Medical isotopes

Global importance and opportunities for the Netherlands

in a European context

NuclearNetherlands

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Foreword

This publication highlights the importance of continuous and reliable supply of medical isotopes to the Netherlands, Europe and the rest of the world. It also describes the substantial efforts taken by all supply chain partners towards breakthroughs that improve future nuclear health care services and treatment of patients. The development of new therapeutic applications of isotopes is illustrated with several examples.

The Netherlands has an internationally recognised unique position: it is the world's largest supplier of Molybdenum-99/Technetium-99m, it hosts all supply chain partners within its borders, it has a long tradition in supply chain collaboration, it is a renowned developer of new international breakthroughs in new therapy and diagnostics and it is progressing well on the new multi-functional facility for medical isotopes, the PALLAS-reactor, the core of the infrastructure for the decades to come.

Stimulating role of Dutch government

The Dutch government has played an important and stimulating role in nuclear medicine research and development over the last decades, and continues to do so today. It supports the PALLAS-reactor initiative both financially (by providing loans for the preparatory phase) and politically. It also supports the OYSTER project of the Reactor Institute Delft. In early 2016, the Dutch presidency of the EU took the initiative to get the political support of all European countries for new EU policies to guarantee long-term supply of medical isotopes and for European countries to implement the OECD-NEA policy principles on Full Cost Recovery.

Europe's crucial role

As shown in this publication, Europe plays a crucial role in international research, in development efforts and in the international supply chain. Compared to other continents it has the huge advantage of hosting four irradiators (in the Netherlands, Belgium, Poland and Czech Republic) and two processing facilities for Mo-99 (in the Netherlands and Belgium). Having multiple reactors allows European irradiators to coordinate the planning of their scarce resources. Moreover, several European medical centres are world-leaders in research and development of medical applications of radioisotopes, both for diagnostics and therapy.
Finally, the industry is very well developed, e.g. in nuclear medicine imaging equipment and services, in radio-pharmaceuticals and in cyclotron production technology.
However, this strong international position of Europe is being challenged: the ageing infrastructure requires new investments (preferably from the private sector). Several non-European governments (as well as some European countries) continue to subsidise different initiatives for Mo-99 production, thus putting pressure on the business case for required private investments. By doing so, European countries demonstrate their national strategies not to be in line with internationally agreed policies, which harms the European providers on the international market.

This publication recommends courses of action for several European stakeholders in several areas for the coming years.

Focus policies and decisions on patient interests

Policy-making and decision-making on the European security of supply of medical isotopes benefit from a patient-driven focus. Worldwide 48,000,000 patient treatments per annum depend on adequate and timely delivery of radioisotopes produced by ageing infrastructure over 50 years old. Independent of technology, building new irradiation infrastructure typically takes 10 years of design, construction and licensing if sufficient funds are available. Realising these future infrastructure requires the strong political commitment of several (consecutive) governments over a long period of time.

Multi-lateral collaboration to overcome market failures

Governments participating in the OECD-Nuclear Energy Agency have agreed on implementing policies ('the six principles'[1]) that introduce normal market mechanisms in the supply chain. Normal market mechanisms are needed to replace the numerous government interventions of the past.
These normal market mechanisms require an international level playing field for private investors, and a steady decrease of state or regional subsidies or other state support that continue to jeopardize the international level playing field.
It is vital for future private investors in the supply chain to be able to rely on a harmonised and synchronised European policy framework in nuclear medicine infrastructure. This is a precondition for them to consider the significant investments that are required.
Europe should collaborate in using existing policy instruments or developing new instruments to stimulate, control and enforce the implementation of (at least) Full Cost Recovery. European requirements on reliability of supply will enable proper pricing of required Outage Reserve Capacity. European governments can remove obstacles and/or provide incentives for the supply chain to invest generated revenues and profits in renewing and maintaining production and research infrastructure for medical isotopes.

Develop a European roadmap for nuclear medicine research and development

While Europe hosts many renowned research groups on nuclear medicine, there is a strong demand for a multi-year, multi-lateral R&D programme that supports the various stages of the development of new medicines. Scaling up from small scale 'phase 1/few patients' trials to full scale 'phase 3/multi-sited/multi-patient' trials has proved to be difficult to coordinate and finance. The involvement of the isotope supply chain in the various research phases has proved equally difficult to organise. The European Commission is encouraged to take the initiative to coordinate multi-lateral programme development as part of the current Horizon 2020 programme and/or its successor. The programme development may include a vision on the required long-term research infrastructure needed for the nuclear medicine research community as well as a profile of the role the European Medicines Agency is to play. Finally, enforcing the role of the European Commission's Joint Research Centre in this area of research and development could be considered.

Fully implement and enforce the conversion to the use of Low Enriched Uranium

For many years international agreement on non-proliferation has existed on policies to ban the use of High Enriched Uranium (HEU) for the production of medical isotopes in the future. Significant investments by many supply chain partners and governments have led to conversion of the major plants worldwide (Australia, South Africa and the Netherlands). Other sites are still working on the conversion of the fuel elements of their reactors and/or the targets used for irradiation. Since the use of Low Enriched Uranium (LEU) leads to lower yields and thus increases inefficiencies (a.o. generating more waste), it is of the utmost importance that all future supply chain partners are committed to or forced to commit to the HEU-LEU conversion to ensure the international level playing field. This requires continued commitment of the European Commission and all member states to the HEU-LEU conversion.

[1] See https://www.oecd-nea.org/med-radio/statement.html

- ***Reconsider reimbursement systems and levels for radiopharmaceutical products***

Several national governments in Europe collaborate in realising a joint market for pharmaceuticals, partly to ensure proper market dynamics by strengthening the procurement of scarce and/or expensive pharmaceuticals, and partly to ensure early access to new pharmaceutical products. Moreover, several countries have taken the initiative to reconsider their reimbursement systems for radiopharmaceutical products. Differences in reimbursement systems throughout Europe may influence equal access to the radiopharmaceutical products in member states. The industry indicates that in many cases reimbursement levels currently do not allow for the implementation of Full Cost Recovery. By implementing the proper procurement mechanisms, the European health care systems can also contribute to the HEU-LEU conversion.

1 Introduction

Every year, around 48 million[2] examinations and treatments involving medical isotopes take place worldwide. In more than 80% of these cases – around 40 million procedures - the medical isotope Technetium-99m is used. This is a radioactive substance produced on a large scale by a handful of nuclear reactors worldwide. The other isotopes can be roughly divided into two equal groups. There is Fluorine-18, which is produced in small quantities by accelerators in or near hospitals (4.2 million procedures) and there is a collective group that includes various other medical isotopes (3.8 million procedures).

For a long time, it was not very relevant for patients and nuclear medicine specialists to know where the medical isotopes came from. They were simply always available. However, this changed completely between 2008 and 2010, when unexpected production limitations in several large reactors caused major disruptions in the supply. In a short period of time, the market and all its complex links became a topic of discussion.

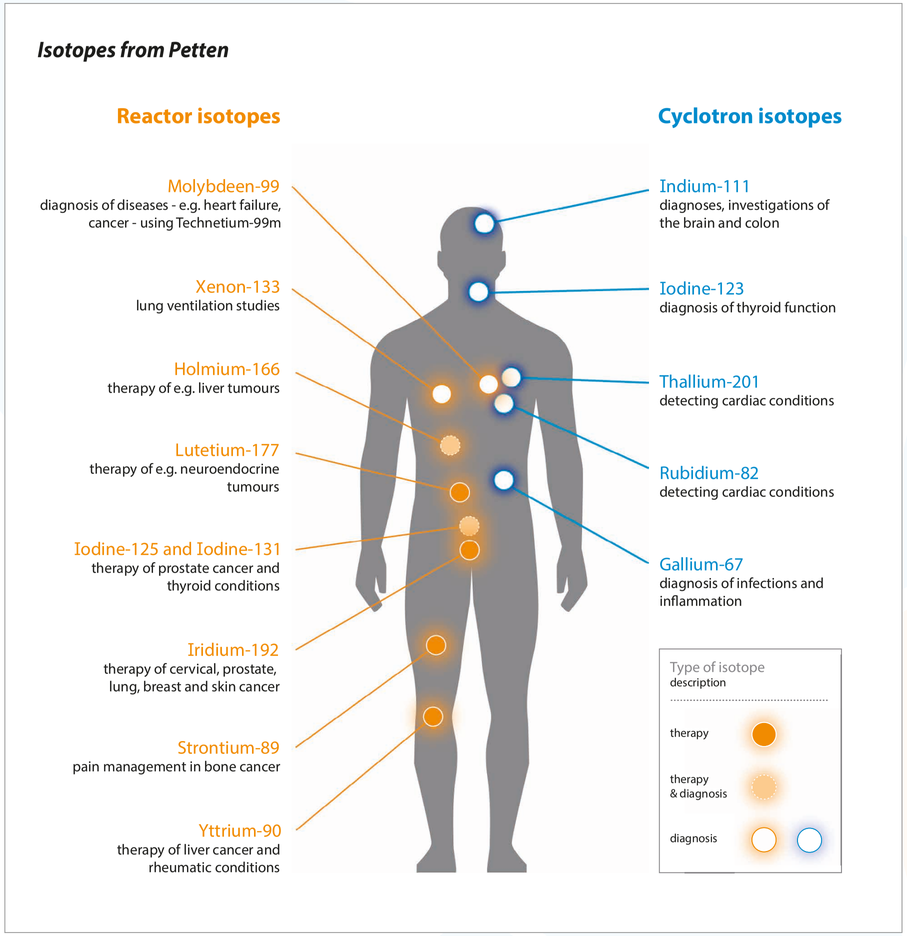
In addition to a widely shared vision that (new) medical isotopes are inherent to modern healthcare and that continuous availability is essential, there are also many contrasting views. This is partly due to the "multi-coloured" landscape that forms the backdrop to the term medical isotopes. There are (political) interests at international, national and local scale. There are public, semi-commercial and commercial parties that depend on each other in one production chain. Professional disciplines that would normally not come into contact have to work together. It is a nuclear activity that is subject to stringent legislation and regulations and where the public interest plays a major role. Finally, it involves a product with a medical use, which is also subject to a large amount of legislation and regulations.

