Alternatives for the production of medical isotopes

A research paper prepared for Greenpeace Netherlands

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Jan Willem van Gelder
Anniek Herder

Profundo
Radarweg 60
1043 NT Amsterdam
The Netherlands
Tel: +31-20-820 83 20
E-mail: profundo@profundo.nl
Website: www.profundo.nl

Summary

The time and investments needed to built the proposed high flux reactor PALLAS, can also be used to develop alternatives for the production and use of medical isotopes. As a nuclear reactor has significant disadvantages because of safety and environmental issues, this report commissioned by Greenpeace, takes a closer look at the advantages and disadvantages of alternatives for nuclear reactors and the period needed for each alternative to become commercially available.

Although the (limited) research has not found detailed information about construction time and costs, it does show that there are interesting alternatives available. Table 1 provides an overview of the alternative production technologies for producing the most widely used medical isotope Technetium-99 (Tc-99m). This isotope is used for imaging technologies and derived from parent isotope Molybdenum-99 (Mo-99), that is produced in a nuclear research reactor.

According to a Dutch study amongst nuclear medicine professionals its use is not expected to decrease the coming fifteen years. But in absolute terms, the demand for Mo-99 is not likely to increase. Moreover, the European imaging association AIPES does believe that a shift towards the use of non-reactor produced radionuclides for imaging and therapy purposes and pain relief, is possible because of the availability and increasing use of alternative imaging technologies. Since the radio-isotope supply crises of 2008 these technologies are increasingly being considered as substitutes instead of complementary to common nuclear medicine procedures. Besides that we also found a report on the increased use of Thallium, the predecessor of Tc-99, that can be made using accelerators.

For therapeutic applications many different medical isotopes are required, that can be made with accelerators or replaced by other isotopes, produced with accelerators.

Based on the conclusions, we recommend:

- to undertake a more thorough research that compares the alternative production technologies for Mo-99 on a set of indicators like costs, construction time needed, the impact on waste, the use of highly enriched uranium for fuel and targets, additional facilities needed, etc.;
- to undertake additional research to assess the future demand and production technologies for other radioisotopes (besides Mo-99);
- to asses if separate solutions or a combined solution for producing Mo-99 and producing other radioisotopes are most desirable.

Table 1 Overview of alternative production technologies of Mo-99

Technology	Stage	Advantage	Disadvantage
Accelerators			
Proton activation	Both research / demonstration stage as well as commercial available (ACSI: in 15 months)	• No use of enriched uranium targets • Local production of Tc-99m in a network of cyclotrons ensures a regular supply • Own or nearby production facility at hospital • No reactor needed: less safety risks, no high level nuclear waste production	• Partial conversion of Mo-100 into Mo-99 and other Mo- isotopes which may lead to harmful Tc-isotopes • Lesser quality of end product • Own or nearby production facility at hospital
Photo-neutron	Research	• Nearly no waste stream, except waste from chemical processing of irradiated targets • Higher predictability of schedule, cost, and licensing than for a reactor • Facility costs and licensing issues should be reasonably low risk • Scalable: it can be built as a small (low power) facility or large facility • No reactor needed: less safety risks, no high level nuclear waste production	• Change in Tc-99m generator technology needed • Facility requires more electrical power than reactor • Approval needed from pharmaceutical authorities • Cost of manufacturing Mo-100 targets and separation likely to be high
Photo-fission	Research (3-4 years needed for design and testing, another 3-4 years for construction)	• Use of natural uranium targets, with lower cost and safety risks • Achieve similar yields from natural uranium or enriched uranium targets • Could use existing processing and generator technologies • No reactor needed: less safety risks, no high level nuclear waste production	• No proof of working of photon production, construction of converter is problematic • Could result in higher target waste volume • Facility requires more electrical power than reactor, and than photo-neutron process because higher-beam requirements • Approval needed from pharmaceutical authorities • Similar hot-cell facility needed for Mo-99 recovery and refinement
Nuclear reactors			
Using LEU targets	Available (adaptation time needed varies from months to	• Compared to using HEU targets: • Same quality	• Conversion to LEU targets is expensive because adaptation production chain

Technology	Stage	Advantage	Disadvantage
	13 years)	• Lower safety risks • Possibly lesser waste stream	• Still needs high security level and maintenance • Radioactive waste from fuel of nuclear reactor
Smaller reactors	Available but adaptation needed	• If many small reactors work together in network, no new reactors needed	• Still needs high security level and maintenance • Radioactive waste from fuel of nuclear reactor
Neutron activation	Available but research needed for improvement (several years)	• Use of natural uranium targets, with lower cost and safety risks • Nearly no radioactive waste stream from the irradiated targets • Smaller reactors can be used	• Major change in Tc-99m generator technology is needed • Viability of proposed separation techniques need to be proven to work in high-volume application • Radioactive waste from fuel of nuclear reactor • Unclear whether technology is scalable
Solution reactors	Demonstration realised, further research needed (5-6 years)	• Targets are unnecessary • Use of LEU for fuel • Far less radioactive waste Efficient use of neutrons for radionuclide production • Extraction processing is simplified • Inherent passive safety	• Development of isotope separation technology is needed • Need to further increase reactor power Approval needed from pharmaceutical authorities • Radioactive waste from fuel of nuclear reactor
Accelerator Driven Systems	Research (reported availability of MYRRHA in 2018)	• Higher level of safety • Could use existing processing and generator technologies	• Radioactive waste from fuel of nuclear reactor • Probably lower utilization ratio than nuclear reactors • Interference in planning of experiments and isotope production
New generator technologies	Sometimes available, sometimes more research needed	• Some methods are proven • Use of waste from nuclear reactors	• Still need for nuclear reactors • Reprocessing of nuclear waste

Samenvatting

De benodigde tijd en investeringen voor het bouwen van hoge flux onderzoeksreactor PALLAS kunnen ook gebruikt worden voor het ontwikkelen van alternatieve productiemethoden en alternatieven voor het gebruik van medische isotopen. Omdat een kernreactor significante nadelen heeft ten aanzien van veiligheid en milieu, onderzoekt dit rapport in opdracht van Greenpeace, de voor- en nadelen van alternatieven voor kernreactoren en de periode die nodig is voordat deze commercieel beschikbaar zijn.

Hoewel dit (beperkte) onderzoek geen gedetailleerde informatie over de benodigde tijd en investeringen voor de ontwikkeling en constructie van alternatieven heeft opgeleverd, heeft het wel laten zien dat er interessante alternatieven beschikbaar zijn. Onderstaande tabel geeft een overzicht van de alternatieve technologieën voor het produceren van de meest gebruikte medische isotoop Technetium-99 (Tc-99m). Dit isotoop wordt in de geneeskunde gebruikt voor beeldvormingtechnologieën en gegenereerd uit moederisotoop Molybdeen-99 (Mo-99), dat wordt geproduceerd in een nucleaire onderzoeksreactor.

