The Production of Medical Isotopes without Nuclear Reactors or Uranium Enrichment

On-Line Supplement

Seth A. Hoedl,[1] Harvard Law School, Cambridge, MA, USA

W. Derek Updegraff, Center for Science, Technology, and Security Policy, AAAS, Washington, DC, USA

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[1] Seth A. Hoedl, Harvard Law School, Cambridge, MA 02138, USA.
E-mail: shoedl@jd15.law.harvard.edu

Introduction

This supplement describes the medical use, medical demand, and production methods for 12 commonly used medical isotopes and 71 other less commonly used radioisotopes that have or did have medical or research applications, including six isotopes for which reactor-based production is likely the only practical choice. Most accelerator-based production estimates are based on published yields. For those radioisotopes for which published yields are unavailable, estimates of the production rate use a very simple model, unless otherwise noted. In the case of production using spallation neutron sources, self-shielding of the targets due to neutron scattering and absorption was neglected so that the total amount of isotope produced, in Bq, is given by:

$$P = \sigma \cdot f \cdot A \cdot l \cdot \rho \cdot N_a/M \cdot (1 - e^{-t/\tau}),$$

where σ is the cross section, in barns, f is the flux, in n/cm^2/sec, A is the target cross sectional area, in cm^2, l is the target thickness, in cm, ρ is the target density, in g/cm^3, N_a is Avrogado's number, M is the molar mass, in g, t is the exposure time, in sec, and τ is the time constant, in sec. In the case of production using charged-particle reactions with cyclotrons, the target thickness was assumed to be half of the continuous slowing down approximation (CSDA) range of the incident particle at the energy of the cross section maximum so that the total amount of isotope produced, in Bq, is given by:

$$P = \sigma \cdot I/e \cdot l \cdot \rho \cdot N_a/M \cdot (1 - e^{-t/\tau}),$$

where I is the beam current, in amps, e is the electron charge, in coulombs, and all other variables are the same as for neutron absorption.

Appendix A describes the 12 most commonly used medical isotopes that were investigated in detail. Appendix B describes 14 radioisotopes that are less commonly used or that may have use in the future. Appendix C lists 56 other radioisotopes that were identified in this study as having potential medical use and that can be produced with a cyclotron or with a spallation neutron source. Appendix D calculates the ability of a molybdenum enrichment facility dedicated to medical isotopes to enrich uranium.

Appendix A
Demand and Production Estimates for Ten Commonly Used Medical Isotopes

Iridium-192

Iridium-192 (Ir-192) is used for high-dose-rate (HDR) brachytherapy as part of an "after-loader." In this treatment methodology, catheters are placed in the patient that penetrate the tumor or tumor bed. The radioactive source is then automatically positioned in the tumor by a machine, the so-called after-loader that locates 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 United States, and each Ir-192 source is replaced four times per year,[1] so that there is a total U.S. need of 14,000 Ci per year, measured at the end of production.

Ir-192 sources are typically fabricated by exposing natural iridium to a neutron flux.[2] Each after-loader source is a cylinder with a diameter and length of 1 mm and 5 mm respectively, although smaller sources with a diameter of 0.34 mm are available.[3] Iridium-191 (Ir-191) has an absorption cross section of 954 barns and represents 37 percent of natural iridium. Because of the high absorption cross section, a natural iridium target will absorb almost all of the incident neutrons. Ignoring self-shielding, a 0.34 mm dia by 5 mm long iridium cylinder, with a mass of 0.01 g, exposed to a thermal neutron flux of 10^{14} n/cm^2/sec would create Ir-192 at a rate of 1.7×10^{12} atoms/sec or 0.4 Ci/day. Because the absorption length, 0.015 cm, is about half the diameter, the actual production rate is likely closer to 0.2 Ci/day. (In comparison, exposure of 0.01 g of Na_2IrCl_6 to a 1.5×10^{13} n/cm^2/sec thermal flux was measured to create 0.05 Ci/day,[4] which suggests that exposure of 0.01 g of Na_2IrCl_6 to a 10^{14} n/cm^2/sec thermal flux would create 0.3 Ci/day.) Considering the half-life, exposure for 30 days would be required to activate a 0.01 g iridium cylinder to 10 Ci. However, the sources are so small that a single 1 cm^2 beam line could irradiate approximately 50 sources if the beam was perpendicular to the cylindrical axis of the sources. Assuming an 80 percent uptime, such a beam line could irradiate 500 sources per year, providing 2,500 Ci.

Ir-192 can also be produced with an accelerator via the Os-192(d,2n)Ir-192 reaction. Tarkayi estimates a production rate on an enriched osmium target of 0.013 Ci/hr at 500 μA,[5] so that, considering the decay time, 10 Ci could be produced in 44 days. Assuming an 80 percent uptime, this rate corresponds to an annual production rate of approximately 60 Ci per osmium target.