As the largest producer of medical isotopes in the world, the Netherlands has to deal with the full extent of all these elements. This document aims to make the reader better informed about the subject, reveal the connections in the chain and discuss the dependence and vulnerability of millions of patients in this context. An analysis will also be provided of the future developments and the many opportunities that the Netherlands has within its borders to perpetuate and expand its role as frontrunner.

The story begins in the hospital with a hypothetical patient suffering from one of the most common diseases. A referral to the nuclear medicine department is probable in at least four out of five cases. What happens here and the instruments and products at the disposal of nuclear medicine are discussed in Chapter 2. Chapter 3 focuses on the trends and developments that ensure that patients will receive even better care in the future.

In Chapter 4, we leave the hospital to review all the steps preceding the patient's treatment. This section explains the various steps in the production chain for medical isotopes and how they are related.
Like Chapter 3, Chapter 5 focuses on the future. This chapter discusses the scenarios for the various parties in the chain. Which (alternative) production routes will form the cornerstones of healthcare in the future? Chapter 6 looks at the situation in the Netherlands, followed by a final chapter (7) with a clear list of recommendations.

[2] MEDraysintell, June 2015



A patient visits the nuclear medicine specialist

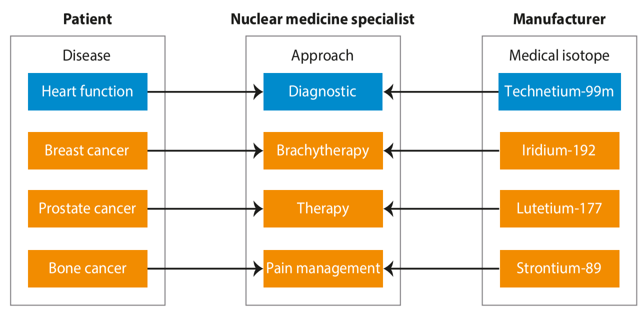
In prosperous countries, most people die of cardio-vascular disease, cancer, diabetes, lung and respiratory tract conditions and dementia. In all these cases – with the exception of diabetes – the specialist is likely to refer his patient to the nuclear medicine specialist. This referral is usually to perform a scan (90% of cases), but increasingly it also involves (cancer) treatment or pain management.

Cancer has a huge and increasing economic impact, according to the World Health Organization in its "top 10 causes of death in prosperous economies" in 2015. In 2012, 14 million new cases of cancer were diagnosed worldwide and 8.2 million people died as a result of this disease. In relation to other causes of death, this is equivalent to approximately 1 in 6. The total costs of treating cancer totalled around 1.16 trillion dollars in 2010[3].

Against this backdrop and with the number of cancer cases predicted to soar (70%) over the next twenty years, all parties involved in innovative nuclear medicine are doing everything they can to find good solutions for these patients.

Disease, approach, isotope

The doctor sets up a treatment plan (diagnosis, therapeutics, follow-up care) for the patient. A nuclear medicine approach is selected for certain diseases. This involves the use of medical isotopes. The use of medical isotopes to tackle cancer is extremely varied. Depending on the type of cancer and the stage of the disease, the diagnosis is performed using medical isotopes, with or without subsequent radiotherapy (external radiation), brachytherapy (radiation from inside the body) and palliative treatment (pain management). The figure below provides a number of examples of diseases, followed by the treatment and the medical isotope involved.



[3] http://www.who.int/features/factfiles/cancer/en/ (fact 8)

2.1 What are medical isotopes

Nuclear medicine specialists use radioactive material to determine whether organs are functioning properly and to detect cancerous growths at an early stage (diagnostics). In addition, so-called therapeutic isotopes are used in the therapy of patients. This chapter will discuss the isotopes for diagnostic purposes and isotopes for therapy.

The radioactive substances used in diagnostics and therapeutics are called medical (radio) isotopes. In order to ensure that they reach the correct organ, the isotope is linked to a non-radioactive substance. By administering this combination to a patient, it is possible to trace a "trail" of radiation using a special camera, allowing the nuclear medicine specialist for example to determine how an organ is functioning or where a cancerous growth is active.

2.2 Diagnostics

Any patient needing medical isotopes for diagnostic purposes is usually scheduled for a nuclear scan. This includes all types of imaging techniques that use radioactivity. These scans are particularly suitable for detecting movement and change, such as the blood flow through the heart or the metabolism in an organ.

When undergoing a scan, the patient is injected with a very small quantity of slightly radioactive liquid. The patient then has to wait several minutes to several days, depending on the examination. Once the liquid has spread through the body via the circulation, the scan can be performed. This provides an image in which the radioactive areas are visible. By detecting the radiation, it is possible to determine whether anything abnormal is going on.

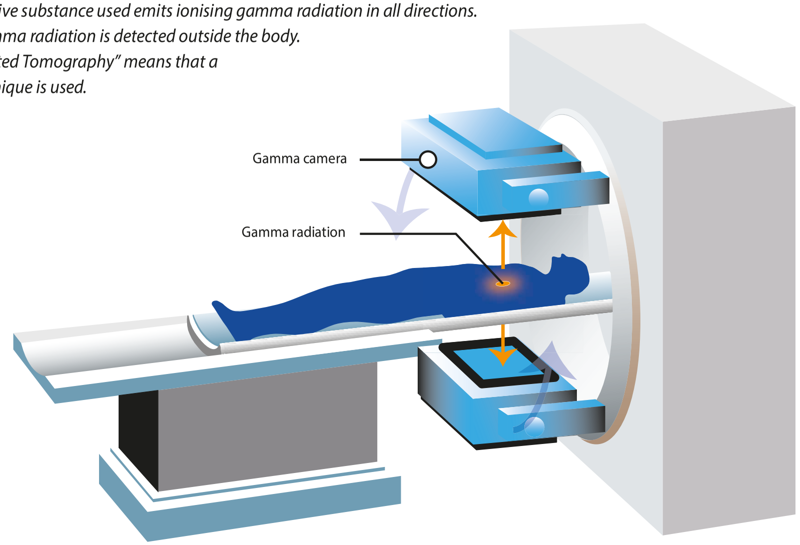
The nuclear medicine specialist has various types of cameras at his disposal. The bed and the camera can be stationary whilst taking pictures, or the bed can pass slowly below the camera or the camera can turn in a circle around the bed. It is possible to record all sorts of images, to obtain a very precise view of what is wrong with the patient.

In modern nuclear medicine, two main imaging techniques are used: PET and SPECT. Both use the gamma radiation emitted by the isotope to produce a series of images of the distribution of radioactivity in the body. Gamma radiation is one type of invisible electromagnetic radiation that a radio-isotope can emit.

PET and SPECT scans generally produce images that can only be interpreted by a specialised doctor. However, by combining them with other techniques (such as "Computed Tomography" also CT or "Magnetic Resonance Imaging" also MRI), we are much better able to generate very precise images of certain functions deep in the body.

