uncertainties in the measurements and losses during radiochemical processing and error. The radiochemical loss for fission-produced and cyclotron-produced Mo-99/Tc-99m has been measured to be 10 percent[69] and 15 percent,[70] respectively. SNS production estimates based on neutron absorption cross sections and cyclotron production estimates based on charged particle cross sections are likely accurate to within 50 percent and a factor of two, respectively. For example, measured neutron absorption yields match cross-section based estimates for Ir-192 and I-131 to within 30 percent and 40 percent, respectively. Measured charged-particle yields match cross-section based estimates for Sm-153 and rhenium-186 (Re-186) to within a factor of 2 and 20 percent, respectively. Radiochemistry loss adds an additional uncertainty of 20 percent.

Although many alternatives to reactor-based production of Mo-99 have been proposed and analyzed, two methods are close to commercialization: electron linear accelerator-based production of Mo-99 and direct cyclotron production of Tc-99m.[71] Linear accelerator-based production uses a photonuclear reaction on molybdenum-100 (Mo-100) to produce Mo-99. Estimates based on modern Monte Carlo calculations suggest that a 35 to 50 MeV, 100 kW elec-

Table 8: Estimated annual capacity of accelerator-based technologies to produce 12 commonly used medical isotopes assuming an 80 percent uptime

	Estimated annual capacity (Ci)		
Isotope	Linear accelerator	Cyclotron	Spallation neutron source
Mo-99	52,000[m]		
Tc-99m		2,700[m]	
Ir-192		60[c]	2,500[c]
I-131		1,000[m]	1,000[m]
Re-188		860[c]	
Sm-153		100[m]	30,000[m]
Re-186		150[m]	50,000[m]
Y-90		1,200[c]	8,000[c]
I-125		200[c]	1,900[m]
Sr-89			12[c]
P-32		900[c]	200[m]
Ra-223		170[m]	90[c]

tron beam impinging on a 1 cm dia. by 2 cm long 98 percent enriched, 15 g, Mo-100 target would produce 180 Ci of Mo-99 per 24 hour exposure or approximately 52,000 Ci per year assuming an 80 percent uptime.[72] Low-power tests of this production method have met the expected yield to within 25 percent.[73] Although natural molybdenum targets could be used, they would reduce the production rate by a factor of 10; commercial operators are only considering enriched targets, which are commercially available.[74] Preliminary measurements suggest that at least 97 percent of the Mo-100 in a 15 g molybdenum target can be recycled when the hospitals or radiopharmacies return the Tc-99m generators to the manufacturer.[75] Thus, the photonuclear method is expected to consume 2.5 mg of Mo-100 per 1 Ci of Mo-99 produced at the end of bombardment. NorthStar is building a commercial facility in Beloit, Wisconsin to pursue photonuclear production of Mo-99. Although the first phase of construction will support Mo-99 sourced from the Missouri Research Reactor, Phase 3 will house electron linear accelerators for photonuclear production.[76]

Tc-99m can be directly produced in cyclotrons via the proton—two-neutron reaction on a Mo-100 target.[77] The thick target yield has been measured to be 16 mCi / μA·hr at 24 MeV and estimated to be as high as 22 mCi / μA·hr at 30 MeV.[78,79] It has been estimated that 85 percent of the Tc-99m can be recovered from a Mo-100 target and that 69 percent of the Tc-99m is lost due to decay between the end of bombardment and clinical use in a patient, so that a 500 μA, 24 MeV cyclotron operating for six hours per day would provide approximately 9 Ci for patient procedures.[80] Assuming an 80 percent uptime, a 500 μA, 24 MeV cyclotron, operated for six hours per day, could provide 2,700 Ci of Tc-99m per year. Much higher production rates at a single cyclotron may be feasible. For example, it may be possible to operate the cy-

clotron for two, six-hour bombardments that would provide Tc-99m to hospitals and clinics twice a day.[81] Larger cyclotrons are also available that would further increase the yield of a single facility. Advanced Cyclotron Systems offers a 30 MeV, 1200 μA cyclotron that in principle could increase the production rate by a factor of 3.3 compared to a 500 μA, 24 MeV cyclotron.[82]

Cyclotron production requires a target to be enriched so that the concentration of molybdenum-95 (Mo-95), molybdenum-96 (Mo-96) and molybdenum-97 (Mo-97) are all below 0.01 percent to increase the Tc-99m production rate and to minimize other radiological contaminants that increase a patient's absorbed radiation dose.[83] Preliminary cyclotron experiments used targets with a mass between 0.5 to 1.2 g and found that approximately 85 percent of the Mo-100 can be recovered from each target after bombardment.[84] Assuming that a 1.2 g target could be used per each six-hour bombardment in the 500 μA cyclotron described above, one would expect that 20 mg of Mo-100 would be consumed per Ci of Tc-99m.

