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Environmental Benefits of NorthStar Medical Radioisotopes' Non–Uranium–Based Production Method for Molybdenum–99/ Technetium–99m

NorthStar MEDICAL RADIOISOTOPES

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INTRODUCTION

The radioisotope technetium–99m (Tc–99m) is the standard of care in diagnostic imaging to assess the extent and severity of heart disease and cancer. Globally, Tc–99m is used in approximately 80% of all nuclear medicine procedures performed each year,[1] and US hospitals alone use this radioisotope in over 40,000 diagnostic imaging procedures each day.[2] Tc–99m is the decay product of molybdenum–99 (Mo–99), another short–lived radioisotope that is traditionally produced via nuclear fission of uranium–235 (U–235) targets. Until recently, the worldwide supply of Mo–99 was entirely dependent on 6 nuclear reactors, most of which are over 50 years old and rapidly becoming less reliable. For instance, in 2009 and 2010, a series of unexpected shutdowns and planned maintenance periods resulted in global Mo–99 shortages. In addition to such supply chain interruptions, a major concern with Mo–99 production via traditional U–235 fission methods is the substantial amount of hazardous waste material generated in the process. Much of this waste is extremely long–lived and may lead to environmental contamination and subsequent human health risks if not disposed of properly. As such, the need for alternative Mo–99 production methods that generate benign and potentially recyclable waste streams is paramount.

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[1] OECD Nuclear Energy Agency. (2019). *The Supply of Medical Radioisotopes: 2019 Medical Isotope Demand and Capacity Projection for the 2019–2024 Period.* (NEA/SEN/HLGMR[2019]1). OECD Publishing, Paris, France.

[2] United States Department of Energy/National Nuclear Security Administration. (2021). *Prevent, Counter, and Respond – NNSA's Plan to Reduce Global Nuclear Threats (FY 2022–FY 2026).* Report to Congress, Washington, DC.

Mo–99 PRODUCTION METHODS AND TARGET MATERIALS

The medical radioisotope Mo–99 does not occur naturally and therefore must be synthesized by irradiating a target material. Mo–99 can then be recovered from the processed targets and prepared for commercial distribution. Currently, 2 primary target materials are used in the commercial Mo–99 industry: uranium–235 (U–235) and molybdenum–98 (Mo–98). Due to the short half–life of Mo–99 (66 hours), production must take place on a continuous basis.

Uranium Target–Based Production

Early production of Mo–99 occurred via neutron capture. Since the late 1980s, Mo–99 has been generated via fission of U–235; targets are irradiated in a nuclear reactor wherein neutrons bombard U–235 to split the nuclei (**Figure 1**).

Though well–established, a major drawback of uranium–based production is the low natural abundance of U–235. When uranium is mined, it contains only 0.7% (by weight) of usable fissile U–235 isotope, while the remaining 99.3% is composed of U–238 and trace amounts of U–234. Consequently, natural uranium ore must undergo enrichment via isotopic separation to increase the relative percentage of U–235 for use in fission targets. High enriched uranium (HEU) has a concentration of 20% or more U–235 by weight, while low enriched uranium (LEU) contains less than 20% U–235.

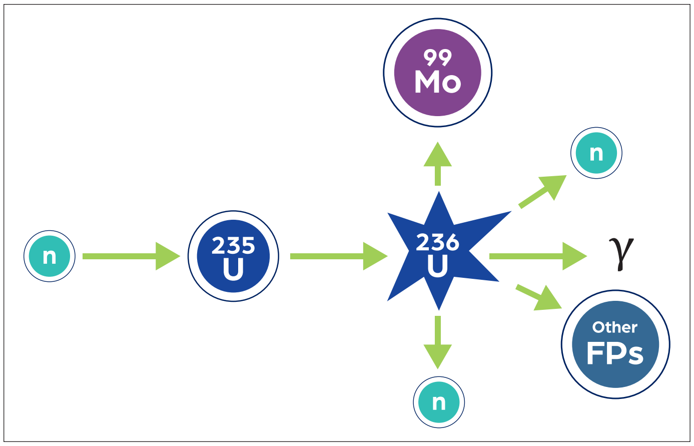

Figure 1. Schematic representation of Mo–99 production from U–235 fission. Note that more than 2 neutrons may be emitted in this process. This represents a typical schematic. n=neutrons and FPs=fission products.[3]

> Compared to U–235 fission–based production methods, NorthStar's neutron capture process generates negligible amounts of waste. Neutron capture by Mo–98 atoms yields approximately 99% useful Mo–99 atoms.

