National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

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Supplement to RIVM Reports 2019-0101
2017-0063 and 2018-0075

RIVM letter report 2020-0171
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L. Roobol (author), RIVM
C. Rosenbaum (author), RIVM
I. de Waard (author), RIVM

Contact:
Lars Roobol
Safety\Measuring and Monitoring
Lars.roobol@rivm.nl

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# Synopsis

**Guaranteed supply of medical radionuclides – additions 2020**

RIVM has carried out additional research into the guaranteed supply of diagnostic and therapeutic radionuclides for the Netherlands. Radioactive substances can be used for making a diagnosis. There are also radioactive substances that can treat various sorts of cancer, or serve as pain relief, the so-called therapeutic radio-isotopes. Together, these substances are called medical radionuclides. Most of these medical isotopes are made in Europe, in six nuclear reactors, one of which is located in the Netherlands (the HFR). All but one reactors are advanced in age and sooner or later they will have to be closed. The Netherlands are considering to build a new reactor: Pallas.

At this moment, the world market is fragile: the unexpected closing of one reactor or one specialised laboratory could already lead to worldwide problems in the supply of medical radionuclides. The other reactors cannot always absorb the increased demand. Moreover, demand for these substances is increasing. Therefore, it is necessary to build new irradiation capacity within the next 10 years, in order to prevent large scale shortages. It is also important to keep Europe self-sufficient by increasing the irradiation capacity. For years, the planning of the projects underway have proven to be too optimistic.

Next to new irradiation capacity, all links of the supply chain are important for guaranteed supply: the supply of raw materials, dependable reactors or particle accelerators, laboratories for making radiopharmaceutical products, dependable and efficient transport between these links, and to the hospitals.

A large part of the supply chain is situated in the Netherlands. This makes that the Netherlands are in a good position to develop new radiopharmaceutical products. The presence of academic hospitals, a reactor and specialised laboratories is contributing to that fact. If the HFR has to close and no other irradiation facility will be developed the Netherlands will lose an important link in the supply chain.

Keywords: isotopes, medical radionuclides, diagnostics, therapy, reactor, particle accelerator, guaranteed supply, employment

# Publiekssamenvatting

## Leveringszekerheid voor medische radionucliden -aanvullingen 2020

Het RIVM heeft aanvullend onderzoek gedaan naar de leveringszekerheid van diagnostische en therapeutische radionucliden voor Nederland.

Radioactieve stoffen kunnen worden gebruikt om een diagnose te stellen. Ook kunnen ze verschillende soorten kanker behandelen of pijn bestrijden, zogenoemde therapeutische radionucliden. Samen heten ze medische radionucliden. De meeste medische radionucliden worden in Europa gemaakt in zes kernreactoren, waarvan er één in Nederland staat (de HFR). Op een reactor na zijn deze installaties oud en zullen ze vroeg of laat moeten sluiten. In Nederland wordt overwogen een nieuwe reactor te bouwen, de Pallas.

De wereldmarkt is op dit moment fragiel: als één grote reactor of één van de gespecialiseerde laboratoria onverwacht uitvalt, kan het wereldwijd een probleem worden om medische radionucliden te leveren. De andere reactoren kunnen de vraag dan niet altijd opvangen. Bovendien neemt de vraag naar deze middelen toe. Nieuwe bestralingscapaciteit is dan ook nodig om te voorkomen dat er binnen 10 jaar zorgelijke tekorten ontstaan. Het is ook belangrijk om Europa zelfvoorzienend te houden door het bouwen van nieuwe bestralingsfaciliteiten. De planning van initiatieven die gaande zijn, blijkt al jarenlang te optimistisch.

Naast nieuwe bestralingscapaciteit zijn alle onderdelen van de leveringsketen belangrijk voor de leveringszekerheid. Het gaat dan om de aanvoer van grondstoffen, betrouwbare reactoren of versnellers, laboratoria die een medisch product kunnen maken, betrouwbaar en efficiënt transport tussen deze schakels, en naar de ziekenhuizen.

Nederland heeft een groot deel van de leveringsketen in eigen land. Hierdoor is Nederland goed in staat om nieuwe radiofarmaceutische producten te ontwikkelen. De aanwezigheid van academische ziekenhuizen, een reactor en gespecialiseerde laboratoria dragen daaraan bij. Als de Pallas-reactor niet wordt gerealiseerd en de HFR moet sluiten, dan verliest Nederland een belangrijke schakel in de leveringsketen

Kernwoorden: isotopen, medische radionucliden, diagnostiek, therapie, reactor, deeltjesversneller, leveringszekerheid, werkgelegenheid

# Contents

# Summary

Medical radionuclides can be used for diagnostic as well as therapeutic purposes. At present, diagnostic examinations are for the most part carried out using molybdenum-99/technetium-99m that is produced in reactors.
There are presently (new) initiatives underway that will increase to future capacity for the production of molybdenum-99/technetium-99m as well as a number of substances used for therapeutic purposes, such as lutetium-177. These initiatives are under development in Belgium, Canada, Germany, France, the Netherlands, and the USA.

**Radionuclide supply and demand**
The global demand for molybdenum-99/technetium-99m will increase over the long term. The projected increase in demand in the developed economies is small, namely 0.5% per year. However, the projected increase in demand in the emerging economies varies between 5% and 8% per year.
The projections for the future supply of radionuclides are uncertain: The timelines given by the producers themselves for the start of production via new initiatives have generally turned out to be overly ambitious. It is uncertain whether the new irradiation facilities will be able to actually produce the quantities specified by them on the given dates.

Besides molybdenum-99, reactors also produce a wide range (more than 50) of other radionuclides in smaller or very small quantities. These radionuclides can be used to cure patients, extend their lives, or alleviate pain. Most of these radionuclides cannot yet be produced using accelerators. Analyses of the type available for molybdenum-99 are not available for the projected production capacity of therapeutic radionuclides for the coming 10 years. A large number of radionuclides are involved, and each of them has its own delivery chain with specific dependencies and vulnerabilities. In 2021, a report will be released on the supply security of therapeutic radionuclides, commissioned by the European Commission.

Market analyses show that the global market share of nuclear therapy (including brachytherapy) in comparison to all diagnostic and therapeutic nuclear medicine procedures grew from 4% in 2013 to 12% in 2016. The prognosis is that this market share will have increased to 20% in 2019 and to 60% in 2030. The new treatments with lutetium-177 and alpha emitters such as actinium-225 have the potential to capture a large part of the therapeutic market.

The market for lutetium-177 is growing. There is room for improvement in terms of efficiency in certain reactors, especially if they are prepared to produce lutetium-177 at the expense of other irradiation activities. However, if the projected annual growth in demand of 7% becomes a reality, then shortages will nevertheless occur within a few years. On the other hand, there are also new market initiatives underway in this sector as well. The reactor of the Laue-Langevin Institute in Grenoble (France) is now also irradiating lutetium-177, and the Canadian company Bruce

Powers claims that by 2022 it will be supplying large (but unknown to us) quantities of lutetium-177 in collaboration with the German biotech-pharmaceutical company ITM (Isotopes Technology Munich).
Production facilities
Almost all the present reactors in Europe that can produce isotopes for medical purposes are 45 years or older. Due to their advanced age, these reactors cannot be counted on to provide a secure supply of isotopes over the coming 10 years. The exceptions in this regard are (1) the German Forschungsreaktor München (FRM-II) and (2) the future French Jules Horowitz Reactor (JHR).

The FRM-II is optimised for carrying out scientific research. It routinely produces lutetium-177 and holmium-166. Starting in 2022, the reactor is expected to also be able to deliver molybdenum-99. However, the reactor's production capacity for making medical radionuclides will remain limited because (1) the main goal is to carry out scientific research, and (2) the reactor is available for irradiation only 180 days per year.
The Jules Horowitz Reactor is still being built, and the project is still subject to various uncertainties. The reactor is expected to be able to start delivering molybdenum-99 at the end of 2025.

An innovative initiative (Smart/Lighthouse, from IRE in Fleurus) to produce molybdenum-99 with an accelerator was recently granted a subsidy by the Belgian government. IRE itself expects to be able to deliver molybdenum-99 using this new technology in 2028.

**Funding**
All existing production reactors in the world are subsidised by governments. This has an impact on the costs charged by the irradiation facilities. In the case of molybdenum-99, it was often sold below the actual cost price. A covenant was drafted in 2012 aimed at selling molybdenum-99 on the market for prices that would cover the production costs. This is known as Full Cost Recovery (FCR).
A failure to achieve FCR makes it more difficult to develop and build new production capacity, as the (artificially) low price charged for the products makes it more difficult to recover the initial investment costs.

**Supply security and delivery security**
Supply security is achieved by optimising the delivery chain. Important links in this chain are: (1) a stable supply of raw materials, which may or may not be isotopically enriched; (2) reliable irradiation facilities (reactors/accelerators) with a high degree of availability; (3) reliable processing facilities (radiochemical "hot cell" laboratories) with a high degree of availability; (4) reliable radiopharmaceutical facilities with a high degree of availability; (5) reliable and efficient transport between these links and, finally, from the pharmaceutical company to the hospitals.

Given the present situation within the industry, the presence of all these links of the chain in one country does not improve the delivery security in that country, as no "first rights" have been established. However, a continent such as Europe does stand to benefit from having the entire chain located on its own territory; after all, during situations such as

Covid 19, transport over land turns out to be more reliable than air transport.

If the HFR were to shut down without the Pallas reactor being built to replace it, then the Netherlands would lose its position within this delivery chain. After all, if the irradiation facility was no longer available, then it is quite likely that the radiopharmaceutical company would also relocate to a site outside the Netherlands.
If the Pallas reactor is not built, it would also have major negative consequences for the (local) job market in the nuclear sector (loss of approximately 1000 jobs at the Petten site, and approximately the same number under suppliers). Generally speaking, it would also have major negative consequences for the nuclear knowledge infrastructure in our country, as about one third of the persons employed in the nuclear sector work in Petten. Together with the loss of physical infrastructure, this means that the services provided to the nuclear industry as well as other industrial sectors and government entities would cease to exist.

If no new initiatives for medical radionuclides appear on the market in the medium-term to long-term (10 years), then worrisome market shortages could occur. The following aspects play a role in that regard:

- Many of the present installations are old. It is not possible to predict when and if the production will (partially) come to a halt. However, the likelihood of such a development occurring increases as the installation becomes older. In addition, the HFR and the BR2 each supplies approximately 30% of the global market. The failure of one of these installations would therefore have a major impact on the global market.
- How long it will take before new initiatives start operating and delivering products cannot be reliably predicted. Without exception, the predictions made by the manufacturers over the last 10 years about when production capacity would become available have turned out to be overly optimistic.
- The initiatives with accelerators (such as SHINE, Lighthouse, …) for producing molybdenum are under development, but none of these initiatives are yet in production. Once one of these initiatives actually start producing, it will be able to supply part of the global demand for molybdenum (SHINE claims 30%).
- If there are new initiatives that succeed in developing a product within a number of years that can be delivered to hospitals, then it would improve the supply security of molybdenum-99 from that moment onwards.
- If one of the global players has to shut down, as has happened in the past, then the capacity at other facilities will be increased in order to raise production levels and be able to make deliveries to hospitals. During the molybdenum-99 shortages of 2009-2010 (due to failure of the HFR), this was not realised within a year, and supply security was re-established only after the HFR again became available.

The experiences of the Dutch hospitals have shown us that the system for the delivery of medical radionuclides is presently less secure than, for example, our power grid. There is an extensive track record available from the Dutch hospitals which makes it clear that the deliveries regularly

experience brief interruptions. As it turns out, this is frequently caused by logistics issues (delayed flights et cetera).