Commercialization of cyclotron production methods are being actively pursued in Canada. On 9 June 2013, the TRIUMF laboratory and Advanced Cyclotron Systems Inc. announced that they had successfully produced 10 Ci of Tc-99m during a six-hour overnight shift on a cyclotron at the British Columbia Cancer Agency, Vancouver Centre.[85] In addition, Advanced Cyclotron Systems sells a 500 μA, 24 MeV cyclotron, the TR 24, capable of producing Tc-99m along with PET isotopes.[86]

The production estimates support several conclusions. A 100 million-person country could meet its need for historically reactor-produced isotopes with a combination of electron linear accelerators, cyclotrons and spallation neutron source beam lines. The exact combination that is appropriate for an individual country will largely depend on the transportation network of that country, the fraction of the population that lives in large metropolitan areas that can be readily served with cyclotron-based production, and the time between when a hospital receives a radioisotope and when it is used in a patient. For example, a 100 million person country that distributed and used the isotopes within three days of production could meet their demand of I-131 and P-32 with approximately three commercially available 500 μA, 24–30 MeV cyclotrons, while supplying Ir-192, Sm-153, Re-186, Y-90, I-125, strontium-89 (Sr-89) and radium-223 (Ra-223) with approximately eight 1 cm^2 10^{14} $n/cm^2/sec$ thermal neutron beam lines. Because of rhenium-188's (Re-188) short half-life, its use would only be practical if it could be distributed the same day that it is produced and would require one or two cyclotron beam lines. Countries that could distribute and use these isotopes faster or slower will require correspondingly greater or fewer accelerators to meet their isotope demand.

The appropriate combination for Mo-99/Tc-99m depends on the urban density of a given country. Cyclotron production of Tc-99m is likely only appropriate for large metropolitan regions that can consume sufficient quantities of Tc-

Table 9: Estimated Tc-99m production costs per dose

Production method	Tc-99m cost per dose (2010 dollars)	Tc-99m cost as percentage of SPECT scan cost
Reactor	$15	5%
Linear Accelerator	$7	2%
Cyclotron	$8 – $13	2% – 4%

99m to justify in-city production. The U.S. demand for Tc-99m is about 1,500 Ci per million people, so that any metropolitan region with a population greater than one million could consume approximately 55 percent of the Tc-99m produced by one 500 μA, 24 MeV cyclotron operated six hours per day. The fraction of a country's population in cities this large varies considerably. In the United States and Iran, approximately 50 percent and 24 percent of the population live in urban regions with a population greater than one million, respectively.[87] A possible combination for an urbanized country to consider for Mo-99/Tc-99m production would be to use cyclotrons to produce 25 percent of its Tc-99m demand and linear accelerators to produce the balance in the form of Mo-99. In this case, assuming that Mo-99 losses are the same as in the present reactor-based Mo-99 supply chain, a 100 million-person country would need approximately 15 cyclotrons and 6 linear accelerators to meet U.S. level demand.

Cost Estimates for Tc-99m and Mo-99

The costs for producing Tc-99m and Mo-99 with cyclotrons and linear accelerators, respectively, are presented in Table 9. These estimates were calculated independently of costs cited in the public literature. Note that these are production costs and not the sale price paid by hospitals or radiopharmacies. Reactor-based production is estimated to cost approximately $15 per dose.[88] Both accelerator-based methods have the potential to produce Mo-99/Tc-99m for approximately this cost. Note that the cost of the isotope itself likely has little impact on the total expense of a SPECT scan, which costs twenty times more than the reactor-based production cost in the United States.[89]

According to a study by the CNRC, a photonuclear Mo-99 production facility employing two 100 kW linear accelerators would have capital costs of $20.7 million. Annual operation and maintenance costs are estimated to be $5.83 million, including the costs of processing and shipping Mo-99, but not the cost of the Mo-100 targets.[90] At $850 per gram of Mo-100,[91] the capital expense would be increased by $1 million for an initial Mo-100 inventory, and the annual Mo-100 expense would be $220,000, so that the overall capital costs for this facility would be approximately $21.7 million, and annual operating costs would be approximately $6 million.

