CORAR

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Good morning, Chairman Bowman, Ranking Member Weber, and members of the committee. I am Michael J. Guastella, the Executive Director of the Council of Radionuclides and Radiopharmaceuticals, Inc. (CORAR). CORAR is an association of companies in the United States and Canada that manufacture and distribute radiopharmaceuticals, radioactive sources, and medical isotopes in the United States for therapeutic and diagnostic nuclear medicine and for industrial, environmental, and biomedical research and quality control.

Thank you for the opportunity to provide the committee with the perspective of the medical and industrial isotope industry. Our supply chain issues have been the focus of several government efforts over the last 15 years to address the lack of a reliable and sufficient supply of domestic medical and industrial isotopes and the recent Russian invasion of Ukraine highlights further these issues. The problem is significant, and my member companies are appreciative of the committees' interest in these issues and our suggestion on what needs to be done.

I want to thank you Mr. Chairman and Ranking member Weber for your support and assistance over the last several years. Your committee has recognized the importance of medical and industrial isotopes and you have advocated for federal policies that would ensure that our patients have the isotopes necessary for the diagnosis and treatment of disease. CORAR member companies greatly appreciate your support and your willingness to work with us.

What is Nuclear Medicine?

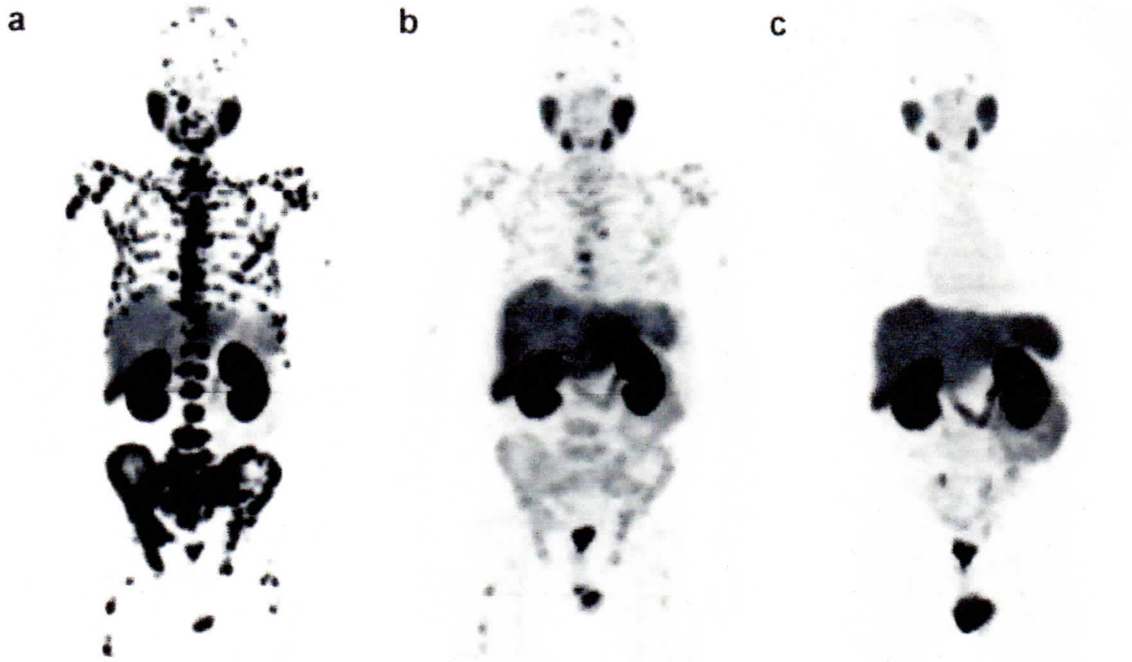
Nuclear medicine involves the injection of radioactive materials (i.e., medical radioactive isotopes, known as medical radioisotopes, and radiopharmaceutical drugs) into a patient's body for diagnostic or therapeutic procedures. These isotopes help provide detailed images of patients' organs, arteries, or certain cells, as well as assessing organ function. Nuclear medicine is integral to the care of patients with cancer, heart disease and brain disorders and offers not only structural images but allows physicians to see how the body is functioning and to measure its chemical and biological processes. To put the use of these isotopes and radiopharmaceuticals into perspective, today we estimate that there are approximately twenty (20) million nuclear medicine procedures performed annually in the United States as reported by the Society of Nuclear Medicine and Molecular Imaging (SNMMI).[1]