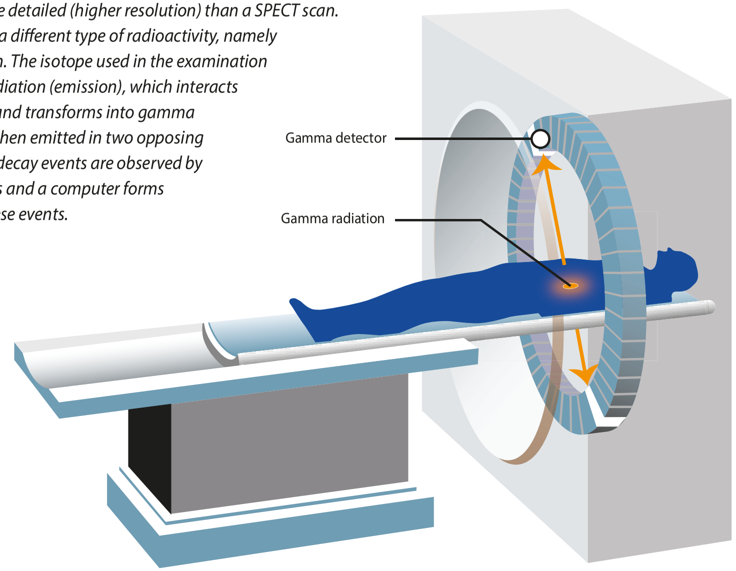
SPECT - "Single Photon Emission Computed Tomography"

A SPECT scan is most commonly used. "Single Photon Emission" means that the radioactive substance used emits ionising gamma radiation in all directions. This gamma radiation is detected outside the body. "Computed Tomography" means that a 3D technique is used.



PET - "Positron Emission Tomography"

A PET scan is more detailed (higher resolution) than a SPECT scan. This camera uses a different type of radioactivity, namely positron radiation. The isotope used in the examination emits positron radiation (emission), which interacts with an electron and transforms into gamma radiation. This is then emitted in two opposing directions. These decay events are observed by a ring of detectors and a computer forms a 3D image of these events.



Medical isotopes are very important, particularly for diagnostic purposes in oncology, cardiology and neurology. It is estimated that more than 10.000 hospitals worldwide use isotopes for diagnosis. The best known isotope for diagnostic purposes is Technetium-99m. This isotope is used annually in more than 40 million diagnostic examinations worldwide, with half of these examinations taking place in North America and around 7 million in Europe. Around 250,000 procedures using Technetium-99m take place each year in the Netherlands.

Technetium-99m is used in the vast majority of SPECT scans. This workhorse of diagnostics has many advantages compared to other isotopes (see 4.1 Molybdenum-99 / Technetium-99m). PET scans primarily use Fluorine-18, which is produced in cyclotrons. PET isotopes have a (very) short half life. They are therefore produced shortly prior to use in a cyclotron that is located in or near a specialised hospital. Fluorine-18 is used to produce the radio-pharmaceutical FDG (18F-fluorodeoxyglucose), which makes the glucose consumption in the body visible. This forms an important part in the detection of growths. Other suitable PET isotopes are Carbon-11, Oxygen-15 and Nitrogen-13.

2.3 Therapeutics

Therapy involving radiation can be divided into radio-therapy, nuclear medicine therapy (including brachy-therapy) and palliative therapy. Radiotherapy uses external sources of radiation, while nuclear medicine therapy involves the administration of a medical isotope to a patient. In both cases, the therapy is aimed at destroying specific tissues. Palliative therapy focuses on pain management. Patients receive an administration of a medical isotope that slows down the disease process, thereby reducing pain and improving quality of life. Brachytherapy is a specific method of administering the radio-isotope, in which the isotope is administered via a catheter or needle to the site of the condition and continues to emit radiation to the diseased tissue for a shorter or longer period.

By linking the correct medical isotope to a suitable tracer, the nuclear medicine specialist is able to deliver the medical isotopes to the correct site in the body, significantly limiting the damage to healthy cells whilst effectively killing the diseased cells. The radiation dose administered during therapy is much higher than the dose used for diagnostics. In some events the patient can be considered radioactive for a while.

The most common therapy in the Netherlands are:

- Iodine-131 for thyroid conditions, in which a capsule of radioactive iodine is administered to the patient. The iodine accumulates in the thyroid, where it emits radiation (therapy).
- Iridium-192 for the treatment of – for example – breast cancer and prostate cancer (brachytherapy).
- Radium-223, (Xofigo®) for the treatment of bone metastases of prostate cancer.
- Lutetium-177, for the treatment of neuroendocrine tumours and on an experimental basis for the treatment of prostate cancer (nuclear medicine therapy).
- Strontium-89, Rhenium-186 or Samarium-153 for pain management of metastasised bone cancer (nuclear medicine therapy).
- Yttrium-90 for the treatment of liver cancer (radio-embolisation) and certain rheumatic conditions.
- Holmium-166 for the treatment of liver cancer (radio-embolisation).

Therapeutic applications are quickly gaining in importance and compared to the diagnostic applications they are mainly of qualitative importance. For example, therapeutics using Lutetium-177 for a patient with neuro-endocrine tumours – a rare and very malignant form of cancer – can extend the patient's life span on average by at least 4 years, with a relatively good quality of life[4]. This therapeutics was developed in the Netherlands and is now used very successfully all over the world. The number of patients who are eligible for therapeutics with Lutetium-177 is expected to rise significantly.

[4] Erasmus MC, http://www.net-kanker.nl/

3 Trends and developments in nuclear medicine

Anyone observing the developments in the use of medical isotopes from a distance will observe three general trends: From the 1960s to 2015, the focus of nuclear medicine was primarily diagnostic. The development of various so-called "cold kits" (tracers), improvements in imaging technology and the availability of cameras were the driving factors in those years. The emphasis during this period was not focused so much on treatment with isotopes, although the first developments did start around that time.

The first therapeutic products were developed in the run-up to 2015, under brand names such as Xofigo® and Zevalin®. The success of these products provided an impulse for the development of other radiotherapeutic products. As it takes some time for these types of new products to reach the market, many new brands are expected to become available to patients over the next ten years.

The new therapeutic products based on Lutetium-177 look particularly promising. They are a tangible example of the frequently mentioned trend of "personalised medicine", which essentially means that a therapy is tailored to the patient. This avoids excessive and ineffective treatment, which could result in cost reductions in healthcare whilst maintaining quality of life.

The third trend involves the so-called alpha emitters, which are isotopes that emit alpha particles. These medical isotopes can be used in future to find smaller "targets" more effectively, making it possible to treat so-called micro-metastases. Alpha emitters are very effective at destroying tumour cells. Various universities and companies are working on their development.

3.1 Developments in diagnostics

Although the most prominent discoveries are now being made in the field of nuclear medicine therapy, the developments in the field of diagnostics are also continuing. Major steps are still taking place in the development of new tracers and further improvements in camera and imaging techniques. This is all aimed at increasing the effectiveness of therapeutics.

The costs of use and purchasing the SPECT or PET cameras also play a role in diagnosis. A PET camera is much more expensive to purchase and use than a SPECT camera. However, a PET camera is often used for complicated examinations due to the higher resolution of the images. Hospitals often work together to purchase and operate the PET technology. The ratio between SPECT and PET cameras in hospitals is currently 5:1.

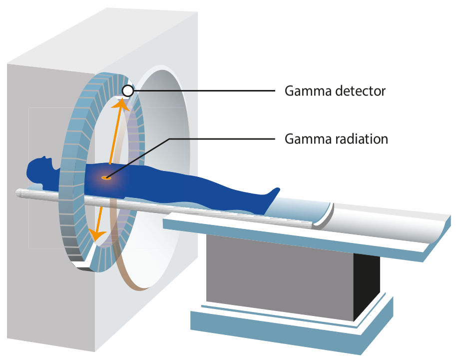
The resolution of SPECT scans is also still improving. The image quality is now approaching that of PET. Research by Technopolis in 2008[5] reveals that the choice of a certain imaging technique varies per medical specialisation. PET is strongly favoured in oncology, while SPECT is dominant in cardiology and for producing bone scans and other organ scans. Despite the growth in the use of PET cameras, Fluorine-18 is not expected to replace Technetium-99m.

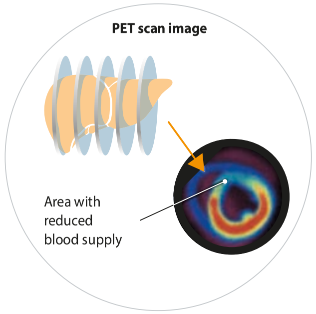
The current state of technology is that these devices are used in combination with CT: SPECT-CT and PET-CT. The CT technology basically provides detailed 3D X-ray images. By combining the data from SPECT or PET with CT, it is possible to combine the information about the functioning of the organs with the exact location in the body.

