

Medical isotope production in Australia:

Should we be using reactor based or cyclotron technology?

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Executive summary

ANSTO (the Australian Nuclear Science and Technology Organisation) is currently planning to dramatically increase the use of the Lucas Heights OPAL reactor to supply a third of the world market with medical isotopes, and is constructing a new facility to be completed by the end 2016. This will result in 97% of the medical isotopes produced at Lucas Heights being sold on the export market, with 3% for Australian use.¹

Recent advances create a choice as to whether we continue reactor manufacture, or develop cyclotron capacity in Australia.

Reactor production of isotopes has been shown to be unreliable with at times worldwide shortages of supply, due to unplanned outages. Cyclotron use would be more reliable, decentralised and both cheaper and cleaner.

Reactor isotope production and sale can only occur with significant subsidies from government. Canada, who supplies over 30 % of the world market, is phasing out reactor isotope production due to concerns about reliability, cost, radioactive waste accumulation and other issues. Cyclotrons, unlike a nuclear reactor, pose almost no accident, proliferation or terrorist risks.

Reactor use generates a significant long-lived Intermediate Level Waste waste burden which must be safeguarded for hundreds of thousands of years. Provision of subsidised reactor based isotopes may slow the uptake of cyclotron technology in many countries.

In contrast, cyclotron technology is cheaper, less prone to shortages of supply, and does not produce any long lived nuclear waste. Canada expects full production of domestic isotopes using cyclotron technology in 3-5 years.

Australia would be better served in the future by following the Canadian example and using cyclotrons to produce medical isotopes.

ANSTO is a tax payer funded organisation. It should be leading the debate on this issue, and providing accurate and up to date information.

The current proposal from ANSTO to markedly increase reactor isotope production should be subject to a public inquiry, given it will have repercussions that include less reliability of supply for nuclear medical care, the need for major subsidies and result in the production of waste that will impact on future generations of Australians for millennia.

¹ <http://www.world-nuclear.org/info/Country-Profiles/Countries-A-F/Appendices/Australian-Research-Reactors/> accessed 13/1/2016

Background

In Australia there are about 560,000 nuclear medicine procedures per year among 21 million people, 470,000 of these using reactor isotopes. Currently these are largely produced by the nuclear reactor at Lucas Heights in NSW, and imported at times when there are reactor outages (due refuelling, service and maintenance resulting in an “uptime” of 80%). Current construction underway at Lucas Heights will enable ANSTO to provide some 15 million doses per year, launching Australia as a major international supplier of Mo-99 isotope, the precursor to the most commonly used isotope in nuclear medicine, Tc-99m . Current world demand is about 45 million doses per year, so the new plant will be capable of meeting about one-third of world demand from late 2016².

Canada, the world's single largest producer of medical isotopes, independently reviewed its nuclear industry in 2009 and decided not to build a new reactor³. This review, titled “Report of the Expert Review Panel on Medical Isotope Production 2009” should be read by all members of the Australian Parliament, as it clearly spells out the many reasons why Canada wished to stop supplying over 30% of the world’s nuclear medicine market.

Several reasons stood out:

