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BACKGROUND PAPER

The 2009–2010 Medical Isotope Shortage: Cause, Effects and Future Considerations

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The 2009–2010 Medical Isotope Shortage: Cause, Effects and Future Considerations

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THE 2009–2010 MEDICAL ISOTOPE SHORTAGE: CAUSE, EFFECTS AND FUTURE CONSIDERATIONS

1 THE NATIONAL RESEARCH UNIVERSAL REACTOR SHUTDOWN

Between May 2009 and August 2010, a global shortage of medical isotopes was caused by the unexpected shutdown of the National Research Universal (NRU) at Atomic Energy of Canada Limited's (AECL's) Chalk River laboratories in eastern Ontario. On 14 May 2009, the NRU reactor shut down automatically 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 was resolved. 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, which the Canadian Nuclear Safety Commission (CNSC) described as "well below CNSC 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 were particularly challenging due to the limited access to the corroded surface, which had to be handled remotely due to high radiation fields.[3] Following 15 months of repair activities, the reactor was finally restarted on 17 August 2010. On 25 August 2010, AECL reported that the NRU had resumed "full production of medical isotopes." [4]

The NRU has three purposes:

- the production of industrial and medical radioisotopes (among the largest global suppliers), used to diagnose and treat a number of diseases, including cancer and heart disease.
- neutron beam research, which examines a wide range of materials, leading to advances in medical, scientific and industrial fields. (The NRU is one of the world's few reactors available for commercial use, and its research facilities receive over 200 professors, students and industrial researchers annually.)
- research and development support for CANDU power reactors.[5]

Table 1 presents a list of medical isotopes produced by the NRU.

Table 1 – NRU Isotope Production for Diagnostic and Therapeutic Use

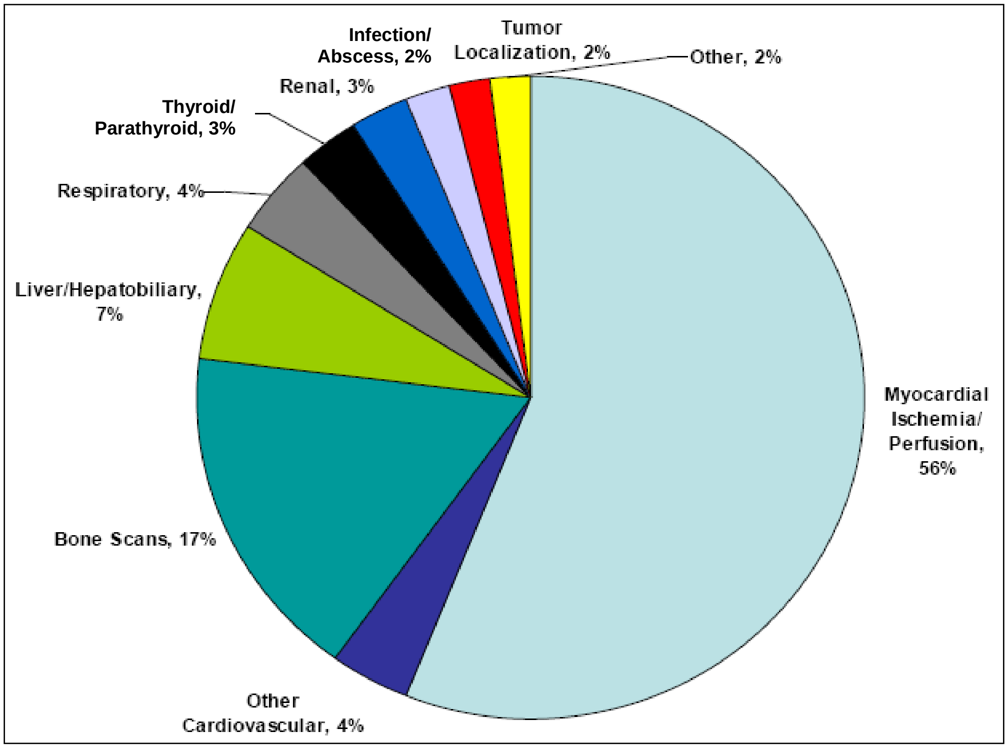
Medical Isotope	Diagnostic and/or Therapeutic Use
Molybdenum-99	Medical diagnosis (imaging) of the brain, heart, liver, kidney, lungs, thyroid, spleen and bone marrow
Iodine-131	Therapy, imaging and diagnosis (mostly for thyroid cancer)
Iodine-125	In-vitro diagnostics, bone densitometry devices, protein 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, *Nuclear Science*, “Medical Isotopes.”