[5] Technopolis-rapport 2008

Comparison of PET and SPECT

Positron Emission Tomography (PET)

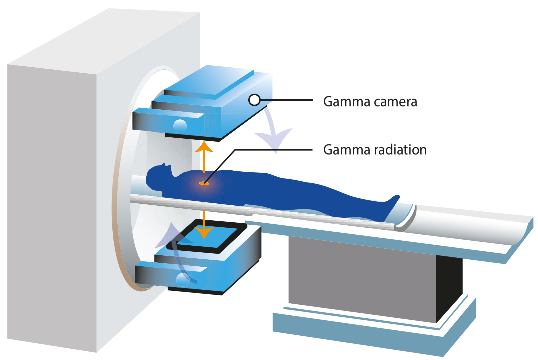


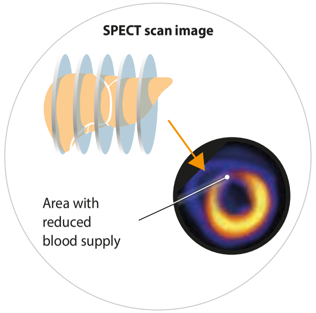


Trends in camera
- Better image quality than SPECT, but also more expensive.
- Technology trend moving towards PET/CT, makes it possible to stack multiple images.
- The global capacity is approximately 4,900 cameras (2015) increasing to 7,000 (2025).

Trends in isotopes
- Most commonly used tracer is Fludeoxyglucose (FDG), based on F-18.
- Other isotopes: Ga-68, Rb-82, C-11, N-13, O-15, Sr-92.
- New research yields new tracers (for example, for Ga-68, Rb-82), which will replace existing tracers.
- PET isotopes require local production in cyclotrons, which is less cost effective than reactor production.

Single Photon Emission Computed Tomography (SPECT)





Trends in camera
- Lower resolution, but also cheaper.
- New SPECT cameras have a similar image quality to PET.
- Same trend as for PET: moving towards hybrid technology SPECT/CT.
- The global capacity is around 26,200 cameras (2015), increasing to 29,000 (2025).

Trends in isotopes
- Most used isotope is Tc-99m, which can be linked to various tracers (available as cold kits)
- Various isotopes produced in reactors and cyclotrons can be used, but Tc-99m is the most common.
- Renewed interest from medical research is resulting in the development of new tracers.

Sources: Wikipedia, Zimmermans workshop 2016

A more recent development is the combination of these cameras with MRI. MRI provides detailed images of tissues and organs. The combination of techniques such as SPECT-MRI and PET-MRI is gaining in popularity.

G-SPECT

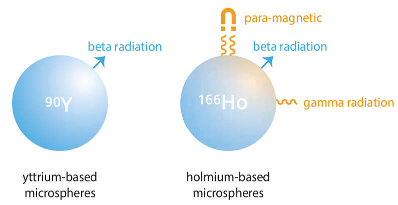
A good example of a prominent development in SPECT is the so-called G-SPECT. This is a new type of camera developed by MILabs, a "spin off" of the UMC Utrecht.
The G-SPECT has an exceptionally high resolution of 3 millimetres (normal SPECT: 7-10 mm), making the image even more clear. In addition, G-SPECT is the first technique to provide insight into a large number of rapid, dynamic processes, such as those associated with Alzheimer's disease or Parkinson's disease. Another important advantage is that G-SPECT has a high sensitivity. This means that the patient can be given a much lower dose of radioactive substance. Furthermore, it is possible to obtain a usable scan even if the patient moves in the scanner.
At the moment, scans often fail and need to be repeated for this reason. In addition, the G-SPECT can convert 3D images into a 4D film. This makes it possible to visualise how substances move in and out of structures, which can be of importance – for example – in investigations of tumours. This opens up a new field that can provide a lot of interesting information for doctors and patients.

3.2 Developments in therapeutics

As mentioned before, nuclear medicine is rapidly following the trends in personalised medicine. Existing methods are aimed at patient groups. Specialists are getting better all the time at determining which therapeutics will or will not work within these groups: "appropriate use". This results in increasingly effective therapeutics in which any unnecessary damage (for example due to side effects of medication or exposure to radiation) can be prevented. This increases both patient safety and the quality of life for patients. In future, the treatments will be more and more targeted at individuals.

Holmium-166

There is increasing interest in the innovative treatment using Holmium-166. The University Medical Centre (UMC) Utrecht recently registered the first indication for this innovative treatment. The Holmium-166 is loaded in microspheres (brachytherapy) to combat primary liver tumours from within. The Holmium-166 also emits gamma radiation, allowing diagnostic images to be recorded.



The development of new therapeutic products and radio-pharmaceuticals takes time. It always involves collaboration between specialists from very different fields and the involvement of scientists. Besides radiochemists, biochemists, pharmacists and organic chemists also play an important role. Nuclear physicists and various engineering disciplines are also required for the production of new radiopharmaceuticals. After all, the production of radiopharmaceuticals places very high demands on the infrastructure of the parties involved.

The combination of therapy and diagnostics, the so-called "theranostics", is an emerging application of medical isotopes that offers a great perspective. The radio-pharmaceutical tracks down the tumour and once it has been absorbed properly, the same molecule is labelled with a therapeutic substance (an alpha or beta emitter). The molecule guarantees the same absorption pattern for both diagnostic and therapeutic applications. This allows the treatment to be targeted and modified for maximum effectiveness and the fewest possible side effects. Examples of this are diagnostics and therapy using the molecule PSMA. Thanks to the diagnostic Gallium-67, it is known where the substance will go to in the body. This same PSMA linked to Lutetium-177 then irradiates only those sites that are visible on the scan. The combination of therapy and diagnostics means that nuclear medicines will make an even greater contribution to personalised medicine.

4 The supply chain of medical isotopes

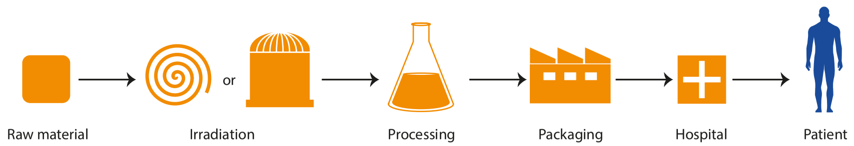
There are various ways in which medical isotopes can be produced. Isotopes can be produced in reactors and accelerators (such as cyclotrons). Both production methods are quite different. In brief: not every isotope can be produced by a reactor and not every isotope can be produced by an accelerator. So far, very few therapeutic isotopes have been produced by accelerators. The two production methods complement each other and clearly cannot replace each other.

In addition to the two aforementioned methods, there has also been an international search specifically for "new" technologies for the production of the widely used Molybdenum-99 / Technetium-99m. ASML's "Lighthouse" project is an example of this.
This chapter will discuss in more detail the current and new production methods.

The irradiation of the raw materials (either in a reactor, or in an accelerator) forms only a small part of the production process of medical isotopes. A series of purification and processing steps takes place in various laboratories after the irradiation. The extent to which reactors can play a role in the production of medical isotopes therefore depends strongly on the vicinity of parties who can quickly prepare the irradiated materials and transport them to the hospitals. Sophisticated logistics are vital due to the short life span of the isotopes (see the box on page 17 about half life and logistics).

The various steps in the chain are essential and must be performed with the greatest possible accuracy. For example, any trace of an undesirable isotope remaining in the final product after purification could result in an excessively high radiation dose for the patient or poor image quality.

Isotopes production chain

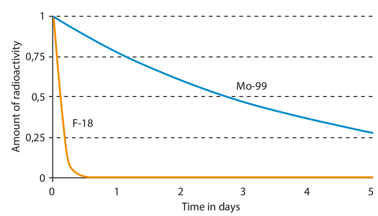


Half life and logistics

Medical isotopes are radioactive. The amount of radioactivity reduces over time as a result of the so-called radioactive decay. This means that the product loses "strength" (= radioactivity) over time. The term "half life" is used to describe this process.

The half life is the time it takes for the amount of radioactivity to halve. For many medical isotopes, this half life is in the range of several hours to several days. As the amount of product decreases rapidly over time, it is vitally important to ensure that the supply is carefully planned. This means that the time at which the medical isotopes are required in the hospital are calculated back to the production time down to the hour. This also means that as little time as possible should be lost in the chain.

Compare it to selling fresh fruit: the figure displays the decay of radioactivity for the isotopes Molybdenum-99 and Fluorine-18. Molybdenum-99 has a half life of 66 hours, approximately 2.5 days, whilst Fluorine-18 has a half life of 109 minutes, just under 2 hours. For this reason, the production facilities (= cyclotrons) for isotopes with a shorter life span such as Fluorine-18 are generally located closer to the patient than the production facilities (= reactors) for isotopes with a longer life span such as Molybdenum-99.