The aspects mentioned above apply to the delivery of molybdenum for diagnostic procedures. For the therapeutic isotopes such as lutetium-177, iodine-131 and iridium-192, the failure of one of the reactors would probably lead to a longer period of shortages. Iridium-192 (for radiotherapy) of the right quality cannot be produced using an accelerator. There are initiatives underway in the world aimed at increasing production capacity for lutetium-177 and iodine-131, for example at Bruce Power and SHINE. However, the demand is also growing rather quickly, and it is not clear whether supply is outpacing demand to such a degree that the increased supply will be able, within several years, to compensate for the closure of a producer such as the BR2 or the HFR. A large scale increase in the production capacity of therapeutic isotopes at other facilities demands a timeline of several years.

In short, if one of the large irradiation facilities presently operating on the global market for molybdenum/technetium were to shut down, the impact on supply security would depend on the timeframe. If these facilities were to stop producing in the near future without any new initiatives being available that are already reliably producing and delivering, then it would lead to a shortage of medical isotopes. If the shutdown took place further in the future, then the initiatives that had already been realised and were reliably producing would probably be able to fill (part of) the production gap. However, this is true only for the diagnostic isotopes. The supply of therapeutic isotopes depends on many factors. We also expect shortages for other important substances such as lutetium-177 and iodine-131. The severity of these shortages will depend on how quickly alternative producers can supply the market and the quantities they can deliver. In the long term, most of the reactors in Europe will be shut down, and Europe will no longer be self-sufficient unless new irradiation capacity is built.

No country in the world has succeeded in building a reactor for the production of medical radionuclides that is fully financed by private means. However, a small 2 MW reactor (in size comparable to the one in Delft), which would cost roughly €100 million, would appear to be feasible in the US on the basis of private funding alone. Other initiatives in the US depend either on knowledge acquired previously or on the capacity of already existing research reactors funded by the government. SHINE, NorthStar and Niowave would seem to be exceptions in this regard, as they each intend to build production capacity in the US with limited subsidies, based on accelerator technology.

The irradiation capacity for the production of medical radionuclides in the other countries has also (largely) been financed by the government. This can be the result of government funding for the construction of a new reactor or facility, or the result of having an existing government-funded facility available where the production of medical radionuclides can be carried out while incurring only marginal additional costs.

# 1 Introduction

## 1.1 Background and motivation

Medical radionuclides are radioactive substances that are used within a hospital setting to diagnose various diseases, such as cancer and heart abnormalities, or for (cancer) therapy. Some of these substances can be produced only with the help of particle accelerators and others only with the help of nuclear reactors.
The nuclear reactors that are presently used for producing these substances are old, so that new initiatives are needed to ensure the supply of these medical radionuclides for the future.
The initiatives that are presently being discussed can be divided into three categories:

1. Building new (production-oriented) nuclear reactors for medical radionuclides.
2. Modifying existing (old) nuclear reactors to make them suitable for the production of radionuclides.
3. Developing new technology that would make it possible to use particle accelerators to produce those medical radionuclides that until now have been produced only by nuclear reactors.

## 1.2 The issues to be investigated

RIVM has been commissioned by the Dutch Ministry of Health, Welfare and Sport to draft a report on the supply reliability of medical radionuclides and the role played by the Pallas reactor in that regard. More specifically, the following questions were asked:

1. Is it necessary to build new production capacity in the Netherlands?
    a. Does Pallas or an alternative play a central role in the development of medicines based on isotopes?
    b. What is the significance of the Pallas reactor, the alternatives and/or their absence for the healthcare sector in the Netherlands?
    c. How important is Pallas or an alternative for high-quality job opportunities and for knowledge infrastructure?
2. When will possible alternatives become available?
3. What partnerships or collaborations are there in other countries and what kind of funding do these initiatives receive (existing initiatives and initiatives under development)?
4. Why are other countries willing to put their faith in the market? In other words, why are they not themselves building a reactor?
5. What policy options are available to the Ministry of Health, Welfare and Sport if no new production facility becomes available in the Netherlands?

These questions were answered by consulting the previous reports written by RIVM on this topic [1-4], by collecting updated public data, and by having a number of stakeholders fill out a questionnaire. For the questions and the answers given by the stakeholders, refer to appendices A and B.

## 1.3 Reading guide

Chapter 2 of this report presents background information about medical radionuclides. It provides insight into the role of medical radionuclides in healthcare and the supply chain. It then explains the present situation with regard to supply reliability (supply and demand) and the prognoses for the future.
Chapters 3 through 7 discuss the issues to be investigated. The discussion is based on the knowledge and information presented in chapter 2 and the results of the questionnaires for the stakeholders. The content of the questionnaires for the stakeholders (production facilities and hospitals) and the answers of the respondents are presented in appendices A and B.

# 2 Background information on medical radionuclides

## 2.1 Medical diagnostics and therapy

Nuclear medicine physicians and radiotherapists use many different types of medical radionuclides for making diagnoses (via medical imaging of the body) and for cancer therapy. These substances have been selected for their specific properties such as the particles or energy that they radiate, how quickly they disintegrate (i.e. transform into a different substance), and how easily they can be chemically linked to other substances. Many of the diagnostic examinations are done with technetium-99m, which is a daughter nuclide of molybdenum-99, which until now has been produced in reactors. Another commonly used radionuclide is fluorine-18, which is used in particular for PET scans. Fluorine-18 is produced using a particle accelerator (a cyclotron) and therefore falls outside the scope of this report.

By linking radionuclides to biological molecules (sugars or proteins for example), it is possible to make targeted images of certain processes inside the body. For example, sugars specifically target muscle tissue (e.g. the heart), and calcium specifically targets bone tissue. In addition, there are complex proteins that specifically bind with a specific type of cancer cell. The biological molecule therefore functions as a carrier vehicle that targets (travels to) a specific site in the body, and the radionuclide functions as a kind of lamp that emits radiation at the site in question. The radiation that is emitted is captured using a special type of camera and then converted into an image for diagnostic purposes.

The radiation that is emitted can also be used to kill cancer cells that may be present. In that case, the radionuclide is used for therapeutic purposes. The newest developments in this field are referred to as theranostics, which is a combination of therapy and diagnostics [5]. In theranostics, one radionuclide can be linked to a tracer for diagnostic purposes (e.g. gallium-68 to dotatoc for neuroendocrine tumours) after which a different radionuclide can be linked to the same tracer for therapeutic purposes (e.g. lutetium-177, again linked to dotatoc). The developments in this area started over 75 years ago with the use of iodide-131 for the diagnosis and treatment of thyroid cancer but have accelerated in recent years, for example for the diagnosis and treatment of prostate cancer using PSMA linked radionuclides [6].

To carry out such procedures using technetium-99m, hospitals purchase a generator. The generator contains molybdenum-99, which disintegrates into technetium-99m. For each procedure, the hospital laboratory can “milk” the necessary technetium-99m from the generator; the generator is therefore also referred to as the “cow”. The speed (half-life) with which molybdenum-99 disintegrates is such that, after roughly one week, the generator no longer contains enough technetium-99m for medical imaging purposes. A new generator then needs to be delivered [2-4].

## 2.2 Production in irradiation facility

There are roughly two groups of medical radionuclides: one group that can be produced efficiently only in a nuclear reactor, and another group that can be produced efficiently only in a particle accelerator such as a cyclotron. A limited category of radionuclides can be produced in a reactor as well as in a particle accelerator (see Figure 2.1).

At present, the most commonly used medical radionuclide, molybdenum-99/technetium-99m, can be produced only in a nuclear reactor. However, many innovative initiatives have been developed in recent years that aim to produce molybdenum-99 in a particle accelerator. These particle accelerators are, however, larger and more complex installations than a cyclotron.

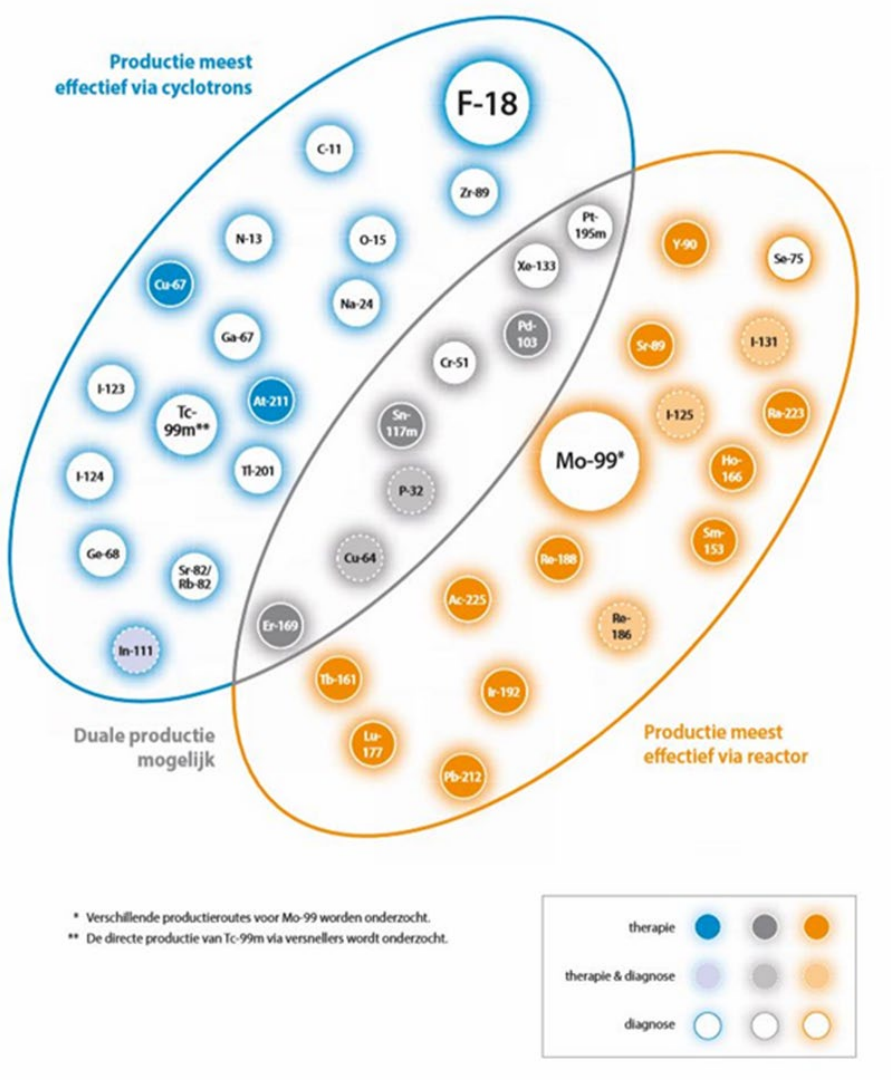



*Figure 2.1 Overview of production methods of radionuclides [7]. Some radionuclides can be produced only in a reactor (yellow group), others only in an accelerator (blue group). A limited category of radionuclides can be made using both production methods (grey group)*

## 2.3 Delivery chain

The irradiation of medical radionuclides is only one part of a complex delivery chain. The most important steps in this chain are:

1. obtaining the (enriched or unenriched) raw material;
2. irradiating that material;
3. radiochemical separation of the desired nuclides from the irradiated material;
4. the radiopharmaceutical process that ensures that the end product meets the quality requirements (including purity).

Figure 2.2 illustrates this complex delivery chain for molybdenum-99 [8]. The irradiation facilities (irradiators), the processors of the irradiated material (molybdenum-99 suppliers), and the pharmaceutical suppliers (Technetium generators) have formed an international network. They have cooperative agreements with each other and purchase from and sell to each other.

The position of the Netherlands within this entire framework is quite special in that a large part of the delivery chain for medical radionuclides is situated within its borders. This includes research & development, the (isotopic) enrichment of raw materials, the irradiation of these materials, and the processing of these intermediate products into radiopharmaceutical ingredients and end products. Nevertheless, the Dutch government has little control over the delivery chain. This is due to the international cooperation of all the partners in the chain and the fact that the network is interdependent to such a high degree.
In case of shortages, caused by the unexpected failure of one of the nodes in the network, the pharmaceutical companies that deliver molybdenum-99/technetium-99m to the hospitals will ration the limited supply on a proportional basis. For example, if there is a global shortage of 10% in a particular week, then all clients will receive 10% less than the amount ordered. Whether or not a country actually contributes to the delivery chain is not relevant in this regard.