2 THE GLOBAL SHORTAGE OF MEDICAL ISOTOPES

The shortage of medical isotopes (mainly molybdenum-99 or Mo-99) triggered by the shutdown of the NRU was 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, bone scans to detect cancers, and general organ scans.[6] 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.[7] Figure 1 presents the composition of nuclear medical procedures where Tc-99m is predominant, based on 2006 data.

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

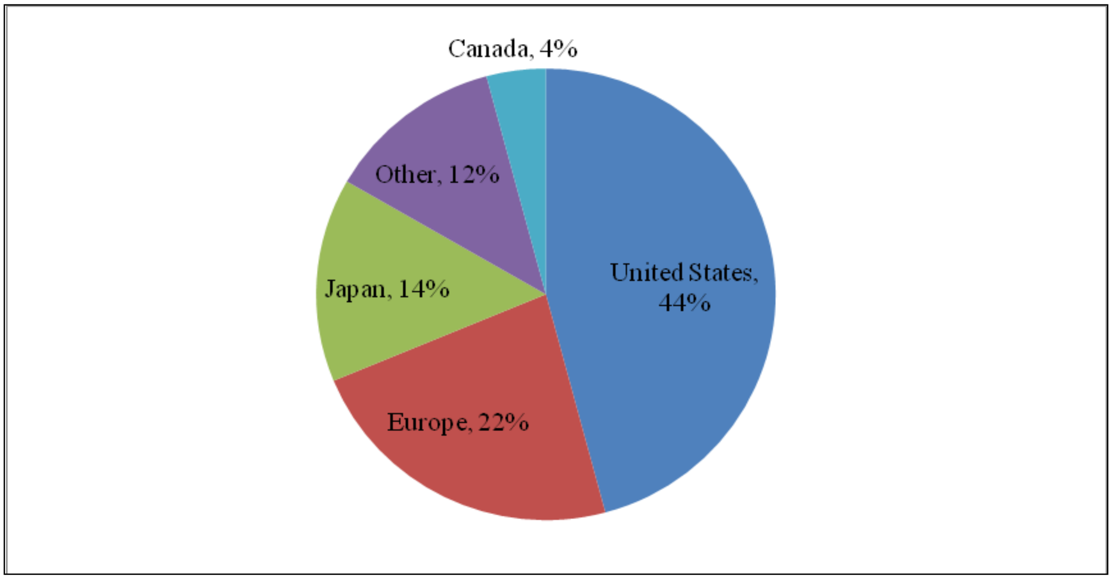


Source: Natural Resources Canada, Document presented to the House of Commons Standing Committee on Natural Resources, Meeting 23, 2 June 2009.

The 2009–2010 isotope shortage limited diagnostic testing (as opposed to therapy), which particularly affected cancer patients, where early and reliable diagnosis is critical.[8] It was estimated that an overall 30% of the global supply was 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, experienced higher shortages than Europe, where other suppliers are more prevalent.[9] The shortage also varied across Canada, since isotope supplies are managed by the provinces and territories.[10]

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[11] (see Figure 2 for a breakdown of the global demand for Mo-99/Tc-99m). According to AECL, the NRU's isotope supplies help more than 76,000 people daily, in over 80 countries.[12] However, even with the NRU reactor in operation, the production of medical isotopes needs to increase to satisfy 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, has explained: "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.[13]