Iodine-131

Iodine-131 (I-131) is used to treat both thyroid cancer and benign hyperthyroid disease. Diagnostic use has been replaced by cyclotron-produced iodine-123 (I-123) because I-123's x-ray emission energy is better suited to SPECT cameras and I-123 delivers a smaller radiation dose than I-131.[6]

Treatment for thyroid cancer typically requires 180 mCi, while treatment for benign disease typically requires 30 mCi.[7] In the United States, thyroid cancer presents in about 65,000 patients per year,[8] and I-131 treatment is prescribed for approximately 40 percent of these patients.[9] Hyperthyroidism presents with an incidence of 0.04 percent of women and 0.01 percent of men per year, so that in the United States one expects 75,000 cases per

year.[10] U.S. physicians prescribe I-131 therapy for 70 percent of benign diseases.[11] Thus, one would expect a maximum U.S. demand at time of treatment of approximately 6,000 Ci of I-131 per year.

I-131 is typically created by neutron capture on tellurium-130 (Te-130), creating tellurium-131 (Te-131) and tellurium-131m (Te-131m), which subsequently beta-decay to I-131. I-131 can also be produced as a fission product. Exposing a 100 g natural TeO_2 (i.e. 34 percent Te-130) target to a 10^{14} n/cm^2/sec flux has been demonstrated to yield approximately 20 Ci of I-131 per 120 hr irradiation.[12] In comparison, based on the Te-130 absorption cross section of 0.24 barns and taking into account the decay of I-131, one would expect a 100 g TeO_2 target to produce 13 Ci of I-131 per 120 hr. Assuming an 80 percent uptime, such a 100 g target would yield approximately 1000 Ci/yr.

I-131 can also be produced via charged-particle reactions. In fact, the first production was accomplished with the Berkeley 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. Thick target yields on an unenriched target have been measured to be approximately 100 μCi / μA·hr at a beam energy of 20 MeV; an enriched target would be necessary to prevent contamination with other iodine isotopes,[13] which would give a yield of approximately 300 μCi/μA·hr. At a beam current of 500 μA and an uptime of 80 percent, one would thus expect an annual production rate per target of 1000 Ci/yr.

Rhenium-188

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. A treatment dose is typically 90 mCi.[14] It is not yet approved for use in the United States and is presently only used as part of clinical studies.

Other radioisotopes for palliative bone treatment analyzed here include rhenium-186 (Re-186), samarium-153 (Sm-153), strontium-89 (Sr-89), and radium-223 (Ra-223). In the United States, approximately 280,000 patients per year are thought to need care for metastatic bone disease.[15] Only a fraction of these patients are likely to be prescribed a radiopharmaceutical for bone pain; alternative treatment options include analgesics, external beam radiotherapy, surgery, and bisphosphonates.[16] Of the patients who are prescribed a radiopharmaceutical, only a fraction will choose one particular radioisotope. If one assumes that the bone pain therapy market is equally divided between the five treatment options and four radioisotopes, then only 11,000 patients per year will choose one particular isotope. A typical patient can be treated up to four times per year,[17] so that at a maximum, one would expect 45,000 annual treatments. For Re-188, that number of treatments corresponds to a U.S. demand of 4,000 Ci/yr.

Re-188 is typically provided by a tungsten-188 (W-188) generator that is created by double neutron capture on tungsten-186 (W-186) in a reactor. Creation of W-188 requires a sustained neutron flux of 10^{15} n/cm^2/sec,[18] which is likely unachievable with a spallation neutron source. Re-188 can be produced via neutron capture on enriched rhenium-187 (Re-187) targets with a cross section of 76 b.[19] A 0.1 cm thick, 1 cm^2 target would be expected to produce 1,300 Ci per three days in a thermal neutron flux of 10^{14} n/cm^2/sec or 380,000 Ci/yr assuming an 80 percent uptime. Considering only absorption, the neutron path length is 0.2 cm. Re-188 can also be produced via the Re-187(d,p)Re-188 reaction. The measured

thick target yield with a 12 MeV, 500 μA deuteron beam is 300 μCi/μA·hr.[20] A 500 μA beam operated with an 80 percent uptime would create 1,000 Ci/yr. However, the specific activity requirements for Re-188 treatment are likely high and may make thermal neutron or deuteron-based cyclotron production difficult.

Re-188 could also be produced in carrier free form via the W-186(α,x)Re-188 reaction with a measured cross section of 55 mb at 43 MeV.[21] Given this cross section, one would expect that a 40 MeV, 500 μA α beam impinging on a 0.01 cm thick target (half the CSDA range) would create 860 Ci/yr at 80 percent uptime.

Samarium-153

Sm-153 is used for palliative bone therapy.[22] The typical prescription dose is 1 mCi/kg, so that a 70 kg patient needs 70 mCi up to four times per year.[23] It is approved for use in the United States under the brand name Quadramet. Assuming that Sm-153 has the same market share as any of the other palliative therapy radioisotopes (see Re-188) and that patients can be treated four times per year, there are 45,000 annual treatments for a total U.S. demand of 3,000 Ci/yr.

