Context

Since 2007, there have been a number of medical isotope shortages that have had a severe impact on the delivery of nuclear medicine. To minimize the effect on patient care, the nuclear medicine community has employed a number of mitigation strategies. Common approaches include prioritizing patients, rescheduling non-urgent scans, and referring patients to alternate diagnostic modalities where possible.

Five nuclear reactors across the world supply more than 90% of the medical isotope that is used in nuclear medicine procedures. Repeated and prolonged closures of one or more of these nuclear reactors have led to ongoing fluctuations in isotope availability. On at least two occasions since 2007, three of the five prominent reactors have been out of commission at the same time. In March 2010, there was a period when none of the reactors was working. The closure of just one of these reactors can disrupt the security of the global medical isotope supply.

There is growing concern that periodic isotope disruptions will become the norm until alternative medical isotope production capabilities can be put into place. There is also concern that within the next decade, one or more of these major reactors could be forced to permanently close. According to the Association of Imaging Producers and Equipment Suppliers (AIPES), technical and licensing requirements will lead to the decommissioning of most of the major reactors within this 10-year time frame. Since the demand for this medical isotope is expected to remain critical during this period, such a scenario could impose major challenges to the nuclear medicine community.

The medical isotope at the centre of this global crisis is technetium-99m (99mTc). This isotope, 99mTc, is used to diagnose and detect a number of conditions, including cancer and heart disease. A delay of even a few days with conditions that 99mTc is used to diagnose could be critical to improved patient outcome or survival.

Objectives

The purpose of this environmental scan is to investigate the global impact of shortages of 99mTc supplies. The following questions will be addressed:

• Which countries were more severely impacted by the 99mTc shortage and why?
• What are the most popular uses of 99mTc?

Results of this report are based on a limited literature search and communications with key informants. As such, the comprehensiveness of this report cannot be guaranteed. This report is based on information gathered as of August 2010.

Findings

Global impact

99mTc is the radioisotope that is used in approximately 80% to 90% of nuclear medicine procedures. It is produced from the decay of molybdenum-99 (99Mo), a by-product of uranium-235 fission. Five nuclear reactors produce approximately 95% of the world’s supply of 99Mo. These include the Chalk River reactor in Canada, the High Flux Reactor (HFR) in the Netherlands, BR2 in Belgium, OSIRIS in France, and SAFARI-1 in South Africa. Each of these industrial scale reactors are government-owned and funded, and provide multiple services to a variety of users, in addition to the production of medical isotopes.

The Canadian reactor produces approximately 30% to 40% of the global demand for 99Mo; the three European reactors and the reactor in South Africa produce a similar quantity, and the smaller reactors support approximately 4% of the world’s demand. The global market share of the five major isotope producing reactors is shown in Table 1.
Environmental Scan

Table 1: Worldwide Production Capacity of $^{99}$Mo, 2009

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Approximate Share (%)</th>
</tr>
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<tbody>
<tr>
<td>Chalk River (Canada)</td>
<td>30% to 40%</td>
</tr>
<tr>
<td>High Flux Reactor (HFR) (Netherlands)</td>
<td>30% to 40%</td>
</tr>
<tr>
<td>OSIRIS (France)</td>
<td>7%</td>
</tr>
<tr>
<td>BR2 (Belgium)</td>
<td>14%</td>
</tr>
<tr>
<td>SAFARI-1 (South Africa)</td>
<td>15%</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>4%</td>
</tr>
</tbody>
</table>

Smaller reactors also produce $^{99}$Mo, but they mostly accommodate local or regional needs. Some regional producers of $^{99}$Mo include Australia, Argentina, Indonesia, and Poland. While these reactors do not produce the commercial quantities necessary to compensate for the closure of a large reactor, they can act as backups when larger reactors experience outages. Collectively, these reactors produce about 5% of the world’s supply. The regional reactors are listed in Table 2.