An area of rapid advancement in nuclear medicine is often referred to in some cases as Radiopharmaeutical Therapy (RPT). RPT is a novel therapeutic modality for the treatment of cancer, providing several advantages over existing therapeutic approaches. In RPT, radiation is systemically or

[1] Society of Nuclear Medicine and Molecular Imaging, http://www.snmmi.org.

locally delivered using radiopharmaceuticals that either bind preferentially to cancer cells or accumulate by physiological mechanisms.[2]

An example is provided below of the clincal response to Lu-177 PSMA-617 in a metastatic prostate cancer patient who had exhausted all standard treatment options.



Groener, D.; Baumgarten, J.; Haefele, S.; Happel, C.; Klimek, K.; Mader, N.; Nguyen Ngoc, C.; Tselis, N.; Chun, F.K.H.; Grünwald, F.; Sabet, A. Salvage Radioligand Therapy with Repeated Cycles of 177Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer with Diffuse Bone Marrow Involvement. Cancers 2021, 13, 4017. https://doi.org/10.3390/cancers13164017

The FDA approved Lu-177 PSMA-617 (Pluvicto®) for the treatment of advanced prostate cancer in 2022 and ^{177}Lu-DOTATE (Lutathera®) for the treatment of neuroendocrine tumors in 2018. In addition to the approved radiotherapies mentioned, we estimate that there are at least 85 clinical trials running to examine a variety of other RPT's based on medical radioisotopes such as copper-67 (Cu-67), actinium-225 (Ac-225), and lutetium-177 (Lu-177).[3]

In addition, oncology patients are benefiting from the development of Theranostics which integrates imaging and therapy using a radiopharmaceutical to characterize the cancer (diagnostic) and then deliver a precise treatment (radiotherapy). It is envisaged that Theranostics will become the 5th pillar of oncology – the other four pillars being surgery, radiation therapy, interventional oncology, and drugs (including chemotherapy and targeted therapies – biologicals and immunotherapy).[4]

The Problem

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[2] Sgouros, G., Bodei, L., McDevitt, M.R. et al. Radiopharmaceutical therapy in cancer: clinical advances and challenges. Nat Rev Drug Discov 19, 589–608 (2020). https://doi.org/10.1038/s41573-020-0073-9
[3] https://www.clinicaltrials.gov/ct2/results?term=Lu-177+OR+Ac-225+OR+Cu-67&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=4&phase=0&phase=1&phase=2&phase=3&Search=Apply
[4] Theranostics: The Fifth Pillar of Cancer Care, The Royal Australian and New Zealand College of Radiologist, Faculty of Radiation Oncology, Version 1.0 25 May 2021

Now let me update the committee on U.S. isotope supply challenges and opportunities.

