PRB 09-04E

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THE MEDICAL ISOTOPE SHORTAGE: CAUSE, EFFECTS AND OPTIONS

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Revised 1 September 2009

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CE DOCUMENT EST AUSSI PUBLIÉ EN FRANÇAIS

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THE NATIONAL RESEARCH UNIVERSAL REACTOR SHUTDOWN

The National Research Universal (NRU) reactor at Atomic Energy of Canada Limited's (AECL) Chalk River laboratories in eastern Ontario shut down automatically on 14 May 2009 due to a power outage. A heavy-water leak at 5 kilograms per hour was subsequently discovered – a result of corrosion on the outside base of one of the reactor's vessels – which led AECL to extend the shutdown until the problem could be addressed. According to AECL, the heavy water was captured and stored in drums, and posed no health or safety risk to the public or the environment.(1) In addition, evaporation resulted in some tritium air emissions at safe levels, "well below CNSC [Canadian Nuclear Safety Commission] regulatory limits."(2)

AECL's preliminary assessment of the extent of corrosion concluded that the available nuclear repair technologies could not provide an immediate or simple solution. Inspection and repair activities are particularly challenging due to the limited access to the corroded surface, which must also be handled remotely due to high radiation fields.(3) By 8 July 2009, the leak site had been "thoroughly analysed," according to AECL, revealing "thinning of the wall at the leak site, and [identifying] a total of nine areas of interest."(4) The same day, Hugh MacDiarmid, President of AECL, announced that the reactor "will not return to service before late 2009."(5)

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(1) Bill Pilkington, Senior Vice-President and Chief Nuclear Officer, Atomic Energy of Canada Limited, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 24, 4 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3959754&Language=E&Mode=1&Parl=40&Ses=2.

(2) Michael Binder, President, Canadian Nuclear Safety Commission, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 24, 4 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3959754&Language=E&Mode=1&Parl=40&Ses=2.

(3) Pilkington (2009).

(4) AECL, "NRU Status Report #11 – Most current assessment of Chalk River NRU reactor allows for revised guidance on timeline for return to service," 8 July 2009, http://www.aecl.ca/NewsRoom/Community_ Bulletins/090708.htm.

(5) CBC News, "Chalk River Reactor Idled to Late 2009 or Longer," 8 July 2009, http://www.cbc.ca/canada/story/ 2009/07/08/chalk-river-nuclear-reactor008.html.

The NRU reactor has contributed to "50 years of Canadian leadership in nuclear science and technology," according to Dominic Ryan, President of the Canadian Institute for Neutron Scattering.(6) The reactor has three purposes:

1. Production of industrial and medical radioisotopes (largest global supply), used to diagnose and treat a number of diseases including cancer and heart disease.

2. Neutron beam research, which examines a wide range of materials, leading to advances in medical, scientific and industrial fields. (NRU is one of the world's few reactors available for commercial use, and receives over 200 professors, students and industrial researchers annually.)

3. Engineering research and development support for CANDU(7) power reactors.(8)

The NRU reactor is 50 years old and is licensed by the CNSC to operate until October 2011.(9) Reactors can be refurbished and maintained with no set lifetime;(10) however, their cost of servicing and vulnerability rise with age.(11) AECL is working with the CNSC to extend the NRU reactor's licence beyond 2011.(12)

THE GLOBAL SHORTAGE OF MEDICAL ISOTOPES

The shutdown of the NRU reactor has triggered a global shortage in nuclear medical isotopes (mainly molybdenum-99 or Mo-99), which has made the situation particularly problematic from a medical standpoint. Technetium-99m (Tc-99m), which is derived from Mo-99, is used for the vast majority of nuclear medical procedures – primarily cardiac imaging,

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(6) Dominic Ryan, President, Canadian Institute for Neutron Scattering, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 27, 16 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3999694&Language=E&Mode=1&Parl=40&Ses=2.

(7) CANDU (Canada Deuterium Uranium) reactors are Canadian-designed nuclear power reactors that are fuelled by natural uranium and use heavy water as a moderator and coolant.

(8) AECL, "Nuclear Science – National Research Universal Profile," n.d., http://www.aecl.ca/Science/CRL/NRU.htm.