Table 2: Small-Scale Producers of $^{99}$Mo, 2010

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPAL</td>
<td>Australia</td>
</tr>
<tr>
<td>CNEA</td>
<td>Argentina</td>
</tr>
<tr>
<td>Maria</td>
<td>Poland</td>
</tr>
<tr>
<td>Rez</td>
<td>Czech Republic</td>
</tr>
<tr>
<td>WWR-TS</td>
<td>Russia</td>
</tr>
<tr>
<td>FRM-II</td>
<td>Germany</td>
</tr>
<tr>
<td>HFETR</td>
<td>China</td>
</tr>
<tr>
<td>HANARO</td>
<td>Korea</td>
</tr>
<tr>
<td>SIWABESS Y MPR</td>
<td>Indonesia</td>
</tr>
</tbody>
</table>

Each of the five major isotope producing reactors, as listed in Table 1, are approximately 40 years old and have already exceeded their planned operating lives by 10 or more years. These reactors require increasing amounts of maintenance that is time consuming and costly. During the last five or so years, unanticipated closures of each of the five major nuclear reactors have occurred approximately twice a year.

According to AIPES, the $^{99m}$Tc shortages experienced in May and July of 2010 have been the worst experienced in medical isotope history. At this time, both the Canadian and Dutch reactors, which together produce two-thirds of the global supply of $^{99}$Mo, were out of service. Other reactors maximized their output to alleviate the isotope supply deficit, but they were unable to compensate for the entire global isotope demand.

With the Canadian and Dutch reactors back in production, the most immediate concerns facing the nuclear medicine community have been alleviated. However, the expected decommissioning of both these reactors in 2016, and the threat of the permanent closure of the other main reactors listed in Table 1, raise questions about the vulnerability of isotope supplies.

To minimize future disruptions, reactors in Belgium, France, the Netherlands, and South Africa have begun to synchronize operating cycles and coordinate routine maintenance plans to ensure that at least one reactor is always in production. In November 2009, the International Atomic Energy Agency (IAEA) published practice guidelines intended to
prevent future global isotope shortages by facilitating coordinated efforts: Optimization of Research Reactor Availability and Reliability: Recommended Practices.\textsuperscript{14}

While the isotope crisis is a global concern, some countries, and even regions within countries, have experienced a more serious impact from the supply crisis than others. The United States, Canada, and Japan\textsuperscript{14,15} are examples of countries that have faced significant challenges with the supply shortage. Korea,\textsuperscript{5} several South American\textsuperscript{16} countries, and the Far East\textsuperscript{16} have also experienced significant shortages.

Some parts of Europe have encountered intermittent but serious problems associated with the isotope crisis. Cancellations or delays in patient services ranged from 20\% to 70\%, depending on the week and location of hospitals.\textsuperscript{7} However, as three of the five major reactors are located in Belgium, Netherlands, and France, and together they supply more than 80\% of the European demand,\textsuperscript{5} Europe has not been as vulnerable as regions that do not have access to local supplies. As well, the Canadian reactor, which is one of the biggest in the world, is not a regular supplier to Europe.\textsuperscript{17} As such, Europe did not experience a direct impact from the shutdown of the Canadian reactor.

The crisis in Europe became most acute when several of its reactors were offline simultaneously. Ordinarily, isotope supplies would have been supplemented by surplus material from the Canadian and South African reactors, but with the Canadian supplier out of commission the pool of alternative producers was severely limited.