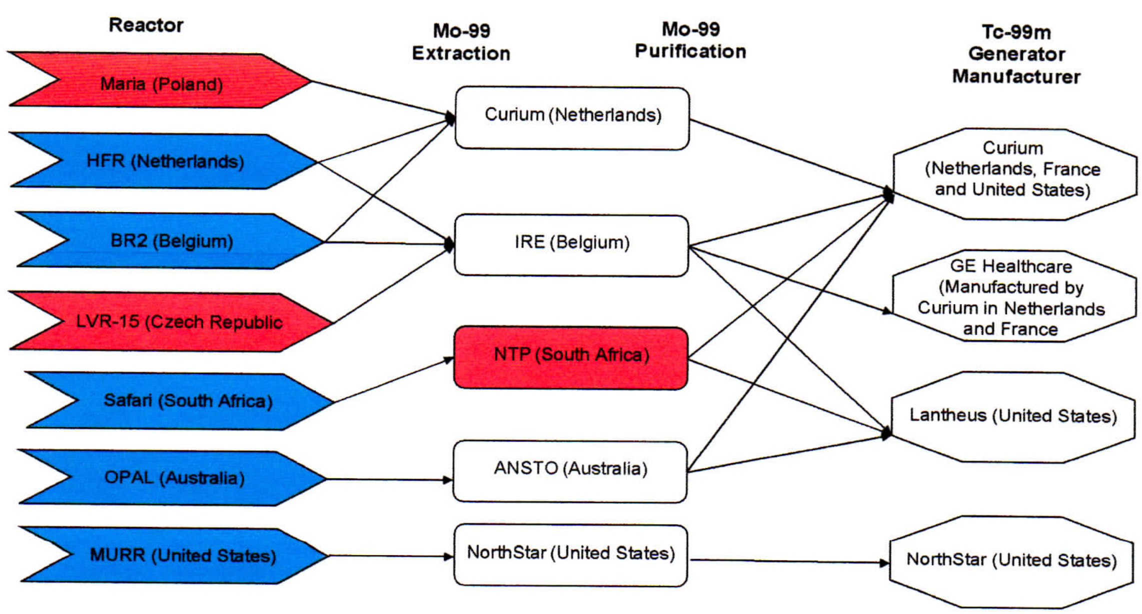
Lack of Domestic Supply

In the mid-1990s, the last U.S. commercially operated research reactor that produced fission based medical isotopes was closed and decommissioned leaving the U.S. without a domestic source of essential medical isotopes. Additionally, the U.S. government closed the stable isotope production facility in Oak Ridge National Laboratory in the late 1990s, leaving the U.S. largely dependent on foreign sources of such isotopes which are often used as target material for the production of radioisotopes. Few in the U.S. government focused on the loss of domestic production until 9-11 as the supply of many radioisotopes coming from abroad was temporarily cut-off due to the cessation of commercial flights into the U.S., echoed years later as commercial flights into the U.S. were halted in March 2020 at the start of the COVID-19 pandemic.

Dependence on Foreign Sources for Medical and Industrial Applications

There are over 40 isotopes that we identify in the list attached (Exhibit 1) to my testimony that are important isotopes for medical or industrial purposes and that the U.S. relies largely on Russian companies to supply as either raw materials or the isotopes themselves. Specifically, the Russian state corporation Rosatom (and affiliates) are critical suppliers of isotopes used in the U.S. for the manufacture of radiopharmaceutical drugs for U.S. patient care and industrial purposes. For example, to serve U.S. patients, a significant portion of the molybdenum-99 (Mo-99) supply chain relies on uranium-235 (U-235) sourced from Rosatom for either research reactor fuel or U-235 used for target fabrication in the Mo-99 production process.[5]

The majority of Mo-99 production is based overseas and handled by a series of long-established research reactors and processors in Europe, South Africa, and Australia. Six multi-purpose research reactors (excluding MURR[6]) and four Mo-99 processors (excluding NorthStar) supply approximately 95% of Mo-99 for patients in the United States[7]. The research reactors and processor filled in red below indicate points in the Mo-99 supply chain that we understand rely on Russian raw materials.



[5] National Academies of Sciences, Engineering, and Medicine Report on Molybdenum-99 for Medical Imaging; https://www.nap.edu/catalog/23563/molybdenum-99-for-medical-imaging
[6] University of Missouri Research Reactor
[7] https://www.nationalacademies.org/news/2016/09/new-report-examines-molybdenum-99-production-and-use

Mo-99 is necessary to produce technetium-99m (Tc-99m). Tc-99m, the most common medical isotope used in nuclear medicine procedures in the United States, is derived from molybdenum-99 (Mo-99), which has a half-life of 66 hours. Tc-99m based radiopharmaceuticals are used by nuclear medicine physicians and radiologists to diagnose diseases, such as heart disease and many forms of cancer, and to inform treatment plans. Of the 20 million nuclear medicine procedures performed annually in the United States, an estimated 15 million of these procedures utilize Tc-99m based radiopharmaceuticals.[8] For example, over 1 million doses of Tc-99m sestamibi, needed to diagnose coronary artery disease, were dispensed to Medicare beneficiaries in CY 2017.[9]

Enriched ytterbium-176 (Yb-176) is used for the production of Lu-177 and enriched zinc-68 (Zn-68) is used for the production of Cu-67 for therapeutic application. Both Lu-177 and Cu-67 are being used to develop the next generation of targeted radiopharmaceutical therapies that will enhance the treatment of disease, especially cancer, as described in the examples above. However, the enriched stable isotopes needed to commercialize these targeted radiopharmaceutical therapies are either sole sourced or predominantly sourced from Russia.