The weak links in the delivery chain are the advanced age of the existing reactors and the availability of the hot cell laboratories (processing labs) where the molybdenum-99 is radiochemically purified from the irradiated uranium plates.
Two of these old reactors, the BR2 in Mol (Belgium) and the HFR in Petten, provide approximately 60% of the global demand for molybdenum-99 between the two of them. In addition, all the molybdenum-99 irradiated in Europe is processed in only two radiochemical (hot cell) laboratories, namely Curium in Petten and IRE in Fleurus (Belgium). In the present situation, the prolonged failure of one of both reactors or laboratories would have serious global repercussions for the delivery of molybdenum-99, namely about 30% of the present global demand. Figure 2.7 in section 2.3 shows that this situation could last for years.
Although there is less information available with regard to the therapeutic radionuclides, it is quite plausible that roughly the same decreases/shortages would apply for therapeutic radionuclides if a reactor had to be shut down. However, there are more hot cell laboratories available in Europe that could possibly process the

therapeutic radionuclides or that could be modified within a few years to make this possible.

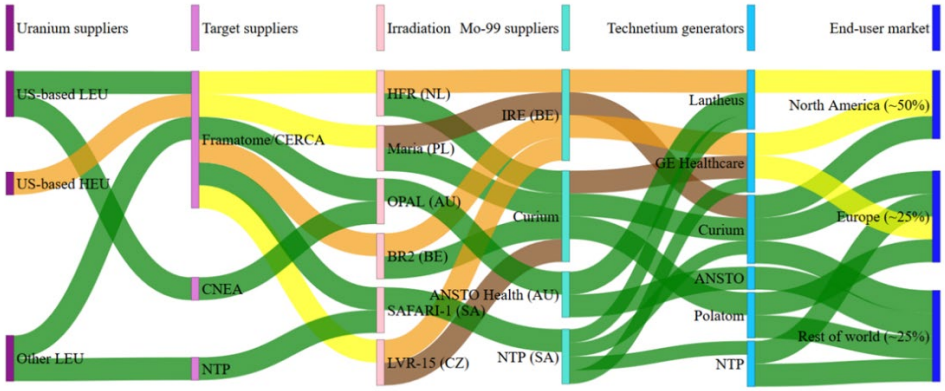



*Figure 2.2 The international delivery network for molybdenum-99/technetium-99m. The green paths show production on the basis of low enriched uranium (LEU), the orange ones on the basis of high enriched uranium (HEU), the yellow ones on the basis of both the above, and the brown ones show backup routes that are deployed only in special situations [source: [8] (Figure 108)].*

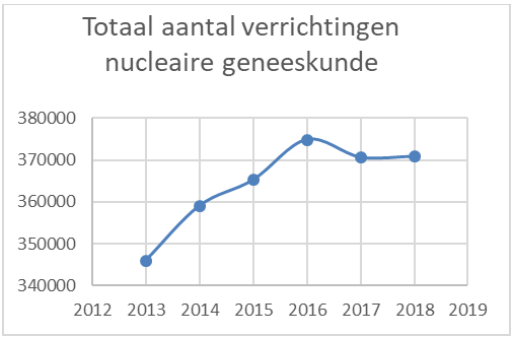
## 2.4 Delivery reliability: present situation with regard to supply and demand

Delivery reliability is achieved by optimising the entire delivery chain. The combination of a reliable supply of raw materials together with a cooperating irradiation facility and a radiochemical and radiopharmaceutical laboratory determines the reliability of the system.

### *2.4.1 Present use of radionuclides in the Netherlands*

A great many different medical radionuclides are utilised in the Netherlands. However, the demand for these substances is very unevenly distributed. Some radionuclides, such as technetium-99m, are utilised to an enormous degree (molybdenum-99/technetium-99m), a total of approximately 300,000 administrations per year, whereas other radionuclides are used much less frequently, sometimes only a few hundred times per year.

In Figure 2.3, the graph on the left shows the total number of nuclear medical procedures carried out from 2013 up to and including 2018. The increase amounts to approximately 1% to 2% per year. The graph on the right in Figure 2.3 shows the number of nuclear medicine therapeutic treatments over time.
Part of the increase in treatments, such as treatments with lutetium-177, has occurred more recently than 2018 and is therefore not shown in this graph. In addition, new therapies are at first not always declared and are therefore not reflected in this data.



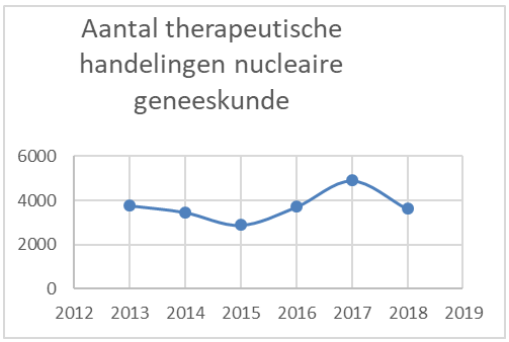




*Figure 2.3 The graph on the left shows the total number of nuclear medicine procedures (diagnostic as well as therapeutic) in the Netherlands from 2013 up to and including 2018. The graph on the right shows the number of nuclear medicine therapeutic procedures [9].*

Table 2.1 applies to the most commonly used reactor-produced medical radionuclides and specifies whether the substances in question are used for diagnostic or therapeutic purposes, the technologies used to produce them, and how frequently they are presently being used in the Netherlands. The number of procedures is not always the same as the number of patients: for most examinations or therapies, a radioactive substance is administered to a patient only once but in some cases several times.

*Table 2.1 The most commonly used reactor-produced medical radionuclides in the Netherlands*

| **Radionuclide** | **Application** | **Production** | **Number of procedures in the Netherlands per year** |
|---|---|---|---|
| Yttrium-90 | Therapy | Reactor | 25 |
| Technetium-99m | Diagnosis | Reactor (Complex accelerator[e]) | Approximately 300,000[a] |
| Iodine-125 | Therapy | Reactor | Approximately 4000[b] |
| Iodine-131 | Therapy | Reactor (Complex accelerator[e]) | 1,394 |
| Iridium-192 | Therapy | Reactor | Approximately 1,100[c] |
| Holmium-166 | Therapy | Reactor | Approximately 50 |
| Lutetium-177 | Therapy | Reactor | Estimated 900[d] |

a Estimate based on the total number of procedures with medical radionuclides.
b This is an estimate based on the care code for 'localising breast tumour' (18,300 instances in 2018) and the numbers from the questionnaire in appendix B. The number of I-125 procedures is less than the number of care code declarations for localisation, as this can also be carried out via a different method such as wire localisation, but is higher than in the questionnaire, as not all hospitals have filled out the questionnaire and there is also presently little information available from radiotherapy for I-125.
c There are presently approximately 700 cervical cancer patients per year in the Netherlands (source: IKNL), half of whom receive iridium brachytherapy (350 patients), 1900 endometrial cancer patients per year, of whom 35% receive iridium brachytherapy (665 patients), and approximately 50 vaginal carcinoma patients who need iridium brachytherapy.
d Estimate based on data from the questionnaire.
e The term complex accelerator used here refers to the class of particle accelerators such as those by Lighthouse, SHINE, etc. In terms of size and complexity, these accelerators fall somewhere in between a cyclotron and a research reactor.

The number of procedures or patients does not tell the whole story. The benefit provided by the procedures in terms of diagnosis, cure, extra life years, and quality of life is also important. Sometimes there are also alternatives for procedures or treatments.

Diagnostic procedures reveal a condition or exclude it. By doing so, the procedure assists the clinical medical specialist in the process of diagnosing the symptoms of the patient. Negative test results, whereby no indication is found of the suspected illness, also help in this regard.

Therapeutic treatments can cure a patient, but they can also extend the life of a terminally ill patient and/or serve to reduce pain. The quality of life during or after a treatment is also important in this regard. The combination of longer life and quality of life is referred to, within a cost-benefit analysis, with the term QALY, i.e. quality-adjusted life year [1]. Answering the question of how many healthy life years are gained in the Netherlands or elsewhere via the application of medical radionuclides falls outside the scope of the assignment at hand and would require a larger-scale investigation than the one requested here.

### *2.4.2 Alternative radionuclides and alternatives for nuclear medicine*

[1] presents an overview of the medical radionuclides used in the Netherlands as well as possible alternatives. An alternative nuclide can sometimes be used for some procedures. However, the resulting disadvantages are a poorer image quality and/or a higher dose. The Dutch Association of Nuclear Medicine states that all alternative techniques or procedures are second-best [1].

### *2.4.3 Present production capacity of molybdenum-99*

Almost all reactors in Europe that are presently capable of making medical radionuclides are 45 years or older and can therefore not ensure a supply of isotopes for the coming 10 years. The exceptions in this regard are the German Forschungsreaktor München (FRM-II) and the future French Jules Horowitz reactor (JHR) [3].

The FRM-II and the JHR will increase the total production capacity of molybdenum-99. The annual production of molybdenum-99 by both these facilities together lies between the production capacity of the HFR

[1] Refer, for example, to the definition given in: https://nl.wikipedia.org/wiki/Quality-adjusted_life_year

and BR2 [3, 8]. A study carried out in 2018 at the request of the European Union [8] concluded that, in the long term, in addition to the FRM-II and the JHR, another reactor will be needed that is specialised in the production of medical radionuclides, as reactors such as the HFR will be shut down in the long term. Pallas is viewed by the experts as the most likely candidate in this regard.
The expert panel also concluded that, if no extra reactor is built, Europe will not be able to supply its own needs. Such a situation could even lead to shortages on the global market [3, 8]. Now, two years after the above study, new data is available, including data on developments in Belgium and the US, that justify once again looking critically at this conclusion. In that regard, read section 2.5 on the future supply and demand of medical radionuclides.

### *2.4.4 Present delivery problems*

As described in appendix B, eight of the nine responding hospitals reported one or more episodes of delivery problems in 2019. In particular, this applies to the delivery of molybdenum-99/technetium-99m. The causes mentioned by the hospitals for these issues include a shortage of molybdenum-99 in Petten. This does not pinpoint the exact location of the problem in the delivery chain (reactor, radiochemical laboratory, or pharmaceutical facility). To clarify this issue, NRG [10] was contacted.

NRG operates the reactor in Petten and also manages the molybdenum production facility (MPF) located there. (The MPF is what the OECD refers to as a "processing" or "hot cell" laboratory.) Two aspects are important for delivery security: availability and reliability.

Availability refers to the number of days each year that the reactor is available for irradiations. The reactor in Petten can perform irradiation 270 days per year, and the radiochemical laboratory (hot cell laboratory) in Petten is available 50 weeks per year.

Reliability refers to the degree to which the facility operates according to planning. In 2019, the reliability of the radiochemical laboratory was 100%, and the reliability of the reactor was 98.1%. In 2019, there were unplanned interruptions at the end of October and beginning of December that lasted, respectively, 2 and 3 days. The delivery problems reported by hospitals may have occurred during planned interruptions.

When asked about the matter, NRG responded as follows: 'A direct relationship between shortages, such as those experienced by hospitals, and the operations of reactors is often not evident. In the first place, there are various links in the production chain after the reactor step, and in the second place it is the radiopharmaceutical companies that take care of distributing the end product to hospitals (all over the world). The reactors cannot influence these parts of the chain. However, the existence of short logistic connections is generally favourable for supply security.'

## 2.5 Supply security: future supply and demand

### *2.5.1 Prognoses for future production capacity of molybdenum-99*

The OECD/NEA in Paris, in collaboration with the industry, prepares annual reports on the prognoses for the supply of the most commonly used medical radionuclide, molybdenum-99. The most recent report was prepared in 2019 and covers the 2019-2024 period [11].

In its 2019 report [11], the OECD/NEA worked out three scenarios regarding the demand for and production of medical radionuclides as well as the (radiochemical) processing capacity. These scenarios are as follows:

- A: uses the present operational irradiation and processing capacity as the point of departure.
- B: adds the new initiatives into the mix. In doing so, the non-reactor initiatives were assigned an operational success probability of 50% within the timeframe specified by the initiators.
- C: same as scenario B, but with a two-year delay, as the planning for most of the initiatives has turned out to be too ambitious.