Volgens een Nederlandse studie onder de nucleaire geneeskundigen zal het gebruik ervan naar verwachting de komende vijftien jaar niet afnemen. Maar in absolute aantallen zal de vraag naar Mo-99 waarschijnlijk ook niet toenemen. Verder verwacht de Europese producentenvereniging AIPES dat een verschuiving naar het gebruik van niet-reactor geproduceerde radionucliden voor beeldvorming, therapie en pijnbestrijding zeker mogelijk is door de beschikbaarheid en het toenemende gebruik van alternatieve toepassingen. Sinds de leveringcrises van radionucliden in 2008 worden deze technologieën steeds vaker beschouwd als vervanging in plaats van een aanvulling op de gebruikelijke nucleaire geneeswijzen. Daarnaast vonden we ook een verslag over het toegenomen gebruik van thallium, de voorganger van Tc-99, dat gemaakt kan worden met behulp van deeltjesversnellers.

Tenslotte kunnen voor therapeutische toepassingen zeer veel verschillende medische isotopen gebruikt worden die nu al gemaakt kunnen worden met deeltjesversnellers óf vervangen kunnen worden door andere isotopen, die wel kunnen worden geproduceerd met deeltjesversnellers.

Op basis van de conclusies, bevelen we aan:

- om een meer diepgaand onderzoek uit te voeren dat de alternatieve productiemethoden voor Mo-99 op een reeks indicatoren zoals kosten en tijd voor constructie vergelijkt met de impact op de afvalstroom, het gebruik van hoog verrijkt uranium voor brandstof en bestralingstargets, extra benodigde voorzieningen, enz.;
- om extra onderzoek te doen naar de toekomstige vraag naar en productie van andere radio-isotopen dan Mo-99;
- om met behulp van onderzoek te beoordelen of de genoemde afzonderlijke oplossingen of een gecombineerde oplossing voor het produceren van Mo-99 en andere radio-isotopen het meest wenselijk is.

Table 2 Overzicht van alternatieve productiemethoden van Mo-99

Technologie	Fase	Voordeel	Nadeel
Deeltjesversnellers			
Protonen-activering	Zowel onderzoek / demonstratie als beschikbaar (ACSI: over 15 maanden)	• Geen gebruik van hoogverrijkt uranium voor targets • Lokale productie van Tc-99m in netwerk van cyclotrons verzekert constante levering • Eigen of nabije productie faciliteit bij ziekenhuis • Geen kernreactor nodig: weinig veiligheidsrisico's en geen hoogactief radioactief afval	• Gedeeltelijke omzetting van Mo-100 in Mo-99 en andere Mo isotopen die kunnen leiden tot schadelijke Tc-isotopen • Minder kwaliteit eindproduct • Eigen of nabije productie faciliteit bij ziekenhuis benodigd is vereiste
Photo-neutron	Onderzoek	• Afgezien van afval voor chemische bewerking van bestralingstargets, bijna geen radioactief afval • Hogere voorspelbaarheid van productieschema, kosten en benodigde vergunningen dan kernreactor • Kosten van faciliteiten en verkrijgen van vergunningen redelijk lage risico's. • Kan zowel als kleine en grote faciliteit gebouwd worden • Geen kernreactor nodig: weinig veiligheidsrisico's en geen hoogactief radioactief afval	• Aanpassing aan Tc-99m generatoren vereist • Faciliteit heeft meer elektriciteit nodig dan kernreactor • Toestemming nodig van farmaceutische autoriteiten • Kosten productie Mo-100 bestralingstargets en scheidings-technieken waarschijnlijk hoog
Photo-fission	Onderzoek (3-4 jaar nodig voor ontwerp en testen, nog eens 3-4 jaar voor constructie)	• Gebruik van natuurlijk uranium voor bestralingstargets, met lagere kosten en veiligheidsrisico's • Behaalt vergelijkbare opbrengst als met hoogverrijkt uranium bestralingstargets • Kan bestaande faciliteiten gebruiken • Geen kernreactor nodig: weinig veiligheidsrisico's en geen hoogactief radioactief afval	• Nog niet bewezen • Bouw van omvormer is problematisch • Kan resulteren in meer radioactief afval • Faciliteit heeft meer elektriciteit nodig dan kernreactor en photo-neutron proces • Toestemming nodig van farmaceutische autoriteiten • Dezelfde hot-cell faciliteiten nodig voor verwerking Mo-99
Kernreactoren			
Gebruik van LEU targets	Beschikbaar (tijd voor aanpassing varieert van paar	• In vergelijking met hoogverrijkte bestralingstargets:	• Overschakelen op LEU bestralingstargets is duur door

Technologie	Fase	Voordeel	Nadeel
	maanden tot 13 jaar)	• Dezelfde kwaliteit • Lagere veiligheidsrisico's • Mogelijk kleinere afvalstroom	aanpassingen in keten • Nog steeds veiligheidsrisico's en hoog niveau van onderhoud • Hoogactief afval door gebruik kernreactor
Kleinere kernreactoren	Beschikbaar maar aanpassingen aan faciliteiten nodig	• Als veel kleine kernreactoren samenwerken in een netwerk zijn er geen nieuwe grote kernreactoren nodig	• Nog steeds veiligheidsrisico's en hoog niveau van onderhoud • Hoogactief afval door gebruik kernreactor
Neutronen-activering	Beschikbaar maar onderzoek nodig voor verbetering van scheidingstechnieken (meerdere jaren)	• Gebruik van natuurlijk uranium voor bestralingstargets met lagere kosten en veiligheidsrisico's • Weinig radioactief afval van bestralingstargets • Kleinere reactoren nodig	• Aanpassing Tc-99m generator vereist • Scheidingstechnieken moet nog worden bewezen in toepassing op grote schaal • Hoogactief afval door gebruik kernreactor • Onduidelijk of techniek kan worden opgeschaald
Homogene kernreactor	Demonstratiemodel gerealiseerd, verder onderzoek nodig (5-6 jaar)	• Geen bestralingstargets nodig • Gebruik van laag verrijkt uranium als brandstof • Minder radioactief afval • Efficiënt gebruik van neutronen voor radionuclide productie • Extractieproces is vereenvoudigd • Inherente veiligheid	• Ontwikkeling van scheidingtechnieken nodig • Straalkracht moet nog verder worden opgevoerd • Toestemming nodig van farmaceutische autoriteiten • Hoogactief afval door gebruik kernreactor •
Accelerator Driven Systems	Onderzoek (gerapporteerde beschikbaarheid van MYRRHA in 2018)	• Hoog niveau van veiligheid • Kan bestaande chemische verwerkingsprocessen gebruiken	• Hoogactief afval door gebruik kernreactor • Waarschijnlijk lager gebruik dan kernreactoren • Interferentie bij de planning van experimenten en productie van isotopen
Nieuwe generator technologieën	Soms beschikbaar, soms meer onderzoek nodig	• Sommige methoden zijn al bewezen • Hergebruik van afval van kernreactoren	• Hoogactief afval door gebruik kernreactor voor productie moederisotopen • Hergebruik van afval van kernreactoren

Contents

Introduction

NRG, the owner of the High Flux Reactor (HFR) in Petten, will soon come with a preliminary proposal for the construction of a new reactor, named PALLAS, that is to replace the old one. However, it will at least take another ten years before the new reactor will be operational. That period can also be used to invest in alternatives for the production and the use of medical isotopes. Greenpeace prefers alternatives that don not need a nuclear reactor for isotope production because of safety concerns and the nuclear waste problem of reactors. The advantages and disadvantages of such alternatives are not yet sufficiently examined to take a decision on the construction of PALLAS.

This report takes a closer look at the production methods for medical isotopes (Chapter 1). Two questions are answered for each alternative:

- what are the advantages and disadvantages of the alternative?
- what is the period needed for the alternative to become commercially available?