There are numerous other medical isotopes used in the diagnosis and treatment of various diseases that are sole sourced or predominantly sourced from overseas, including Russia. For example:

- Palladium-103 (Pd-103) is primarily used in early-stage prostate cancer treatment and a primary source of Pd-103 is Russia. Restrictions on access to Pd-103 will impact the ability of oncologists to treat patients.
- Xenon-133 (Xe-133) is produced overseas and shipped to the U.S. for the diagnosis of lung disease.
- Much of the iodine-131 (I-131) used to treat thyroid disease in the U.S. is sourced from overseas.
- Gadolinium-153 (Gd-153), and cobalt-57 (Co-57) are isotopes used in sealed sources, calibrating devices required for nuclear medicine cameras in order for medical isotopes to be measured accurately. Due to the half-life of these isotopes, hospitals need to replace sealed sources frequently and Russia is the sole source provider in the world of Gd-153 and the majority supplier of Co-57.

Please note that Exhibit 1 includes a number of isotopes produced through a supply chain heavily reliant on Russian production[10].

Industrial Applications

CORAR members supply industrial isotopes as well as medical isotopes and foreign supplied radioisotopes also play a crucial role in supporting U.S. oil and gas production – interruption of supply would quickly result in shortages and cause significant revenue losses to American energy sector producers.

- Radioisotopes such as iridium-192 (Ir-192) and selenium-75 (Se-75) assure operational safety in refineries and pipelines to test for corrosion, leaks, and cracks. Also, Ir-192, has medical applications for the treatment of cancer. Ir-192 is procured from two powerful high-flux reactors in Russia.
- Foreign produced americium-241 (Am-241) is used in the manufacture of smoke detectors. Russia is the largest source for Am-241with very limited amounts produced domestically since the late 1970s.

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[8] US Department of Energy, https://www.energy.gov/nnsa/nnsa-s-molybdenum-99-program-establishing-reliable-supply-mo-99-produced-without-highly
[9] *Center for Medicare and Medicaid Claims data*
[10] Information available through Russian selling entities public websites

- Russian reactors also provide barium-133 (Ba-133), used in extraction and refining to separate oil, water, and gas. Ba-132 is an enriched stable isotope and is only available from Russia.

The Solution

CORAR members have been working for numerous years to develop a sufficient and reliable domestic supply of essential isotopes.

The U.S. Government recognized that essential medical procedures were postponed due to flight cessations post 9-11 with serious potential health consequences. Following 9-11, the American Medical Isotope Production Act of 2012 (AMIPA) was enacted. AMIPA has focused the U.S. Department of Energy (DOE) on the conversion from the use of highly enriched uranium (HEU) to low enriched uranium (LEU), and assisting in the development of a domestic medical isotope industry from non-HEU sources, which led to a close relationship between several CORAR member companies and the DOE in the government effort to aid in the development of a domestic supply of medical isotopes and to meet the needs of our researchers and drug developers for the next generation of medical isotopes. These public-private relationships include several awards of Cooperative Agreements with Government cost-share by the National Nuclear Security Administration (NNSA).

Considering the current need to enhance domestic production of other medical and industrial isotopes, the DOE leadership has been a supportive and a constructive partner through efforts of the Office of Science, Isotope Program (DOE Isotope Program). Unfortunately, current U.S. production of enriched stable isotopes and radioactive isotopes is not sufficient to meet domestic needs and highlights the U.S. reliance on Russia for a number of these isotopes.

To paraphrase the committee's question, "what foundational research would be relevant for isotope production and supply and what policies should the Congress and the Administration consider going forward?"

CORAR members believe that there are a few essential elements that would move us closer to a reliable domestic supply of isotopes and to reduce our dependence on Russia and other foreign suppliers. As a brief overview these elements are:

- Fully fund the proposed U.S. Stable Isotope Production and Research Center (SIPRC), the Radioisotope Processing Facility (RPF), and the Clinical Alpha Radionuclide Producer (CARP) projects and accelerate the appropriations for these three facilities.
- Retain the Committee's COMPETES provision establishing an advisory Committee for the DOE Isotope Program. CORAR is appreciative of the committee for already addressing this.
- When commercial production is adequate to satisfy U.S. demand, retain the language to continue to ensure that the DOE Isotope Program will preserve and appropriately allocate its resources by not competing with commercial isotope producers.
- When the DOE Isotope Program provides commercial isotopes to the domestic market, when commercial production is non-existent or insufficient to meet U.S. demand, ensure that the DOE Isotope Program is required to continue to satisfy the principles of full cost recovery for commercial isotopes.
- To increase flexibility for the DOE Isotope Program to identify opportunities to expedite domestic production of important medical and industrial isotopes currently sourced from Russia, include language that would allow the DOE Isotope Program to identify additional opportunities for Federal investment, including through potential public-private partnerships, as appropriate.
- Continue to support the DOE Isotope Program Research and Graduate training programs, through appropriated government grants and other government educational programs, to help fill the pipeline with knowledgeable and trained individuals in research, development, and commercialization to meet the current and future needs of the medical and industrial isotope industries.