This photonuclear facility would be able to produce approximately 104,000 Ci per year, enough for 1.35 million doses. The facility would use 260 g of Mo-100 per year. Targets would be recycled after about 40 days to allow the target material to decay to safe levels. An initial supply of 1200 g of Mo-100 would be required.[92] Assuming a five percent interest rate and a 30 year useful-life, this investment and operating expense is equivalent to a $7.36 million annual cost. Assuming an average Tc-99m dose of 30 mCi and a generator cost of $0.05/mCi,[93] the overall production cost is approximately $7 per dose. This estimate is very close to the $7.50 per dose suggested in the CNRC paper.[94]

A 24 MeV, 500 μA cyclotron for charged-particle production of Tc-99m likely costs about $7.8 million.[95] The facility to house this accelerator costs about $4 million,[96] and the OECD NEA has estimated that the Tc-99m processing facility would cost about $0.45 million.[97] The annual operating expenses would be $0.3 and $0.25 million for the cyclotron[98] and the processing facility,[99] respectively. Assuming a 30-year useful-life and a five percent interest rate, the overall annualized cost of such a cyclotron would be about $1.35 million, not including expenditures for consumed Mo-100.

The cost per dose for cyclotron-produced Tc-99m depends greatly on how much Tc-99m is produced with the cyclotron per day. A 24 MeV, 500 μA cyclotron that was operated for two, six-hour bombardments would annually produce 5,400 Ci of Tc-99m, provide material for 180,000 procedures and consume 108 g of Mo-100. The Mo-100 consumption would add an annual operating expense of $0.09 million so that the total annual expenditure would be $1.44 million, and the cost per dose of Tc-99m would be about $8. This cost is comparable to both the estimate for linear accelerator-produced Mo-99, and results from other studies which have estimated the cost of production on smaller cyclotrons to be approximately $7.80–8.10.[100]

A cyclotron that was operated differently would have a different production cost per dose. For example, a cyclotron that only operated for one six-hour bombardment would produce half the Tc-99m, but would also use half the Mo-100 and incur half the operating expense, so that the production cost would be approximately $13 per dose. On the other hand, the production of PET isotopes using the same cyclotron would spread the capital and operating costs to other imaging procedures and likely reduce the Tc-99m cost dramatically.

PROLIFERATION RISK OF ACCELERATOR-BASED MEDICAL ISOTOPE PRODUCTION

Particle accelerators can be used to create plutonium-239, and thus, in principle could be a proliferation risk. In fact, for several decades, numerous countries pursued an accelerator-based plutonium-239 production program.[101] However, calculations performed here demonstrate that accelerators and the

Table 10: Plutonium-239 production capabilities of medical isotope production technologies

Machine/Accelerator	Neutron rate (n/sec)	Minimum years to produce 10 kg of Pu-239
Heavy water 40 MWth research reactor[118]	—	1
SINQ-scale spallation source with a uranium target	—	20
50 MeV, 100 kW electron linear accelerator	1.5×10^{14}	7,000
30 MeV, 500 μA cyclotron	10^{14}	10,000
1 cm^2 10^{14} n/cm^2/sec thermal neutron beam line	10^{14}	10,000

enrichment infrastructure to support them are capable of producing far less plutonium-239 or HEU than reactor-based medical isotope production infrastructure. In fact, except for large, specially engineered accelerator/reactor combinations called accelerator-driven systems, accelerators for medical isotope production are not capable of producing significant quantities of plutonium-239, so that accelerator-based medical isotope production is very unlikely to present a proliferation risk.

The capacity of accelerator-based medical isotope production facilities including linear accelerators, hospital scale cyclotrons and spallation neutron sources to produce plutonium-239 was estimated based on the neutron flux that such a facility could produce. Plutonium-239 is produced via thermal neutron capture on uranium-238. Annual production of 10 kg of plutonium-239 with a machine that has an 80 percent uptime requires a neutron production rate of at least 10^{18} n/sec. 50 MeV linear accelerators built for Mo-99 production could be repurposed by replacing the Mo-100 target with a uranium target. Hospital-based 30 MeV cyclotrons could make neutrons by bombarding beryllium targets with deuteron ions. Spallation neutron sources can create plutonium-239 by either replacing the spallation target with uranium or by exposing a uranium target to a neutron beam line. Table 10 lists the results of this analysis. See the online supplement for calculation details.