4.1 Reactors as producer of isotopes

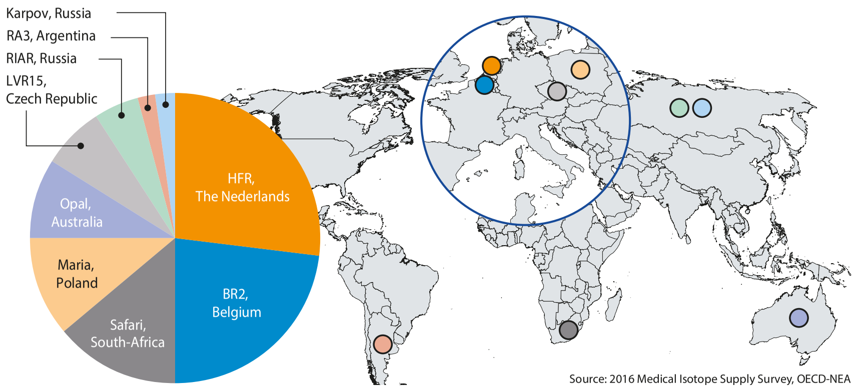
The core of a nuclear reactor constantly produces neutrons. Neutrons are atomic particles that carry no charge and they can be used to produce radioactive substances. By temporarily placing materials in the reactor, they are exposed to these neutrons and isotopes are subsequently formed. A large variety of medical isotopes can be produced using this method. The best known isotope currently produced by reactors is Molybdenum-99 / Technetium-99m.

Molybdenum-99/Technetium-99m

The widely used Technetium-99m is a metastable radio-isotope with a half life of 6 hours. It is a decay product of Molybdenum-99, which has a half life of 66 hours. This is the time it takes for half of the Molybdenum-99 to decay to form Technetium-99m. Molybdenum-99 is therefore called the mother isotope. The long half life of Molybdenum-99 means that it can be transported over a large distance. In practice, a delivery to the hospital only needs to take place about once a week. Doctors can have access to Technetium-99m at any time of the day, seven days a week.

The Technetium-99m is "tapped" in the hospital from a generator that the manufacturer has loaded with the mother isotope. The generator is a heavy cylinder that contains a vial of liquid. During the tapping process – also called elution – a chemical separation takes place. The main benefit of generators is that – due to the longer half life of the mother isotope – the generator can be used for a longer period to produce an isotope with a shorter life span. This means that a hospital does not have to place a new order every day for isotopes with a short life span, but instead has a source of isotopes that can be used for a longer period. Examples of radionuclide generators are Mo-99/Tc-99m, Ge-68/Ga-68, Rb-81/Kr-81m or Rb-82/Sr-82. The generators are used for both SPECT and PET applications.

Global reactor capacity for Molybdenum-99



Currently available global reactor capacity for medical isotopes (OECD-NEA).
N.B.: The Russian and Argentine reactors only produce isotopes for local use.

Over 80% of the procedures performed in the hospital use Technetium-99m. In addition, nuclear reactors produce a wide range of other medical isotopes that are of importance to nuclear medicine. The most important are Lutetium-177, Iodine-131 and Iridium-192.

There are only a few (old) reactors worldwide that account for the lion's share of medical isotope production. The most important reactor is the HFR in Petten (the Netherlands), closely followed by the BR2 reactor in Belgium. The Safari reactor in South Africa and the OPAL reactor in Australia account for a smaller share of the global production. The Maria reactor in Poland and the LVR15 reactor in the Czech Republic are mainly important as so-called spare capacity and also serve a specific local market.

4.2 Accelerators as producer of isotopes

In accelerators, charged particles (protons) are accelerated in combination with a magnetic field and an electric field, after which they collide with a target containing the raw material. This activates the raw material, thereby converting it to an isotope. Most products created in an accelerator have a short half life.

Due to the fundamentally different process in an accelerator, this device produces isotopes that are not produced in a reactor. Known isotopes that can be produced using an accelerator are Fluorine-18, Oxygen-15, Iodine-123 and Iodine-124, Carbon-11, Nitrogen-13, Zirconium-89, Gallium-68 and Rubidium-82.

Europe is closely monitoring the developments in Canada. It appears that the United Kingdom in particular will want to follow the Canadians, if they see a technical and commercial success in Canada. In other countries, the developments are being monitored primarily by the owners of existing accelerators (large enough to be able to produce Technetium-99m).

In the Netherlands, accelerators for the production of medical isotopes are located in Amsterdam, Eindhoven, Petten, Alkmaar, Groningen, Nijmegen and Rotterdam.

Canada

As an alternative to building a new multi-purpose research reactor, the Canadian government opted in 2009 to release CAD 35 million for the "Non-reactor-based Isotope Supply Contribution Program" (NISP), followed in 2011 by CAD 25 million for research within the so-called "Isotope Technology Acceleration Program" (ITAP). The developments within these programmes in Canada focus mainly on the production of Technetium-99m by cyclotrons. Recent scientific publications and public reporting about the progress reveals that they are still working on this solution for Canada[6]. Despite the many investments, there is still no approved and certified producer using cyclotrons for the production of Technetium-99m[7]. As the new production method results in a new pharmaceutical product, the entire process for the registration of new pharmaceutical products has to be completed. It has since been reported that the authorities are now working on these admission requirements.

[6] See among others - the TRIUMF presentation during the 2016 Mo99 Topical Meeting in St Louis, http://mo99.ne.anl.gov/2016/pdfs/presentations/S7P3_Presentation_Buckley.pdf
[7] This is in contrast to what LAKA claims in http://www.laka.org/nieuws/2017/pallas-tussen-krimpende-vraag-en-groeiende-capaciteit-6336

5 Trends and developments in the supply chain

Medical isotopes can be produced using reactors and accelerators. This chapter will discuss why these production routes complement each other and which developments are taking place in both "routes".

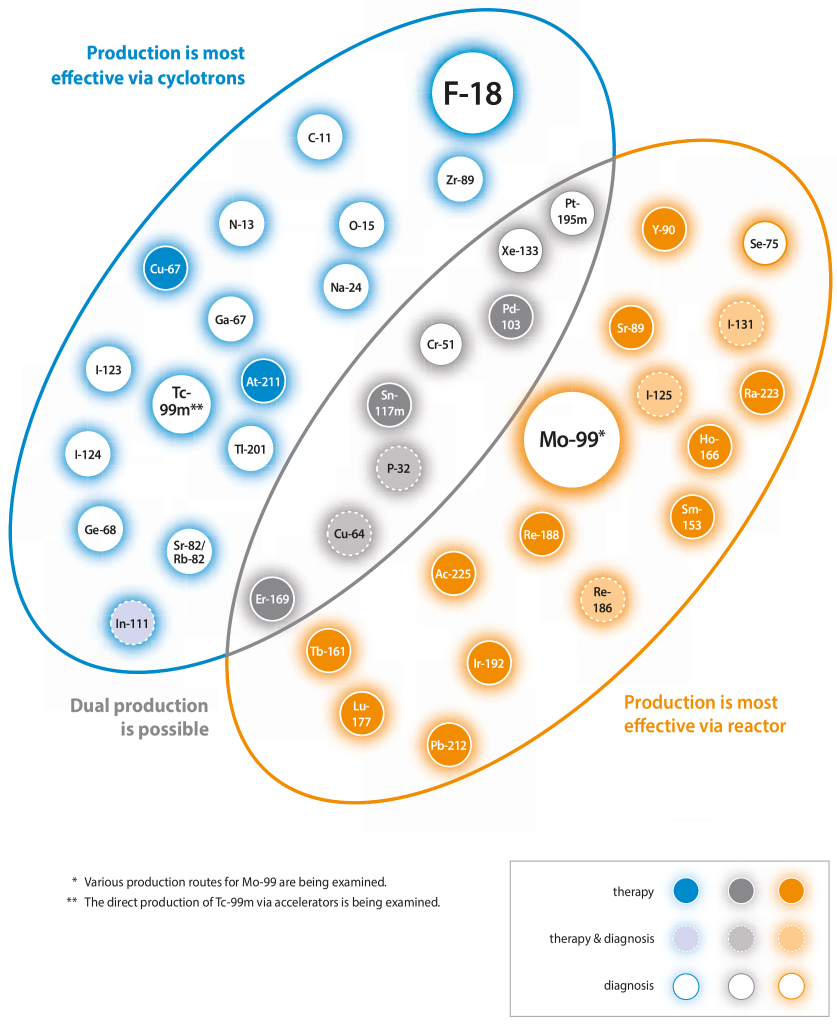
Can every medical isotope that is currently produced in a reactor also be produced in an accelerator? The answer is: No, that is not possible. The reverse is also true: not every medical isotope that is produced in an accelerator can also be produced in a reactor. This is due to the properties of the raw materials in relation to the radiation generated by an accelerator or reactor. These are physical properties that determine how much radioactivity can be generated using a reactor or an accelerator. In addition, it is also important to consider whether the medical isotope can be generated with the correct quality (purity, specific activity) and in the correct quantity (radioactivity).