In Britain, where isotope shortages were at times severe,\textsuperscript{5} the Department of Health there introduced weekly situation reports to monitor supplies when they fell below 30\% of regular isotope activity. At the height of the crisis in March 2010, when each of the main five reactors was offline, 14 National Health Service hospitals reported receiving less than 30\% of normal isotope supplies. It is believed that less than 30\% is an insufficient amount to manage urgent clinical cases.\textsuperscript{18}

With limited options for managing the supply of $^{99m}$Tc, the British medical community, like other global medical communities, implemented mitigation strategies to manage restricted supplies. The British Nuclear Medicine Society recommended treating priority patients, maximizing clinical activity to fit in with the delivery of $^{99m}$Tc supplies, rescheduling non-urgent tests, and where possible referring patients to other diagnostic modalities. Myocardial perfusion imaging was being performed with thallium-201, and bone scans were being performed with fluorine-18 sodium fluoride, a radioisotope that was used for the task before the introduction of $^{99m}$Tc-methylene diphosphonate molecule and other diphosphonate agents in the 1960s.\textsuperscript{19} Priority cases include sentinel lymph nodes, pediatric cases, situations in which other imaging modalities are specifically contraindicated (e.g., patients in renal failure where intravenous contrast may not be given for computed tomography scan or magnetic resonance imaging), and clinically urgent studies as determined by managing clinicians.\textsuperscript{20}

The Society of Nuclear Medicine, an international scientific and professional organization, released short-term recommendations for dealing with isotope shortages. The recommendations focus on the maximization of existing supplies by scheduling patients around $^{99m}$Tc availability, performing imaging studies throughout the week, and lowering doses and extending imaging times. It was suggested that where possible, alternate isotopes replace $^{99m}$Tc; for example, iodine-123 was recommended as a common alternative for thyroid scintigraphy; for myocardial perfusion imaging $^{99m}$Tc should be used only when appropriate for stress test imaging. Thallium-201, rubidium-82 by positron emission tomography (PET), coronary computed tomography scans, and echocardiographic or electrocardiographic stress tests were also recommended as replacement diagnostic procedures.\textsuperscript{21}

While the location of a reactor is closely linked to a country’s security of supply, a fully functional $^{99}$Mo supply chain requires processing capacity and availability, geographic alignment between $^{99m}$Tc processors and reactors, improved efficiency of the distribution system, and regulatory approvals.\textsuperscript{8}
There is no domestic production of $^{99}$Mo in Japan\textsuperscript{22} and the US,\textsuperscript{23} the two largest markets for nuclear medicine products.\textsuperscript{23,24} Japan, which consumes approximately 14\% of the global market share of $^{99m}$Tc,\textsuperscript{25} relies almost exclusively on one provider, Canada. The US, which consumes 44\% of the global demand,\textsuperscript{25} receives virtually all of its supply from Canada (52\%) and the Netherlands (45\%). Canada, which consumes 4\% of the global market of $^{99m}$Tc\textsuperscript{25} relies mostly on its domestic supply, but also, to a much smaller extent, on two other providers (Netherlands 10\%, Belgium 2\%).\textsuperscript{8} Canada’s primary reliance on a domestic supply of $^{99m}$Tc may account for why Canada’s isotope shortfall was around 65\% of its overall average, while the general global isotope shortfall was around 35\%.\textsuperscript{26} Similarly, Japan’s lack of supplier diversity may have contributed to its vulnerability during the isotope crisis.

The situation may have been worse for Japan, if it had not been for its significant adoption of PET technology.\textsuperscript{27}

Europe, which consumes approximately 22\% of the global demand of $^{99m}$Tc,\textsuperscript{25} is supplied by six providers (Netherlands 30\%, Belgium 16\%, France 12\%, South Africa 32\%, Canada 5\%, and other 5\%).\textsuperscript{8} Thus, if one or even two reactors are offline, there are still a number of other providers who can supply the European market.

Several surveys have been conducted in specific countries and regions that have collected anecdotal information on the impact of the $^{99m}$Tc shortages. The main findings of these studies are captured here.