The neutron flux of these accelerators can be greatly increased by engineering a subcritical assembly of natural uranium and neutron moderator around an accelerator beam target. In such a machine, called an accelerator-driven system (ADS), the neutrons created by the accelerator drive fission reactions in the uranium that, in turn, liberate more neutrons. The exact neutron multiplication factor depends on the geometric details of the uranium and moderator. A U.S. Department of Energy study determined that a simple, natural uranium and light-water moderated and cooled subcritical assembly could am-

plify the plutonium-239 capture rate by a factor between 13 and 17 depending on the size of the assembly.[102] Although a determined proliferator could, in principle, build an ADS around an accelerator, deployment of such a system would have no purpose for medical isotope production. Furthermore, only a spallation neutron source at the scale of SINQ modified into an ADS would have the potential to create 10 kg of plutonium-239 within a time frame that would be practical for a proliferator. All other accelerator technologies would require at least 350 years per accelerator.

Clandestine deployment of an ADS would also be difficult. First, diversion of uranium for an ADS 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.[103] In contrast, a light water-moderated subcritical assembly in the form of a 2.4 m cube that is capable of multiplying neutron capture by a factor of 13 requires 100 tons of natural uranium.[104] IAEA report IAEA-CN-184/308 presents an analysis of how the IAEA would be involved with an ADS in Belgium.[105] Second, an ADS would involve substantial engineering and site modification that could be easily discovered. An ADS must be cooled, and the radiation output (including gammas, neutrons, and radioactive gases) would be quite different from the output from an accelerator dedicated to medical isotope production. Furthermore, in terms of cost, construction time, ease of concealment, and technical difficulty, an ADS is far more complicated than a reactor. A country determined to acquire plutonium-239 could much more readily build a small heavy water or graphite-cooled natural uranium reactor than an ADS.

An enrichment infrastructure to support accelerator-based isotope production may be needed because accelerator-based production often requires enriched isotopes as the beam targets. Although these isotopes are stable and can be easily shipped worldwide, if a country chose to domestically enrich such isotopes, the infrastructure for such enrichment could be repurposed for HEU production.

The scale of enrichment required for medical isotopes can be set by the demand for Mo-99 and Tc-99m because both cyclotron and linear accelerator-produced Tc-99 and Mo-99 require enriched Mo-100 targets. A 100 million-person country that met its clinical need for Tc-99m by producing 40,000 Ci of Tc-99m with cyclotrons and 300,000 Ci of Mo-99 with linear accelerators per year would need approximately 1.6 kg of enriched Mo-100, which corresponds to an enrichment capacity of 41 kg-SWU/yr. A centrifuge-based facility with this capacity, could, in principle, be capable of producing 0.2 kg of 90 percent HEU per year, which is not a proliferation risk (see Appendix D, online supplement). By comparison, a 1 GWe PWR consumes 28.5 metric tons of 3.75 percent LEU per year and requires an enrichment capacity of 150,000 kg-SWU/yr. that could produce 730 kg of 90 percent HEU per year.[106]

CHALLENGES FOR EXPANSION OF ACCELERATOR-BASED PRODUCTION

Although accelerator-based production is feasible for at least 76 different radioisotopes and is actually used for producing 29 different isotopes, there are a number of steps that must be taken before other specific accelerator-produced isotopes can be commercially available for patient use. These steps include technical challenges, such as target design and radiochemistry, medical challenges, such as demonstrating and convincing physicians that the accelerator-produced radioisotope can meet the same clinical needs as the reactor-produced isotope, and regulatory challenges, such as achieving FDA clearance. Two paths to develop new non-HEU sources of Mo-99 illustrate these steps.

Accelerator-Based Production of Mo-99

Accelerator-based, photonuclear production of Mo-99 has been pursued in the United States as part of a private-public partnership between NorthStar and the NNSA. In 2007, NorthStar realized that a 1999 Idaho National Laboratory proposal for photonuclear Mo-99 production was feasible if combined with radiochemistry technology that NorthStar had previously licensed from another company and that could produce Tc-99m with low specific activity Mo-99.[107] Since that time, NorthStar has developed five generations of its radiochemistry technology, now called "RadioGenix." It submitted a new drug application to the FDA in March 2013 and the approval process is ongoing.[108] Both Argonne and Los Alamos National Laboratories have assisted NorthStar with technical issues associated with target construction, target cooling, and chemical processing after irradiation.[109] NorthStar has recently partnered with a radiopharmacy company, Triad Isotopes, to help bring their RadioGenix technology to market.[110]