Reactors and accelerators

Substances can become radioactive when they are exposed to high-energy particles. This can be achieved in many different ways, but the most relevant routes are those using neutrons or charged particles. The fission process in the reactor produces neutrons that can activate these substances. For example, non-radioactive lutetium (Lu-176) can be converted to radioactive Lu-177 when exposed to neutrons.

Charged particles, such as positively charged hydrogen particles (protons), can be accelerated to high speeds (= high energy) in an accelerator. This energy can be selected in such a way that these particles make other substances radioactive. There are both round accelerators (cyclotrons) and straight accelerators (LINAC, "linear accelerator"), but their function is always to accelerate charged particles. Through exposure to protons, non-radio-active Oxygen-18 can be converted to radioactive Fluorine-18, a widely used accelerator isotope. This Fluorine-18 is used for diagnostic purposes using PET cameras.

It is and-and



* Various production routes for Mo-99 are being examined.
** The direct production of Tc-99m via accelerators is being examined.

The "and-and" figure provides an overview of the most important reactor isotopes and accelerator isotopes. The overlapping space indicates which isotopes can be produced both in a reactor and in an accelerator. This overview clearly emphasises the important of the use of reactors in the production of therapeutic isotopes.

5.1 (New) production routes for Molybdenum-99

There are various ways in which Molybdenum-99 can be produced. In the figure, these production methods are presented with the irradiation facility (reactor or accelerator) and the raw material (uranium or molybdenum). At the moment, the global demands for Molybdenum-99 are met almost exclusively via the reactor route. In this process, uranium is irradiated in a nuclear reactor and the Molybdenum-99 is then harvested from the fission products. This is the process that is performed on a large scale in Petten.

Another method that is being examined is the use of Molybdenum-98 as a raw material in a nuclear reactor. This results in Molybdenum-99 of a different quality, for which a special new generator has to be used. Other options that were examined were the fission of uranium (into a form of a salt) by neutrons from an accelerator and the conversion of molybdenum by photon bombardment. Again, a new generator is required due to the quality of the resulting Molybdenum-99. An accelerator can produce Technetium-99m directly by targeting molybdenum with protons.

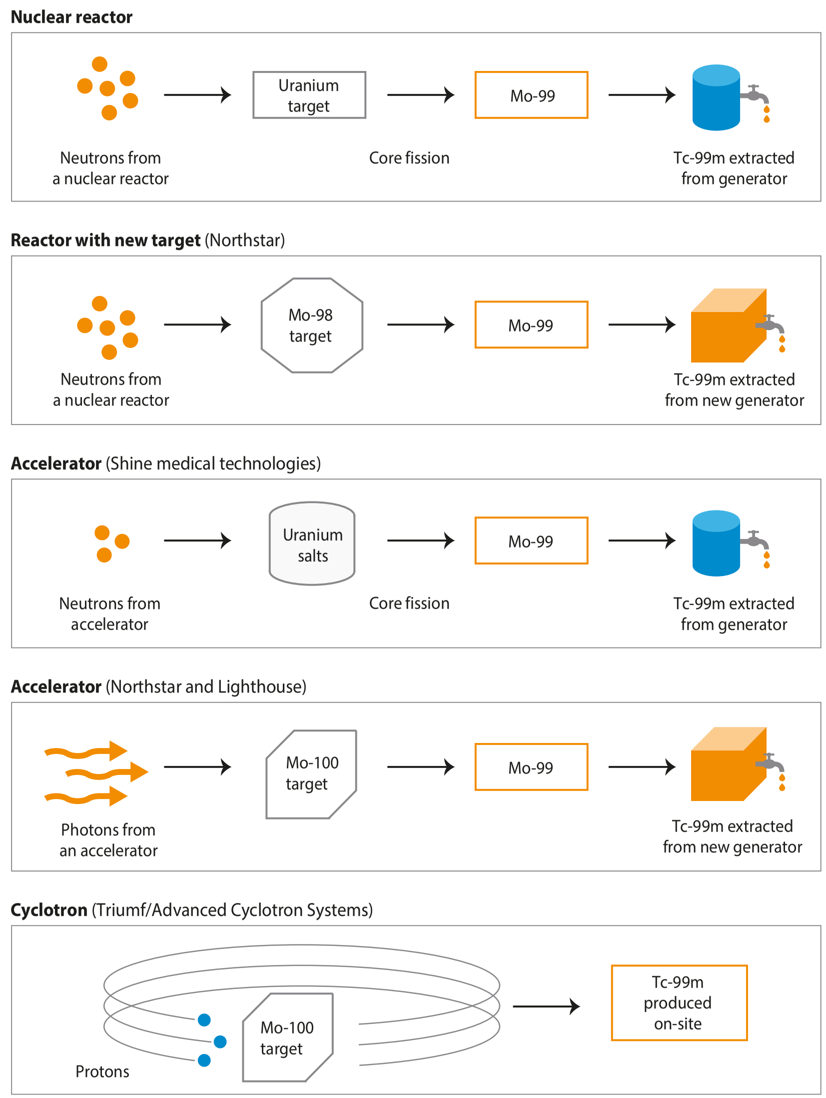
Various projects have been started over the last few years, particularly in the United States, with the aim of producing Molybdenum-99 via a different technique. Some projects have already stopped, such as the project by Babcock & Wilcox with the former Covidien (now Curium) to create a new type of reactor and an initiative by GE Hitachi Nuclear Energy to produce Molybdenum-99 in nuclear power plants.

At the moment, the initiatives by Shine Medical, Northstar and Northwest Medical Isotopes are attracting the most international attention. The American government is supporting both Shine Medical and Northstar with subsidies up to $25 million per project. The (old) MURR also plays a role in some projects, as this reactor's licence was recently renewed for twenty years.

ASML Lighthouse

A special application of an accelerator is the so-called Lighthouse initiative by ASML. In this initiative, a special, intense electron accelerator is used to create very high-energy light (photons) via a converter. This light is targeted at enriched molybdenum (Mo-100) and this is used to form Molybdenum-99. This production technology does not use Uranium, but does use enriched molybdenum. Urenco Netherlands has developed the technology to product this enriched molybdenum. The Lighthouse initiative, which was proclaimed a National Icon in 2016, is still in the early phase of development.

Process



6 The Dutch situation

Since the closure of the Canadian NRU reactor, the Netherlands has become the largest manufacturer of medical isotopes in the world. As Technetium-99m dominates by market share, the expectations for this market are crucial. A slight growth is expected over the next twenty years. This growth can be attributed mainly to countries where nuclear medicine is currently still not matured. In Western countries, there is mainly an increase in demand for therapeutic isotopes. For example, there are high expectations for Lutetium-177 and Holmium-166.

In the slightly longer term, the focus is primarily on alpha emitters, which are now showing very promising results in research projects.

Global use of reactor isotopes in nuclear medicine and expected trend over the next 20 years

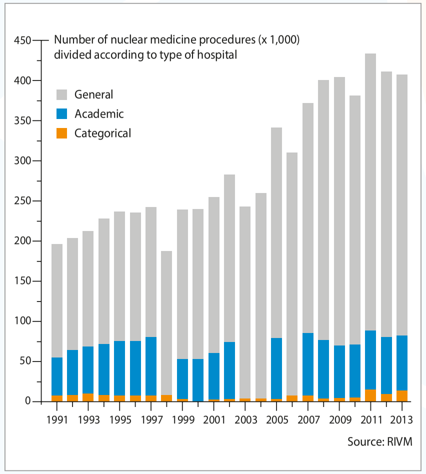
Isotope	Number of procedures using medical isotopes worldwide in 2017	Expected trend in the next 10 years
Tc-99m	35 million	+
I-131	1 million	=
Ra-223	10,000	++
Xe-133	100,000	- -
Y-90	20,000	+
Ho-166	400	++
Lu-177	15,000	+++
Ir-192	120,000	-
Alpha emitters	2,000	+++
Sr/Re/Sm	10,000-20,000	- - -
I-125	27,000	+

Drafted based on data from OECD, IAEA and NRG

The number of nuclear medicine procedures in the Netherlands has doubled over the past twenty years. The total number of procedures involving medical isotopes in the Netherlands is approximately 436,000 per year. This number includes both diagnostics and therapeutics. This figure includes both reactor isotopes and accelerator isotopes.