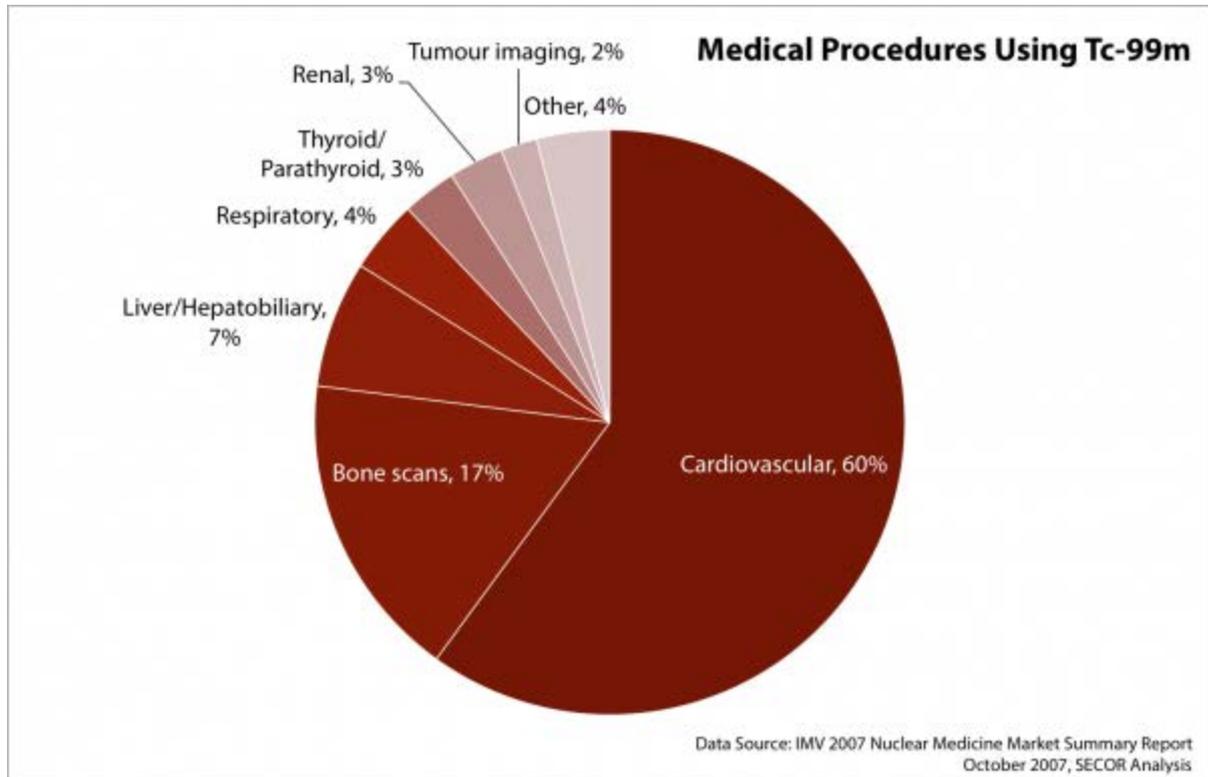
- reactor based production created worldwide isotope supply vulnerabilities due to the inherent unreliability of a linear supply chain, where single point failures create unplanned outages,
- investment in reactor production of medical isotopes would crowd out investment in innovative alternative production technologies both domestically and internationally,
- Canada did not want to continue being the radioactive waste site for other countries' nuclear medicine industries,
- and at no stage was reactor production commercially viable without massive taxpayer subsidies.

² <http://www.world-nuclear.org/info/Country-Profiles/Countries-A-F/Appendices/Australian-Research-Reactors/> accessed 13/1/2016

³ Report of the Expert Review Panel on Medical Isotope Production 2009 Presented to the Minister of Natural Resources Canada
https://www.google.com.au/search?q=Canadian+review+nuclear+isotope+production&ie=utf-8&oe=utf-8&gws_rd=cr&ei=SE-XVvHLFMbA0gSL4YrAAw accessed 14/1/16

Why do we need isotopes?

There are multiple isotopes used in nuclear medicine, but over 85% of procedures use Technetium-99m (Tc-99m).⁴ It is the world's most highly used medical isotope and is the critical component driving over 76,000 imaging procedures per day.



Nuclear Reactors and Isotope Production

Using nuclear reactors to produce medical isotopes introduces a number of challenges.⁵ Most critical is reliability of supply. Aging reactors are becoming increasingly unreliable and outages contribute to ongoing shortages. More modern reactors also have unplanned outages.

The infrastructure of reactor production of medical isotopes is that of a linear supply chain, which is inherently unreliable since it is vulnerable to single point failures. Once a failure occurs in this chain, recovery is logistically very difficult until this failure is rectified. This vulnerability has been shown repeatedly over the last decade due to unplanned outages from major isotope producers.