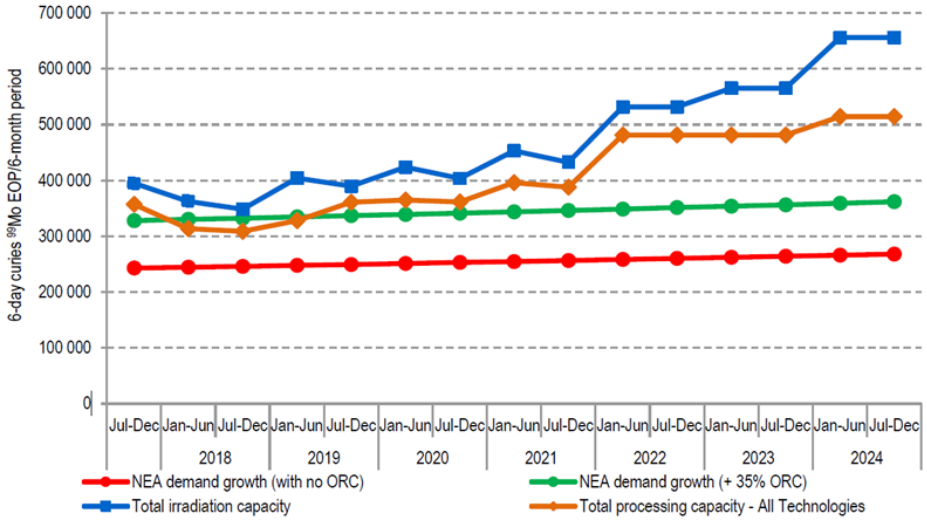



*Figure 2.4 Projected supply and demand for molybdenum-99 per six months [11]. The assumption made here is that the data provided by manufacturers on when the extra capacity will become available is always two years earlier than the actual date realised. Figure from the 2019 report; data points from 2018 with regard to capacity realised, data points from 2019-2024 on expected capacity. ORC stands for outage reserve capacity.*

Figure 2.4 shows scenario C from the OECD-NEA 2019 report. The data points from 2018 show the capacity actually realised here, and the data points from 2019 onwards show the expected capacity. The red line is the projected demand for molybdenum-99. The green line lies 35% (ORC: outage reserve capacity) above the red line. This is considered to be an adequate safety margin in terms of capacity, which ensures that the demand can always be satisfied even if one of the irradiation or processing facilities suffers an unplanned temporary shutdown.

Figure 2.4 makes it clear that the supply of molybdenum-99 in the coming years will not be limited by the available irradiation capacity (blue line) but rather by the processing capacity available in radiochemical laboratories (the orange line lies below the blue line). In 2018, the orange line was below the green line but still above the red line. This means that, in 2018, processing capacity was tight and that the 35% safety margin was not guaranteed during that period. In other words, the unexpected shutdown in 2018 of only one producer could have resulted in shortages in global supply.

In this prognosis for the 2019-2024 period, the orange line does lie above the green line, which represents the demand (plus a safety margin of 35%). Further on in this section, the reliability of such prognoses is discussed.

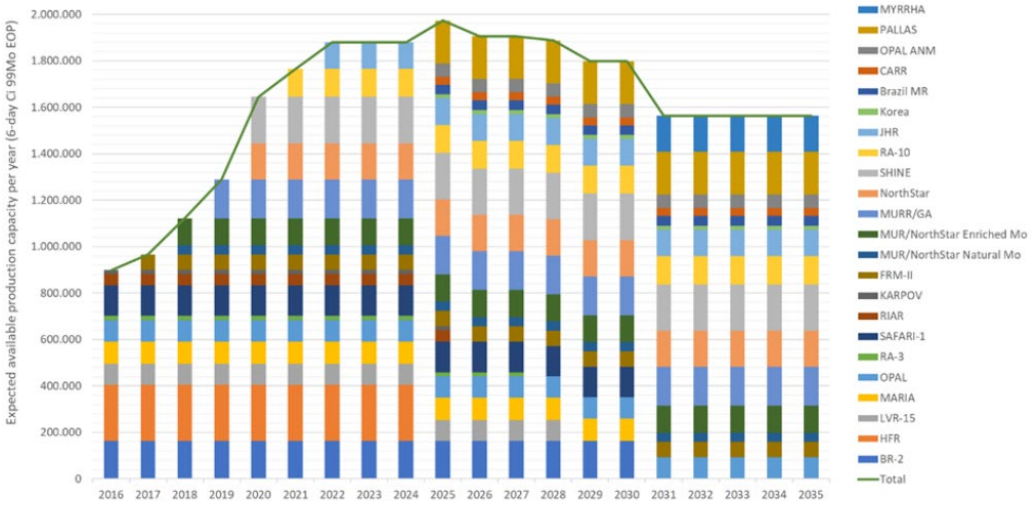



*Figure 2.5 Prognosis until 2035 for the annual production capacity of molybdenum-99 [source: [8], Figure 110] as stated by manufacturers in 2016.*

In its 2019 report, the SAMIRA (European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology) initiative looks further into the future and provides a prognosis for production capacity until 2035 [8]. Figure 2.5 shows the relevant figure from that report, with the projected irradiation capacity of molybdenum-99 until 2035 as specified by the manufacturers (in 2016).

If all these predictions were to come true, then Figure 2.5 shows that, starting in 2020, an enormous excess production capacity would develop on the molybdenum-99 market. After all, the annual demand for molybdenum-99 is approximately 500,000 6-day curie (the numbers in Figure 2.4 are per six months), whereas the numbers in Figure 2.5 add up to a number between 800,000 (2016) and 1,900,000 6–day curie (2025).

This situation is not likely to actually occur. It is more likely that a number of major players will dominate the market, and that other projects will generate a smaller turnover or even be halted altogether. New players who succeed in supplying the market with reliable and significant quantities of good quality molybdenum-99 between now and

the next five years will have the advantage of being the first movers and will make it difficult for players who arrive later on the scene to obtain a significant market share.

Similarly, the players who now dominate the market for molybdenum-99 have a more comfortable position than possible newcomers who will still have to obtain a share of the market. The important factors in that regard are product quality, reliability, and price.

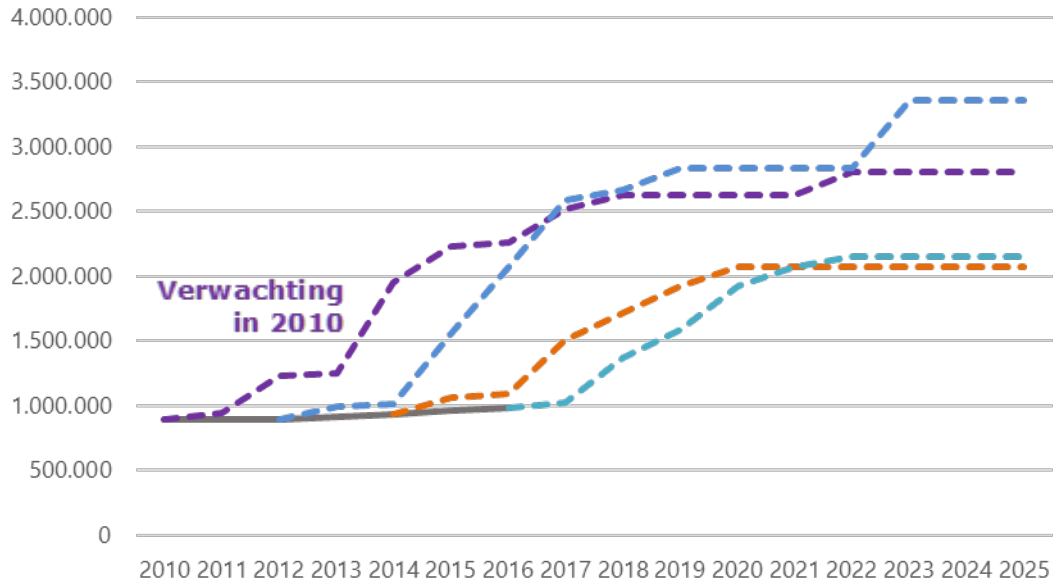



*Figure 2.6: Prognosis of the amount of production capacity (in 6-day curie after completion of processing) for molybdenum-99 that is expected to become available in 2010, 2012, 2014 and 2016 [source: OECD/NEA, [1]].*

By comparing the prognoses of irradiation capacity from successive OECD-NEA reports, one can obtain insight into the delays experienced by large-scale technical projects such as production facilities for radionuclides. Figure 2.6 illustrates this for the prognoses of irradiation capacity for molybdenum-99 up to and including 2025, as projected in 2010 (purple line), in 2012 (dark blue line), in 2014 (orange line) and in 2016 (light blue line). Accordingly, the dates on which irradiation capacity was projected to increase kept on moving forwards into the future: in 2010, capacity was projected to increase in 2011, and in 2016, capacity was projected to increase in 2017.

In addition to the projected starting date for production, the size of the projected capacity expansion was also regularly modified. According to Figure 2.6, in 2012, capacity was projected to increase to 3.4 million curie per year in 2025, but in 2016 that figure was adjusted downwards to 2.1 million, a decrease of over 30%.

The prognoses for molybdenum-99 irradiation and processing capacity presented in the OECD-NEA reports also make it clear how difficult it is to predict the future. The numbers from the 2015 up to and including 2019 reports are compared to each other in Table 2.2.

The OECD-NEA report from 2015 [12] (data from 2014) projects that the irradiation capacity would increase from 490 in 2015 to 620 units in 2019, and that the processing capacity would increase from 380 to 530 units. In reality, both numbers actually decreased to, respectively, 390 and 350 units.

*Table 2.2 Irradiation and processing capacity for molybdenum-99 (in kilocurie per year) according to the OECD-NEA prognoses.*

| **Year of OECD-NEA report** | **Irradiation capacity in year in question** | **Projected irradiation capacity in 5 years** | **Processing capacity in year in question** | **Projected processing capacity** |
|---|---|---|---|---|
| 2,015 | 490 | 620 | 380 | 530 |
| 2,016 | 420 | 690 | 410 | 660 |
| 2,017 | 480 | 705 | 410 | 605 |
| 2,018 | 390 | 630 | 350 | 570 |
| 2,019 | 390 | 660 | 350 | 510 |

*Table 2.3 Irradiation capacity for molybdenum-99 (in kilocurie (kCi) per year) according to the OECD-NEA prognoses. The years in the top row are the years in which the OECD-NEA reports were published. The other years in the table indicate when the extra irradiation capacity will become available on the market according to the (future) producer, in the year in question. The last column 'Delay' indicates by how many years the projected implementation date was moved into the future, between 2015 and 2019. Complete data is not available for all facilities (empty fields).*

| | **2,015** | | **2,016** | | **2,017** | | **2,018** | | **2,019** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **kCi** | **year** | **kCi** | **year** | **kCi** | **year** | **kCi** | **year** | **kCi** | **year** | **delay** |
| OPAL | 108 | 2,017 | 75 | 2,017 | 58 | 2,018 | 58 | 2,019 | 58 | 2,020 | +3 years |
| FRM-II | 67 | 2,018 | 67 | 2,018 | 67 | 2,020 | 67 | 2,020 | 67 | 2,022 | +4 years |
| MURR/NS | 39 | 2,015 | 39 | 2,017 | 39 | 2,018 | 39 | 2,019 | 39 | 2,019 | +4 years |
| MURR/NS* | 117 | 2,017 | 117 | 2,018 | 117 | 2,018 | 117 | 2,020 | 117 | 2,021 | +4 years |
| NorthStar | 156 | 2,018 | 156 | 2,018 | 156 | 2,020 | 156 | 2,021 | 132 | 2,023 | +5 years |
| MURR/GA | | | 218 | 2,019 | 166 | 2,019 | | | | | - |
| SHINE | 175 | 2,019 | 200 | 2,020 | 200 | 2,020 | 200 | 2,021 | | | - |
| Korea | 17 | 2,019 | 17 | 2,020 | 17 | 2020+ | 17 | 2023+ | | | +4 years |
| Brazil | 41 | 2,020 | 41 | 2021+ | 41 | 2022+ | 41 | 2023+ | | | +3 years |
| RA-10 | 120 | 2,020 | 120 | 2,020 | 120 | 2,021 | 120 | 2,021 | 120 | 2,021 | +1 years |
| JHR | 154 | 2,021 | 154 | 2,021 | 115 | 2,022 | 115 | 2,023 | 115 | 2,023 | +2 years |
| China RR | 34 | 2019+ | 34 | 2021+ | 34 | 2022+ | 34 | 2023+ | | | +4 years |

A final illustration of the uncertainties in the prognoses of irradiation capacity is presented in Table 2.3. This table shows how the estimates made by various (future) producers vary over the years with regard to the start of irradiation operations and the projected irradiation capacity [11].