Prior to 2012, most targets for Mo–99 production were fabricated from HEU; however, due to the proliferation–sensitive nature of HEU, government initiatives have since prompted a global industry–wide shift to the use of LEU. Although the conversion to LEU has alleviated the proliferation risks posed by HEU, there is an important trade–off to note: the use of LEU–based target material creates significantly more waste overall in the production of Mo–99. LEU targets are composed of a greater percentage of non–fissile U–238 and other materials that do not undergo fission but still must be properly disposed. In addition, it is estimated that alkaline processing of irradiated LEU targets generates 200% more intermediate–level liquid waste (ILLW) per 10,000 Ci Mo–99 produced compared to HEU.[4] After either HEU or LEU targets have been irradiated, Mo–99 accounts for only about 6% of atoms produced by the fission reaction. I–131 and Xe–133 account for a small fraction of the usable products (< 10%) from the fission process that generates Mo–99, while the bulk of the remaining products end up as some form of waste.[5]

[3] National Research Council (US) Committee on Medical Isotope Production Without Highly Enriched Uranium. (2009). *Medical Isotope Production without Highly Enriched Uranium*. National Academies Press, Washington, DC.

[4] Center for Nuclear Safety and Innovation. (2022, April 25–28). *Current Developments in Fluorine–Based Dry–Chemical Molybdenum Separation* [Presentation]. IAEA Technical Meeting on the Management of Irradiated Uranium Waste from Molybdenum–99 Production Using Low Enriched Uranium Targets, Vienna, Austria.

[5] International Atomic Energy Agency. (n.d.). *Nuclear Data for Safeguards*. Retrieved March 24 from https://www-nds.iaea.org/sgnucdat/c1.htm#92-U-235

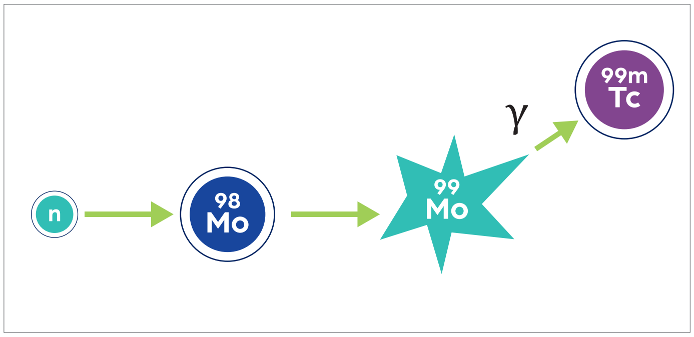

Figure 2. Schematic representation of Mo–99 production from neutron capture.[6]

Molybdenum Target–Based Production

NorthStar is currently the only commercial supplier of Mo–99 to utilize a Mo–98 target and the neutron capture approach. When targets are irradiated in a nuclear reactor, some Mo–98 nuclei absorb or "capture" a neutron to produce Mo–99 (Figure 2).

NorthStar's method for Mo–99 production entirely eliminates the use of uranium target material and, subsequently, many of the drawbacks associated with traditional uranium–based production processes. Mo–98 is a stable, safe, and naturally abundant (~25%) isotope that is easily derived from molybdenite in the earth's crust for use in target manufacturing. Mo–98 targets can be safely enriched to a concentration of over 95% Mo–98, and no weapons–grade or otherwise hazardous material is involved. When Mo–98 targets are irradiated with neutrons, about 99% of the radionuclides produced by neutron capture are usable Mo–99 atoms. Notably, any nonactivated Mo–98 can potentially be recovered and reused.

The irradiated targets are then dissolved, and the Mo–99 is processed and filled into tungsten–shielded source vessels. These source vessels are shipped to radiopharmacies, where Tc–99m is separated and eluted from Mo–99 using NorthStar's proprietary RadioGenix® System (technetium Tc–99m generator). The source vessels are then returned to NorthStar, where they are recycled for reuse.

Waste Production and Environmental Implications

Regardless of the method used, Mo–99 production will always generate other radionuclides that are considered waste by–products, as no reaction yields 100% Mo–99. Such radioactive waste materials are hazardous both to the environment and to human health, and thus require careful management according to guidelines mandated by the US Nuclear Regulatory Commission (NRC). The differences in waste profiles resulting from NorthStar's method compared to those from uranium–based methods, however, are extensive and worth examining in depth.