(9) Serge Dupont, Associate Deputy Minister, Natural Resources Canada, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3946111&Language=E&Mode=1&Parl=40&Ses=2.

(10) Binder (2009).

(11) Dupont (2009).

(12) Hugh MacDiarmid, President and Chief Executive Officer, Atomic Energy of Canada Limited, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 24, 4 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3959754&Language=E&Mode=1&Parl=40&Ses=2.

bone scans to detect cancers, and general organ scans.(13) Introducing radioisotopes into the body (as opposed to external imaging) allows an earlier and more complete diagnosis by tracking the location and movement of the isotopes into diseased tissues. In the case of cancer, radioisotopes can also be used for treatment by emitting energy that kills diseased cells.(14)

Table 1 – NRU Isotope Production for Diagnostic and Therapeutic Use

Medical Isotope	Diagnostic and/or Therapeutic Use
Molybdenum-99	Medical diagnosis (imaging) of the brain, heart, liver, kidney, lungs, thyroid, spleen and bone marrow
Iodine-131	Therapy, imaging and diagnosis (mostly for thyroid cancer)
Iodine-125	In-vitro diagnostics, bone densitometry devices, protein iodination, therapeutic seed (implants often used to treat prostate cancer)
Xenon-133	Lung scanning
High Specific Activity (SA) Cobalt-60	Cancer treatment
Carbon-14	Radio-tracing in biological compounds
Iridium-192	Cancer therapy and radiography

Source: AECL, http://www.aecl.ca/Science/CRL/NRU/Isotopes.htm.

The current shortage limits diagnostic testing (as opposed to therapy), which particularly affects cancer patients, where early and reliable diagnosis is critical.(15) It is estimated that an overall 30% of the global supply is lacking due to the NRU shutdown, with variations across countries and regions. For example, North America, which depends largely on Canada's Mo-99 supply, is experiencing higher shortages than Europe, where other suppliers are more prevalent.(16) The shortage also varies across Canada, since isotope supplies are managed

(13) Meena Ballantyne, Assistant Deputy Minister, Health Products and Food Branch, Health Canada, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3946111&Language=E&Mode=1&Parl=40&Ses=2.

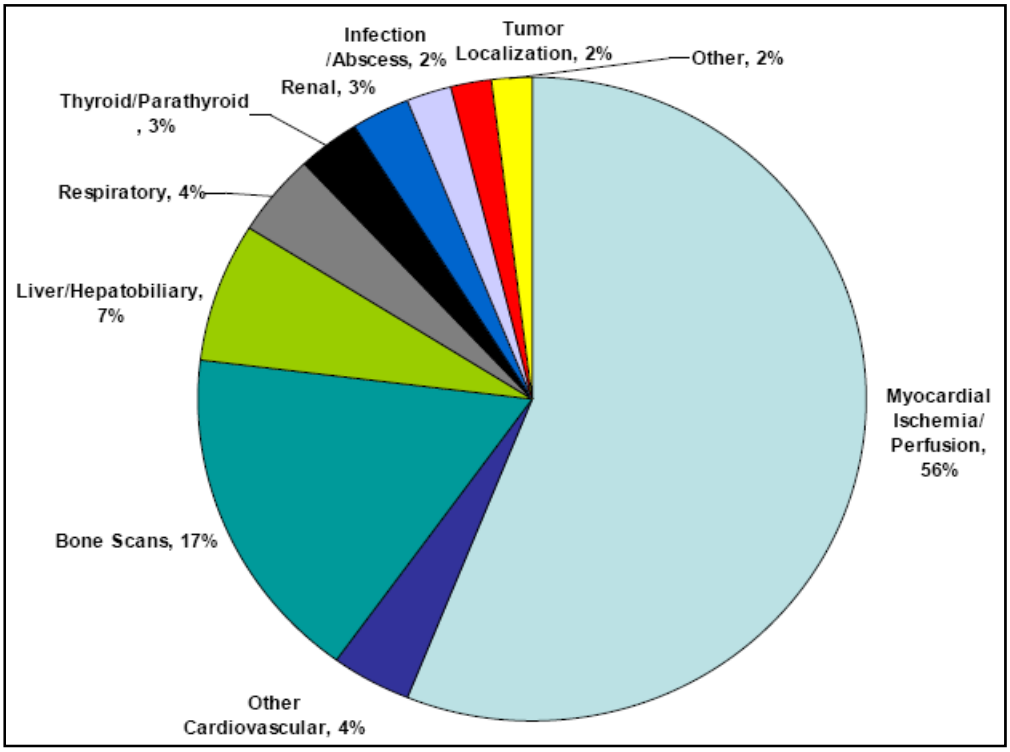
(14) Medical Isotopes, *Frequently Asked Questions*, 12 March 2008, http://www.medicalisotopes.org/faq.html.