For example, in 2015, the FRM-II projected that it would be able to deliver approximately 67,000 curies extra of molybdenum-99 per year by 2018. In 2019, they stated that the estimate of extra capacity was still correct but that they would be able to deliver that quantity only in 2022. So over a period of 4 years, the expected starting date was pushed 4 years forward into the future. As is evident from the last column, Delay, this is true of many of the initiatives.

The graphs and tables in this section make it clear that the uncertainties in these prognoses for molybdenum are quite large, both with regard to the starting date as well as the production capacity.

### 2.5.2 *Available irradiation capacity*

If we look at the OECD/NEA analyses over the years, several striking aspects become noticeable:

- The date on which new capacity is projected to come ONLINE always moves several years forward into the future.
- The date on which existing capacity is projected to go OFFLINE also always moves several years forward into the future.
- The (projected) amounts of capacity that come online and go offline are large and of the same order of magnitude. The addition and subtraction of such large numbers makes the prognosis for the total number very uncertain.

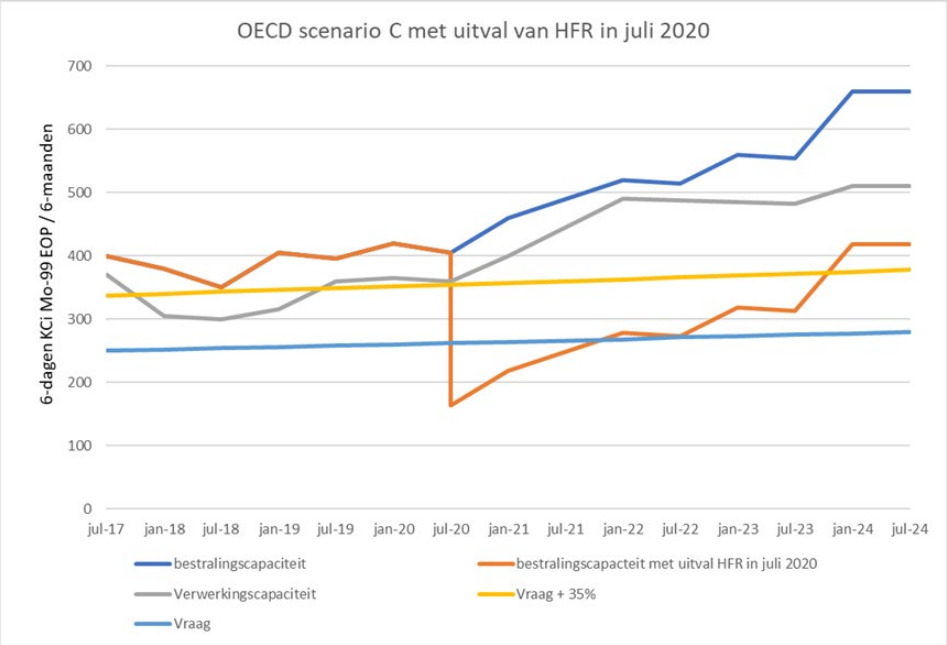



*Figure 2.7: supply and demand for molybdenum-99, based on the OECD-NEA [13] prognoses. The orange line has been added, representing the scenario in which the HFR is definitively shut down in July 2020.*

Figure 2.7 shows exactly the same data as Figure 2.4: the projected supply and demand for molybdenum-99 over the 2019-2024 period, as presented in the OECD-NEA 2019 report [13]. However, one scenario has been added, namely the irradiation capacity in case the HFR (or the BR2) definitively shuts down in July 2020 (orange line). In that scenario, the available capacity decreases almost immediately to 60%-70% of the global demand, and then increases over the next two years to approximately the nominal demand. This is an undesirable situation, as every production interruption, for example due to a maintenance break, would then lead to shortages. The OECD-NEA asserts that an overcapacity of +35% (yellow line) is needed to more or less guarantee supply security, which means that, in this simulation, this situation would be realised only after four years in 2024.

Within the above context, it should be noted that this simulation is based on data provided by the (present and future) manufacturers themselves, in other words their own projections for their future production capacity. However, section 2.5.1 made it clear that these projections are more often wrong than right, and that almost all the projects referred to experience many years of delays in comparison to the originally projected timeline. In actual fact, it will therefore probably take longer for the production capacity to recover than the timeline indicated in figure 2.7.

A calamity (such as the definitive shutdown of a reactor such as the HFR or BR2) would lead to a response from the market, whereby attempts would be made to make up for the shortages. That also occurred in 2009-2010, when molybdenum-99 was in very short supply due to unplanned repair activities on the HFR. At the time, it became clear that the market was not able to quickly expand the production capacity of the other suppliers within a timeframe of one year. The shortages disappeared only after the HFR was again available for irradiation operations. As no significant changes have as yet been made with regard to irradiation and processing capacity (globally), the consequences of a following lengthy interruption of an important reactor will likely be roughly the same as they were in 2009-2010.

### 2.5.3 *Prognoses of future production capacity for therapeutic radionuclides*

Besides molybdenum-99, reactors also produce a wide range of other radionuclides (more than 50) in smaller quantities. These radionuclides can be used to cure patients, extend their lives, or alleviate pain. Most of these radionuclides cannot yet be produced using accelerators. Analyses of the type available for molybdenum-99 are not available for the projected production capacity of therapeutic radionuclides for the coming 10 years. A large number of radionuclides are involved, and each of them has its own delivery chain with specific dependencies and vulnerabilities [3, 4]. It is also not the case that a reactor which, for example, supplies 10% of the global market for molybdenum-99 can also supply 10% of all medical therapeutic radionuclides.

In addition, molybdenum-99 is the most commonly used radionuclide, so that delivery failures are very visible, as made clear by past experience. A High Level Management Group for molybdenum-99 that works to improve molybdenum-99 supply security was therefore

established, and the OECD-NEA has prepared reports on the projected global supply of molybdenum-99 [3, 4, 11].
The EU has recently started to focus more attention on the issue of supply security for therapeutic radionuclides [14, 15]. Although it is now recognised that the supply security of medical therapeutic radionuclides needs to be adequately investigated and, if necessary, improved, the efforts made in this regard have until now remained limited to general reports and a few meetings. A research report by Technopolis (commissioned by the European Commission) is expected to be released in 2021 focusing on the supply security of therapeutic radionuclides.

The production capacity depends on various factors such as the design and purpose of a reactor. Reactors that are designed and built as a research reactor, such as the FRM-II and the JHR, facilitate experiments that make use of the neutrons from the reactor. These neutrons are emitted by the core in beam lines, and these beam lines occupy space that could otherwise be used as irradiation positions for the production of medical therapeutic radionuclides.

Research activities and radionuclide production can also compete with each other in other ways. Every experiment and the production method of every radionuclide has a specific influence on the neutron balance in the reactor core. If experiments and radionuclide production both take place, whereby extreme demands are made of the neutron flux, it may not be possible to combine both these activities from a physical point of view.
The choice of what should be given priority is up to the managers of the facility and, with regard to the experiments, possibly dependent on pressure from other (European) countries, in view of the steadily shrinking number of research reactors in Europe.

In addition, many research reactors are operational for only a limited number of days each year and can therefore not produce radionuclides at any given moment [3, 4].

Besides the physical production capacity, commercial considerations also have an effect on the supply of radionuclides. In informal conversations with representatives of existing or partially built reactors, it was made clear that the price that a reactor operator can receive for the radionuclides is also an important limiting condition for production [3, 4].

### *2.5.4 Prognosis of demand for diagnostic medical radionuclides*

According to the most recent market analyses, the growth in demand for molybdenum-99 (for diagnostic purposes) remains stable at 0.5% for the existing market and is 5% for the developing market [3, 4, 16]. Based on these increases, the estimated quantity of molybdenum presently needed for the global market is 9400 6-day curie[2] of

[2] In the market for molybdenum-99, the quantity of radioactivity is measured in units called '6-day curie'. As molybdenum-99 disintegrates relatively quickly and the quantity diminishes every hour (after 66 hours only half of the original quantity is left), this unit of measure also includes the time at which the activity is measured. This is 6 days after the material is produced. In fact, the substances in question are delivered to the hospitals approximately 6 days after production. It is therefore a measure of the minimum quantity of radioactive molybdenum-99 that is still present upon delivery.

molybdenum-99 per week (or 244,400 per 6 months; see Figure 2.3) [11].

### 2.5.5 *Prognosis of demand for therapeutic medical radionuclides*

Market analyses show that the global market share of therapeutic medical radionuclides (including brachytherapy) in comparison to all (diagnostic and therapeutic) nuclear medicine procedures grew from 4% in 2013 to 12% in 2016 [3]. This market share is projected to grow to 60% in 2030 [3].

The new treatments with lutetium-177 and alpha emitters such as actinium-225 have the potential to capture a large part of the therapeutic market [3]. In addition, there are a number of promising therapeutic radionuclides for the future.

Table 2.4 lists the medical radionuclides that are presently seen as holding promise for the future. This list was prepared on the basis of contacts with medical specialists and a review of the scientific abstracts of the Congress of the EANM (European Association of Nuclear Medicine) in 2019 [17]. The number of treatments per year presently being given is not relevant. If the radionuclide (linked to beneficial proteins) is registered as a therapy, the market for the radionuclide can become quite large within a few years.

A large group in Table 2.4 involves therapeutic alpha emitters such as terbium-161, astatine-211, bismuth-213, radium-223 and actinium-225. Of these, terbium-161 for example is interesting for theranostics, due to its radiation properties, and could be expected to eclipse Lu-177 in importance [18]. Many of these alpha emitters (or their parent nuclides) are produced in a reactor, but a number of promising ones (actinium-225 and astatine-211) can actually be produced quite effectively in cyclotrons.