Sm-153 can be produced via neutron capture on Sm_2O_3 targets enriched in samarium-152 (Sm-152). The thermal neutron absorption cross section is very large (206 b), but the specific activity requirement for the Sm-153 product is very high: 10^3 to 10^4 Ci/g.[24] Seven days in 2×10^{14} n/cm^2/sec flux has been demonstrated to reach the required specific activity.[25] Assuming that the yield is on the low side of the required specific activity in a 10^{14} n/cm^2/sec flux, a 0.1 cm thick, 1 cm^2 area target that contains 0.73 g of Sm-152 would create 730 Ci of Sm-153 per seven days. (Considering only absorption, the neutron path length is 0.2 cm.) Assuming an 80 percent uptime, that rate corresponds to an annual production of 30,000 Ci.

Production via Nd-150(α,n)Sm-153 has been measured at 25 MeV to be 30 μCi/μA·hr.[26] In comparison, given the measured cross section of 0.045 b at 20 MeV, one would crudely estimate a production rate of approximately 14 μCi/μA·hr on a 0.07 cm thick, natural neodymium target. According to the measured yield, a 500 μA beam operated with an 80 percent uptime would create 100 Ci/year. Given the different chemistries of the target and Sm-153, the specific activity of Sm is likely not a limiting factor for cyclotron production.

Rhenium-186

Re-186 is used for bone pain palliative care.[27] The average prescription dose is 40 mCi administered up to four times per year.[28] It is not yet approved for use in the United States and is presently only used as part of clinical studies. Assuming that Re-186 has the same market share as any of the other palliative therapy radioisotopes (see Re-188) and that patients can be treated four times per year, there are 45,000 annual treatments for a total U.S. demand of approximately 2,000 Ci.

Re-186 can be produced in a neutron flux via neutron capture on an enriched rhenium-185 (Re-185) target. In a 10^{14} n/cm^2/sec neutron flux, the production of a 10^3 Ci/g specific activity Re-186 after six days of exposure has been demonstrated.[29] The neutron absorption cross section is very large, 100 b. A 10^{14} n/cm^2/sec flux impinging on a 0.05 cm thick, 1 cm^2 area target that contained 1 g of Re-185 would create 1,000 Ci of Re-186 per six days.

Assuming an 80 percent uptime, this rate corresponds to 50,000 Ci/yr. Self-shielding effects should be small because the neutron absorption path length is 0.15 cm.

Re-186 can also be produced via a p,n reaction on WO_3 targets enriched in W-186. Measurements suggest that one could create 0.5 Ci per day of target exposure using a 15 MeV, 500 μA proton beam.[30] (In comparison, a 500 μA proton beam would be crudely expected to produce 0.4 Ci/day from a 0.01 cm thick target. The CSDA range of a 10 MeV proton beam, at which the cross section peaks at 0.06 b, is 0.023 cm). Assuming an 80 percent uptime, this rate corresponds to an annual production of approximately 150 Ci.

Yttrium-90

Yttrium-90 (Y-90) is most commonly used as a form of palliative care for unresectable liver cancer.[31] 30,000 patients per year present with liver cancer in the United States,[32] but only a fraction of those are likely to use Y-90 therapy. The typical dose is approximately 100 mCi for a 1.5 kg liver.[33] If 10,000 patients per year chose Y-90 therapy, the maximum annual U.S. demand would be 1,000 Ci/year.

Historically, Y-90 has been produced from decay of strontium-90 (Sr-90), which is a fission product.[34] However, Y-90 can be created by neutron capture on yttrium-89 (Y-89), with a cross section of 1.3 b. Exposing a 1 cm cube (approximately 5 g), natural yttrium target to 10^{14} n/cm^2/sec flux would create Y-90 at a rate of 1.1 Ci/hr. Assuming an 80 percent uptime, that rate corresponds to 8,000 Ci/year.

Y-90 can also be created via the d,p reaction on Y-89 with a cross section of 0.1 b at 20 MeV.[35] Given this cross section, one would expect that a 20 MeV, 500 μA d beam impinging on a 0.06 cm thick target would create 1,200 Ci/year.

Iodine-125

Iodine-125 (I-125) is used as the therapeutic isotope in low-dose rate brachytherapy devices, mostly to treat prostate cancer. Each I-125 prostate cancer treatment requires on average 50 mCi.[36] In the United States, about 200,000 men develop prostate cancer per year, and 10,000 of them will be treated with I-125 therapy.[37] The U.S. demand for I-125 brachytherapy is thus about 500 Ci/yr.

I-125 is typically made by neutron capture on an enriched xenon-124 (Xe-124) target (165 b cross section) that subsequently decays to I-125. Measurements demonstrate that exposing 0.4 g of enriched Xe-124 to a 10^{14} n/cm^2/sec neutron flux can create 6.4 Ci per day.[38] At an 80 percent uptime, such a target would produce 1,900 Ci/yr.

I-125 can also be produced by the reaction Te-125(p, n)I-125. It has been estimated that a 30 MeV cyclotron could produce I-125 at a rate of 54 μCi/μA·hr.[39] Assuming an 80 percent uptime and a 500 μA beam current, such a facility could create approximately 200 Ci/yr.

Strontium-89

Strontium-89 (Sr-89) is used for palliative care of metastatic bone disease with a typical treatment of 4 mCi.[40] It is approved for use in the United States under the brand name Metastron. Assuming that Sr-89 has the same market share as any of the other palliative therapy radioisotopes (see Re-188) and that patients can be treated four times per year, there are 45,000 annual treatments for a total U.S. demand of approximately 200 Ci.