Studies used to answer this questions are amongst others, a report of Technical University Delft (TU Delft), commissioned by the Dutch ministry on Environment, VROM, to help them decide whether a new reactor should be built or not. This report cannot be seen as independent source of information, because the institute will probably benefit from PALLAS itself.

We also reviewed some studies on expectations for the future of, and alternatives for, the common use of medical isotopes (Chapter 2).

A summary in both English and Dutch can be found on the first pages of the report.

We hope this report contributes to the debate on the desirableness of a new reactor.

Chapter 1 Medical isotope production

1.1 What are medical isotopes

Atoms consist of electrons and nuclei, also known as nuclides. The latter include two types of nuclear particles, positively charged protons and uncharged neutrons. In chemistry and physics, the atomic number, Z, is the number of protons found in the nucleus of an atom and uniquely identifies a chemical element. In an atom of neutral charge, the atomic number is also equal to the number of electrons.

This atomic number should not be confused with the mass number, A, which is the total number of protons and neutrons in the nucleus of an atom. The number of neutrons, N, is known as the neutron number of the atom; thus, A = Z + N. Isotopes are different types of nuclides of the same chemical element, each having a different number of neutrons. Most naturally occurring elements exist as a mixture of isotopes, and the average atomic mass of this mixture determines the element's atomic weight.

A radionuclide is an atom with an unstable nucleus, and characterized by excess energy. The radionuclide undergoes radioactive decay, and emits a gamma ray(s) and/or subatomic particles that constitute ionizing radiation. Radionuclides may occur naturally, but can also be artificially produced. They are often referred to by chemists and physicists as radioactive isotopes or radioisotopes and used for industrial or medicine purposes. The wording medical isotopes, instead of radioisotopes, is used in nuclear medicine.

Medical isotopes can be used for molecular imaging, therapy, pain palliation and radioimmunotherapeutics. The table below describes the major radioisotopes suitable for medical purposes and used on a large scale.

Figure 1. Radioisotopes for large scale use in nuclear medicine during 2010-2020

Imaging: conventional, single photon emission tomography SPECT, SPECT/CT	Imaging: positron emission tomography (PET, PET/CT, PET/MRI)	Therapy, pain palliation, radioimmunotherapeutics	
^{67}Ga (a)	^{18}F (a)	^{67}Cu (a)	**^{131}I (r)**
^{99m}Tc/^{99}Mo (r)(g)	^{61}Cu (a)	**^{89}Sr (r)**	**^{153}Sm (r)**
^{111}In (a)	^{64}Cu (a)	^{89}Zr (a)	^{169}Er (r)
^{123}I (a)	^{68}Ga/^{68}Ge (a)(g)	**^{90}Y/^{90}Sr (r)(g)**	**^{177}Lu (r)**
^{131}I (r)	^{82m}Rb/^{82}Sr (a)(g)	**^{90}Y (r)**	**^{186}Re (r)**
^{133}Xe (r)	^{89}Zr (a)	^{117m}Sn (r)	**^{188}Re/^{188}W (r)(g)**
^{201}Tl (a)	^{124}I (a)	^{123}I (a)	alpha emitters, e.g. ^{213}Bi/ ^{225}Ac (g)(a)

production route: **(r)** = reactor, **(g)** = generator, **(a)** = accelerator

Source: Verbeek, P., "Report on Molybdenum 99 Production for Nuclear Medicine 2010-2020 - State of the Art", AIPES, November 2008.

Technetium-99m (^{99m}Tc or Tc-99m) has become the most widely used radioisotope for diagnosing diseased organs using single photon emission computed tomography (SPECT). Tc-99m is generated from molybdenum-99 (^{99}Mo or Mo-99). About 80-85% of nuclear medicine procedures use Mo-99. [1]

According a survey of the Association of Imaging Producers and Equipment Suppliers (AIPES) Tc-99m will remain the main medical isotope the coming years. As the production of Tc-99m is a good example of the issues relevant to nearly all other radioisotopes produced by nuclear fission and activation in neutron reactor flux they further argue that if supply of Mo-99 is secured, supply for most other radioisotopes from reactors may also be secured. [2]

This study focuses on production alternatives of Mo-99 and Tc-99m, but will also show alternative options for other medical isotopes. Especially when this presents interesting possibilities for the production of Mo-99 or Tc-99m.

1.2 Common production technology

The common production technology for radioisotopes involves nuclear reactions with the so-called neutron-fission process. The basic setup involves using a beam of particles (for example from a nuclear reactor core) to strike a target. Nuclear (as opposed to chemical) reactions within the target then create the radioisotope atoms from the atoms of the target material. After irradiation by the beam, the target is then removed to recover the radioisotopes of interest using mechanical and chemical procedures by the producers of radioisotopes. A refinement step then isolates and purifies the radioisotope so that it is ready for transport to, for example, the producer of radiopharmaceuticals.

Radioisotopes are produced both by using a nuclear research reactor or an accelerator. Nuclear reactors and particle accelerators are complementary in the production of radioisotopes for medical applications because different radioisotopes made in either an accelerator or a nuclear reactor are made for specific purposes. [3]

1.2.1 Production of Tc-99m

Derived from the man-made element technetium, Tc-99m emits radiation without causing significant damage to the patient and its six-hour half-life is long enough for a medical examination and short enough to allow a patient to leave the hospital soon afterwards. More importantly, Tc-99m is generated from molybdenum-99 (^{99}Mo or Mo-99), whose half-life of 66 hours allows for transport over long distances.

Mo-99 is mostly produced at nuclear reactors where the beam of neutrons comes from the fission reaction in uranium in the reactor core. Also the target material contains uranium (U-235) that after irradiation, is split in various completely different elements including Mo-99. The raw irradiated target material from the reactor, containing a variety of radioisotopes, then travels to a separate facility.[4]

It is dissolved in either nitric acid or alkaline solutions for one to three hours, after which the Mo-99 can be recovered and purified by a variety of processes. Mo-99 is send to the manufacturer of Tc-99m generators, which is often located close to the Mo-99 producer.

The Tc-99m generators must then quickly be forwarded to hospitals and other users. A radio pharmacy in the hospital will recover Tc-99m from the generator and add this to the nonradioactive components of radiopharmaceuticals. In case of molecular imaging, Tc-99m will be combined with the relevant biomolecules to form the specific radiopharmaceutical for administration to a patient.[5]

1.3 Present medical isotope producers

While radioisotopes, and especially Mo-99, are at present commonly produced in research reactors, not all research reactors in the world are able or willing to produce them. The analytical and research capabilities of a research reactor are determined primarily by the available thermal neutron flux. The database of International Atomic Energy Agency (IAEA) keeps record of operational research reactors in the world and categorises them as a low flux, medium flux, or high flux reactor according to the following levels of thermal neutron flux: [6]

- 107 low flux reactors ($\leq 1 \times 10^{12}$ n/cm^2/s)
- 85 medium flux reactors ($> 1 \times 10^{12}$ n/cm^2/s and $< 1 \times 10^{14}$ n/cm^2/s)
- 55 high flux reactors ($\geq 1 \times 10^{14}$ n/cm^2/s)