(15) Karen Gulenchyn, Medical Chief, Department of Nuclear Medicine, Hamilton Health Sciences and St. Joseph's Healthcare Hamilton, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 25, 9 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3971702&Language=E&Mode=1&Parl=40&Ses=2.

(16) Steve West, President, MDS Nordion, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 26, 11 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocID=3985256&Language=E&Mode=1&Parl=40&Ses=2.

by the provinces and territories.(17) The cost of a millicurie (a unit of measurement) of Tc-99m has risen from $0.19 to $0.54, which, for example, represents $5 million in added expenditures for Ontario.(18)

Figure 1 – Composition of Nuclear Medical Procedures Where Technetium-99m is Predominant, 2006



Source: Natural Resources Canada, Document presented to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009.

The global demand for Mo-99/Tc-99m is approximately 40 million doses per year, 30% to 40% of which is normally supplied by the NRU reactor.(19) According to AECL, NRU's isotope supplies help more than 76,000 people daily, in over 80 countries.(20) However, even with the NRU reactor in operation, the production of medical isotopes needs to increase to satisfy

(17) Jean-Luc Urbain, President, Canadian Association of Nuclear Medicine, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 25, 9 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3971702&Language=E&Mode=1&Parl=40&Ses=2.

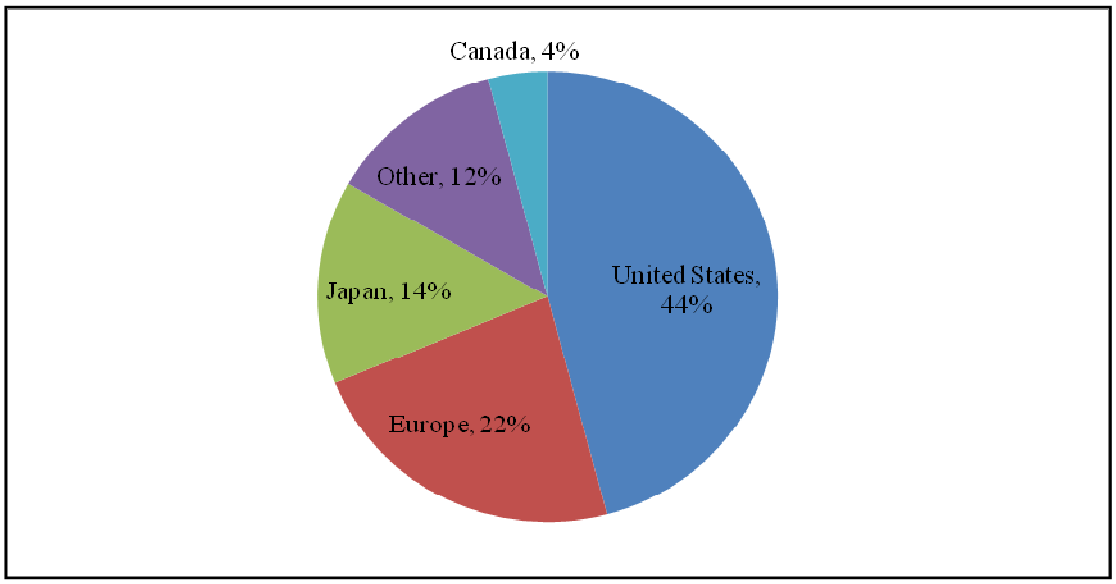
(18) François Lamoureux, President, Quebec Association of Nuclear Medicine Specialists, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 25, 9 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3971702&Language=E&Mode=1&Parl=40&Ses=2.

(19) Dupont (2009).