- Finally, in light of the Russian invasion in Ukraine, request that the administration institute a White House level supply coordinating effort to ensure that there is an interagency coordination to bring about an enhanced, reliable domestic supply of these essential medical and industrial isotopes.

CORAR supports your committee's work contained in Section 311 of the America Creating Opportunities for Manufacturing, Pre-Eminence in Technology, and Economic Strength Act of 2022 (America COMPETES Act of 2022). Provisions of the COMPETES Act will improve the mission of the DOE Isotope Program including the establishment of a new Advisory Committee to provide expert advice to help define the nation's isotope needs and help identify opportunities to increase domestic isotope production. Also, CORAR acknowledges that the authorization of appropriations for the DOE Isotope Program includes escalating authorization through 2026 that should be used to support the new DOE SIPRC, RPF, and CARP projects. However, this level of funding supports project timelines that would have the SIPRC and RPF facilities completed in the early 2030s. CORAR encourages the committee to consider accelerating the authorization of appropriation rate for the DOE Isotope Program that would allow these projects to be completed on an accelerated timeline (ideally over the next four to five years).

CORAR wants to emphasize that the DOE Isotope Program plays a critical role in producing and distributing isotopes needed in scientific research and for initial medical clinical development, as there are not sufficient commercial incentives for production of such isotopes. However, CORAR and its member companies believe that where commercially feasible, medical, and industrial isotopes should be produced by the private sector. Several companies are currently developing reactor and non-reactor capabilities to help scale up domestic production of essential medical radioisotopes such as Mo-99, I-131, and Xe-133. In addition, private sector projects are underway to increase domestic supply of actinium-225 (Ac-225), Lu-177, and Cu-67 for targeted radiotherapies. CORAR believes that when diverse commercial production sources can meet U.S. demand, the DOE Isotope Program should exit the market for such isotopes, consistent with the mission of the DOE Isotope Program.

CORAR is aware of additional opportunities being explored by industry stakeholders in North America to augment the domestic supply of essential medical and industrial isotopes such as the use of current nuclear power reactors as neutron sources for isotope production. The Canada Deuterium Uranium (CANDU) commercial power reactors are currently being used for certain medical isotope production in Canada. For example, BWXT Medical has publicly disclosed that they will be using the Ontario Power Generation (OPG) Darlington Nuclear Generating Station to produce the medical isotope Mo-99.[11] Also, ITM Medical Isotopes GmbH has publicly stated that they are using Bruce Power Reactors to produce the therapeutic radioisotope Lu-177[12]. Both OPG and Bruce Power reactors utilize CANDU design technology which provides unique capabilities to irradiate targets for isotope production that commercial reactors in the U.S. don't currently possess.

However, these commercial activities may not be adequate to address the immediate risks to the radioactive and stable isotope supply chains posed by the Russian invasion of Ukraine and potential sanctions being considered on Russian suppliers by the U.S. and its allies.

Any U.S. Government sanctions on Rosatom, or its subsidiaries (and affiliates), will significantly disrupt the supply of many of our essential medical and industrial isotopes. For a number of those isotopes where commercial domestic production has not been established or is not sufficient to meet U.S. medical and industrial needs, the DOE Isotope Program can potentially provide a bridge to ensure domestic supply. To better prepare the DOE Isotope program to meet the isotope needs of U.S. health care and industry, CORAR supports accelerating the completion timelines of both the RPF, SIPRC, and CARP projects mentioned above.