A global shortage of medical isotopes arose in 2009 when Canada's National Research Universal (NRU) reactor at Chalk River Laboratories was shut down unexpectedly on May 14,

⁴ <http://www.triumf.ca/cyclomed99/problem> accessed 13/1/2016

⁵ <http://www.triumf.ca/fag-medical-isotopes> accessed 13/1/2016

2009, following the discovery of a leak of heavy water. It was out of commission for 15 months. Another shortage occurred in 2011 following a shutdown of the NRU for regular maintenance. Australia's own OPAL research reactor, which officially opened in April 2007 was unable to produce sufficient medical isotopes for the domestic market until 2009 as fuel supply and engineering deficiencies were addressed.⁶

In addition, having a single central production source creates waste due to delays in shipping. Since half of the Mo-99 decays every 66 hours, much more needs to be shipped, and as a result Tc-99m ends up being wasted as it decays during shipment from far-flung reactors, to pharmaceutical companies, and finally to hospitals. Isotope-generating reactors create other by-products besides Mo-99 that persist as long-lived nuclear waste.

Historically, Tc-99m has been produced in a select number of nuclear reactors around the world. These reactors produce large quantities of molybdenum-99 (Mo-99), which undergo radioactive decay to form Tc-99m within special generators as they are shipped and stored at local hospitals.

Only a few reactors around the globe are capable of producing Mo-99 at an appreciable amount, and many of these reactors are ageing and require more frequent shutdowns for maintenance and repairs.

A Nuclear Energy Agency/OECD report from 2015 titled “The supply of medical radioisotopes”⁷ outlines a number of differing supply scenarios between 2015 and 2020, particularly in reference to Technetium-99m which is 80-85% of medical isotopes used. It notes that demand has fallen over 10% in the last year, from 10,000 6-day curies per week to 9,000 6-day curies per week. It states “*The reasons behind market demand being now lower than previously estimated are not fully clear.*” They suggested increased efficiency of use, some reduction in the average injected dose and some changes in clinical procedures. Despite this observed drop in demand, they continued to model 0.5% increase in demand for mature markets, and 5% increase in demand in developing markets. This persistent growth modelling was done to “*maintain continuity*”.

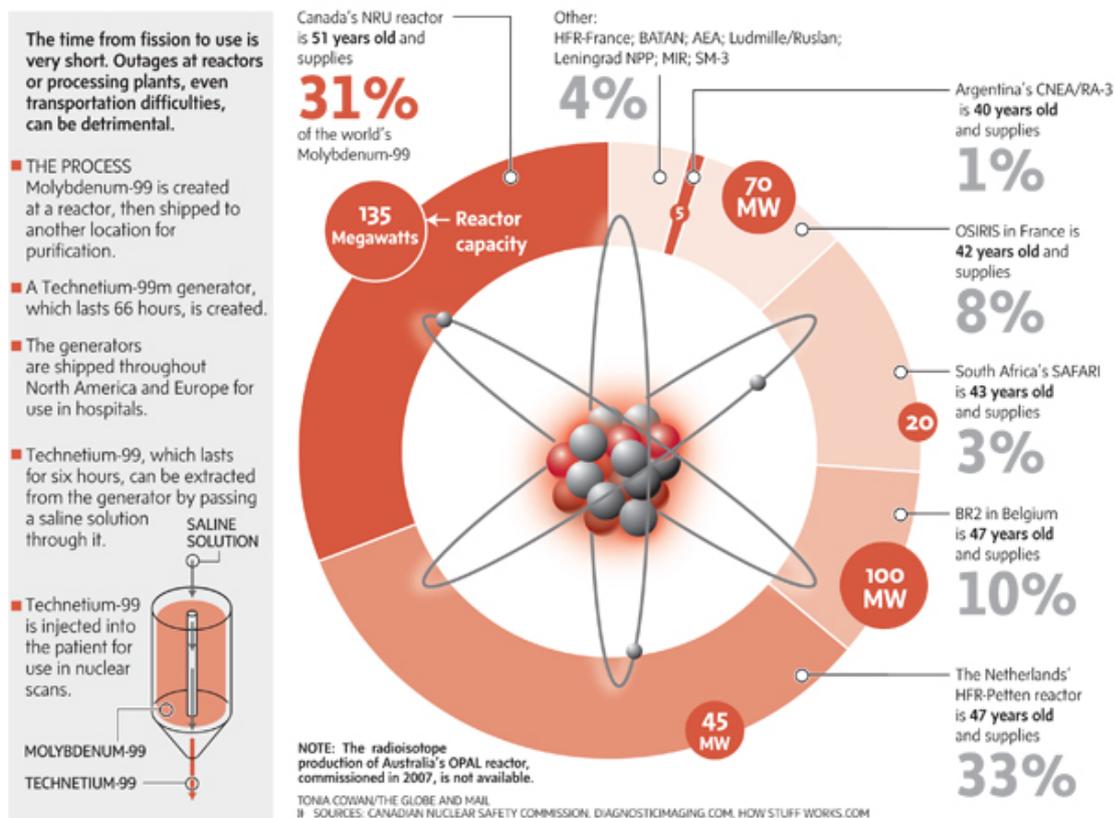
This report acknowledges the important role of alternative technologies; “*From 2017 the additive irradiation capacity from ‘alternative technology’ projects primarily in the US is progressive and quite substantial throughout the period, indicating that the additive capacity of ‘alternative technology’ will support overall security of supply during the 2017 to 2020 period.*”