(20) AECL, "Nuclear Science – Medical Isotopes," n.d., http://www.aecl.ca/Science/CRL/NRU/Isotopes.htm.

projected future demands. Tc-99m is in rising demand worldwide due to the aging populations of Europe and North America, and the growing use of the isotope in emerging countries. Furthermore, as Jean Koclas, Nuclear Engineering Professor at the École polytechnique Montréal, explains: "Technetium 99 has the immense advantage of being a non-invasive technique … [with] an ever-increasing number of applications" – which further augments the global demand for the isotope.(21)

Figure 2 – Approximate Global Demand for Molybdenum-99/Technetium-99m



Note: Totals may not sum, due to rounding.

Source: Serge Dupont, Associate Deputy Minister, Natural Resources Canada, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009.

Five government-owned reactors supply about 95% of the global demand for Mo-99: the NRU reactor (the largest), the Petten reactor in the Netherlands, the BR2 reactor in Belgium, the OSIRIS reactor in France, and the SAFARI reactor in South Africa. Several other smaller reactors provide local and regional supplies with no major influence on the global market.(22) Since there are no manufacturers of Tc-99m in Canada, Mo-99 is exported to the United States and Japan where Tc-99m generators can be produced. Exports to the United States are partly reimported as Tc-99m generators for medical use in Canada.(23)

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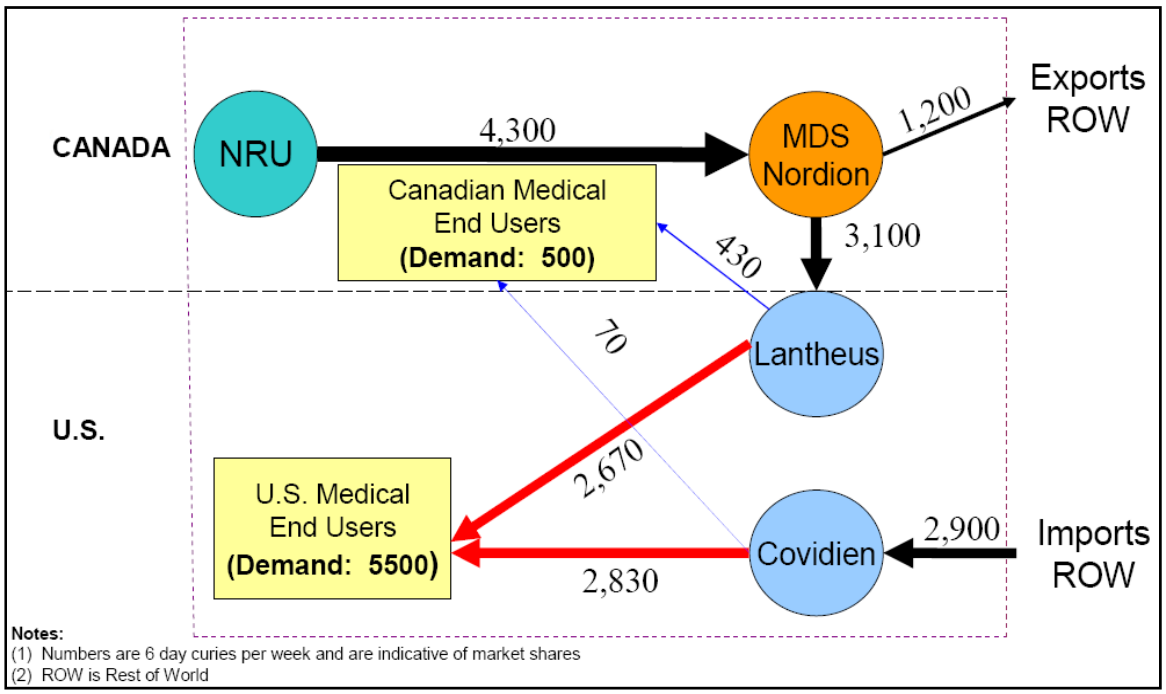
(21) Jean Koclas, Professor, Nuclear Engineering Institute, Engineering Physics Department, École polytechnique Montréal, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 28, 18 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=4009510&Language=E&Mode=1&Parl=40&Ses=2.

(22) Dupont (2009).

(23) Ibid.