The European Association of Nuclear Medicine conducted a survey among 34 of its member countries to determine the impact of the $^{99m}$Tc supply of $^{99}$Mo for nuclear medicine. The survey reported that 14 countries were seriously affected by the isotope deficit (Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Iceland, Ireland, Lithuania, Netherlands, Slovakia, Switzerland, and the United Kingdom). Nine countries were found to experience some impact (Austria, Bulgaria, Denmark, Italy, Luxembourg, Malta, Portugal, Slovenia, and Turkey). Eleven countries reported no impact (Cyprus, Estonia, Finland, Israel, Latvia, Norway, Poland, Romania, the Russian Federation, Serbia, and Ukraine).\textsuperscript{5}

The Society of Nuclear Medicine (SNM) conducted a survey of nuclear pharmacies. The survey included information from 13 countries, with the US accounting for 93\% of all responses.\textsuperscript{28} The survey reported that approximately 70\% of physicians and nuclear medicine technicians have experienced the impact of the recent shortage; almost 50\% have postponed patient tests and 20\% of procedures were cancelled. In more than one out of three of the postponed cases, tests were delayed for longer than one month.

A similar survey was conducted in Canada in 2010. Two-thirds of all nuclear medicine sites participated in the survey. The survey reported on cardiac, bone, and lung diagnostic tests and found a decrease in the number of these tests by approximately 22\% in October 2009 compared with a year earlier. This represents about 12,000 fewer exams.\textsuperscript{29}

The survey also reported on the economic impact of the ongoing shortage. Almost 67\% of participants reported that costs had gone over budget because of vendor surcharges that had inflated monthly invoices by $5,000 to $30,000, 23\% of participants reported managing, but with reduced services, and 2\% reported no economic impact.\textsuperscript{29}

The survey examined staff management changes during the crisis and found a moderate to high degree of change in increased weekend work, extended shifts, and overall staff scheduling practices. Staff morale rates were reported to be lower because of the uncertainty and nature of the shortage. The findings corroborate those of another study completed by the Canadian Association of Medical Radiation Technologists.\textsuperscript{30} This survey examined the impact of the isotope shortage on human resources at 119 out of 245 Canadian nuclear medicine facilities. The results indicated that 45\% of respondents made changes to staffing arrangements, with 62\% of technologists working longer hours when $^{99m}$Tc was available and 68\% working weekend shifts to make the best use of limited supplies.

A survey on the impact of isotope shortages was also conducted in hospitals in the Japanese region of Saitama Prefecture.\textsuperscript{22} The results indicated that 52\% of the respondents reported a reduction in the number of nuclear medicine
Environmental Scan

studies: the reduction, however, was small, with a decrease per month of less than 20 studies in two-thirds of the nuclear medicine facilities. Lung perfusion studies were the most seriously affected, followed by renal, bone, brain, and myocardial scans. Alternative procedures were performed at almost half of the hospital facilities with myocardial perfusion using thallium-201 being the most commonly substituted isotope.

Popular Uses of Technetium-99M

Each year more than 20 million people in the US, two million in Canada, 10 million in Europe, and 14 million in the rest of the world benefit from nuclear medicine tests involving medical isotopes.31 The top five most frequently performed nuclear medicine procedures include cardiac imaging, bone scintigraphy (including tumour metastases), lung investigations, and thyroid, parathyroid and kidney function and analysis imaging. Each of these procedures uses 99mTc as the preferred isotope.5 Table 3 provides a breakdown of nuclear medicine procedures that use 99mTc.

Approximately 60% of the tests that use 99mTc are cardiac-related procedures for which other imaging options may be acceptable.32 Thallium-201 is used as an alternative SPECT myocardial imaging agent. However, it was originally replaced by 99mTc agents two decades ago because its imaging properties were considered to be poorer than 99mTc,24 especially in overweight patients,33 its dosimetry was believed to be inferior,24 and it has a slightly increased radiation dosage.34

Bone scans are typically the most common use for 99mTc in cancer centres.6 Patients with metastatic disease are usually tested every six to eight weeks to determine whether a particular treatment therapy is working. 18F fluorine is a PET agent used for bone scanning that is believed to be an excellent clinical substitute for 99mTc. However, it is at least 10 times more expensive24 and it is not universally accessible because it requires a PET camera, radiochemistry, and a local cyclotron.5