Sr-89 can be made by neutron capture on Sr-88 with a cross section of 0.058 b.[41] Sr-89 can also be made via a fast neutron reaction on Y-89.[42] For this treatment modality, specific activity is likely critical to achieve therapeutic effect. Metastron has a specific activity of at least 0.08 Ci/g.[43] In a 10^{14} n/cm^2/sec neutron flux, at least five days of exposure would be required to reach that specific activity. A 1 cm^3 target would be expected to create 0.2 Ci per five days. Assuming an 80 percent uptime, that rate corresponds to an annual production of 12 Ci/yr.

Cyclotron production of Sr-89 is unfeasible; the d,2p reaction on Y-89 has a cross section of 0.0003 b.[44]

Phosphorus-32

In the past, phosphorus-32 (P-32) was used for types of ovarian cancer, blood disease, and metastatic bone cancer. It is no longer recommended for palliative bone cancer therapy due to myelotoxicity.[45] Today, it is mostly a niche isotope used for a certain type of cystic brain tumor called cystic craniopharyngiomas; each treatment requires on average 0.5 mCi of P-32.[46] A total of 20,000 patients present with brain cancer in the United States per year. Only a fraction of these patients will likely need P-32 therapy. Assuming a conservative upper bound of 10,000 patients per year gives a total U.S. demand of 5 Ci.

P-32 is typically made by neutron capture on sulfur-32 (S-32). Measurements indicate that a 10^{14} n/cm^2/sec neutron flux impinging on a 5 g, 1 cm^2 natural sulfur target would create 4.5 Ci per week long exposure.[47] Assuming an 80 percent uptime, this rate corresponds to approximately 200 Ci per year.

Cyclotron production of P-32 has a long history: early supplies of P-32 were created with the Berkley cyclotron.[48] A d,2p reaction on S-32 has a cross section of 0.139 b at an energy of 18 MeV.[49] One would expect that a 500 μA beam impinging on a 0.13 cm thick target would create 900 Ci per year.

Radium-223

Ra-223 is used for palliative treatment of prostate origin metastatic bone disease at a recommended dose of 1.4 μCi / kg.[50] A 70 kg patient would require a dose of 0.1 mCi. Ra-223 has recently been approved for use in the U.S. under the brand name Xofigo.[51] Assuming that Ra-223 has the same market share as any of the other palliative therapy radioisotopes (see Re-188) and that patients can be treated four times per year, there are 45,000 annual treatments for a total U.S. demand of approximately 5 Ci.

Ra-223 is typically produced as a daughter product of actinium-227 (Ac-227), which itself is created via neutron capture on radium-226 (Ra-226).[52] Because radium-223 (Ra-223) is eluted from an Ac-227 generator, the demand for Ra-223 sets the scale for the amount of Ac-227 that must be available for hospital or radiopharmacy use. Ac-227 has a half-life of 22 years. If one assumes that the Ra-223 is eluted every seven days and that the loss between elution and clinical use is 50 percent, then to provide 0.1 Ci of Ra-223 per seven days for clinical use requires 0.6 Ci of Ac-227. Ra-226 has a 12.8 b thermal neutron absorption cross section. Exposure of 1 cm^3 of Ra-226 to a 10^{14} n/cm^2/sec neutron flux would produce 0.6 Ci every 17 days. Assuming an 80 percent uptime, such a beam line could produce 10 Ci of Ra-226 per year, 1.6 Ci of Ra-223 per week, or approximately 90 Ci of Ra-

223 per year. However, the half-life of Ac-227 is so long that one 20 day exposure of a 1 cm^3 of Ra-226 could meet U.S. level demand for at least five or ten years.

Particle accelerator alternatives have been investigated; Weidner et al. demonstrated that 9 Ci of thorium-227 (Th-227) could be produced with a 10 day exposure of a 70-90 MeV 250 μA proton beam on a natural thorium target.[53] If this quantity of Th-227 were eluted three times, every seven days, a total of approximately 6 Ci of Ra-223 would be produced from each target. Operating the accelerator at 80 percent uptime would yield a total of approximately 170 Ci of Ra-223 per year.

Appendix B
Less Commonly Used Isotopes

Actinium-225

Actinium-225 (Ac-225) is an alpha emitter with a 10 day half-life that is used for targeted alpha therapy. [54] The isotope is harvested as a product of the uranium-233 (U-233) decay chain. U-233 is produced by neutron capture on thorium-232 (Th-232). Ac-225 can be produced in cyclotrons or linear accelerators with a radium-226 (Ra-226) target. Proton cyclotrons would make use of the (p,2n) reaction. Linear accelerators can use bremsstrahlung gammas to produce Ra-225 via the (γ,n) reaction. Ra-225 decays to Ac-225 with a 15 day half-life.

Americium-241

Americium-241 (Am-241) is an alpha emitter with a 432 year half-life and is produced as a daughter of plutonium-241 (Pu-241), which has a half-life of 14 years. Pu-241 is produced in reactors by three successive neutron captures on uranium-238 (U-238) or in cyclotrons via the (α,n) reaction on uranium-238.[55] Historically, it has been used in cardiovascular imaging, osteoporosis detection,[56] and thyroid scans.[57] For these imaging modalities, Am-241 has been replaced by technicium-99m (Tc-99m), iodine-127 (I-127), and positron emission tomography (PET) isotopes.