Figure 3 – Supply Chain of Molybdenum-99/Technetium-99m Between Canada and the United States



Source: Natural Resources Canada, Document presented to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009.

Throughout the supply chain, specific steps must be followed in face of a number of technical and regulatory challenges, adding to the complexity of responding to the global isotope shortage. After being processed at the NRU reactor, Mo-99, which has a half-life of about 66 hours, is shipped to MDS Nordion in Kanata, near Ottawa, to be extracted and purified. It must then be exported to the appropriate Tc-99m manufacturer before the radioactive material decays and is no longer useful. The Tc-99m generators are produced with a useful life of 10 to 14 days and must be shipped to hospitals and radio pharmacies within an appropriate timeframe. Tc-99m itself has a half-life of only six hours, and therefore cannot be stockpiled. All stages of the supply chain are also subject to nuclear and medical health and safety regulations.[24]

Since all reactors must undergo systematic outages for maintenance, there is a critical need for harmonization between isotope suppliers to maintain the global supply balance. The unexpected outage of the NRU reactor has thus created a serious imbalance within a complex supply chain, which undermines current medical procedures and emphasizes the incentive for additional technologies to secure or substitute the future supply of medical isotopes.[25]

(24) Ibid.

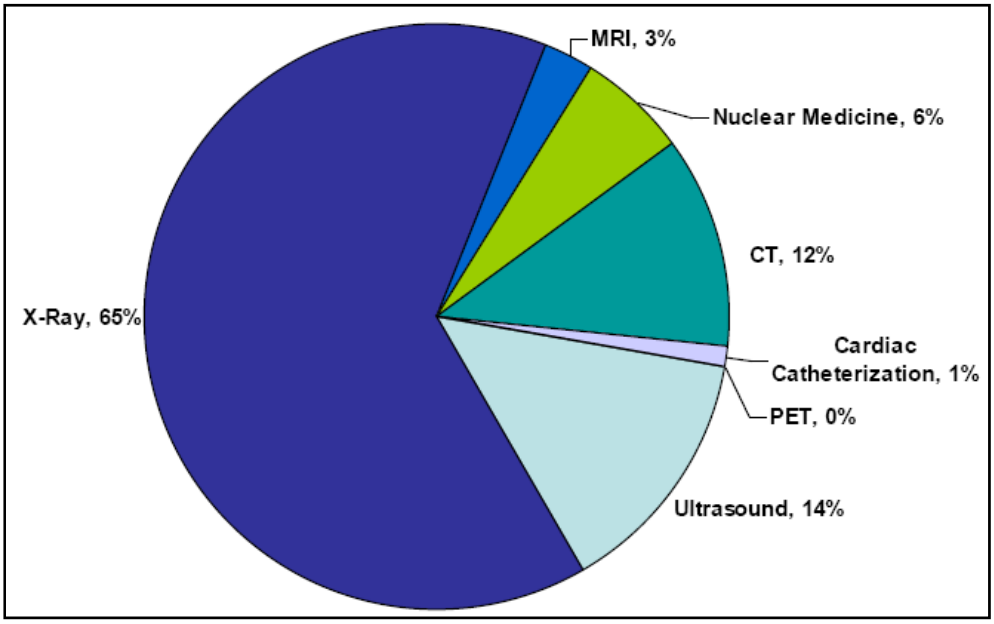
(25) Ibid.

OPTIONS

A. Alternative Medical Procedures

Nuclear medicine is one of many imaging technologies, and Tc-99m is not the only isotope used for diagnosing cancer – although it typically accounts for 80% of nuclear medical procedures. Alternatives to Tc-99m include thallium-201 for cardiac imaging, 18-F fluoride (using positron emission tomography, PET) for bone scanning, iodine-123 for kidney imaging, gallium-67 for the detection of Hodgkin's disease and lymphomas, PET scanning for other cancers and some small heart conditions, as well as X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans and ultrasounds.(26)

Figure 4 – Medical Imaging Procedures in Ontario Hospitals, 2007



Note: Totals may not sum, due to rounding.

Source: Natural Resources Canada, Document presented to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009.