The amount of radioactivity of radioisotopes formed is proportional to the neutron flux: the higher the neutron flux, the higher the radio activity. This explains the importance of nuclear research reactors with high power or high neutron flux for the production of radioisotopes, especially Mo-99. [7]

The worldwide production of Mo-99 basically depends on six nuclear reactors: the OPAL in Australia, the BR2 reactor in Belgium, the NRU in Canada, the High Flux Reactor (HFR) in The Netherlands, SAFARI-1 in South Africa and, to a lesser extent, the OSIRIS in France. The production schedules of these reactors are matched to comply with the need for medical isotopes. These producers of medical isotopes are aging. In 2009 the NRU was shut down again for necessary, but unscheduled, repairs. Because of the risk that a possible break down of more than one reactor at the same time will result in medical isotope shortage, many people involved argue that new reactors are needed to safeguard the supply of medical isotopes. Plans for new reactors are being developed, taking a lot of time and investments. For example, the construction of Pallas (Netherlands) is estimated at € 500 million and Jules Horrowitz (France) at € 500 million.[8]

Besides these six major producers other reactors do produce radioisotopes for application by nuclear medicine, but only in small amounts and for the national market. However, most reactors are dedicated for research and are not equipped with the necessary facilities to regularly produce medical isotopes.[9]

When looking for alternative production methods to avoid the disadvantages of nuclear reactors, the challenge is to identify those techniques which have high yields of ^{99}Mo and high specific radio activity. It is also important to consider the necessary facilities for the production of Tc-99m generators and the infrastructure for transport to hospitals, because a constant and reliable supply of Mo-99 is critical for nuclear medicine.

Chapter 2 Alternative medical isotope production technologies

2.1 Introduction

In this chapter alternative medical isotope production technologies are reviewed. All of these technologies should be able to produce high yields of ^{99}Mo with high specific radio activity, guaranteeing a constant and reliable supply of Mo-99 to the manufacturers of Tc-99m generators and from there to hospitals and other users.

The alternative technologies are grouped in four groups, based on the basic technology used:

- Accelerators (paragraph 2.2);
- Nuclear reactors (paragraph 2.3);
- Accelerator driven systems (paragraph 2.4);
- Generators (paragraph 2.5).

The basic characteristics of each technology are described and as far as possible an overview is given of the costs, advantages and disadvantages of each technology as well as the period needed to get the technology operational.

2.2 Accelerators

An accelerator or accelerating machine (also called cyclotron) is a high voltage machine to accelerate particles and is developed for use in "atom-smashing" experiments. The energy of the utilized particles ranges from a few electronvolts (eV) up to nearly teraelectronvolts (1000 billion eV). Electrons, protons, and all kind of charged particles are accelerated to produce X-rays, neutrons, charged particle beams and radioisotopes for use in research and technology. Accelerators can vary in size between one small enough to fit on a table, up to huge machines tens of kilometres in length. They can be linear or circular, can operate in continuous or pulsed modes, and utilize many techniques to accelerate ion beams. [10]

A few hundred accelerators are used worldwide to produce short-lived medical isotopes, needed for producing medical isotopes required for PET (positron-emission tomography) procedures (^{11}C, ^{13}N, ^{15}O, ^{18}F). These isotopes cannot be produced in nuclear reactors.[11] An accelerator based approach has some major advantages over nuclear reactors: [12]

- The accelerator can be turned on and off at will and without consequence
- The accelerator does not produce radioactive waste from its operation although waste from chemical processing of irradiated targets to recover and extract the Mo-99 would be similar to a reactor-based approach
- An accelerator is safe, no risk of nuclear accidents
- The technology is scalable: additional accelerators can be built or turned on and off as needed
- Higher predictability of schedule, cost and licensing than for a reactor. The main facility costs and licensing issues should be reasonably low in risk
- At end-of-life, an accelerator is comparatively inexpensive to decommission as major components are less prone to become radioactive over time than occurs in the high neutron environment of an operating reactor

Due to technical reasons, until now few accelerators were capable of producing Mo-99 and none are suitable for producing more than a small fraction of the required amounts. Considering above mentioned advantages, the challenge is to make accelerators able to produce ^{99}Mo on the scale needed for nuclear medicine. The next sub-paragraphs discuss some of the options.

2.2.1 Proton activation

Irradiation of stable elements with protons in accelerators also results in radionuclides of the irradiated element. An accelerator can for example be used for facilitating the ^{100}Mo(p,pn)^{99}Mo reaction, taking one neutron from the stable Mo-100.

An accelerator with high beam power can only produce 0,64 Ci ^{99}Mo/hour from 100% enriched ^{100}Mo. This means that there are about 160 accelerators needed to produce an equivalent of ^{99}Mo as for example the High Flux Reactor in Petten is able to produce through fission of uranium targets. With the current available accelerators it is not (yet) possible to produce the amount of ^{99}Mo that hospitals need. A disadvantage is that besides ^{99}Mo also other Mo-isotopes are being produced and this will cause competitive reactions, such as the production of ^{96}Tc which - when applied in the hospital - may lead to a double dose and bad images. More research is needed to find a solution to this problem.

Proton activation in an accelerator can also be used for direct production of ^{99m}Tc. The yield of two cyclotrons using this process is equivalent to the yield of a fission process in a reactor, but the half-life of Tc-99m is that short that a hospital would need its own cyclotron or a cyclotron located within two hours driving distance. Also, the hospital would need facilities for separating ^{99m}Tc from the ^{99}Mo target. Of course, this can be seen as an advantage too, as a hospital or radio pharmacy would not be dependent on a major radioisotope producer and its infrastructure anymore. [13]

This idea is brought into practice by Advanced Cyclotron Systems Inc (ACSI). The Canadian company proposed to use its new 24 MeV, TR-24, cyclotron to produce technetium-99m directly from enriched molybdenum-100 and use existing distribution networks. The ACSI TR series cyclotrons are already used for the commercial production and distribution of PET and SPECT radioisotopes by the world's leading radioisotope producers. According to ACSI, the TR-24 cyclotron is commercially available and recently has been licensed by Canadian Nuclear Safety Commission. With several participating organizations already planning installation of TR-24 cyclotrons in the very near future this network can start supplying technetium-99 and other medical isotopes in 15-16 months. It is expected that in 2 to 3 years it could meet the entire Canadian technetium-99m demand. [14]

It is unclear how ACSI addresses some disadvantages mentioned by TRIUMF and the Dutch Technical University of Delft (TU Delft). They say that the quality of technetium produced from enriched Mo-100 is not good enough because it exists of only 25% Tc-99m together with 75% Tc-99. Thus, three times more of the normal dose is needed for treatment and this is, due to medical reasons, not desirable. Finally, only part of the expensive ^{100}Mo will convert into the useful ^{99}Mo and a separation technique is not available (according to TU Delft) or very costly (according to the Canadian laboratory TRIUMF). [15]

- **Estimated costs**
  Building a cyclotron facility will cost approximately CA$ 2.5 million (€1,7 million) to CA$ 6 million (€ 4 million).[16]

- **Estimated time for design and construction**
  ACSI cyclotrons can start supplying in 15-16 months.