To make the most efficient use of available sources of 99mTc, many nuclear physicians and specialists are decreasing the dose and prolonging the imaging time. However, if the 99mTc dose is too low it will result in both false-negative and positive results that could potentially lead to less effective imaging scans.12 Some physicians have been conducting tests that require higher doses of 99mTc (e.g., bone and parathyroid scans) as soon as 99mTc generators are delivered and scheduling less demanding scans (e.g., thyroid imaging) when the 99mTc generator’s activity diminishes,6 in an effort to optimize 99mTc’s yield. One factor that helps to determine which patients receive 99mTc is body weight, as it has less penetration in larger patients. Given this information, smaller doses may be administered to patients who fall under a threshold weight.

For some procedures where there really is no alternative, such as hepatobiliary scanning for suspected gall bladder disease, sentinel lymph node determination for cancer surgery, and kidney function investigations, a shortage of 99mTc may be critical.2,5

New pressures on the health care system have emerged as a result of the implementation of alternative short-term strategies. Wait-times for substitute imaging modalities have increased because of the increased volume of patients who would previously have been scanned with 99mTc. As well, patient rescheduling has led to pressures on health human resources by requiring weekend shifts and overtime.27 This too has boosted hospital operational budgets. Patient referrals to

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### Table 3: Nuclear Medicine Procedures that Use 99mTc

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial perfusion</td>
<td>56%</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>4%</td>
</tr>
<tr>
<td>Bone scans</td>
<td>17%</td>
</tr>
<tr>
<td>Liver, hepatobiliary</td>
<td>7%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4%</td>
</tr>
<tr>
<td>Thyroid, parathyroid</td>
<td>3%</td>
</tr>
<tr>
<td>Renal</td>
<td>3%</td>
</tr>
<tr>
<td>Infection, Inflammation</td>
<td>2%</td>
</tr>
<tr>
<td>Tumour imaging</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
</tbody>
</table>
diagnostic imaging departments have also suffered as a result of $^{99m}$Tc shortages, with a 10% to 25% decrease in referrals even when $^{99m}$Tc supplies have improved.\textsuperscript{27} This is largely due to the fact that referring physicians are still using alternative diagnostic methods, even with improved isotope availability.

The reduced supply of $^{99m}$Tc has had other negative consequences on nuclear medicine and its health human resources. The Royal College of Physicians and Surgeons of Canada reported a decrease in the number of nuclear medicine residents. Similarly, the Canadian Association of Medical Radiation Technologists reported that some nuclear medicine professionals had lost their jobs and that there had been a decrease in the number of admissions to related technologist programs.\textsuperscript{27}

**Conclusion**

Several countries have experienced an impact from the isotope crisis; some more seriously and for longer periods than others. Canada, the US, Japan, Korea, and a number of South American nations have experienced the impact more intensely than many other regions. This is believed to be linked to their heavy reliance on isotopes produced at the Canadian reactor. These countries were forced to seek alternate supplies from other reactors during the 16-month closure of the Canadian facility. There may be a relationship between the number of suppliers a country has and isotope vulnerability; with more severity associated with fewer suppliers.

Some European countries experienced more shortage than others; the United Kingdom, Belgium, Netherlands, France, Germany, Greece, Croatia, the Czech Republic, Hungary, Iceland, Ireland, Slovakia, and Switzerland are European countries that were the most severely affected. However, as three of the five largest commercial reactors serve these countries, and numerous small reactors supplement their surplus requirements, the shortages may not have been as acute or prolonged in Europe as they were in countries with access to fewer suppliers.

The nuclear medicine procedures that were most affected by shortages in $^{99m}$Tc include, cardiac imaging, bone scintigraphy (including tumour metastases), lung investigations, and thyroid, parathyroid and kidney function and analysis imaging. Each of these procedures uses $^{99m}$Tc as the preferred isotope.

**References**


34. **Solution to isotope shortage lies in domestic production.** RSNA News [Internet]. 2010 Jul [cited 2010 Sep 9].


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