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

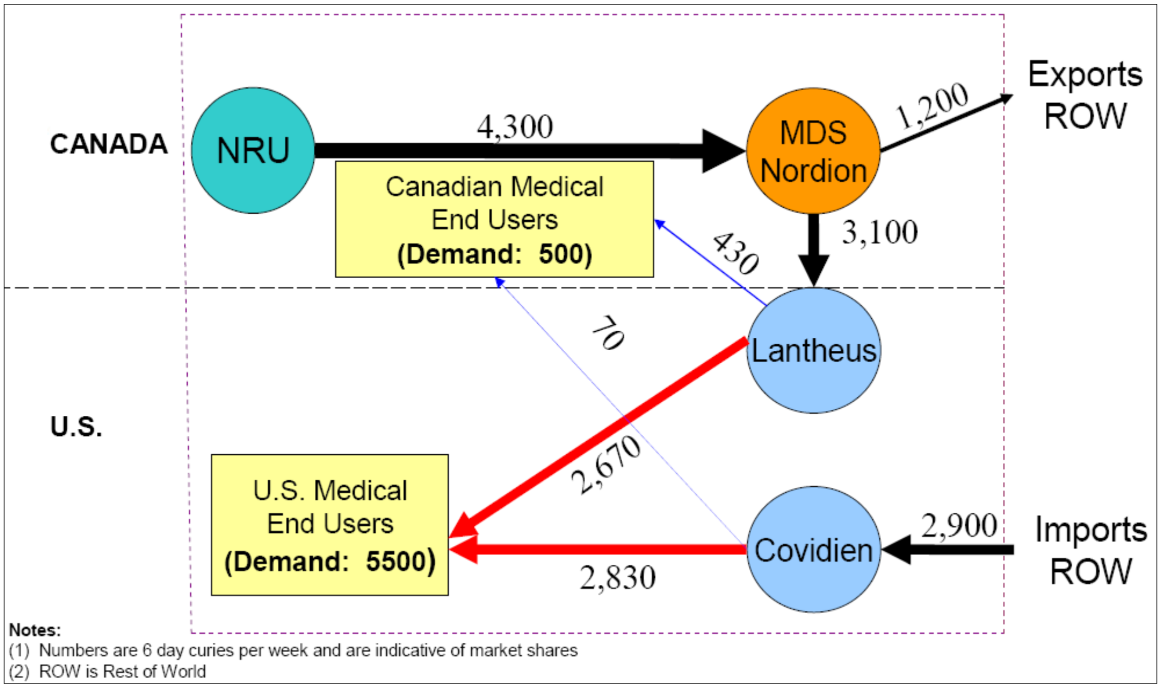


Note: The sum of the totals may not equal 100, due to rounding.

Source: Natural Resources Canada, Document presented 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 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.[14] 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.[15] Throughout the supply chain, specific steps must be followed in the 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, Mo-99, which has a half-life of about 66 hours, is shipped to MDS Nordion in Ottawa (Kanata), 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.[16] Figure 3 presents the supply chain of Mo-99/Tc-99m between Canada and the United States.

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



Notes:
(1) Numbers are 6 day curies per week and are indicative of market shares
(2) ROW is Rest of World

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

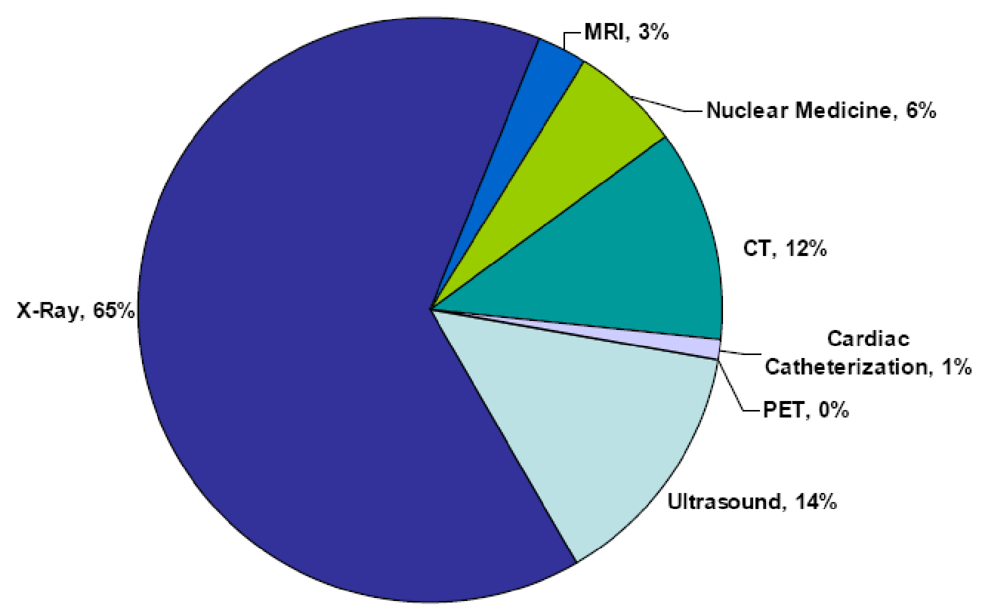
Since all reactors must undergo systematic outages for maintenance, there is a critical need for harmonization between isotope suppliers to maintain the global supply balance. As a result, the unexpected outage of the NRU reactor created a serious imbalance within a complex supply chain, which emphasizes the incentive for additional technologies to secure or substitute the future supply of medical isotopes.[17]