⁶ <http://www.world-nuclear-news.org/newsarticle.aspx?id=14530> accessed 15/1/2016

⁷ <https://www.oecd-nea.org/med-radio/supply-series.html> accessed 7/3/2016

Medical isotopes: How they work and who supplies them

Molybdenum-99 decays into Technetium-99m, a short-lived medical radioisotope used in 80% of nuclear medicine procedures. Canada's NRU reactor at Chalk River, Ont., and the Netherlands' HFR-Petten reactor together account for nearly two-thirds of the world's supply.



Sources of Tc-99m from conventional nuclear reactors, courtesy the Globe & Mail.

Australia currently produces just over 1 % of global supply of Tc-99⁸

For many years, Canada's NRU reactor supplied approximately one third of the world's demand of Mo-99 for Mo-99/Tc-99m generators used in hospitals for diagnostic nuclear medicine. The NRU shutdowns in 2009 and 2011 created major problems in supplying Tc-99m to nuclear medicine sites in many countries, including Canada, and illustrated the existing system's single point of failure vulnerability. The Canadian NRU reactor is scheduled to close in 2018. New reactor and non-reactor based projects are coming on line in the 2015-2020 period in Europe, North and South America and the far East⁹.

The Canadian Government Expert Review Panel on Medical Isotope Production in 2009 considered building a new reactor when examining options for future isotope supply, but concluded:

⁸ <http://www.world-nuclear.org/info/Country-Profiles/Countries-A-F/Appendices/Australian-Research-Reactors/> accessed 13/1/2016

⁹ <https://www.oecd-nea.org/med-radio/supply-series.html> accessed 7/3/2016

“Research reactors are shared facilities that have all the benefits associated with multi-use facilities, including the benefit of costs being spread over a large base of activities. However, this is the most expensive of the options, with high capital and operating costs. Costs associated with the processing facility, training, licensing requirements, security, and waste management are also very significant.

*Revenue from isotope production would likely offset only approximately 10–15% of the costs of the reactor”.*¹⁰

A 2010 OECD/Nuclear Energy Agency report titled “The Supply of Medical Radioisotopes- An economic study of the Molybdenum-99 supply chain”¹¹ found reactor based production of Mo-99/Tc-99m requires significant taxpayer subsidies, as the cost of sale does not cover the cost of production. This study was very comprehensive, and in its opening acknowledgements states:

“This report would not have been possible without input from a significant number of supply chain participants and stakeholders including all major reactor operators, all major processors, generator manufacturers, representatives from radiopharmacies and nuclear medicine practitioners. The input from the supply chain participants was essential for completing this study, and the NEA greatly appreciates the information provided by interviewees.”

The report goes on to conclude: “In many cases the full impact of Mo-99/Tc-99m provision was not transparent to or appreciated by governments who were financially supporting research reactors’ 99Mo production. The full costs of waste management, reactor operations, fuel consumption, etc. were not included in the price structure, thus providing a significant deficiency in the pricing mechanism. This is a subsidisation by one country’s taxpayers of another country’s health care system. Many governments have indicated that they are no longer willing to provide such subsidisation.

Overall, it is clear that there is a market failure in the 99Mo supply chain. This market failure has contributed to a supply chain that is economically unsustainable. This pricing structure has resulted in a lack of investment in current and new infrastructure to reliably supply 99Mo.”