The number of therapeutic treatments in the Netherlands is relatively low. Based on figures from the RIVM and an inventory by reactor operator NRG (Petten), it is estimated that the current figure is over 6,700 treatments per year. It is hard to measure a total, as many treatments take place on an experimental basis and are not always included in the figures issued by insurance companies or the RIVM.

Medical nuclear procedures in the Netherlands



The importance of PET scans is also expected to rise in the Netherlands compared to SPECT scans. As SPECT is cheaper, simpler and faster, the ratio between these imaging modalities is expected to stabilise at 60:40 or 50:50.

Use of medical isotopes for nuclear medicine procedures in the Netherlands

Isotope	Production	Objective	Indication	Numbers per year
Tc-99m	Reactor	Diagnostic	SPECT	220,000
F-18, In-111, I-123, Ga-67	Cyclotron	Diagnostic	PET	129,000*
Rb82	Reactor	Diagnostic	Myocard PET	4,200
I-131	Reactor	Therapy	Hyperthyroidism	1,846
Ir-192	Reactor	Therapy	Breast/prostate cancer	1,724
Ra-223	Reactor	Therapy	Metastasised prostate cancer	1,100
Y-90	Reactor	Therapy	Liver cancer, Non-Hodgkin's Lymphoma	225
Lu-177	Reactor	Therapy	NE tumours, PSMA	670
Ho-166	Reactor	Therapy	Liver cancer	40
I-125	Reactor	Therapy	Prostate cancer, marker strands	> 1,000
Re-186	Reactor	Pain management	Bone metastases	10-15
Sm-153	Reactor	Pain management	Bone metastases	120
Sr-89	Reactor	Pain management	Bone metastases	22
Er-169	Reactor	Pain management	Bone metastases	10-15

Source: RIVM: Production and use of medical radio-isotopes in the Netherlands, 2017-0063.

**The figures for PET diagnostics are not provided in the RIVM report, but are derived from the Open Dis database.*

The RIVM performs a yearly inventory of the number of medical nuclear procedures that take place. This has revealed a growth in the number of diagnostic procedures.

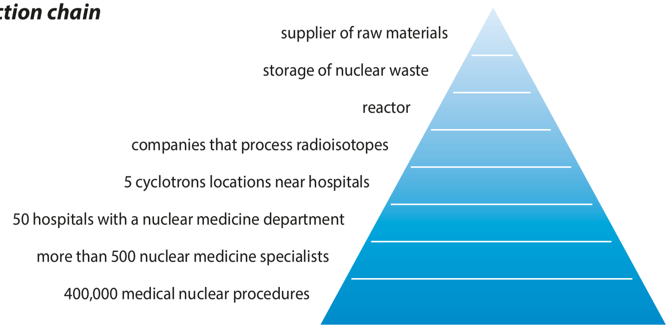
6.1 The nuclear medicine infrastructure

The Dutch nuclear knowledge infrastructure[8] includes strong expertise and extensive applications in the field of medical, materials science, energy and dealing with nuclear facilities and materials. As a result of this excellent knowledge and infrastructure, the Netherlands is in a very good international starting position in the field of medical isotopes, both in production and in use. The complete supply chain for the production, processing and delivery of medical isotopes is represented in the Netherlands. In addition, the Netherlands has a very well equipped nuclear medicine infrastructure.

A survey amongst participants in the previously mentioned Technopolis study (2016) revealed that safeguarding the Dutch nuclear knowledge infrastructure is deemed important for healthcare and safety in the Netherlands. The participants in the survey state that the Netherlands occupies a leading position in the field of medical isotopes. The nuclear and medical infrastructure is ideal for performing fundamental and applied scientific research in the field of medical isotopes. All steps in the chain are present in order to perform own research, but also to contribute to international developments and "clinical trials".

[8] Nuclear knowledge infrastructure in the Netherlands, Inventory and relation to public interests, Technopolis (2016), and position paper Nuclear knowledge infrastructure in the Netherlands, published by Nucleair Nederland (2016)

Dutch production chain

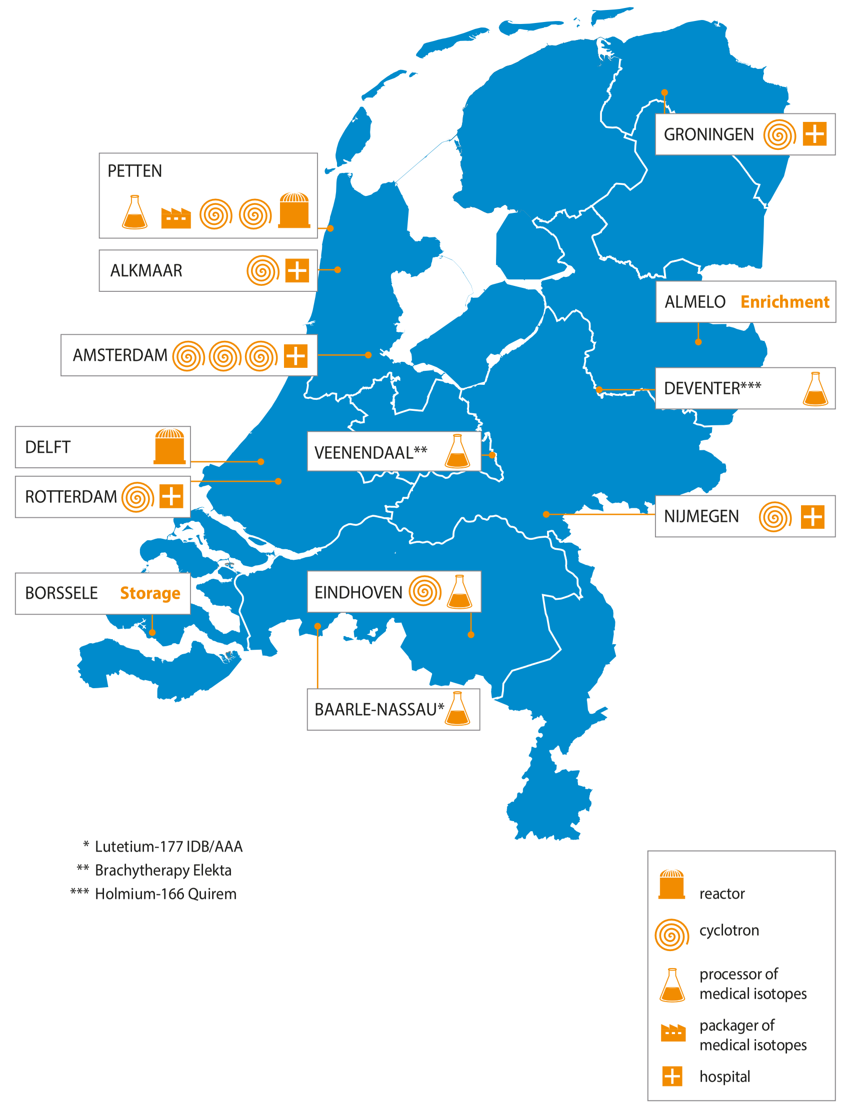


The Dutch nuclear and medical infrastructure provides a production chain in which medical isotopes can be supplied to patients worldwide. In addition, the Netherlands has an extensive nuclear medicine service, resulting in more than 400,000 procedures being performed in the Netherlands annually.

- Together with its radio-pharmaceutical partners, reactor operator NRG is the largest producer of Molybdenum-99 in the world. The Petten-based company develops and optimises the production of Molybdenum-99, supplies various therapeutic isotopes and conducts research into the production of isotopes for new radio-pharmaceuticals, particularly for therapeutic applications.
- TU Delft (Reactor Institute Delft) conducts research into alternative techniques for the production of Molybdenum-99, examines generator chemistry and studies the radio-chemistry of other production processes.
- The Stichting Voorbereiding PALLAS-reactor (Foundation for preparation of the PALLAS-reactor) is working on the successor to the High Flux Reactor in Petten. The PALLAS-reactor will focus strongly on the production and development of (new) medical isotopes. In addition, the PALLAS-reactor offers a flexible infrastructure to perform (medical) nuclear research.
- Processor Curium supplies and distributes a wide range of medical isotopes to hospitals all over the world.
- IBD Holland/AAA processes and distributes Lutetium-177.
- With its stable isotope department, Urenco has developed production routes for enrichment of raw materials for the production of medical isotopes. Examples of this include the enrichment of iridium and xenon for the production of Iridium-192 and Iodine-125. Urenco has also developed a production route for Mo-100.
- Various academic centres are working on their own research and are participating in international studies. Some examples:
  - Holmium-166 was developed in the UMC, in collaboration with TU Delft and NRG, among others.
  - the Erasmus Medical Centre is internationally renowned as an expert in the field of Lutetium-177. The development of Lutetium-177 (production process) was initiated by Erasmus MC and NRG.
  - The NKI and Radboud University Medical Centre are working together with NRG to develop the clinical application of Pt-195m for the treatment of head & neck cancer and lung cancer.
  - Through its cyclotrons and a radio-therapeutic centre, the VU Medical Centre has specialised in the development of medical isotopes.
  - The LUMC performs fundamental research into carriers/tracers with fluorescent techniques.
  - GE Healtcare, Eindhoven

International institutes, companies and medical centres know how to seek out Dutch companies and medical centres, to gain access to their expertise, products and input for clinical research.