The medical community has used some of these alternative procedures as a short-term contingency response to the shutdown of the NRU reactor. However, such alternatives can replace the role of Tc-99m only temporarily, since they are often less effective, available or reliable.(27) For example, CT and MRI scans have limited availability, and echocardiography (a potential alternative for cardiac function tests) may not be suitable for 15% to 20% of patients.(28)

(26) Ballantyne (2009).

(27) Ibid.

(28) Gulenchyn (2009).

According to the Canadian Agency for Drugs and Technologies in Health, "the necessary infrastructure is not currently sufficient for PET to replace the work of Tc-99m isotopes for heart ailments, and cancer diagnosis and staging."[29] There were 28 centres performing publicly funded scans in seven Canadian provinces as of July 2009,[30] with the greatest access in Quebec.[31] Jean-Luc Urbain, President of the Canadian Association of Nuclear Medicine, says that the technology is more widely available in Australia, China, Europe, India, Kuwait, Singapore, South America, and the United States.[32] However, even if PET scanning were to become used more extensively in Canada, it could not replace Tc-99m for paediatric bone scanning for cancers due to the procedure's intense level of radiation.[33] It is also a more expensive technology. According to Karen Gulenchyn, Medical Chief at the Department of Nuclear Medicine at Hamilton Health Sciences and St. Joseph's Healthcare Hamilton, a dose of fluorodeoxyglucose would cost at best $250 to $300, as opposed to $15 to $20 for a Tc-99m-based product.[34]

B. Alternative Canadian Suppliers

There is potential for new suppliers of Mo-99 or alternative products in Canada. However, most new supply options are not suitable as a short-term solution. New suppliers must meet a number of criteria, including:

- technical and business feasibility to expand to commercial scale;
- ability to provide a solution within a reasonable timeframe;
- ability to work within an international supply chain; and
- capacity to meet regulatory requirements, including health, safety and waste management provisions.[35]

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(29) Canadian Agency for Drugs and Technologies in Health, "Future Alternatives to Molybdenum-99 (Mo-99) Production for Medical Imaging," *Health Technology Update*, Issue 11, August 2009, http://www.cadth.ca/index.php/en/hta/reports-publications/health-technology-update/ht-update-11/future-alternatives.

(30) Information on the status of publicly funded Canadian PET scans is found in Canadian Agency for Drugs and Technologies in Health (August 2009), Table 2, Location of Publicly Funded PET Scanners and Cyclotrons in Canada (2009), http://www.cadth.ca/media/healthupdate/Issue11/table2_e.pdf.

(31) Canadian Agency for Drugs and Technologies in Health (August 2009).

(32) Urbain (2009).

(33) Ballantyne (2009).

(34) Gulenchyn (2009).

(35) Dupont (2009).

1. The MAPLE Reactors

The MAPLE (Multipurpose Applied Physics Lattice Experiment) reactors 1 and 2 at AECL's Chalk River laboratories were designed and built exclusively for the production of medical isotopes. They were originally meant to replace the aging NRU reactor, but were never commissioned due to a technical discrepancy. "[T]he actual behaviour of the reactor did not mirror the modelled behaviour of the reactor," which reduces its safety provisions below what is acceptable, according to AECL.(36) To restart the reactors, the discrepancy must be explained "to the satisfaction of AECL … [and] the CNSC."(37) The total cost of the discontinued MAPLE project was approximately $250 million, according to Hugh MacDiarmid.(38)

The feasibility of restarting the project is controversial. Steve West, President of MDS Nordion, quoted a report by the National Academy of Sciences, stating that AECL could contract with another organization to provide the necessary technical expertise or resources to repair the MAPLE reactors. The report's authoring committee "assumes that the worst-case scenario for fixing the MAPLE reactors involves the replacement of the reactor cores," which would likely cost less than building a new reactor.(39) John Waddington, a nuclear safety consultant, confirms that the reactors could be started in principle, but would require "much human and financial effort."(40) According to Hugh MacDiarmid, the MAPLE reactors are not a viable short-term option since it would take "many years and many hundreds of millions of dollars before [they] would be licensable and could be put into service."(41)

2. The McMaster Nuclear Reactor

The McMaster nuclear reactor in Hamilton, Ontario, is a 5-megawatt materials test reactor (MTR). The university has proposed to produce about 20% of North America's Mo-99 demand in the medium term – a supply about four times Canadian demand. The reactor is licensed until 2014, and is currently operating at 3 megawatts, 16 hours a day, five days a week. To produce the proposed volume of isotopes, the McMaster reactor would need to operate

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(36) MacDiarmid (2009).