¹⁰ **Report of the Expert Review Panel on Medical Isotope Production** 2009 Presented to the Minister of Natural Resources Canada

https://www.google.com.au/search?q=Canadian+review+nuclear+isotope+production&ie=utf-8&oe=utf-8&gws_rd=cr&ei=SE-XVvHLFMbA0gSL4YrAAw accessed 14/1/16

¹¹ https://www.google.com.au/search?q=The+supply+of+medical+isotopes+An+economic+study+of+the+Molybdenum+supply+chain&ie=utf-8&oe=utf-8&gws_rd=cr&ei=d2yYVr-uE8zP0ATX_KegBQ accessed 15/1/2015

Cyclotron isotope production

A cyclotron is an electromagnetic device (about the size of a four wheel drive car) used to accelerate charged particles (ions) to sufficiently high speed (energy) so that when it impinges upon a target the atoms in the target are transformed into another element.¹² In other words, it uses electricity and magnets to shoot a narrow beam of energy at elements, e.g. molybdenum-100, a natural material, and this produces technetium-99.

A cyclotron differs from a linear accelerator in that the particles are accelerated in an expanding spiral rather than in a straight line.

The Canadian approach

In 2009 the Canadian Government Expert Review Panel on Medical Isotope Production recognised that cyclotron technology could readily be adapted to produce isotopes.

Drawing from expertise in physics, chemistry, and nuclear medicine, the team of Canadian researchers (Triumf Cyclomed99 group¹³) set out to develop a reliable, alternative means of production for a key medical isotope Technetium-99m (Tc-99m). In early 2015 they announced they had developed technology that uses medical cyclotrons already installed and operational in major hospitals across Canada to produce enough Tc-99m on a daily basis. They also successfully addressed issues for several other less commonly used isotopes.¹⁴

This production method for Tc-99m can be used by retrofitting various brands of conventional cyclotrons already in use in hospitals and health centres across Canada. They have had successful pilot projects producing commercial quantities of isotopes in three different cyclotron models (from GE and ACSI). More cyclotron types will be demonstrated shortly. They state proposed upgrades to existing medical cyclotrons and production sites can be done quickly and cost effectively. This allows for rapid deployment of the technology which can be scaled to meet regional demands.

Depending on the machine capability, a large metropolitan area could be supplied by a single dedicated, or a handful of partially dedicated, medical cyclotrons. By enabling regional hospitals to produce and distribute isotopes to local clinics, widespread supply disruptions can be avoided.

The Canadians also believe cyclotrons create new opportunities to export technology to international partners and across multiple business sectors. Other uses exist for nearly all

¹² <http://www.triumf.ca/faq-medical-isotopes> accessed 13/1/2016

¹³ <http://www.triumf.ca/cyclomed99> accessed 15/1/2016

¹⁴ <http://www.triumf.ca/cyclomed99/articles-and-media> accessed 13/1/2016

aspects of this technology, with potential applications that have benefits toward other aspects of nuclear medicine, molecular imaging and non-related fields.

By the completion of the project, the research team will be producing Tc-99m on three different brands of medical cyclotrons at a commercial scale. Production and distribution of this most commonly used isotope from a regional supply hub will de-centralize the process, helping to avoid future isotope shortages.

Clinical trials began in 2014 and are proceeding toward full market approval through Health Canada (equivalent to the US FDA).¹⁵ In Canada there are plans to have 24 cyclotrons operating by 2018. But it is likely to be several years before cyclotron production is able to fully substitute for the reactor based isotope production. The Canadian example is useful given some similarities in population, geographic size and city size.

Worldwide many hospitals in major urban centres operate cyclotrons. There are currently over 950 small medical cyclotrons manufactured by several companies (ACSI, GE, IBA, Siemens, Sumitomo, Best, etc.) installed around the world. Approximately 550 of these machines operate above 16 MeV and are capable of producing appreciable quantities of Tc-99m. Existing cyclotrons would need to be upgraded to maximize beam current onto a single target. It is important to note that cyclotron production still needs considerable work to become mainstream.