*Table 2.4: Medical radionuclides that hold promise for the future*

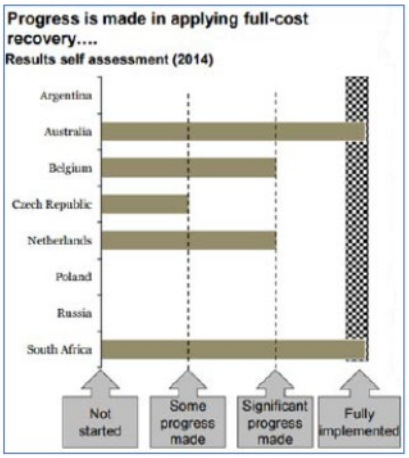
| **Radionuclide** | **Application** | **Production** |
|---|---|---|
| Carbon-11 | Diagnosis | Cyclotron |
| Oxygen-15 | Diagnosis | Cyclotron |
| Scandium-44 and -47 | Diagnosis / therapy | Cyclotron respectively reactor (cyclotron) |
| Chromium-51 | Diagnosis | Reactor |
| Copper-64 and -67 | Diagnosis / therapy | Cyclotron |
| Rubidium-82 | Diagnosis | Cyclotron (82Sr/82Rb generator) |
| Zirconium-89 | Diagnosis | Cyclotron |
| Indium-111 | Diagnosis | Cyclotron |
| Tin-117m | Therapy | Reactor (cyclotron) |
| Terbium-161 | Therapy | Reactor |
| Erbium-169 | Therapy | Reactor |
| Renium-188 | Therapy | Reactor (188W/188Re generator) |
| Astatine-211 | Therapy | Cyclotron |
| Lead-212 | Therapy | Reactor (224Ra/212Pb generator) |
| Bismuth-213 | Therapy | Reactor (225Ac/213Bi generator) |
| Radium-223 | Therapy | Reactor |
| Actinium-225 | Therapy | Cyclotron (reactor) |

The medical therapeutic radionuclide that is expected to show the most growth in the coming 10 years in terms of demand is lutetium-177. Only a rough estimate is available with regard to the prognosis for the production capacity of this radionuclide based on market surveys [1-4] and informal discussions with experts. The general impression is that it should be possible, in the medium to long term (approximately 10 years), to double the existing production capacity for lutetium-177. This will be done in part by optimising the production process and in part by sacrificing production capacity of other radionuclides that are less in demand or less profitable.
This will make it possible to accommodate an annual growth in demand of 3%. However, if the demand for Lutetium-177 does increase as rapidly as expected from now on (by 7% or more per year), then the global production capacity for this radionuclide is expected to be inadequate within five years and shortages will occur [3. 4].
Theoretically, there is still some flexibility available to increase the present production of medical therapeutic radionuclides at the FRM-II, but the reality is that the demand for lutetium-177, for example, already exceeds the capacity of the FRM-II [3, 4].
If Bruce Power, as claimed [19], in 2022 actually starts supplying large (but as yet unknown) quantities of lutetium-177 to the German pharmaceutical company ITM, then the situation described above could change quite drastically.

## 2.6 Full Cost Recovery

Previous reports [1-4] have already dealt with the topic of full cost recovery (FCR). This concerns being able to realise a price for isotopes that covers the costs involved. Traditionally, the trade in medical radionuclides did not operate as a free market, as not all the costs involved were discounted in the price charged by the reactors for their isotopes. After all, these reactors were mostly built in the 1950s and 60s for other purposes (carrying out material-based experiments) and paid for by the government of the country where the reactor is located. When they started to produce radionuclides on a large-scale, these reactors had therefore already been paid for, and for many of them the costs of dismantlement had also been taken care of. Accordingly, the costs already incurred were not included in the price that had to be paid for the radionuclides. In the case of molybdenum-99, it was often sold below the actual cost price.

Since 2011, the OECD-NEA recommends implementing full cost recovery throughout the entire supply chain of medical radionuclides. If all countries were to do this, it would in fact ensure a healthy business case for building, safely operating and maintaining existing and new facilities, as well as their dismantlement at the end of their technical lifetime [3, 4]. For the irradiation facilities, this means that they should include all the costs that they incur (including construction, operation, maintenance and dismantlement of the reactor) in the price for the irradiated products. According to the OECD-NEA, this would lead to only a small increase in the price paid at the end of the chain in the hospital, but it would greatly improve supply security for the medical radionuclides, as new initiatives could become cost-covering and therefore possibly more attractive for investors [2-4].




- Argentina's new plant is paid by government funds and at the current plant support is granted for capex and waste management
- Australian's government granted a loan to construct a new production plant and a waste processing plant, but the parties are now discussing if this loan can be waived off
- Belgian's new plant, MYRRHA, 40% funded by Belgian Ministries and currently Belgian Government pays for waste and security
- Czech republic's capital, overhead and decommissioning costs are not covered in the price
- Netherlands got a loan for the last refurbishment of the HFR. FCR is planned to be used in new PALLAS reactor
- Poland did not start yet, so assuming government funding. Intends to seek private funds for a new processing plant
- Russia applies its own FCR method for irradiations, processing and generator manufacturing
- South Africa does not grant financial support

*Figure 2.8 Steps made towards Full Cost Recovery [3]*

Figure 2.8 shows the results of a self-assessment with regard to full cost recovery by a number of countries that play an important role in the global production of molybdenum-99. Although some progress has been made, there are still many countries that have not yet completely implemented full cost recovery.

## 2.7 Knowledge and the job market

If the Pallas reactor is not built, it will have negative consequences for the (local) job market in the nuclear sector: a loss of approximately 1000 jobs at the Petten site, and approximately the same number under suppliers.

In general, it will also have negative consequences for the nuclear knowledge infrastructure in our country, as about one third of the persons employed in the nuclear sector work in Petten. Together with the loss of physical infrastructure, this means that the services provided to the nuclear industry as well as other industrial sectors and government entities would cease to exist [3, 4].

# 3 Question 1 - Is the construction of a new production facility in the Netherlands necessary?

The sub-questions asked in this question are:

a. Does Pallas or an alternative play a central role in the development of medicines based on isotopes?
b. What is the significance of the Pallas reactor, the alternatives and/or their absence for the healthcare sector in the Netherlands?
c. How important is Pallas or an alternative for high-quality job opportunities and for knowledge infrastructure?

## 3.1 Role in the development of medicines based on isotopes

Globally, 40 million nuclear medicine procedures are carried out each year, 80% of which are carried out with technetium-99m, a daughter nuclide of molybdenum-99. The annual growth in demand for radionuclides is as much as 5%, depending upon the specific substance [20]. Together with the BR2 in Belgium, the HFR in Petten provides 60% of the global demand for molybdenum-99 [3]. The HFR also produces various other diagnostic and therapeutic radionuclides.

In order to develop and produce advanced new cancer therapies using radioactive substances and to implement them in hospitals, persons with various areas of expertise are needed, including: nuclear physicists, radiochemists, biochemists, microbiologists, medical specialists (oncologists, radiologists, nuclear medicine physicians, radiotherapists), chemists, process technologists, pharmacists, logistics experts et cetera. The development of new therapies therefore flourishes best in a setting where a pharmaceutical company, a company producing radioactive substances, an airport, and a university hospital are not too far from each other in order to ensure optimum collaboration between the above disciplines [2-4].

The Netherlands is in a unique position to have a large part of the production & development chain located within the country's borders. The development of new therapies is more likely to succeed if the above areas of expertise can collaborate effectively and efficiently. It is therefore no accident that the lutetium-177 therapy was developed in the Netherlands. If a new irradiation facility were to be established in the Netherlands, the position of the Netherlands within the above framework would be maintained.

## 3.2 Significance of a Dutch production facility for the Dutch healthcare sector

Approximately 370,000 procedures with radionuclides are carried out each year at Dutch nuclear medicine departments. Approximately 3800 of these procedures (about 1%) are of a therapeutic nature, whereas the rest involve diagnostic examinations. Diagnostic examinations that are frequently carried out using technetium-99m are, for example, the sentinel lymph gland procedure (often in the case of breast cancer, over

17,000 procedures in 2018), bone scans (approximately 28,000 scans in 2018), and stress tests in case of cardiac symptoms (over 35,000 tests in 2018) [9]. If technetium-99m were no longer available or less readily available, these procedures would no longer be available or only on a delayed basis. The rest of the process chain in the hospital, for example scheduled breast cancer operations, would not be impacted by this issue. There is no reasonable alternative available for the sentinel lymph gland procedure without the use of radionuclides, and this is also true of many examinations that are carried out with radionuclides.

Therapeutic options in the field of nuclear medicine are expected to increase more rapidly in the coming years (see appendix B). Medical specialists now expect that, in any case, lutetium-177 will witness a rapid rise in use (as a therapeutic agent for prostate cancer), and that demand will increase tenfold. An international clinical trial is presently underway (Vision trial, NCT03511664[3]) on the use of 177Lu-PSMA-617 for patients with metastasised and castration-resistant prostate cancer. Patients in Dutch hospitals are also being included in the trial. The results are expected to become available in 2021 [21]. The results of the questionnaire under Dutch hospitals with regard to the use of medical radionuclides and their expectation for the future are presented in appendix B.

In the past, the US in particular experienced problems due to an insufficient supply of radionuclides, caused by the closure of the airspace after 9/11 and during the eruption of the Eyjafjallajökull in March 2010. In 2009 there was a global shortage due to the interruption of production by two major irradiation facilities. The presence of a production facility in the Netherlands (or at a location accessible via a land route) would, in that respect, provide a greater degree of supply security.

In summary, we can conclude that the presence or absence of an irradiation facility in the Netherlands would not have a major impact on the supply security of medical radionuclides. However, the Covid-19 pandemic has recently made it clear that the location of such a facility on the European continent can be very useful, as transport over land often remains possible even when air transport becomes more difficult or even impossible. The considerations presented in section 3.1 (development of new medical radionuclides) do argue for the construction of an irradiation facility in the Netherlands.

## 3.3 Employment and knowledge infrastructure

As described in an earlier RIVM report [3], the Energy & Health Campus in Petten provides work for approximately 1600 employees, 86% of whom work in the nuclear sector. In addition to these jobs that are directly affected in Petten, there are also jobs indirectly affected, for example jobs at suppliers of goods to the campus. Over the next 5 to 10 years, the construction of a new reactor would create 400 to 700 extra (externally contracted) jobs.

[3] https://clinicaltrials.gov/ct2/results?cond=&term=NCT03511664&cntry=&state=&city=&dist=

It makes sense to ensure that the entire chain of organisations involved is present near a production facility. This provides benefits in terms of logistics, collaboration, and efficiency. It reduces dependence on third parties and can contribute to further technological and scientific developments, in addition to benefits of an operational nature. Such a location can serve as an example of a place where the knowledge economy and knowledge infrastructure come together.

In addition to the present Energy & Health Campus in Petten, facilities also exist in Ontario, Canada (Bruce Power), in Garching bei München, Germany (FRM-II), and in Lucas Heights in Sydney, Australia (ANSTO-OPAL) which are organised in this fashion.

This justifies the conclusion that the presence of such a production and research campus, which includes an irradiation facility, is of substantial importance. The production generates revenues in the present, and the research activities create opportunities for future revenues.

## 3.4 Discussion and conclusion

The supply security of medical radionuclides was recently focused on by the European Commission, which aims to create a (European) Strategic Agenda for Medical, Industrial and Research Applications of nuclear and radiation technology (SAMIRA). A study carried out within this context [8] comes to the conclusion that, in spite of the current initiatives aimed at expanding the existing production capacity for medical radionuclides and building new production capacity, it is necessary to build an additional reactor within the EU in order to guarantee the self-sufficiency of the EU and to prevent global shortages of medical radionuclides. The study designates Pallas as the candidate that is ready to guarantee the necessary production capacity in the coming decades.
As is clear from the scenario described in 2.5.2, a disruption of the HFR would cause available capacity to almost immediately shrink to 60% of global demand, after which it would take two years for capacity to increase to approximately the nominal demand. The OECD-NEA sees supply security as being guaranteed only in case there is +35% overcapacity. A disruption of the production by the HFR would lead to a shortage on the global market of 40%. This would have consequences for carrying out diagnostic and therapeutic procedures with radionuclides.
The question of whether the construction of a new production facility in the Netherlands is necessary is difficult to answer. The above makes it clear that, in the long term, additional global production capacity has to be created in order to be able to guarantee global supply security. Production capacity also needs to be expanded within the land borders of the EU in order to have a guaranteed supply of medical radionuclides in case of incidents such as a volcano eruption or virus outbreak.
It is difficult to predict which planned initiatives will actually take place and what their timeframe and capacity will be. The decision on whether or not to build a production facility is an assessment made on a national (and not EU) level and depends on political and administrative considerations.

# 4 Question 2 - Which alternative production facilities are available or will become available?

## 4.1 Present production facilities

Table 4.1 presents an overview of the reactors presently in use for the production of medical radionuclides. The HFR and BR2 together account for 60% of the global production of molybdenum-99. However, these reactors are also nearly the oldest on the list, and they could very well have to close down within 10 to 20 years. The FRM-II research reactor in Germany is involved in expanding its molybdenum production capacity and is expected to be able to produce more molybdenum-99 starting in 2022. The Bundesministerium für Gesundheit has contributed €1 million for the construction of the molybdenum-99 irradiation facility out of a total budget of €5.4 million [22]. How the remainder of the budget is being financed is not known. This table does not include the reactors that produce only small amounts of radionuclides or only on a very regional basis, such as those in Argentina, Brazil, Russia, China, and South Korea.