(37) John Waddington, Nuclear Safety Consultant, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 26, 11 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3985256&Language=E&Mode=1&Parl=40&Ses=2.

(38) MacDiarmid (2009).

(39) West (2009).

(40) Waddington (2009).

(41) MacDiarmid (2009).

24 hours a day, seven days a week. AECL has also pointed out logistical issues associated with transporting certain materials around the Greater Toronto and Hamilton Area.(42)

AECL supports the proposal "to the extent it is possible"; however, the McMaster option is not viable as a short-term solution.(43)

3. The Canadian Neutron Centre

The Canadian Neutron Centre is a proposed new research reactor to replace the aging NRU. It is planned to perform multi-purpose research, and could produce Mo-99 upon conception.(44) According to Dominic Ryan, an estimate that was presented in the Senate in early 2008 put the cost of a fully qualified replacement for the NRU at about $800 million. However, he indicated that this is only a rough estimate. "[A] proper engineering costing design" is required to determine a precise cost.(45)

4. Other Production Methods

The TRIUMF group at the University of British Columbia has proposed an alternative method of producing Mo-99, through an accelerator-based process using photo-fission of U230A (a kind of uranium). The development of this concept requires time and testing, and cannot be considered as a short-term solution. The technology would cost about $50 million.(46)

In addition, the National Research Council has proposed producing Mo-99 by removing a neutron from Mo-100. Similarly, Advanced Applied Physics Solutions (part of the TRIUMF group) has proposed producing Mo-99 by adding a neutron to Mo-98, which is already done around the world, according to TRIUMF's director Nigel Lockyer.(47)

C. Alternative Global Suppliers

The other four major reactors (Belgium's BR2, France's OSIRIS, the Netherlands' Petten, and South Africa's SAFARI) may be able to supplement the current isotope

(42) MacDiarmid (2009).

(43) Dupont (2009).

(44) Ibid.

(45) Ryan (2009).

(46) Nigel Lockyer, Director of TRIUMF, Presentation to the House of Commons Standing Committee on Natural Resources, Meeting 27, 16 June 2009, http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=3999694&Language=E&Mode=1&Parl=40&Ses=2.

(47) Ibid.

shortage in the short term.(48) However, the four reactors are of similar vintage to the NRU and the sustainability of their isotope production is uncertain. They must also undergo their scheduled maintenance. The Petten reactor, for example, which is the second largest after the NRU, plans a five- to six-month shutdown in early 2010 to repair a water leak.(49) Other options include:

- ***Australia:*** The OPAL reactor has already been commissioned to produce and export Mo-99, with ongoing discussion to supply the North American market. While the reactor can potentially increase its production capacity (by two to three times) in the long term, it can produce only about a quarter of NRU's capacity in the short term.
- ***Argentina:*** Can supply modest quantities to the North American market.
- ***France:*** The Jules Horowitz reactor, which is expected to come on-stream by 2015, can produce Mo-99. However, the reactor was built for other uses and is not likely to limit its activity to the production of Mo-99.
- ***The United States:*** The University of Missouri research reactor may be brought on-stream to produce Mo-99. However, there are no specific commitments to make this a reliable option.(50)

CONCLUSION

The medical isotope shortage is an ongoing issue of national and global concern. There is currently no evidence of reliable short-term solutions beyond the augmented production by the four other major global reactors to replace the NRU supply. Considering the aging condition of global reactors and the uncertain sustainability of their production, long-term projects and/or alternative technologies are required to address the growing demand for technetium-99m-based diagnosis and therapy. In Canada, key long-term considerations include: new isotope-producing reactors, the restarting of the MAPLE project, and alternative technological options such as PET scanning and TRIUMF's accelerator-based proposal to produce molybdenum-99.

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(48) CBC News, "Global Supply Under Pressure," 11 June 2009, http://www.cbc.ca/health/story/2009/05/19/f-medical-isotopes.html.

(49) West (2009).

(50) Dupont (2009).