3 FUTURE CONSIDERATIONS

3.1 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.[18] Figure 4 presents the breakdown of medical imaging procedures in Ontario hospitals, based on data from 2007.

Figure 4 – Medical Imaging Procedures in Ontario Hospitals, 2007



Note: The sum of the totals may not equal 100, due to rounding.

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

During the isotope shortage, the medical community used some alternative procedures as a short-term contingency response to the shutdown of the NRU reactor. However, such alternatives could replace the role of Tc-99m only temporarily, since they are often less effective, available or reliable.[19] 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.[20]

Furthermore, 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." [21]

There were 28 centres performing publicly funded scans in seven Canadian provinces as of July 2009,[22] with the greatest access in Quebec.[23] According to Dr. Jean-Luc Urbain, President of the Canadian Association of Nuclear Medicine, the technology is more widely available in Australia, China, Europe, India, Kuwait, Singapore, South America, and the United States.[24] However, even if PET were to be used more extensively in Canada, it could not replace procedures that use Tc-99m for paediatric bone scanning for cancers due to the intense level of radiation produced by PET scanning.[25] PET is also a more expensive technology than traditional Single Photon Emission Computed Tomography (SPECT), which uses Tc-99m. Dr. Karen Gulenchyn, Medical Chief at the Department of Nuclear Medicine at Hamilton Health Sciences and St. Joseph's Healthcare Hamilton, has stated that a dose of fluorodeoxyglucose (used in PET procedures) would cost a minimum of $250 to $300, as opposed to $15 to $20 for a Tc-99m-based product.[26] Further commercialization of PET technology in Canada may reduce the cost of PET procedures.

3.2 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 short-term solutions. 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.[27]

3.2.1 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 they were never commissioned due to a technical discrepancy. As described by Hugh MacDiarmid, President and Chief Executive Officer of AECL, "[T]he actual behaviour of the reactor did not mirror the modelled behaviour of the reactor," which, according to AECL, renders the safety of the reactors below acceptable levels.[28] To restart the reactors the discrepancy must be explained "to the satisfaction of AECL … [and] the CNSC." [29] The total cost of the discontinued MAPLE project was approximately $250 million, according to MacDiarmid.[30]

The feasibility of restarting the project is controversial. Steve West, President of MDS Nordion, has 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.[31] Waddington has confirmed that the reactors could be started in principle, but that this would require “much human and financial effort.” [32] According to 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.” [33]

3.2.2 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, in the medium term, about 20% of the demand in North America for Mo-99. Such production would be equivalent to about four times of Canada’s demand for the isotope. 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 24 hours a day, seven days a week. There may also be technical issues with integrating McMaster isotopes into the existing supply chain due to a design discrepancy between the pin-shaped NRU targets and the McMaster targets, which are a pleat design.[34] AECL has pointed out logistical issues associated with transporting certain materials around the Greater Toronto and Hamilton Area; but has supported the proposal “to the extent it is possible.” [35]

3.2.3 THE CANADIAN NEUTRON CENTRE

The Canadian Neutron Centre is a proposed new research reactor to replace the aging NRU. As currently planned, it would perform multi-purpose research, and could produce Mo-99 upon conception.[36] According to Dominic Ryan, President of the Canadian Institute for Neutron Scattering, 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 has indicated that this is only a rough estimate, stating that “a proper engineering costing design” would be required to determine a precise cost.[37]

3.2.4 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.[38]