Cyclotrons in Australia¹⁶

A new medical production facility in Australia is the twin PETNET cyclotrons at Lucas Heights. These are small cyclotrons dedicated to making fluorine-18 for FDG synthesis.

Two small cyclotrons are operated commercially in Melbourne by Cyclotek while others are based at the Royal Prince Alfred Hospital (NSW), Peter MacCallum Cancer Institute (VIC), Austin Health and Medical Imaging Australia (VIC), Royal Brisbane Hospital (QLD), Wesley Hospital (QLD) and Sir Charles Gairdner Hospital (WA). Another will be integrated into a new building complex at the Macquarie University Hospital in NSW. It remains to be seen how many of these will be sufficiently powerful to adopt the Canadian retrofit technology to produce isotopes in a decentralised way. Australia should look to partner with the Canadians to jointly progress and implement the cyclotron technology.

¹⁵ <http://www.triumf.ca/cyclomed99/how-it-works> accessed 13/1/2016

¹⁶ <http://www.ansto.gov.au/NuclearFacts/AboutNuclearScience/ReactorsandAccelerators/Cyclotrons/> accessed 13/1/2016

It is interesting to note that the current ANSTO web page states:

*“A recent report (2010) from the OECD Nuclear Energy Agency indicates that non-reactor technologies for Mo-99 production are still decades away from fruition, and expresses strong doubts as to whether they could ever substitute for reactor technologies. A 2010 article in the European Journal of Nuclear Medicine and Molecular Imaging comes to the same conclusion”.*¹⁷

Clearly in 2016 this is not the case. It is surprising and concerning that the enormous and very well publicised technological advances made in Canada are not acknowledged. It is also surprising given the 2015 OECD/NEA report “The Supply of Medical Isotopes” acknowledges the significant and rapidly growing role of alternative technology projects, and notes their contribution to world supply is modelled as progressive and quite substantial from 2017 on.

It is important that ANSTO provides up to date and balanced information to government and the public, so that it is not perceived as behaving like a vested interest.

Conclusion

Australia’s proposal to increase production of isotopes at the OPAL Lucas Heights reactor comes at a turning point in the technology. We have a choice as to whether we continue reactor manufacture, or develop cyclotron capacity in Australia.

Reactor production of isotopes has been shown to be unreliable. On a number of occasions it has resulted in worldwide shortages of supply, due to the unplanned outages that have occurred. Cyclotron use would enable more reliable decentralised isotope production, which will be both cheaper and cleaner.

Reactor production and sale can only occur with significant subsidies from the government (i.e. taxpayers). It is more costly than cyclotron manufacture. Subsidisation of other countries’ health systems at a time when Australia is already financially constrained seems ill advised.

In addition, reactor use for the production of isotopes creates a significant waste burden. 97% of the increased reactor isotope production is planned to be for international sale, so Australia will be left with the reactor waste from this international use. This waste is long-lived Intermediate Level Waste which must be safeguarded for tens of thousands of years, as well as shorter-lived Low Level Waste which requires formal disposal.

¹⁷ <http://www.ansto.gov.au/NuclearFacts/AboutNuclearScience/ReactorsandAccelerators/Cyclotrons/>
accessed 13/1/2016

Cyclotrons, unlike a nuclear reactor, pose almost no accident, proliferation or terrorist risks.

Provision of heavily subsidised reactor based isotopes internationally is also likely to slow the uptake of cyclotron technology in many countries.

In contrast, cyclotron technology is cheaper, less prone to shortages of supply, and does not produce any long lived nuclear waste, and will be commercially feasible in the near future. To develop cyclotron manufacture in Australia, a suitable research team needs a champion with the appropriate political connections, along with a hospital in Australia willing to serve as a test site. Once the Australian cyclotron and medical community are able to test the technology, it will be possible to make a well informed decision.

ANSTO is a tax payer funded organisation. The information it provides to the community via its website is significantly outdated. It should be leading the debate on this issue, and has a responsibility to provide accurate and up to date information.

The decision to markedly increase reactor isotope production should be subject to a public inquiry, given it will have repercussions that include the need for major subsidies, less reliability of supply for nuclear medical care and result in the production of waste that will impact on future generations of Australians for millennia.