- **Advantages of this approach**
  - No use of HEU or LEU for targets
  - No high level radioactive waste, because no reactor is operated
  - In case of Tc-99m production, local and regular production is possible

- **Disadvantages of this approach:**
  - Only part of the expensive Mo-100 converts into Mo-99, other Mo-isotopes will cause competitive reactions and production of harmful Tc-isotopes
  - Lesser quality of end product than reactor produced Mo-99 or Tc-99m
  - A hospital would need its own production and manufacturing facilities

2.2.2 Photo-neutron process

The photo-neutron process uses a high-powered electron accelerator to irradiate a high-Z converter target such as liquid mercury or water-cooled tungsten. High-energy photons (known as Bremsstrahlung) radiation are produced by the electron beam as it interacts and loses energy in the converter target. The photons can then be used to irradiate another target material placed just behind the convertor, in this case Mo-100, to produce Mo-99. In short: an intense photon beam generated by an electron accelerator removes a neutron from a Mo-100 target to produce Mo-99 (stimulating the reaction $^{100}Mo(\gamma,n)^{99}Mo$). [17]

According to the Task Force on Alternatives for Medical Isotope Production "some research and development work to examine the Mo-100 target chemistry for direct extraction of Tc-99m could be considered. If successful, it could make the possibility of very small, self-contained generator systems being possible for central radio-pharmaceutical labs for a group of hospitals, very similar to PET cyclotrons." [18]

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  Unclear

- **Advantages of this approach**

  - There would be nearly no waste stream, except waste from chemical processing of irradiated targets to recover and extract the Mo-99
  - Higher predictability of schedule, cost, and licensing than for a reactor
  - The main facility costs and licensing issues should be reasonably low risk
  - Scalable: it can be built as a small (low power) facility or large facility, because technology is equally useful over a wide range of powers
  - No high level radioactive waste, because no reactor is operated

- **Disadvantages of this approach**

  - A major change in the generator technology would be needed because of the different target
  - An accelerator-based production facility would require substantially more electrical power than a reactor-based facility
  - Pharmaceutical authorities like Health Canada needs to approve these new products
  - The cost of manufacturing Mo-100 targets and the cost of separating Mo-100 from Mo-99 would likely be quite high, because Mo-100 comprises less than 10% of naturally occurring molybdenum and the separated isotope presently costs dollars per milligram

2.2.3 Photo-fission

The present-day technique uses a neutron to split uranium. An alternative solution uses a photon instead to fission the uranium nucleus. The proposed photo-fission accelerator approach would produce high-energy photons to split natural uranium U-238 with the same fractional production of Mo-99 as produced by neutrons. According to a 2008 study of TRIUMF, the photo-fission accelerator technique has several key advantages and the authors highly recommends further research and investments. This technology is expected to generate sufficient quantities of Mo-99 to supply a significant fraction of the North American demand.[19]

The conceptual design is not established yet and there are substantial uncertainties in the capital cost and eventual operating costs. However, according to TRIUMF construction of such an accelerator will be much faster than design and construction of a new reactor, such as Pallas (which will take probably ten years). Vice versa NRG, the owner of HFR Petten and initiator of Pallas, thinks that TRIUMF will need about ten to twenty years before their ideas are realised.[20]

TU Delft emphasizes that this accelerator technology would be quite focused: it would not allow for production of other non-fission-based medical isotopes and would not provide many of the additional R&D and commercial opportunities associated with present-day research reactors.[21]

- **Estimated costs**
  Design of a demonstration machine will cost about C$ 10 million (€ 6.7 million), and the construction costs are estimated at C$ 50 million to C$ 125 million (about € 33.8 million to € 84.6 million). The report speaks of “a half-dozen multi-megawatt machines could be built that would meet about 30-50% of North-American demand”. [22]

- **Estimated time for design and construction**
  From 2008 about 3 to 4 years is needed for design and testing plus an additional 3-4 years for construction.

- **Advantages of this approach**
  - Use of natural or depleted uranium targets which have lower cost, no concerns about shipping and handling HEU, and would reduce security required for waste-storage site
  - The proposed technology can achieve similar yields from natural uranium, LEU, or HEU targets because the photo-fission process is not very sensitive to the neutron number of uranium
  - Could use existing processing techniques, although the volume of the dissolved uranium solution used for Mo-99 recovery could be larger than present (depending on the target designs), but once recovered, the Mo-99 refinement and purification steps should be identical
  - Could continue to use existing generator technologies
  - No high level radioactive waste, because no reactor is operated

- **Disadvantages of this approach**
  - No proof of working of photon production technology (demonstration machine needs to be built first) and the construction of converter is still problematic
  - Could result in higher target waste volume than HEU reactor target technology because of low concentration of the product per gram of target material used (depending on the target design). The specific activity of the actual Mo-99 product should be similar to the value obtained from neutron-fission of HEU, but the total target volume may be significantly higher because of thermal or mechanical issues associated with handling beam power

- An accelerator-based production facility would require substantially more electrical power than a reactor-based facility
- Higher operating and capital costs for the accelerator than the photo-neutron process because of higher beam-power requirements
- The facility would likely be similar to existing hot-cell facilities used in Mo-99 recovery and refinement
- Because this is a new technology, pharmaceutical authorities like Health Canada, the U.S. Food and Drug Administration, the European Medicine Agency or the Dutch Medical Evaluation Board, will probably need to approve the final Mo-99 product for clinical use

2.3 Nuclear reactors

2.3.1 Neutron-fission process with LEU targets

As explained earlier, the most common and large scale production method of Mo-99 radioisotopes is to stimulate fission of uranium (^{235}U) in high flux research reactors by irradiation of uranium targets with neutrons. The targets contain highly enriched uranium (HEU) which lead to nuclear non-proliferation and security concerns. Discussions around the world about this concerns lead to the wish of moving away from the traditional use of HEU as reactor fuel and in targets for the production of Mo-99. The alternative is the transition to low enriched uranium (LEU) for reactor fuels and targets. This approach has made significant progress, but large-scale viability of LEU targets is still under development.[23]

In an article in Nonproliferation Review, Christina Hansell points out that the technology to produce Mo-99 using LEU targets is proven, available, and has been used routinely by two smaller producers for a number of years (Argentina and Australia). Moreover, the Argentine Mo-99 producer has observed an improvement of radionuclide purity and yield since changing to LEU. With conversion, other useful isotopes such as iodine 131 (I-131) can be recovered, instead of leaving them as waste in the Mo-99 production process. [24]
To supply the US nuclear medicine community with medical isotopes Lantheus Medical Imaging announced in the first half of 2009, that it has finalized an arrangement with the Australian Nuclear Science and Technology Organisation (ANSTO) to receive Mo-99 produced from its low-enriched uranium targets in ANSTO's new OPAL reactor. This supply arrangement makes Lantheus, which had relied heavily on the Canadian Chalk River reactor, the first company to supply Tc-99m derived from low-enriched uranium to the U.S. market.[25]

The IAEA is assisting a number of countries in examining and testing the use of LEU targets and several American reactors are launching pilot projects using LEU targets. In 2008, Nuclear Research & consultancy Group (NRG) - the operator of the HFR Petten - would begin work to develop LEU targets in cooperation with France's CERCA. The new Pallas reactor, scheduled to replace HFR in 2015, will be designed to use LEU fuel and targets from the outset. CERCA believes it can create an industrial production capacity to produce these targets in three to four years, but it needs partner companies or governments to help fund this investment. [26]

Besides NRG, CERCA has been in talks with the Missouri University Research Reactor (MURR) on developing LEU targets. The MURR facility itself is a research reactor and needs to be converted into a medical isotope producer. The plan was to start construction of a new production facility for LEU targets in 2009, but in July 2009 Radiology Today wrote that the project has not yet received adequate funding. [27]

Full-scale industrial production of LEU targets is not likely to be set up without either a government mandate or government funding. But political determination and financial support to convert the major producers' isotope production to LEU has been lacking. There are currently no commercial incentives for these producers to convert from HEU use. High up-front costs, low profit margins, and difficult licensing processes mean that the establishment of new facilities is extremely difficult without government intervention. [28]

According to the Dutch research institute Reactor Instituut Delft it indeed seems technically possible to use LEU targets for production of ^{99}Mo. But the research institute also emphasizes the downside of the transition of HEU to LEU targets: significant investments in terms of money (tens of millions of dollars) and time (several months to 13 years) are needed, because the facilities for separation, purifying and refinement throughout the chain need to be adjusted. [29]

- **Estimated costs**
  The American reactor MURR estimates construction of a new production facility for LEU targets at about US$ 35 million (€ 24.8 million).