Californium-252

Californium-252 (Cf-252) decays by alpha emission (97 percent of the time) and spontaneous fission (3 percent) with a half-life of 2.6 years. It is produced by 14 successive neutron capture reactions on uranium-238,[58] and thus, accelerator-based production of Cf-252 would be difficult. The spontaneous fission decay mode makes Cf-252 an attractive neutron source because it liberates 3.75 neutrons per fission.[59] Although historically, neutron therapy was explored as a treatment for many cancers, it is now used mostly for salivary gland tumors.[60] Neutron therapy in the United States is delivered almost exclusively by cyclotron-produced protons bombarding a beryllium target.

Cesium-131

Cesium-131 (Cs-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.[61] It can be produced in cyclotrons by proton activation of xenon-131 (Xe-131).[62]

Cesium-137

Cesium-137 (Cs-137) is a beta and gamma emitter with a half-life of 30.2 years. It is produced as a fission product. It would be difficult to produce with accelerator-based technology. Historically, it was used as a source of high-energy x-rays for both external x-ray therapy and internal high-dose-rate brachytherapy. Although in the past Cs-137 was commonly used for gynecological brachytherapy, modern practice in the United States uses Ir-192 instead.[63] Ir-192 is readily used with commercial "after-loaders" that automatically remove the source from a shielded container and minimize exposure to medical personnel.

In addition, Ir-192 treatments can be performed on an outpatient basis, whereas Cs-137 gynecological treatment requires an inpatient hospital stay and several days of continuous sedation. Small-scale electron accelerators have replaced Cs-137 in external beam applications. A country looking to provide the most modern radiation treatment would be unlikely to use Cs-137. A National Academies' report has called for the complete replacement of all Cs-137 sources in the United States due to the security risk of misuse.[64] Cs-137 blood irradiators are also in the process of being replaced by accelerator alternatives, at least in developed countries.[65]

Xenon-133

Xenon-133 (Xe-133) is used in lung ventilation-perfusion studies and is typically produced as a fission product.[66] It would be difficult to produce with accelerator-based technologies. However, xenon-127 (Xe-127) has been demonstrated to be superior: its higher x-ray emission energy provides better resolution, its decay mode (electron capture instead of beta decay) reduces patient dose, and its longer half-life increases its shelf life.[67] In addition, Tc-99m-based aerosols are also usually superior to Xe-133 and used more frequently.[68]

Chromium-51

Chromium-51 (Cr-51) is a gamma emitter with a 28 day half-life that is used to label red blood cells and quantify gastro-intestinal protein loss. It is produced via neutron capture on chromium-50 (Cr-50).[69] Cyclotron-produced indium-111 (In-111) is likely a more efficient blood labeler.[70]

Cobalt-60

Cobalt-60 (Co-60) is a gamma emitter with a 5.27 year half-life. It is fabricated by neutron capture on cobalt-59 (Co-59).[71] Historically, it has been used for external beam radiotherapy, brachytherapy, and equipment sterilization. As with Cs-137, brachytherapy Co-60 sources have been replaced by Ir-192, and radio-surgery Co-60 sources have been replaced by 6 MeV electron accelerators. Co-60 is still used in some developing countries for external beam radiotherapy and is used worldwide for sterilization.[72] Co-60 is used as the radiation source for medical device sterilizers. The quantities of Co-60 required for sterilization or external beam therapy are so large that accelerator-based production would be unlikely to meet worldwide demand. However, x-ray based medical device sterilizers are now commercially available and have been deployed in Europe.[73] The costs of these facilities is expected to be comparable to Co-60 sterilizers.

Iodine-132

Iodine-132 (I-132) is both a beta and gamma ray emitter with a half-life of 2.3 hrs. It is typically produced by the decay of the fission product tellurium-132 and historically was used for imaging.[74] I-132 has been replaced by the other iodine isotopes for clinical use. It can be produced in a cyclotron by alpha bombardment of natural tellurium.[75]

Lutetium-177

Lutetium-177 (Lu-177) is a beta and gamma emitter with a 6.7 day half-life. It can be used for simultaneous imaging of and therapy for tumors. The isotope has shown promise for treating neuroendocrine tumors,[76] and clinical trials are ongoing.[77] Lu-177 is typically produced by neutron activation of natural or enriched Lu-176 targets. Cyclotron production via deuteron bombardment of enriched ytterbium-176 (Yb-176) targets at 12.5 MeV can produce high specific activity Lu-177.[78] Cyclotron production has the advantage of avoiding the undesirable contaminant lutetium-177m (Lu-177m).