Uranium Waste Profile

As previously mentioned, fissions resulting from the irradiation of U–235 atoms with thermal neutrons yield only about 6% Mo–99. Other than the I–131 and Xe–133 atoms produced, the remaining fission yield distribution represents various types of waste, a substantial portion of which are long–lived and highly radioactive. In fact, approximately 35% of the long–lived fission reaction products are problematic radioisotopes.[7]

> Beyond greatly reducing the amount of radioactive waste generated in the target irradiation process, NorthStar has implemented steps to ensure that other unused materials resulting from the production and processing of Mo–99 are recycled and reused where possible.

[6] National Research Council (US) Committee on Medical Isotope Production Without Highly Enriched Uranium. (2009). *Medical Isotope Production Without Highly Enriched Uranium*. National Academies Press, Washington, DC.

[7] International Atomic Energy Agency. (nd). *Nuclear Data for Safeguards*. Retrieved March 24 from https://www-nds.iaea.org/sgnucdat/c1.htm#92-U-235

WASTE PRODUCTS	DESCRIPTION	WASTE ACTIVITY (mCi)* (per 3000 6-day Ci of Mo-99 produced)	
		U-235–Based Methods	NorthStar's Method
Activation	Primary activation products of NorthStar's method have half-lives of 65 days (Zr-95) and 35 days (Nb-95) Primary activation products of uranium-based methods have half-lives of ~10 years (eg, Co-60)	51	0.16
Fission	Half-lives of ~30 years (eg, Cs-137, Sr-90)	189,000	0.0
Transuranics/Actinides	Half-lives of >250,000 years (eg, uranium and plutonium waste)	2.7	0.0
Total Waste		**189,000 mCi**	**0.16 mCi**
Uranium-based methods generate far more radioactive waste than NorthStar's method.†			

*The values listed indicate activity levels 1 year after target irradiation. †Data on file at NorthStar.

The hazardous radioactive fission waste products fall into 3 categories: fission products, transuranics/actinides, and other activation products apart from Mo-99. The half-lives of these radionuclides vary; on average, fission products (eg, Cesium-137 [Cs-137] and Strontium-90 [Sr-90]) have half-lives of about 30 years, transuranics or actinides (ie, the long-lived uranium and plutonium waste products) have half-lives of greater than 250,000 years, and activation products (eg, Cobalt-60 [Co-60]) have half-lives in years.[8]

Typical commercial shipments of Mo-99 currently contain ~3000 Ci.[9] For every 3000 Ci of Mo-99 produced from uranium-based target material, an estimated 189 Ci of fission products, and 2.7 mCi of transuranics/actinides, and 51 mCi of activation products remain 1 year following irradiation.[10]

It is also worth noting that U-235 target irradiation does generate 2 other useful medical radioisotopes: Iodine-131 (I-131) and Xenon-133 (Xe-133). Since I-131 and Xe-133 can be produced less expensively from other sources, both are regarded as waste material in fission, thereby adding to the overall radioactive waste inventory for uranium-based Mo-99 production.

Molybdenum Waste Profile

Compared to U-235 fission-based production methods, NorthStar's neutron capture process generates negligible amounts of radioactive waste. Mo-99 atoms account for approximately 99% of the neutron capture reaction products, and while not all Mo-98 atoms in a target undergo neutron capture during a single irradiation, the remaining Mo-98 can be reclaimed (or recovered) and irradiated again. Since NorthStar's methods do not rely on fission to produce Mo-99, there are no radioactive fission by-products. Additionally, no transuranic waste is generated as the target material is free of uranium. The only waste isotopes resulting from neutron capture by Mo-98—which account for only 1% of the total reaction products—are trace amounts of other activation products including Zirconium-95 (Zr-95), Antimony-124 (Sb-124), and Niobium-95 (Nb-95), all of which have half-lives of 65 days or less.

For every 3000 Ci of Mo-99 produced by NorthStar for commercial distribution, the activation waste products generated amount to less than 600 mCi. The majority of this waste is very short-lived, especially relative to fission or transuranic waste products. In fact, less than 17 mCi (ie, less than 6×10^{-4}%) of the total waste products generated via

[8] Kondev FG, Wang M, Huang WJ, Naimi S, Audi G. (2021). The NUBASE2020 evaluation of nuclear properties. *Chinese Physics C*. 45(3), 030001.
[9] This and all subsequent mentions of "Ci" refer to 6-day curies.
[10] International Atomic Energy Agency. (1998). *Management of waste from Mo-99 production*. (IAEA-TECDOC-1051). IAEA, Vienna, Austria.