Dutch nuclear value chain for medical isotopes



* Lutetium-177 IDB/AAA
** Brachytherapy Elekta
*** Holmium-166 Quirem

7 Recommendations

This publication has described how important it is that patients in the Netherlands, Europe and worldwide can rely on a continuous availability of medical isotopes. This publication also makes clear that the entire supply chain is working hard on innovations that should ensure that patients receive even better care in the future. The development of new therapeutic isotopes is a good example. The Netherlands occupies a unique position in this situation: it is the largest international producer of Technetium-99m, it accommodates all chain partners within its own borders, it has a long-standing tradition of collaborations in the chain, internationally groundbreaking new treatments and examinations are being developed and work is being put into achieving a new multi-functional facility for medical isotopes, the PALLAS-reactor.

In recent years, the Dutch government has played an important active and stimulating role in the nuclear medical field. There is support for example for the PALLAS-reactor, both financially and at a policy level, the financial challenges at ECN/NRG are being examined and tackled and the Reactor Institute Delft has received funding for its OYSTER project. Furthermore, active contributions are being made to a new international policy for a healthy price for medical isotopes (under the name "Full Cost Recovery"). The Netherlands has an important voice in forums such as the OECD-NEA and the European Commission.

However, the preservation and expansion of the Dutch position is not a given. Therefore, this publication will conclude with a number of recommendations to everyone who is active in this field. This includes the medical sector, the pharmaceutical sector, the industry, governments and stakeholder groups.

- **Always act in the interests of the patient**
  It is essential and directly in the patients' interests to offer long-term supply security for medical isotopes. The supply chain for medical isotopes is fragile and currently cannot function without active government involvement. Neither is it in patients' interests to think in terms of contradictions. For example, alternative production routes (accelerators) do not make the current reactor routes redundant. As has been clearly stated in this publication, the routes are clearly complementary. The realisation of the PALLAS-reactor in Petten is useful and necessary and should be actively encouraged through government policy and international cooperation.

- **Stimulate European cooperation and profiling**
  Large research and production facilities for medical isotopes should be created per continent (and not per country). European harmonisation and the coordinated use of available public funding is therefore urgently required. It is important to profile "Petten" as the leading European centre of expertise in the field of medical isotopes (production and research). Placing the PALLAS-reactor on the long-term agenda of the "European Strategy Forum on Research Infrastructures" (2018) offers the opportunity to gain access to European infrastructure and research resources.

- **Set up a national research agenda**
  A national agenda for research needs to be developed in order to remain a leading player in the development of customised therapeutic applications. This can be incorporated in the European research agendas. The involvement of university hospitals (UMCs) and patient organisations is vital. The agenda should also be aligned with the Top Sectors policy. On a European scale, the Netherlands can form a leading group with other European countries that have production facilities (particularly Belgium, followed by Poland, Czech Republic, France and Germany). The research programme of the European Joint Research Centre in Petten can also be developed further towards research in the field of medical isotopes. This will form a stronger connection with the agenda of the European Commission's.

- **Claim the Dutch leader's position**
  The Netherlands could do more to profile itself internationally as one of the few countries in the world that has fully implemented a non-proliferation policy for research reactors and the production of medical isotopes. The purchasing policy for medical isotopes in an increasing number of countries should take this into consideration.

- **Remain committed to the efforts of achieving a healthy market**
  An internationally recognised problem is the role that subsidies play in (a part of) the market for medical isotopes. These subsidies impede the process of attracting private funding for both facilities and for product development and block the growth towards a "mature" market. The "OECD NEA High Level Group on Medical RadioIsotopes" has been working on international harmonisation of the policy regarding this matter for eight years. The Dutch government successfully placed this topic on the agenda of the European Commission during its EU Presidency in 2016. It is equally important to follow through on this. The playing field for private investors should be levelled, at least on a European scale. This also means that the care sector will gradually have to accept higher rates, in exchange for a sustainable market that is able to attract private investments. However, this does not automatically mean that prices will increase for the patient. The costs for using radioisotopes currently only account for 3% of the costs for the total "end product". Instead, a shift in the cost-benefit ratio within the chain itself will have to take place.

- **Stimulate cooperation in the Dutch nuclear sector**
  The most important players in the nuclear field in the Netherlands (NRG, PALLAS, TU Delft, Urenco, various UMCs, NWO, TI Pharma and the other parties) should increase their efforts to develop a joint research and innovation agenda for improved nuclear medicine applications. The government can contribute by stimulating this cooperation.

- **Invest in university curricula**
  In order to boost the knowledge and skills in the Netherlands on an ongoing basis, university curricula can be developed in the field of the application of nuclear medicine, specifically focusing on the nuclear technology for the production of medical isotopes.

- **Strengthen the international profile of the nuclear sector**
  The Dutch nuclear industry can further strengthen the international profile of the Netherlands in the field of medical isotopes by working together on research, development and production of (new) medical isotopes and their applications. Also focus on the knowledge and skills required to optimise the process and reduce the waste flows. The further promotion of Petten as a leading "Centre of Excellence" in the field of nuclear medicine can also form part of this cooperation. Finally, there should be a greater focus on public information campaigns about medical isotopes.

A Overview of international developments in the production chains

Canada, once the world's largest producer of medical isotopes with the NRU reactor, has decided to stop production medical isotopes permanently in 2018. In anticipation of this move, Canada terminated the production of isotopes in October 2016 and the NRU reactor is only available until 2018 for the production of medical isotopes in situations of a global shortage. The company Nordion's adjacent chemical factory (the "molybdenum processing facility") has also been decommissioned and is on "stand-by" until 2018. Canada has decided to focus completely on research into alternative production methods and will limit itself in future to the home market. There are political reasons underlying this decision. In the past, Canada has built two isotope reactors (the MAPLE reactors). However, these reactors could not be commissioned due to design errors. There is no support, either political or social, for the repair of these errors.

The ***United States*** does not have a large-scale production capacity for molybdenum produced in reactors. They have always relied on deliveries, primarily from Canada and the Netherlands. The American "Medical Isotopes Production Act" was passed in 2012, a so-called technology neutral law that aims to reduce dependence on foreign suppliers. This Act released $163 million for research. This budget will be used to ensure that producers of medical isotopes worldwide will switch from using Highly Enriched Uranium ("HEU") to Low-Enriched Uranium ("LEU"), both as a fuel for research reactors and for the uranium "targets" that are irradiated to produce Molybdenum-99. In the Netherlands, the HFR reactor started using LEU fuel in 2006. A licence was requested in the Netherlands at the end of 2016 as part of the Nuclear Energy Act for the conversion to LEU targets.

A large-scale producer of medical isotopes is located near Sydney, ***Australia***: ANSTO. The OPAL reactor is relatively young (has now been operating for 10 years) and the government institute ANSTO is currently investing in replacing the old molybdenum processing facility. As a result, Australia will soon have the most modern infrastructure in the world.

Europe traditionally plays an important role in the production of medical isotopes by reactors. Not only are there various reactors contributing (mainly in the Netherlands, Belgium, Poland and Czech Republic in 2017), but there are also two molybdenum processing facilities in Europe (in the Netherlands and Belgium). In the future, the FRM2 reactor in Germany and the JHR reactor in France that is currently under construction should be able to contribute.

The Netherlands occupies a special position in Europe: not only is the Netherlands currently the largest producer of medical isotopes in the world, along with Australia it is also the only country that has the reactor and the molybdenum-processing facility in the same location. This offers many advantages, not least the fact that radioactive materials do not need to be transported by road. As transportation times are non-existent, the yield of the entire production process is also higher (less decay of molybdenum during the process) and this results in less waste.

In ***Africa***, only the SAFARI reactor in South Africa – in combination with NTP Radioisotopes, both in government hands – is globally active in the production of medical isotopes.

In ***Russia, China, Korea*** and ***Argentina***, the production of medical isotopes takes place on a small scale using reactors. These countries usually produce only for the local market, which is still small in each of these countries.

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