Manganese-54

Manganese-54 (Mn-54) decays by electron capture with a half-life of 312 days. It has been used as a radiotracer in nutrition studies.[79] The isotope can be produced in reactors via a (n,p) reaction on iron-54 or with cyclotrons via the (d,n) reaction on chromium-53 (Cr-53).[80]

Ruthenium-106/Rhodium-106

Ruthenium-106 (Ru-106) is a beta emitter with a 374 day half-life that is used for brachytherapy. The beta emitted by Ru-106 has too short a range to be therapeutically effective. However, its daughter, Rh-106, has a 30 s half-life and emits a beta with sufficient range. Ru-106 is a fission product and has traditionally been produced along with fission-produced molybdenum-99 (Mo-99).[81] Historically, Ru-106 was used to treat skin cancers and choroidal melanomas (cancer of the retina).[82] However, surface brachytherapy is now most commonly performed with either Ir-192 sources [83] or electronic x-ray sources. Ru-106 continues to be used to treat cancers of the eye.[84] The typical eye plaque has a maximum activity of 1.6 mCi.[85] Alternatives include so-called eye plaques loaded with either I-125 [86] or palladium-103 (Pd-103).[87] In North America, Ru-106 treatment is disfavored for treatment of ocular melanoma; a 10 year 9,000 patient multi-center study chose to use I-125 instead of Ru-106.[88] Some studies have found that Ru-106 treatment has a higher cancer recurrence rate for choroidal melanoma.[89] The market for Ru-106 is very small because of the long half-life and the limited number of patients; only 2,700 individuals per year in the United States develop cancers of the eye.[90]

Ru-106 can be produced with either a spallation neutron source, a high energy cyclotron, or a photo-fission process. Exposure of a 1 cm^3 natural uranium target to a 10^{14} $n/cm^2/sec$ neutron flux would be expected to generate about 6 Ci of Ru-106 per year, equivalent to at least 3,600 eye plaques. A spallation reaction on lead can generate Ru-106. At 50 MeV, the cross section is about 1 mb.[91] With a 0.1 cm thick target, a 500 μA proton beam operating with 80 percent uptime would produce 0.15 Ci or 90 eye plaques per year. Photofission production of Ru-106 by bombardment of a natural uranium target with electrons from a linear accelerator would be similar to photo-nuclear production of Mo-99. It has been estimated that a 30 MeV, 100 kW electron beam could generate 3×10^{13} fissions per sec using a natural uranium target.[92] Given the Ru-106 fission yield of 2.5 percent and an 80 percent uptime, such a beam line could generate 11 Ci or at least 7,000 eye plaques per year.

Selenium-75

Selenium-75 (Se-75) decays by electron capture with a 120 day half-life. It is produced via thermal neutron capture on selenium-74 (Se-74).[93] It is used in the form of seleno-methionine to study the production of digestive enzymes and can be produced with a cyclotron by irradiating natural bromine with protons in the 60 MeV range.[94]

Ytterbium-169

Ytterbium-169 (Yb-169) decays by electron capture with a 32 day half-life. It can be produced in a reactor via neutron capture on ytterbium-168 (Yb-168).[95] Historically, it has been used for cerebrospinal fluid studies in the brain.[96] There is renewed interest in the isotope for brachytherapy; it can be produced in a 30 MeV cyclotron via a p,n reaction on natural thulium.[97]

Appendix C
Other Radioisotopes

Table 1: Radioisotopes, not discussed elsewhere in the online supplement that have potential medical use and that can be created with a small spallation neutron source. Unless otherwise noted, the example production reaction is taken from the IAEA's reactor production manual.

Isotope	Example Production Reaction	Example medical use
Calcium-45	(n,γ)	Tracer for calcium metabolism studies.[98]
Cobalt-58	(n,p)	Vitamin B-12 labeling.[99]
Dysprosium-165	(n,γ)	Radiation treatment of arthritis (synovectomy).[100]
Erbium-169	(n,γ) [101]	Radiation therapy of inflammatory joint disease.[102]
Gadolinium-153	(n,γ)	Calibration source for SPECT cameras.[103]
Gold-198	(n,γ) [104]	Brachytherapy and radiopharmaceuticals for therapy.
Holmium-166	(n,γ)	Bone cancer palliation therapy.[105]
Iron-59	(n,γ)	Diagnosis of hematopeietic disorders.[106]
Osmium-191 / Iridium-191m	(n,γ)	Angiocardiography.[107]
Palladium-109	(n,γ)	Radiolabeled monoclonal antibody for cancer therapy.[108]
Phosphorous-33	(n,p)	Tracer for molecular biology research.
Platinum-195m	(n,γ)	Tracer for biodistribution studies of labeled drugs.[109]
Potassium-42	(n,γ) [110]	Tracer for potassium metabolism research.[111]
Promethium-149	(n,γ) [112]	Therapeutic radiopharmaceutical.[113]
Rhodium-105	(n,γ)	Therapeutic radiopharmaceutical.[114]
Samarium-145	(n,γ) [115]	Brachytherapy.[116]
Scandium-46	(n,γ)	Blood flow research.[117]
Scandium-47	(n,p) [118]	Labeling of monoclonal antibodies.[119]
Silver-111	(n,γ)	Radio-synovectomy.[120]
Sodium-24	(n,γ)	Tracer for sodium metabolism research.
Sulfur-35	(n,p)	Tracer for molecular biology research.
Tantalum-182	(n,γ) [121]	Historically used for brachytherapy wires.
Tellurium-123m	(n,γ)	SPECT isotope.[122]
Terbium-161	(n,γ) [123]	Therapeutic radiopharmaceutical.[124]
Thorium-227	(n,γ) [125]	Therapeutic radiopharmaceutical.[126]
Thulium-170	(n,γ) [127]	Bone pain radiopharmaceutical.[128]
Tin-113 / Indium-113m	(n,γ)	Historic SPECT isotope.[129]
Tin-117m	(n,n′)	Bone pain palliation therapy.[130]

Table 2: Radioisotopes, not discussed elsewhere in the online supplement that are typically produced with accelerators. Unless otherwise noted, production reaction and medical use are taken from the IAEA list of established and emerging isotopes, IAEA cyclotron production manual, and medical literature.