*Table 4.1 Existing reactors for the production of medical radionuclides*

| **Name** | **Country** | **Facility** | **Status** | **Number of operational days per year [13, 23]** | **Planned closure** |
|---|---|---|---|---|---|
| OPAL | Australia | Reactor | In operation since 2006 | 300 | Not yet determined |
| FRM-II | Germany | Reactor | In operation since 2005 | 240 | 2,054 |
| Maria | Poland | Reactor | In operation since 1974 | 200 | 2,035 |
| ILL | France | Reactor | In operation since 1967 | 100 | Not yet determined |
| SAFARI-1 | South Africa | Reactor | In operation since 1965 | 305 | Not yet determined |
| HFR | The Netherlands | Reactor | In operation since 1961 | 270 | Not yet determined |
| BR2 | Belgium | Reactor | In operation since 1961 | 147 | Not yet determined |
| LVR-15 | Czech Republic | Reactor | In operation since 1957 | 210 | 2,028 |

## 4.2 Future production facilities

Table 4.2 provides an overview of the new production facilities whose future construction has already been announced. The table includes not only reactors but also several initiatives aimed at producing molybdenum-99 using an accelerator. The information in the table has for the most part already been presented in previous RIVM reports [3, 4]. There is generally little or no information available in publicly available sources about planned production starting dates, unless the facility seems to be nearing its opening date.

The planned starting date for NorthStar shown in the table is 2021, but this seems to be optimistic. The groundwork for the US location of SHINE started in May 2019, and it is expected to become commercially operational in 2022. The starting date for the Bruce Power reactor in Canada appears to be more realistic, as it involves a relatively limited technical modification of an irradiation facility at an existing reactor (more or less similar to what is now being done at the FRM-II) in order to make it suitable for the production of new medical radionuclides [24]. Bruce Power will initially focus on the production of lutetium-177 (in addition to the production of cobalt-60, which has been taking place there for a very long time). Construction of the French Jules Horowitz reactor has been going on since 2009. The Northwest initiative has developed a new technology for the production of molybdenum-99, which makes use of already existing (older) research reactors. Molybdenum-99 will be purified from reactor-irradiated low enriched uranium in a Radioisotope Production Facility specially designed for that purpose [15]. There is not much publicly available information on the present status of the Belgian SMART/Lighthouse project, with the exception of a planned starting date in 2028. It should be noted in this regard that, when the RIVM report 2019-0101 [3] was drafted, the planned starting date was still in 2025. The starting date for the Belgian Myrrha initiative is even further off in the future. However, the beamline will be built in earlier construction phases (first planned delivery date in 2026), and this will also make it possible to produce radionuclides [25].

However, the information available on the projected numbers of operating days for the new facilities to be built is far from complete. The projected number of operational days for Pallas is >300 days per year. That number is more than for the HFR (270 days/year), in part because a new reactor requires fewer maintenance stops and in part due to technological progress.

*Table 4.2 New production facilities to be built for medical radionuclides. A question mark means that it is not known or uncertain whether this radionuclide will be produced at this facility.*

| Name | Country | Facility | Status | Planned start | Mo-99 | I-131 | I-125 | Other | Financing |
|---|---|---|---|---|---|---|---|---|---|
| Niowave [26] | USA | Accelerator | Built | Testing Mo-99 production in 12/2019 | x | x | - | Sr-89, Y-90, Xe-133, Act-225 | $ USD from NNSA* |
| NorthStar [27] | USA | Accelerator | Unknown | 2,021 | x | - | - | Ga-68, Re-188, Bi-213, Ac-225 | $15 million USD from NNSA* |
| SHINE [28] | USA and Europe | Accelerator | USA: groundwork started in 2019 | USA: 2022 | | | USA and Europe | Xe-133, Lu-177* | $15 million USD from NNSA* |
| Bruce Power [24] | Canada | Reactor | Refurbishing existing reactor | 2,022 | - | ? | ? | Co-60**, Lu-177 | Collaboration agreement with The Saugeen Ojibway Nation (SON); Memorandum of Understanding with ITM in München. |
| Jules Horowitz Reactor (JHR) [29] | France (Cadarache) | Research reactor | Under construction since 2009 | 2,023 | x | x | ? | Xe-133 | € 250M from CEA* (50%) |
| Northwest [15] | USA | Production facility | Unknown | 2,023 | x | - | - | - | $15 million USD from NNSA |
| SMART / Lighthouse [30, 31] | Belgium (Fleurus) | Accelerator | Unknown | 2,028 | x | x | - | Ga-68, Xe-133, Re-188 | € 52M from Belgian government |
| Myrrha [25] | Belgium (Mol) | Reactor | Accelerator design and construction | 2,036 | x | ? | ? | Not further specified | € 506M from Belgian government |

| Name | Country | Facility | Status | Planned start | Mo-99 | I-131 | I-125 | Other | Financing |
|---|---|---|---|---|---|---|---|---|---|
| ARTMS / TRIUMF [32, 33] | Canada | Accelerator | Unknown | Unknown | Tc-99m | - | - | Cu-64, Ga-68, Zr-89 | $ 4.1M CAD deal with Quark Venture<br>$ 26.4M CAD collected in series A funding round |
| Eden [34] | USA | Reactor | Investment agreement in 2019 | Unknown | x | ? | ? | ? | Investment agreement with Abo Empire |

*NNSA: National Nuclear Security Administration, CEA: Commissariat à l'énergie atomique, EDF: Électricité de France.
** Cobalt has been produced in large quantities for a very long period of time by Bruce Power.
? It is not known whether this radionuclide will be produced or not.

## 4.3 Complex accelerators in combination with nuclear reactors

A possible future scenario is that the molybdenum-99 producing reactors in Europe will generate much less turnover due to competition from other reactors in the US and/or from the complex accelerator projects such as Lighthouse (Belgium) and SHINE (US and later also Europe), which also aim to bring substantial quantities of molybdenum to the market. If, in future, molybdenum-99 were to be produced exclusively with complex accelerator installations, it is not yet clear whether the present collection of research reactors would be sufficient to make Europe independent with regard to the supply of therapeutic radionuclides. It is also not clear whether these reactors would still be able to cover their costs if they were to produce only these radionuclides.

This question can be answered only with the help of a large-scale and lengthy study. After all, there is a reason for the study presently being carried out by Technopolis (see section 2.5.3), which focuses specifically on supply and demand developments with regard to therapeutic radionuclides. The results of this study are expected to become available in 2021.

However, a number of general comments can already be made:

- Bruce Power (Canada) claims that it will be able to supply large (but not further specified) quantities of lutetium-177 in 2022.
- Generally speaking, the production of each therapeutic radionuclide requires its own irradiation process and often its own irradiation facility (a rack with holders for the material to be irradiated). This needs to be designed, contracted out, and validated - a process that often requires a few years.
- It is not likely that the market for therapeutic nuclides will automatically align itself in a manner that will ensure supply security for all therapeutically needed radionuclides. Each research reactor can produce for only a certain number of days per year, and not every reactor has the equipment required to irradiate all the radionuclides needed.
- International coordination is needed to ensure a continuous supply of therapeutic radionuclides, as is the case for molybdenum-99 via OECD-NEA.
- Finally, it should be noted that, in this scenario, the production of therapeutic radionuclides is left in the hands of the same collection of older research reactors (with the exception of the Jules Horowitz reactor once it becomes available), and that this will provide temporary relief but not a definitive solution for the issue of supply security of therapeutic radionuclides in the long term.

# 5 Question 3 - Partnerships and forms of financing

The third research question is as follows:

What partnerships or collaborations are there in other countries and what kind of funding do these initiatives receive (existing initiatives and initiatives under development)?

Partnerships exist in the area of radiopharmaceuticals, including agreements with irradiation facilities. The structure of that network is discussed in section 2.3. The collaboration is based on delivery contracts or memoranda of understanding and depends on private financing.

The following discussion is limited to the relationships between irradiation facilities in leading countries in Europe, North America, and Australia. Taken together, this provides a good picture of the irradiation capacity situation.

## 5.1 The Netherlands

The High Flux Reactor (HFR, operated by NRG in Petten) presently produces approximately 30% of the global demand for medical radionuclides. The grounds in Petten also house a hot cell (radiochemical) laboratory where the required product can be purified from the irradiated raw materials as well as a radiopharmaceutical company (Curium) which supplies the medical end products to hospitals. The HFR was originally financed by the Dutch government and is now owned by the European Commission. This means that, at the start, establishing a production chain for molybdenum-99 was relatively inexpensive. After all, the reactor had already been paid for, and the remaining costs incurred were for building an irradiation facility in the reactor and setting up a hot cell laboratory where the molybdenum could be radiochemically purified from the uranium plates irradiated in the reactor.
The decades-long collaboration between the various links in the production chain at the same location was one of the factors behind the successful organisation of the molybdenum-99 deliveries from Petten. It also laid the basis for the development of new medical radionuclides, of which lutetium-177 is the most striking example.
In 2019, the Advancing Nuclear Medicine consortium (consisting of NRG, Antoni van Leeuwenhoek Hospital, the Pallas Preparation Foundation, Radboudumc, Erasmus MC, Amsterdam UMC, NucMed, and FutureChemistry) received a subsidy of €6.8 million for the creation of Field-Lab, an "incubator for nuclear medicines" [35]. This binds the nuclear infrastructure more tightly to the (medical) research community.

## 5.2 Belgium

The Belgian BR2 reactor (operated by the SCK in Mol) produces the same amount of molybdenum-99 as the HFR. Together, they supply 60% of the global market. In 2019, it was announced that the Belgian government was investing €558 million in its nuclear research infrastructure.

The SCK in Mol and IRE/IRE Elit are foundations of public utility that are overseen by the Belgian Federal Minister of Energy. Approximately one third of SCK's revenue comes from the Belgian government. The Belgian federal government has a participation of almost 50% in the daughter company IRE Elit [36].

€506 million of the €558 million is earmarked for the MYRRHA project of SCK in Mol. A research reactor is being built there that is scheduled for completion in 2037. The subsidy from the Belgian government covers approximately one third of the required amount. This research reactor is a new type of nuclear reactor, which is capable of using what is now called "nuclear waste" as fuel.
One of the innovative aspects of the design is that the reactor is powered by a large accelerator. This accelerator can also be used simultaneously for the production of a broad range of medical radionuclides.
The remaining €52 million is being invested by the Belgian government in the IRE in Fleurus, where a large particle accelerator is being built based on the ASML Lighthouse concept. Here the Belgian government is also funding approximately one third of the total investment [37]. Starting in 2028, IRE aims to produce large quantities of molybdenum-99/technetium-99m using this new technology [31].

## 5.3 France

In Cadarache in France, the Jules Horowitz Reactor is already being built. The concrete foundation was poured in 2009. The heat exchangers were installed in January 2020 [29]. The reactor is scheduled to be "switched on" for the first time between 2022 and 2025 [38, 39]. According to the owners, the reactor will be able to produce substantial quantities of molybdenum as well as other medical radionuclides 18 months after it is first switched on [40].
This research reactor is being presented as a modern replacement of the research reactors in the EU, almost all of which were built in the 1960s. The necessary funding is being provided by a consortium of research institutes (Belgium, Finland, France, Spain, Czech Republic, United Kingdom, and the European Commission) as well as parties from the business community such as EDF, Vattenfall and Areva. Japan and India also have a share in the project, which was originally budgeted at €500 million.
The CEA, which is affiliated with the French government, contributes 50% of the investment for the construction, and the French energy company EDF also contributes 20%. The various European research institutes together contribute 20%, and Areva, a French company at the time largely owned by the government, also contributes 10% [16].