To date, NorthStar has been funded by a mixture of a 50–50 cost share agreement with the NNSA and private investment in which the NNSA has contributed approximately $15 million.[111] Although the majority of that sum is to offset construction costs of a new facility dedicated to processing neutron-capture produced molybdenum targets,[112] development of the linear accelerator method is continuing, and there are plans to build accelerators in the new facility.[113]

LEU-based production of Mo-99

Worldwide efforts to eliminate HEU from medical isotope production have been ongoing for over 40 years. Nevertheless, today, most Mo-99 is still pro-

duced with HEU targets. There are technical, regulatory, and economic challenges for the LEU conversion. Producers must build capacity to handle an increased waste volume associated with LEU targets; they must redesign the targets, and develop new process parameters for the exposure and radiochemistry of the targets.[114] Producers must also be granted clearance from agencies, such as the FDA, to sell the LEU-produced Mo-99. To date, the FDA has approved LEU-produced Mo-99 from ANSTO, an Australian producer, and NTP, a South African producer, while European regulators have yet to approve either source.[115] Economic barriers can be significant. In the past, producers, such as Nordion, have argued that the increased facility size required for LEU processing makes LEU conversion uneconomical.[116] In addition, the continued sale of HEU-produced Mo-99, which tends to be cheaper than LEU-produced Mo-99, undercuts the price and makes LEU-produced Mo-99 uncompetitive.[117]

The 40-year effort to replace HEU is now starting to succeed as most producers have near term plans to eliminate HEU. Nevertheless, the HEU story illustrates the difficulty of driving a technology shift based on non-proliferation concerns alone. Accelerators are most likely to be deployed as new sources of medical isotopes, instead of replacements for operating reactors. However, steps recently taken by Mo-99 producers to switch to LEU targets also suggest that a concerted policy effort can influence and achieve a technology switch.

CONCLUSIONS AND POLICY SUGGESTIONS

Accelerator-based technology is now an economic and technically viable source of medical isotopes. Twenty-nine isotopes are already commercially produced using accelerator-based technologies, while accelerator-based production of Mo-99/Tc-99m is so close to commercialization that several countries worldwide are now pursuing accelerator-based production of Mo-99/Tc-99m. Thus, a country building new medical isotope infrastructure has a viable choice between reactors and accelerators, with the latter providing distinct waste, safety, capital cost, and proliferation advantages.

Crucially, accelerator-based technologies have minimal proliferation risk. Unlike reactors, accelerators for medical isotope production cannot be used to produce weapons scale quantities of plutonium-239, and enrichment facilities dedicated to medical isotope production are not of sufficient scale to produce weapon-scale quantities of uranium. In addition, a switch to production of Mo-99/Tc-99m with accelerators that do not use uranium would obviate the problem of false positives for IMS radioxenon detectors.

Countries that seek to minimize the global proliferation risk of medical isotopes should invest in commercializing accelerator-based production technology, possibly using the successful public-private partnerships in the United States as an example. Although 76 isotopes can be produced with accelerators,

commercial scale production has not been demonstrated for many of these isotopes. The case of LEU or accelerator-based production of Mo-99 demonstrates the challenges of commercializing new isotope production methods, but also illustrates that such challenges can be overcome. To commercialize isotope production with linear accelerators or cyclotrons, a targeted public investment on order of $20 million over five to ten years per isotope is likely required because market incentives alone have been insufficient to bring accelerator-based production to market. However, commercializing many of these isotopes simultaneously could likely lower the cost per isotope. Spallation-based production of radioisotopes requires a larger investment to design a facility specifically for medical isotope production. However, for spallation produced radioisotopes, the radiochemistry is very similar to reactor-production and the development costs would be spread over a number of isotopes so that the total development cost per isotope is likely comparable to development costs of cyclotron-production.

Although the time-scale for development is between five and ten years, the need for accelerator-based production is likely to increase in coming decades as the existing reactor fleet ages and requires replacement.

For countries needing to expand their isotope production infrastructure or replace aging infrastructure, accelerators should be considered. Accelerator-based infrastructure can be built in the same or less time than that required to build a new reactor. Such infrastructure could immediately provide 31 medical isotopes, including Mo-99/Tc-99, for domestic consumption and would entail minimal, if any, proliferation risk.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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