Isotope	Example Production Reaction	Example Medical Use
Arsenic-73	Germanium-nat(p,xn)	Environmental tracer.[131]
Astatine-211	Bismuth-209(α,2n)	Radiopharmaceutical therapy.[132]
Bismuth-213	Actinium-225 generator	Radiopharmaceutical therapy.[133]
Bromine-76	Selenium-76(p,n)	PET
Cobalt-55	Nickle-58(p, α)	PET
Cobalt-57	Nickle-nat(p, x)	SPECT
Carbon-11	Nitrogen-14(p, α)	PET
Copper-60	Nickle-60(p,n)	PET
Copper-64	Nickle-64(p,n)	PET
Fluorine-18	Oxygen-18(p,n)	PET
Copper-67	Zinc-68(p,2p)	Radiopharmaceutical therapy.[134]
Gallium-66	Zinc-66(p,n)	PET
Gallium-67	Zinc-68(p, 2n)	SPECT
Gallium-68	Germanium-68 decay	PET
Indium-111	Cadmium-111(p,n)	SPECT
Indium-114m	Cadmium-114(p,n)	Radiopharmaceutical therapy.[135]
Iodine-123	Tellurium -124(p,2n)	SPECT
Iodine-124	Tellurium-124(p,n)	PET
Nitrogen-13	Oxygen-16(p, α)	PET
Palladium-103	Rhodium -103(p,n)	Brachytherapy
Oxygen-15	Nitrogen-14(d,n)	PET
Rubidium-82	Rubidium-85(p,4n)	PET
Technicium-94m	Molybdenum-94(p,n)	PET
Terbium-149	Tantallum-nat (p,x) at 1 GeV	Radiopharmaceutical therapy.[136]
Thallium-201	Thallium-203(p,3n)	SPECT
Xenon-127	Iodine-127(p,n)	SPECT
Yittrium-86	Strontium-86(p,n)	PET
Zirconium-89	Yttrium-89(p,n)	PET

Appendix D
Proliferation Risk of Accelerators for Medical Isotope Production

This section estimates the proliferation potential of accelerator-based medical isotope production facilities including linear accelerators, hospital scale cyclotrons and spallation neutron sources by calculating the annual rate of plutonium-239 production in each type of facility and the capacity of enrichment infrastructure needed to support the accelerator-based facilities.

As in a reactor, accelerators can produce plutonium-239 via thermal neutron capture on uranium-238. Neutrons can be created with accelerators via photo-nuclear, charged-particle, or spallation reactions. However, only a fraction of these neutrons will be captured by uranium-238 because accelerator-produced neutrons have energies in the MeV range and must be moderated to thermal energies, and only a fraction of the initial neutron flux will be successfully moderated. Nevertheless, one can place an absolute upper bound on accelerator production of plutonium-239 by assuming that all neutrons created by the accelerator are captured by uranium-238. With this assumption, 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.

Electron Linear Accelerators

The same photo-nuclear reaction that transmutes molybdenum-100 (Mo-100) into Mo-99 also creates neutrons. Uranium is a better target for neutron production than molybdenum. If a molybdenum target was replaced with a natural uranium target that was designed to optimize neutron production, then a 50 MeV electron beam could liberate 0.024 neutrons per incident electron.[137] Thus, a 50MeV, 100 kW linear accelerator built for Mo-99 production could be repurposed to generate about 1.5×10^{14} n/sec. Such a machine would require at least 7,000 years to fabricate 10 kg of plutonium-239.

Cyclotrons

Hospital-scale cyclotrons that create medical isotopes can also be used to create neutrons through a charged-particle reaction. At a 30 MeV ion energy, the greatest neutron yield is achieved by bombarding beryllium targets with deuteron ions (protons have a 25 percent smaller yield).[138] The neutron yield is approximately 0.03 neutrons per incident deuteron so that a 30 MeV, 500 μA cyclotron for medical isotope production could be repurposed to generate about 10^{14} n/sec. Such a machine would require at least 10,000 machine-years to fabricate 10 kg of plutonium-239.