NorthStar's method have a half-life of greater than 65 days.

To summarize, in the process of producing one 3000 Ci shipment of Mo-99, NorthStar's neutron capture technology generates several orders of magnitude less radioactive waste compared to traditional U-235 fission methods.

Beyond greatly reducing the amount of radioactive waste generated in the target irradiation process, NorthStar has implemented steps to ensure that other unused materials resulting from the production and processing of Mo-99 are recycled and reused where possible. Recyclable, used Mo-99 source vessels are shipped from radiopharmacies back to NorthStar. Any nonactivated Mo-98 remaining in solution in these source vessels is recovered, processed, and used in the manufacture of new targets. After the unused Mo-98 has been reclaimed,[11] the source vessels themselves are cleaned, refilled with freshly prepared Mo-99, and again shipped to customers. Additionally, nonactivated Mo-98 is recovered from several other points in NorthStar's Mo-99 production stream for reuse as target material.

Waste Management Requirements

The activation, fission, and transuranic by-products created when irradiating target materials to produce Mo-99 must all be handled as radioactive waste. The appropriate waste management approaches for these materials as determined by the NRC are based on radioactive decay rates, quantities produced, and hazardousness of each product. As such, the requirements for the handling, storage, transport, and disposal of Mo-99 production waste differ greatly between NorthStar's method and uranium-based methods.

Uranium Waste Storage

The amount and type of waste created by fission-based Mo-99 production requires a high degree of rigor and expense, regardless of whether HEU or LEU targets are used. The proliferation-sensitive long-lived transuranic waste material generated via U-235 target irradiation is classified as greater than Class C waste, necessitating the most exacting levels of management. In most cases, deep geological disposal of these materials is required, as long-term secure storage is mandatory.[12] Furthermore, at some waste storage facilities, security measures such as metal enclosures built to withstand the impact of a jet liner are in place to ensure the uranium waste is not accessible. The disposal of fission and activation waste must adhere to stringent guidelines as well, due to the high levels of radioactivity and quantities of these materials produced.

Molybdenum Waste Storage

As previously discussed, NorthStar's Mo-99 production process generates significantly lower quantities of radioactive waste; furthermore, this waste is comparatively benign and short-lived. As a result, management of the waste streams generated by NorthStar is straightforward and far less rigorous. All of NorthStar's activation waste products can be safely disposed of in standard Class A radioactive landfills. Importantly, NorthStar's process entirely eliminates any national security risks posed by the handling and long-term storage of uranium waste material.

Conclusion

To date, NorthStar's FDA-approved RadioGenix® System[13] has generated well over 1 million doses of Tc-99m, a critical radioisotope for patients undergoing diagnostic tests across the United States. NorthStar's technology uses stable isotopes of molybdenum (Mo-98 in current production methods) to produce Mo-99 without incurring the hazardous waste associated with traditional Mo-99 production methods that use HEU or LEU. NorthStar's production methods not only eliminate the use and/or creation of long-lived and proliferation-sensitive radioactive materials but also reduce the amount of radioactive waste generated by several orders of magnitude when compared with uranium-based methods. Consequently, Mo-99 sourced from NorthStar is considered an Environmentally Preferable Product (EPP) as defined by the US General Services Administration.[14] From an environmental and human health perspective, NorthStar's innovative Mo-99 production process is decidedly cleaner than current industry standards.

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[11] Reclamation of Mo-99 is pending US Food and Drug Administration (FDA) submittal.

[12] Storage and Disposal of Radioactive Waste. (May 2021). *World Nuclear Association*. Retrieved March 24, 2022 from https://world-nuclear.org
Radioactive Waste. (June 2020). *Nuclear Regulatory Commission*. Retrieved March 24, 2022 from https://www.nrc.gov

[13] The FDA approved NorthStar's New Drug Application (NDA) 202158 in February 2018.

[14] The US General Services Administration website contains the following definition, "'*Environmentally preferable' means products or services that have a lesser or reduced effect on human health and the environment when compared with competing products or services that serve the same purpose.*"