- **Estimated time for design and construction**
  Estimates vary from several months to 13 years. US reactor MURR estimates that after construction of a new production facility starting in 2009, commercial operation could commence in four years, and is expected in 2012.

- **Advantages of this approach**

  - Produces 100% Mo-99 with high radioactivity in the same quality as when using HEU targets
  - Production method available and proven
  - No criticality issues and concerns about shipping and handling HEU
  - Use of LEU targets at first sight seems to increase radioactive waste (there is five times more uranium in the LEU targets, which means five times more uranium in liquid target waste), but the total volume of waste from LEU is not greater, and may even be slightly less, than in the current HEU process

- **Disadvantages of this approach**

  - Conversion to LEU targets is expensive even in the case of building new reactors because the whole production chain needs to be changed
  - Production process is delicate, still needs a high security level and many maintenance activities.
  - A nuclear reactor is still required to provide the intense flux of neutrons, producing high level radioactive waste

2.3.2 Neutron-fission process in smaller reactors

The amount of radioactivity of radionuclides formed is proportional to the neutron flux: the higher the neutron flux, the higher the radio activity. This explains the importance of nuclear research reactors with high power or high neutron flux for the production of radionuclides.[30] But the IAEA concluded some years ago that many low and medium flux reactors can attribute to the production of ^{99}Mo and other isotopes after adaptation. This involves construction of facilities and infrastructure of the reactors for recovery and refinement of Mo-99 and the production of Tc-99m generators.

In the past few years several projects have started to invest in the facilities and infrastructures of several low and medium flux reactors: Chile, Egypt, Kazakhstan, Libya, Pakistan and Romania.[31] These reactors can be part of a network attributing to the production of medical isotopes and serving as a backup in case other major reactors shut down.

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  Unclear, but depending on available facilities for recovery and refinement of Mo-99 and producing Tc-99m generators

- **Advantages of this approach**

  - Production method proven
  - If many small nuclear reactors work together in a network, no new high flux reactors are needed

- **Disadvantages of this approach:**

  - Adaptation and building of necessary facilities for recovery and refinement of Mo-99 is expensive
  - Continued usage of nuclear reactors for radioisotope production, and thus production of high level radioactive waste from reactor fuel

2.3.3 Neutron activation

In the traditional process, Mo-99 is produced by irradiating uranium targets with neutrons. But production of Mo-99 is also possible by irradiating Mo-98, using neutron activation (also called neutron-capture process) and gel-generators. Bombarding stable elements with neutrons will result in radioactive cores of the irradiated element. An intense neutron beam generated by a nuclear reactor adds one neutron to a Mo-98 target to produce Mo-99. The main advantage is that natural molybdenum can be used, although enrichment of natural molybdenum to over 90% of ^{98}Mo, will result in a nearly four times higher yield of ^{99}Mo. [32]

The main countries using this technology and supplying to local users are China, India, Iran and Kazakhstan. India has commissioned a production facility for gel generators. Besides that, Brazil is awaiting a reactor upgrade to make this process possible and Egypt has plants under construction with Chinese technology. An IAEA Coordinated Research Project to help countries begin small-scale production of Mo-99 using LEU targets or gel generators started in 2004. Since that time, research contracts and agreements have been concluded with institutions in Argentina, Chile, India, Indonesia, Kazakhstan, Libya, Pakistan, Poland, Romania, South Korea, and the United States.[33]

Radioactivity of the end product is lower than ^{99}Mo from fission of uranium (^{235}U) because of the presence of non-radioactive ^{98}Mo in the end product. But in 2008 prof. dr. Bert Wolterbeek of the Technical University Delft (the Netherlands) applied for a patent on a way of separating stabile ^{98}Mo from radioactive ^{99}Mo. More research is needed to confirm the 'proof of principle' under different conditions and to find a possibility for mass production. In 2010 it is expected to become clear whether this method is successful, and regular production process can be designed. This process will take several years. [34]

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  For application of a new isotope separation technology, several years after confirmation of the 'proof of principle'

- **Advantages of this approach**

  - Because (enriched) natural molybdenum is used, HEU or LEU targets are no longer necessary for the production of ^{99}Mo with the same desired radio activity of fission produced ^{99}Mo
  - There would be nearly no radioactive waste stream from the irradiated targets
  - Smaller reactors can be used

- **Disadvantages of this approach:**

  - A major change in the generator technology (the Tc-99m generator for radio pharmacies) would be needed because of the very low specific activity product and the need to separate Mo-98 from Mo-99: neutron-capture generators are different than fission generators of Mo-99
  - The viability of proposed separation techniques for separation of the Tc-99m from the parent Mo-99, will also need to be proven to work in a high-volume application
  - Unclear whether technology is scalable
  - A nuclear reactor is still required to provide the intense flux of neutrons, and thus producing high level radioactive waste from reactor core

2.3.4 Homogeneous aqueous liquid nuclear reactors

Several organizations have worked on the development of technologies to produce Mo-99 in homogenous aqueous liquid nuclear reactors (or solution reactors), a type of nuclear reactor in which soluble nuclear salts (usually uranium sulfate or uranium nitrate) have been dissolved in water. Mo-99 production is possible without the use of targets. [35]

Demonstration production of Mo-99 was realised twice at the Russian Argus reactor: "After the reactor has been shutdown and the fission power or radiation has decayed for at least one day, the reactor solution is pumped through a sorption column. The chemicals in the sorption column pass through the uranyl sulphate solution and fission products other than molybdenum. They bind the molybdenum to the sorbent material of the column. This operation takes about 6 hours. As a final step, the column is washed with distilled water. The column containing Mo-99 is then disconnected from the extraction loop and placed in a shielded container. " [36]

Further research and exchange of knowledge under the auspices of the IAEA is recommended, because the homogeneous reactor has great potential for the future. The IAEA is seeking funding for such an activity. In January 2009, the American company Babcock & Wilcox Technical Services Group announced an agreement with radioisotope producer Covidien, to develop the liquid core reactor technology to produce Mo-99, using LEU for fuel. If successful, the program could supply more than half of the demand. [37]

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  Given funds, B&W experts estimate that an operation could be up and running in five to six years.