Spallation Neutron Reactions

Neutrons created at a spallation neutron source could be used to create plutonium-239. The SINQ source described above provides an operating example that could likely meet the isotope needs of a 100 million person country and bounds the proliferation risk of this technology. Although SINQ could produce plutonium-239 by simply blanketing the lead spallation target with natural uranium, the most efficient method of producing plutonium-239 would be to replace the lead in the target with uranium. A Monte Carlo study estimated the production potential in such a scenario for a variety of target geometries.[139] In SINQ, a 570 kW, 590 MeV proton beam strikes a target, which can be approximated as a

10 cm radius, 50 cm long cylinder.[140] Applying the Monte Carlo study to the SINQ geometry, a uranium target in SINQ would make 10 kg of plutonium-239 in 20 years. In contrast, a 1 cm^2 thermal neutron beam line itself, with a flux of 10^{14} $n/cm^2/sec$ would require 10,000 years to produce 10 kg of plutonium-239.

Enrichment

Accelerator-based isotope production often requires enriched isotopes as the beam targets. Both cyclotron and linear accelerator-produced Tc-99m and Mo-99 require enriched Mo-100 targets. Natural molybdenum is 9.6 percent Mo-100, with the balance consisting of seven stable isotopes. For cyclotron Tc-99m production, the concentration of Mo-100 must be at least 97 percent, and the concentration of isotopes molybdenum-95, molybdenum-96, and molybdenum-97 must all be below 0.01 percent in order to minimize radiological contaminants.[141] Linear accelerator-produced Mo-99 requires 98 percent enriched Mo-100.[142] The linear accelerator method is estimated to require 2.5 mg of Mo-100 per Ci of Mo-99 produced at the end of bombardment, whereas the cyclotron method is estimated to require 20 mg of Mo-100 per Ci of Tc-99m provided for patient diagnosis.

The effort required to produce enriched material from unenriched material is typically expressed as "separative work" given by:[143]

$$\delta U = P\left[\mathcal{V}(n_p) + \left(\frac{n_p - n_f}{n_f - n_w}\right)\mathcal{V}(n_w) - \left(\frac{n_p - n_w}{n_f - n_w}\right)\mathcal{V}(n_f)\right], \qquad (1)$$

where δU is measured in kg-SWU/year, P is the product feed flow, in kg/year, n_p, n_w and n_f are the enrichment fractions of the product, waste and feed flows respectively, and V(n) is a dimensionless "value function," given by:

$$\mathcal{V}(n) = (2n - 1)\ln\left(\frac{n}{1-n}\right). \qquad (2)$$

For a given enrichment technology, the energy and money required to operate an enrichment facility is typically proportional to the separative work capacity of that facility.

It is much easier to enrich molybdenum than uranium because natural molybdenum has a much higher concentration of Mo-100 than natural uranium has of uranium-235. Although strictly speaking, Equation 2 only applies to binary isotope mixtures, such as U-235/U-238, one can nevertheless approximate the separative work required to enrich Mo-100 by treating all other molybdenum isotopes as a single contaminant. Assuming a Mo-100 concentration of two percent in the waste stream, production of 1 kg of 99.97 percent Mo-100 requires 29 kg-SWU, while production of 1 kg of 98 percent Mo-100 requires 24 kg-SWU. In contrast, 1 kg of 90 percent uranium-235 (n_p = 0.90, n_w = 0.0025, n_f = 0.00711) requires 210 kg-SWU.

The separative work power of a given technology depends on the details of the machine itself and also on the process gas and isotope. For some machines, it may not be possible to convert from one process gas to another. For example, lubricants used in some centrifuges may be compatible with some process gasses but not with others. Nevertheless, a simple estimate of the ability of a centrifuge-based molybdenum enrichment facility to enrich uranium can be made by comparing a generic centrifuge's ability to enrich uranium using UF_6 to its ability to enrich molybdenum using MoF_6. The separative work of a generic gas centrifuge to isolate 1 kg of an enriched isotope is estimated to be:[144]

$$\boldsymbol{\delta U = 50 \cdot \rho D_{PG} \cdot M_{TI} \left(\frac{\Delta M}{M_{PG}}\right)^2 V^2 Z e_E,} \quad (3)$$

where ρD_{PG} is the self-diffusivity coefficient of the process gas in units of kg/m/s, M_{PG} and M_{TI} are the molar masses of the process gas and target isotope, respectively, in g/mole, $\boldsymbol{\Delta M}$ is the molar mass difference between the isotopes the centrifuge is separating, in g/mole, V is the peripheral speed of the rotor, in m/s, Z is the length of the rotor in meters, and e_E is a dimensionless measure of the centrifuge's efficiency and typically ranges from 0.6 to 1.6. The mass ratios and self-diffusivity coefficients of MoF_6 and UF_6 are such that a generic centrifuge has the same separative work power for either isotope (see Table 3).

Table 3: Process gas parameters and estimated separative work capacity of a generic centrifuge for enriching either uranium-235 or Mo-100. 〖ρD〗_PG is taken from Zarkova, assuming an operating temperature of 310 K.

Isotope	$\boldsymbol{\rho D_{PG}}$ (kg/m/s)	$\boldsymbol{\Delta M}$ (g/mole)	$\boldsymbol{M_{PG}}$ (g/mole)	$\boldsymbol{M_{TI}}$ (g/mole)	$\boldsymbol{\delta U/V^2 Z e_E}$
U-235	2.32×10^{-5}	3	352.0	235	2×10^{-5}
Mo-100	1.94×10^{-5}	3	209.9	100	2×10^{-5}

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