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[11] https://www.bwxt.com/bwxt-medical/news/2020/09/24/OPG-and-BWXT-Make-Significant-Progress-in-Production-of-Life-Saving-Medical-Isotope-at-Darlington-Nuclear-Generating-Station

[12] https://itm-radiopharma.com/news/press-releases/press-releases-detail/bruce-power-and-isogen-set-first-critical-milestone-for-exclusive-irradiation-service-provided-to-itm-for-its-production-of-no-carrier-added-lutetium-177-201

Accordingly, CORAR wants to thank the committee for the opportunity to highlight these issues and commends the committee for your work to date and encourages the Committee to continue to support the DOE's research, development, and production activities.

I thank you for the opportunity to testify today, and I would be pleased to answer any questions.

Respectfully Submitted,

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Exhibit 1

Medical Isotopes	Stable	Isotope Details
Actinium-225 (Ac-225)		Cancer treatment
Cobalt-56 (Co-56)		Calibration standard
Cobalt-57 (Co-57)		Medical Imaging
Cobalt-60 (Co-60)		Cancer treatment and medical product sterilization
Cobalt-60 (Co-60)		Cancer treatment and medical product sterilization
Cesium-137 (Cs-137)		Cancer treatment, Thickness gauging, flow dectection
Cadmium-112 (Cd-112)	Stable	Target material for In-111 production
Erbium-168 (Er-168)	Stable	Production of Er-169 used for radiation synovectomy
Gadolinium-153 (Gd-153)		*Medical Imaging Quality Control Source (SPECT)*
Germanium-68 (Ge-68)		PET imaging, cancer treatments
Iodine-131 (I-131)		Therapy for hyperthyroidism and thyroid cancer
Manganese-54 (Mn-54)		Calibration standard
Nickel-64 (Ni-64)	Stable	Target material for Copper-64 production which is used for cancer diagnosis
Palladium-103 (Pd-103)		Treatment for Prostrate Cancer
Rubidium-85 (Rb-85)		*Cancer treatment, target for Sr-82*
Ruthenium-106 (Ru-106)		*Brachytherapy for treatment for ocular melanoma*
Thallium-203 (Tl-203)	Stable	Target material for Thallium-201 production used in heart imaging.
Tin-112 (Sn-112)	Stable	Cancer diagnosis of brain , liver kidney tumors
Molybdenum-98 (Mo-98)	*Stable*	*Target material for Mo-99 production*
Molybdenum-100 (Mo-100)	*Stable*	*Target material for Mo-99 production*
Rhenium-185 (Re-185)	Stable	Production of Re-186 for cancer treatment
Samarium-152 (Sm-152)	Stable	Production of Sm-153 used in cancer treatment
Strontium-90 (Sr-90)		Cancer treatment
Uranium-235 (U-235)		Research reactor fuel and irradiation targets for Mo-99 production
Ytterbium-176 (Yb-176)	Stable	Production of non-carrier added Lutetium-177 for cancer treatment
Yttrium-88 (Y-88)		Medical diagnostics, LED's
Xenon-124 (Xe-124)	Stable	Production of Iodine-123 and Iodine-125 radioisotopes for imaging and cancer treatment
Xenon-133 (Xe-133)		Production of Xe-133 for evaluation of pulmonary function and lung imaging
Zinc-67 (Zn-67)	Stable	Target material for Ga-67 and Cu-67 production
Zinc-68 (Zn-68)	Stable	Target material for Ga-67 and Cu-67 production

Please note: highlighted italic isotopes are single sourced from Russia.

Industrial Isotopes	Stable	Isotope Details
Americium-241 (Am-241)		Oil/Gas exploration
Barium-133 (Ba-133)		Oil/Gas exploration
Barium-132 (Ba-132)	*Stable*	*Target Material to US DOE for Ba-133 production*
Cadmium-109 (Cd-109)		*Metal analysis/lead in paint*
Cerium-139 (Ce-139)		Used in Metal production
Helium-3 (H-3)		*Oceanic transient tracer, fuel for nuclear fusion reactions*
Iridium-192 (Ir-192) Disks		Industrial Radiography
Iridium-192 (Ir-192) Disks		Industrial Radiography
Krypton-85 (Kr-85)		*Radioactive tracer, Arc discharge lamps, exit signs*
Polonium-210 (Po-210)		Static remover
Selenium-75 (Se-75)		Industrial Radiography
Tellurium-122 (Te-122)	Stable	Target material for I-122 gamma imaging
Xenon-124 (Xe-124)	Stable	Instrumentation for radiation detection

Please note: highlighted italic isotopes are single sourced from Russia.