- **Advantages of this approach**

  - Targets are unnecessary
  - Use of LEU for fuel is possible
  - There is far less waste (one-hundredth of the total produced in the normal method for a given quantity of Mo-99)
  - Efficient use of neutrons for radionuclide production
  - The extraction processing is simplified (since no uranium dissolution is required)
  - Inherent passive safety

- **Disadvantages of this approach**

  - Development of isotope separation technology is needed
  - Need to increase reactor power beyond operating experience
  - Pharmaceutical authorities like Health Canada, the U.S. Food and Drug Administration, the European Medicine Agency or the Dutch Medical Evaluation Board will probably need to license production of medical isotopes in such a system, because relevant regulations do not currently exist
  - A nuclear reactor is still required, producing high level radioactive waste

2.4 Accelerator Driven Systems

A combination of an accelerator and a sub-critical nuclear reactor is an accelerator driven system (ADS). The neutron flux of an accelerator is an alternative for high flux nuclear reactors and are safer: as the accelerator is turned down, also the reactor stops. The production of radionuclides in an ADS still needs ^{235}U targets (LEU) and looks a lot like the production process of ^{99}Mo in a nuclear reactor. No ADS is yet constructed anywhere in the world, but research on this method has been undertaken by the Kharkiv Institute of Physics and Technology, in Ukraine, as well as by the Belgian Nuclear Research Center. Resulting Mo-99 would reportedly be of standard (good) quality, though the system is as yet unproven.[38]

The design of ADS system 'MYRRHA' in Belgium has, according to a study of TU Delft, not enough potential to also serve as a neutron source for production of medical radionuclides. There is currently insufficient basis to rely on availability around 2018, apart from the moment of actual routine production of ^{99}Mo and other neutron-rich radionuclides. Estimates of its capacity are only based on older models of the ADS concept, and not actually on MYRRHA's facilities for the production of medical radionuclides. Moreover, there are already indications that the ADS will exhibit a lower availability (3 months business, 1 month preventive maintenance) than is usual in nuclear reactors. And as other research reactors, the MYRRHA is a multi facility for which the planning of scientific experiments and the production of medical radionuclides interfere with each other. However, after realisation of this concept it might be possible that ADS systems can be an alternative for nuclear reactors. [39]

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  Reported availability for MYRRHA is 2018

- **Advantages of this approach**
  - Higher level of safety: the accelerator can be turned on and off without consequences
  - Expected to fit easily in already existing supply chain and facilities for Tc-99m generators, because uses same production process

- **Disadvantages of this approach**
  - Generates same waste stream as high flux research reactors
  - Probably a lower utilization ratio than usual for nuclear reactors
  - Interference in planning of scientific experiments and production of medical radioisotopes, as the first priority is scientific research, not radioisotope production

2.5 New generator technologies

Some radioisotopes can be created easily by the use of radionuclide generator systems. Such systems utilize parent radionuclides with long physical half-lives of months or years. The daughter can be extracted from these radionuclide generators at periodic intervals to obtain short lived radionuclides for formulation of therapeutic radiopharmaceuticals. Because the use of short lived radionuclides is often restricted to places with local production or places that are well connected to production facilities this is an important additional strategy for the production of radioisotopes. An well-known example is the $^{99}Mo/^{99m}Tc$ generator that is produced for radio pharmacies so that they can generate Tc-99m and make their radiopharmaceuticals. Likewise, generator systems can be used to produce medical isotopes instead of production in nuclear reactors.

The IAEA implemented a coordinated research project (CRP) on the development of generator technologies for therapeutic radionuclides from 2004-2007. The recent IAEA report about the results of this CRP described $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$ generator systems. Radionuclide generators prepared from these long lived parents (Strontium-90 has a physical half-life of over 28 years, and W-188 has a physical half-life of 69 days) can serve as convenient production systems to provide the therapeutic radioisotopes Y-90 and Re-188 on a routine basis. [40]

As Sr-90 is a major fission waste product that can be obtained by isolation from spent fuel of nuclear reactors it is very interesting to use it as a generator for Y-90 instead of irradiating Y-89 in a reactor. The development of $^{90}Sr/^{90}Y$ generators could increase availability of Y-90 and be located in national radiopharmaceutical production centres. There was also need for the development of a 'real time' quality control method for estimating the radionuclidic purity of Y-90 prior to patient administration to make the method also available for hospital pharmacy. The CRP succeeded in developing technologies for the preparation of Y-90 and developing reliable analytical techniques for quality control. [41]

Rhenium-188 can be prepared either by irradiation of enriched Re-187 in a nuclear reactor or as the daughter product of the $^{188}W/^{188}Re$ generator. The specific activity of the reactor produced Re-188 is generally low and will depend on the irradiation conditions. There could also be radionuclidic impurities present from Re-186. This depends on the enrichment of the target, but highly enriched Re-187 targets are expensive. On the other hand, the

Re-188 obtained from the generator is of high specific activity (near theoretical) and, potentially, high radionuclidic purity. The main problem with this technology is the need for high specific activity of W-188, but the CRP succeeded in developing a protocol for the preparation of a $^{188}W/^{188}Re$ generator with high specific activity W-188 (>3 Ci/g) using the existing hardware of the $^{99}Mo/^{99m}Tc$ generator. The procedure can be adapted for generator production. Moreover, adsorbents were studied for adsorption of W-188 in order to increase the radioactive concentration of eluted Re-188. Post-elution concentration techniques were also developed by the participants to increase the specific volume of Re-188. These technologies can be adapted for the preparation of Re-188 for radiopharmaceutical production. [42]

The project shows two successful examples of developing generator technology. Utilizing waste products into a useful medical isotope is an interesting idea that can be developed further. But it would be even more interesting to develop generators based on parent isotopes produced by accelerators..

- **Estimated costs**
  Unclear

- **Estimated time for design and construction**
  Unclear

- **Advantages of this approach**
  - Specific methods of $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$ generator systems is proven
  - Waste from nuclear reactors is used to produce useful medical isotopes (in case of the $^{90}Sr/^{90}Y$ generator system)

- **Disadvantages of this approach**
  - Still need for nuclear reactors for production of parent isotopes, producing high level radioactive waste
  - Reprocessing of nuclear waste is necessary to produce certain parent isotopes has a negative environmental impact

Chapter 3 Substitution of medical isotopes

3.1 Introduction

According to AIPES the future expectations of the medical community and the mixed attitude of many public authorities towards the use of nuclear reactors, even for medical purposes, might result in a shift towards non-reactor radionuclides for both imaging and therapy purposes, and pain relief. The medical community might gradually use alternative radionuclides that can be made with accelerators, and alternative imaging technologies, such as e.g. ultrasonic echography, positron emission tomography, imaging techniques based on magnetic resonance, and others. These techniques already show an exponential growth and since the supply crises of 2008 are increasingly being considered as substitutes instead of complementary to nuclear medicine procedures.[43]

3.2 Imaging technology

Molecular imaging - the imaging of molecules, biochemical processes, and physiological activity within the human body - is rapidly becoming one of the most powerful tools for diagnosis and staging of disease in modern healthcare. The main tools for molecular imaging are the SPECT and PET scans that tag specific biologically active molecules (biomolecules) with medical isotopes, that are, as explained in paragraph 1.1, radioactive nuclides. When the radioisotope decays, it emits a particle that can be detected and used to pinpoint its location. By chemically connecting the medical isotope to a biomolecule and introducing the compound into the human body, one can then “see” where the body is using the biomolecule.[44]

Various technologies are available: [45]

- CT-scan (computed tomography), uses X-rays
- MRI-scan (magnetic resonance imaging), uses electromagnetic radiation
- Ultrasonic echography
- Optical imaging
- Planar nuclear technology, based on reactor produced radionuclides
- SPECT (single photon emission computed tomography), based on reactor produced radionuclides
- PET (positron emission tomography), based on radionuclides with short half-lifes and needs cyclotron within reach

Only SPECT and planar nuclear technology need reactor produced radionuclides (reactor isotopes). Moreover the use of these technologies varies per hospital department. A study by the Dutch consultancy Technopolis surveyed experts from hospitals about current use of the various modalities and their expectations for the future, resulting in the overview presented in Table 3.