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.[39]

3.3 ALTERNATIVE GLOBAL SUPPLIERS

Meeting the global demand for medical isotopes is dependent on the performance of the world's main producing reactors. The major reactors (Belgium's BR2, France's OSIRIS, the Netherlands' Petten, and South Africa's SAFARI) are of vintages similar to that of the NRU, making the sustainability of their isotope production uncertain. Furthermore, maintaining the global supply of medical isotopes during a scheduled shutdown of one reactor depends on the ability of the other major reactors to produce isotopes.[40] In addition to these reactors, reactors that may have the potential to contribute to the global supply of medical isotopes 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.
- ***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.
- ***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.[41]

NOTES

1. House of Commons, Standing Committee on Natural Resources [RNNR], *Evidence*, Meeting 24, 4 June 2009 (Bill Pilkington, Senior Vice-President and Chief Nuclear Officer, Atomic Energy of Canada Limited).
2. Ibid. (Michael Binder, President, Canadian Nuclear Safety Commission).
3. Ibid. (Pilkington).
4. AECL, "NRU Status Report #73 – AECL provides update on NRU activities," News release, 25 August 2010.
5. 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. For more details on the NRU reactor, see AECL, *Nuclear Science*, "National Research Universal Profile."
6. RNNR, *Evidence*, Meeting 23, 2 June 2009 (Meena Ballantyne, Assistant Deputy Minister, Health Products and Food Branch, Health Canada).
7. Citizens for Medical Isotopes, *Frequently Asked Questions*.
8. RNNR, *Evidence*, Meeting 25, 9 June 2009 (Karen Gulenchyn, Medical Chief, Department of Nuclear Medicine, Hamilton Health Sciences and St. Joseph's Healthcare Hamilton).
9. RNNR, *Evidence*, Meeting 26, 11 June 2009 (Steve West, President, MDS Nordion).
10. RNNR (9 June 2009) (Jean-Luc Urbain, President, Canadian Association of Nuclear Medicine).

11. RNNR (2 June 2009) (Serge Dupont, Associate Deputy Minister, Natural Resources Canada).
12. AECL, *Nuclear Science*, "Medical Isotopes."
13. RNNR, *Evidence*, Meeting 28, 18 June 2009 (Jean Koclas, Professor, Nuclear Engineering Institute, Engineering Physics Department, École polytechnique Montréal).
14. RNNR (2 June 2009) (Dupont).
15. Ibid.
16. Ibid.
17. Ibid.
18. Ibid. (Ballantyne).
19. Ibid.
20. RNNR (9 June 2009) (Gulenchyn).
21. Canadian Agency for Drugs and Technologies in Health [CADTH], "Future Alternatives to Molybdenum-99 (Mo-99) Production for Medical Imaging," *Health Technology Update*, Issue 11, August 2009.
22. Information on the status of publicly funded Canadian PET scans is found in Table 2, "2009 Location of Publicly Funded PET Scanners and Cyclotrons in Canada" in CADTH (2009).
23. CADTH (2009).
24. RNNR (9 June 2009) (Urbain).
25. RNNR (2 June 2009) (Ballantyne).
26. RNNR (9 June 2009) (Gulenchyn).
27. RNNR (2 June 2009) (Dupont).
28. RNNR (4 June 2009) (Hugh MacDiarmid, President and Chief Executive Officer, Atomic Energy of Canada Limited).
29. RNNR (11 June 2009) (John Waddington, Nuclear Safety Consultant).
30. RNNR (4 June 2009) (MacDiarmid).
31. RNNR (11 June 2009) (West).
32. Ibid. (Waddington).
33. RNNR (4 June 2009) (MacDiarmid).
34. RNNR, *Evidence*, Meeting 27, 16 June 2009 (Christopher Heysel, Director of Nuclear Operations and Facilities, McMaster Nuclear Reactor).
35. RNNR (4 June 2009) (MacDiarmid).
36. Ibid.
37. RNNR (16 June 2009) (Dominic Ryan, President, Canadian Institute for Neutron Scattering).
38. Ibid. (Nigel Lockyer, Director of TRIUMF).
39. Ibid.
40. RNNR (11 June 2009) (West).
41. RNNR (2 June 2009) (Dupont).