Table 3 Use of modalities for imaging by hospital departments in 2008

Department	Main use of modality	Total use of reactor isotopes
Cardiology	SPECT (32%) and Echo (26%)	50%
Oncology	CT (28%)	23%
Neurology	MRI (40%) and CT (29%)	22%
Bonescans	Planar nuclear technology (43%)	55%
Other organ scans	Planar nuclear technology (57%)	74%

Source: Technopolis, "Het medisch gebruik van radioisotopen tot 2025, Een toekomstverkenning," Technopolis, in opdracht van VROM, Directie Risicobeleid, 19 december 2008.

Respondents expect that the current rapid development of PET will continue and that this will cause a relative decline in the use of reactor isotopes. However, due to the low cost and relative simplicity of SPECT and planar nuclear technologies, these technologies continue to exist and to be used in the same quantities as they are now. This expectation is supported by the experience that not one modality was substituted by another, because all technologies added new possibilities to the existing methods. The use of imaging in general will increase strongly because of aging and growing population. The overall expectation is that the use of the isotope Technetium will stabilize or even increase a bit until 2015 and decrease slightly in the period of 2015-2025.[46]

It is interesting to note that an alternate for Technetium that can be produced with accelerators is not mentioned at all in the report of Technopolis. The American journal *Radiology Today* of July 2009 observed that due to the poor supply of reactor isotopes more cardiologists shift to the use of thallium-201, that is produced using accelerators. Because of that, American medical isotope producers Lantheus and Covidien have ramped up production of thallium at their sites in respectively Billerica and St. Louis. These accelerators are operating at expanded capacity to meet the demand for this alternate cardiac imaging agent. Before Tc-99m agents, with better decay characteristics, came along, thallium had been used for imaging. Now there's a generation of nuclear medicine technologists and some physicians who are not that experienced with using thallium, which is a little different. [47]

This shows that there is increased interest in the use of cyclotrons for the production of medical isotopes. It is acknowledged by the IAEA, who reports that "the expansion in the number of cyclotrons during the last ten years has been driven by:

- the advent of advances in medical imaging instrumentation (PET, SPECT and more recently PET/CT);
- the introduction of user friendly compact medical cyclotrons from several companies that manufacture cyclotrons; and
- recent decisions in the developed world that some PET-radiopharmaceuticals are eligible for reimbursement by government or insurance companies." [48]

The IAEA continues its conclusion of the report about the possibilities for the production of radioisotopes with cyclotrons with: "It is expected that this rapid growth will continue and that the demand for new radionuclides that can be applied in industry, as well as medicine, will continue to expand. With this expansion, there will be a greater need for cyclotrons and the radionuclides they can produce."[49]

3.3 Nuclear therapy

More than 90% of reactor isotopes is used for imaging, but in therapy their role is of great importance in terms of quality of life for a smaller group of patients. Expectations of respondents in the Technopolis survey regarding reactor isotopes used for treatment are clear. The use of Iodine-131 and Iridium-192 is much appreciated and will likely stay the same. Due to the availability and development of new therapeutic applications the use of Lutetium-166 and Yttrium-90 will increase and from 2010 onwards also the need for Holmium-166 and Samarium-153 will increase. [50]

Technopolis also emphasizes that a small fraction of medical isotopes can only be made in nuclear reactors and at the same time, are the only available medical treatment. This would be the case with pain relief of bone metastases (with morphine as the only alternative) and with Iodine-131 for treatments of thyroid cancer.[51]

Doing so, this study focuses very much on the expectations regarding Technetium-90m and other reactor produced isotopes. It does not reflect the advantages of accelerators that can produce short lived isotopes for PET as well as for therapeutic applications. In many cases reactor based isotopes can be made with accelerators or replaced by other isotopes, produced with accelerators. [52]

Some examples:

- Cyclotrons with large beam currents can produce Pd-103, used for brachy therapy applications; [53]
- Production of alpha particle emitting isotopes, notably At-211 and Bi-213, for targeted therapy of cancer;[54]
- An alternative therapy for treatment of liver metastases of tumors is the Peptide Receptor Radionuclide Therapy using isotopes produced by accelerators; [55]

Chapter 4 Conclusions and recommendations

Due to safety risks, generation of high level radioactive waste and problems related to maintenance, high flux research reactors are a costly and unreliable production method of medical isotopes. Greenpeace prefers alternative production methods and commissioned this report to provide a summary of studies about such alternatives.

The overview of alternative production technologies in this report reveals a fairly large number of options. It leads to a number of, mostly complementary, solutions for safeguarding the supply of Mo-99 and other isotopes. It also raises questions about the need for a new nuclear reactor. For example, one might question the idea whether it is really necessary to build a nuclear research reactor because it can produce various radioisotopes, while the immediate need for a large scale Mo-99 production technology is more urgent (as 80% of nuclear medicine is based on Mo-99). Once technology is ready, an accelerator or series of accelerators, suitable for the production of solely Mo-99 could also secure the supply of Mo-99. Other existing, and perhaps even smaller, reactors could be sufficient to produce other and less often used radioisotopes. This combination of production technologies is worth considering the need of a new nuclear research reactor.

This report shows that each alternative production technology, including different types of nuclear reactors, has its own advantages and disadvantages. These advantages and disadvantages are not properly presented by the report of TU Delft which concludes that a new high flux research reactor is necessary. Based on a first comparison of the technologies described in Chapter 2, it seems to be too early to conclude that the best option for replacement of HFR would be a nuclear reactor. Especially, the costs and construction times of the different technologies are far from clear, making it impossible to conclude that a nuclear reactor would the cheapest or most early available solution.

A first review of the literature on market developments in radioisotope market, shows that the replacement of Mo-99-based imaging technologies by other imaging technologies is not likely. But in absolute terms, the demand for Mo-99 is not likely to increase as PET imaging - which uses different types of radioisotopes not produced in nuclear reactors - is likely to account for the increase of the total imaging market.

In the field of nuclear therapy, new developments in treatment technologies are likely to increase demand for other radioisotopes. Some of these radioisotopes are produced in nuclear reactors at present, but might possibly be produced by other technologies in the future.

Based on the above conclusions, we recommend:

- to undertake a more thorough research that compares the alternative production technologies for Mo-99 on a set of indicators like costs, construction time needed, the impact on waste, the use of highly enriched uranium for fuel and targets, additional facilities needed, etc.;
- to undertake additional research to assess the future demand and production technologies for other radioisotopes (besides Mo-99);
- to asses if separate solutions or a combined solution for producing Mo-99 and producing other radioisotopes are most desirable.

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