The Laue-Langevin Institute (ILL), located in Grenoble, has a high-flux research reactor that started operating in 1967. Like many research reactors in the world, the ILL started utilising a part of its reactor capacity for the production of medical radionuclides only decades after it first started operating. The facility produces a large number of nuclides, of which lutetium-177 presently appears to be the most important. The institute has plans to expand production and is presently preparing the

new irradiation facilities. The planning is to complete this expansion in 2024.

However, the reactor has only a limited number of production days per year. In 2019 and 2020, this was two periods of 48 days each, or a total of 96 days per year. In 2021, this is projected to be three periods, or a total of 144 days [23].

Like all research reactors in the world, the ILL high-flux reactor was established and funded by the (French) government. The extent to which full cost recovery (see section 2.6) is realised is not known.

## 5.4 Germany

The FRM-II, a research reactor in Garching (near Munich), is one of the newest such facilities in Europe. Part of the reactor capacity is earmarked for the production of medical radionuclides, including molybdenum-99 and lutetium-177. A programme is presently underway to increase production capacity. The extra capacity will become available in 2022.

Like all research reactors in the world, the FRM-II was established and funded by the (German) government. The extent to which full cost recovery (see section 2.6) is realised is not known.

## 5.5 Czech Republic

The Czech Republic has a nuclear research Institute in Řež, with a research reactor (LVR-15) that is also used for the production of medical radionuclides. The reactor has been operating since 1957 and received an upgrade at the end of the 1980s. The reactor has been in operation in its present upgraded form since 1995. As the company itself makes clear (see appendix B), it is not certain how long the reactor can continue to operate in view of the increasing costs of maintenance.

Like all research reactors in the world, the LVR-15 was established and funded by the government. The extent to which full cost recovery (see section 2.6) is realised is not known.

## 5.6 Poland

The Polish Maria reactor is relatively young, having first started operating in 1974. After the major molybdenum-99 shortages in 2010 and the announcement that the Canadian NRU reactor would be shutting down, the Maria reactor announced in 2010 that, with the help of the pharmaceutical company Covidien (now named Curium), which operates the molybdenum-99 hot cell laboratory in Petten, it would make the reactor suitable for the irradiation of molybdenum-99. The reactor has a licence to continue operating until 2040.

Like all research reactors in the world, the Maria Reactor was established and funded by the government. The extent to which full cost recovery (see section 2.6) is realised is not known.

## 5.7 Canada

Canada is a country that believes in nuclear technology. Four of the northern provinces are now working together to promote the development of small modular reactors that would deliver electricity and heat in remote areas within 10 years.

With regard to medical radionuclides, their preference for the time being would seem to be for cyclotrons (small particle accelerators), with the high-energy cyclotron at the TRIUMF institute in Vancouver serving as their flagship [41]. Canada also has the CNL (Canadian Nuclear Laboratories) Chalk Rivers laboratories located in Ontario.

Also located in Ontario are the eight Bruce Power nuclear reactors, the oldest of which was connected to the power grid in 1977 and the youngest in 1987. These are nuclear reactors that produce electricity. A unique aspect of this so-called CANDU design is that it is possible to place materials close to the reactor core and also remove them without shutting down the reactor. This means that the CANDU reactors can irradiate isotopes, so that the Canadian CANDUs also supply the world with cobalt-60, which is often used to irradiate and to sterilise.
At the end of 2019, Bruce Power entered into an agreement with the German company ITM for the production of lutetium-177 using the substance ytterbium-176 as a starting material. The plans call for the first irradiation operations to start as soon as 2022 [42]. The company recently announced that a mock-up installation for the lutetium irradiation is now in the last phase of design and testing [19]. This will make it possible to produce large (but further unspecified) quantities of lutetium-177.
The company is also working on a major maintenance programme that would enable their six youngest nuclear reactors, which started delivering electricity in the 1980s, to continue operating until 2064 [43].

The Canadian government supports the development of medical radionuclide production with the help of subsidies. The Bruce Power nuclear reactors have the advantage that they have already been paid for in full and that only marginal costs are incurred for the development of new business.

## 5.8 United States of America

As mentioned previously in this memorandum, the United States has decided to again become capable of supplying its own needs when it comes to the production of medical radionuclides, starting with molybdenum-99. In 2019, four companies that aim to supply the US with molybdenum-99 received a subsidy of $40 million from the American government [20]. These are [44]:
SHINE, producing molybdenum-99 by splitting uranium with the help of neutrons from a particle accelerator.
NorthStar, producing molybdenum-99 by irradiating natural molybdenum in a research reactor (MURR). Eventually, this facility aims to produce molybdenum-99 with the help of a particle accelerator.
Niowave, producing radionuclides, including molybdenum-99, by splitting uranium with the help of a particle accelerator.

Northwest, producing molybdenum-99 by irradiating uranium in a research reactor (primarily in the MURR).

In addition, there is the EDEN project, which involves the construction of a small (2 MW) nuclear reactor for the production of medical radionuclides. As such a small reactor can be built with only limited resources, it is quite likely that this initiative will get off the ground. The design is based on a design from Sandia National Laboratories, which did not get off the ground at the time [45].

In the US, various strategies have therefore been adopted to set up molybdenum-99 production facilities in the country itself. Sometimes a modest co-financing arrangement of 15 million US dollars [20] is involved, and at other times various tax benefits apply if the facility is built in a specific state or county [46]. Contributions in kind are also often involved, such as allowing companies to share in already existing knowledge, such as the Eden reactor design [45, 47], or actually being able to develop new knowledge with public funding [48-50].

## 5.9 Australia

The Opal reactor, the associated radiochemical laboratory and a radiopharmaceutical company on the grounds in Lucas Heights near Sydney have been a reliable producer of medical radionuclides for many years. In the initial period, they primarily had a regional function supplying Australia, New Zealand, and Southeast Asia/Polynesia.

The Australian Nuclear Science and Technology Organisation (ANSTO), the owner of the facilities, is part of the Australian government. The activities in the area of medical radionuclides and the medical research into these substances are carried out with financial support from the government. The extent to which full cost recovery (see section 2.6) is realised is not known.

## 5.10 Conclusion

No country in the world has yet succeeded in building a reactor for the production of medical radionuclides that is fully financed by private means (see section 2.6). However, a small 2 MW reactor (in size comparable to the one in Delft), which would cost roughly €100 million, would appear to be feasible in the US on the basis of private funding alone. Other initiatives in the US depend either on knowledge acquired previously or on the capacity of already existing research reactors funded by the government. SHINE, NorthStar and Niowave would seem to be exceptions in this regard, as they are building production capacity in the US with limited subsidies, based on accelerator technology.

# 6 Question 4 - Why do countries not build their own reactor?

The question of why each country does not build its own reactor for the production of medical radionuclides is difficult to answer, as many factors play a role in that regard.
It is illustrative to first ask a broader question: why doesn't every country build its own facility to produce (for example) conventional (nonradioactive) medicines or a factory for solar panels or medical facemasks?

The answer of course is that there is confidence in world trade, thereby ensuring that goods are produced in locations where that can be done most efficiently (and cheaply). And for a great many products that we, as a country, depend upon, that does not happen in the Netherlands. Nevertheless, there are products or producers that are so important for our society that policy is proactively implemented to ensure that production occurs in our own country.

A possible reason for a country to build an irradiation facility within its own borders is that it wishes to have supply security even in times of crisis. For example, the closure of the airspace after the attacks on the Twin Towers on 11 September 2001 was the motivation for the US government to implement a policy aimed at the production of medical radionuclides in the US itself. Until then, these had been imported from Europe and, once air traffic stopped, the supply of these medical substances was also cut off. The unforeseen interruption of the reactor in Petten in 2009-2010 and the resulting shortages, the explosion of the Eyjafjallajökull volcano in Iceland in 2010 and the resulting limitations of air traffic, and more recently the corona crisis have strengthened the Americans in their conviction.

With regard to medical radionuclides, the corona crisis has made it clear that it is an advantage to have irradiation facilities, processing facilities, and pharmaceutical companies located on the mainland of Europe so that all transport from and to these facilities can be carried out by road. Traffic by road experienced considerably less interference from Covid - 19 than air traffic. As a result, during the period from March up to and including September 2020, Europe did not have any known delivery problems, whereas the delivery of medical isotopes in Asia and North America became substantially more complex. In addition, reactors and production facilities located outside of Europe, such as those in South Africa and Australia, experienced problems in distributing their products.

The decision to produce medical radionuclides can therefore involve (1) a purely economic decision by a specific producer, or (2) a policy decision based on the public interest of ensuring that the goods are produced within the borders of the country or inside Europe.

However, a reactor is not the determining factor that ensures supply security. That depends upon the entire chain, from the delivery of the starting material, to the irradiation of the material and the chemical

purification of the desired substance in a hot cell laboratory, until the manufacture of the medicine itself under pharmaceutical conditions.

The production of medical radionuclides is a specialty that requires several areas of expertise that will not be found in every country. Knowledge of nuclear technology is needed, preferably a nuclear reactor for research purposes that is available, and a vibrant research community. That research community must be of a very multidisciplinary nature and include reactor technology, irradiation technology, radiochemistry and radiobiology, and oncology for example. In other words physical, chemical, biological, and pharmacological/medical disciplines. The production of medical radionuclides presently in use and the development of future medical radionuclides as well as the proteins and other biological substances that transport them to their target in the human body therefore depends on a strong research culture in the above professional disciplines.

Finally, the decision to build a reactor depends on having a sound business case. In this regard, it is striking that no research or radionuclide production reactor has ever been built that was completely funded by private sources. All reactors that now produce medical radionuclides were originally built as research reactors and paid for by the government.
The countries that have this type of reactor also have the relevant associated infrastructure and experts in house and were, in the 1990s, well positioned to produce medical radionuclides. That could be accomplished relatively cheaply. After all, the reactor and much of the associated infrastructure had already been paid for.

This poses a barrier for countries without a research reactor who would now like to start up their own production, as building a research reactor presently demands a great deal of capital. The exception in this regard would appear to be those companies who wish to produce molybdenum-99/technetium-99m in the future with the help of accelerator technology. The US initiatives in particular would, at present, seem to be capable of reaching full maturity with the help of relatively modest subsidies.

# 7 Question 5 - What policy options are available to the Ministry of Health, Welfare and Sport if no new production facility becomes available in the Netherlands?

If no new production facility becomes available in the Netherlands, whether or not that is a reactor or a (complex) accelerator such as the SHINE concept, then the irradiation operations that now take place in the Netherlands would have to be carried out elsewhere. On the other hand, there would then still be a lively research community present in the Netherlands in the area of medical radionuclides, a research reactor (in Delft), and various radiopharmaceutical companies such as Curium, IDB Holland, and Quirem.

In the following, based on RIVM's expertise, we provide the Ministry of Health, Welfare and Sport with a few options for consideration.

- Just as the United States is aiming to achieve self-sufficiency in the area of medical radionuclides, it would also be an option for the European Union to aim for that as well. That would also make the EU more resilient, in the long term, in the face of incidents whereby importing medical radionuclides from other continents would be temporarily difficult or even impossible. The EU presently also has a good mix of researchers, suppliers of raw materials, irradiation facilities, hot cell laboratories, and radiopharmaceutical companies present within its borders. Coordinated within a European framework, this network would be able to ensure that the entire palette of radionuclides could be produced and delivered on European soil.
- Formulating policy focused on maintaining the rest of the supply chain for medical radionuclides in the Netherlands If new irradiation capacity is not realised, the result would probably be that the radiochemical laboratory, also referred to as the processing or hot cell laboratory, would also have to shut down. That in turn would make it less attractive for the radiopharmaceutical companies to remain based in the Netherlands.
- Commissioning an analysis that would make it clear what is needed to ensure that the existing (High Flux) reactor in Petten can continue to operate reliably for a few decades longer.
- The Netherlands could participate in already existing commercial initiatives elsewhere in Europe that aim to produce medical radionuclides via complex accelerator techniques. This collaboration would have to focus on strengthening those parts of the supply chain and research still present in the Netherlands.
- The Netherlands could participate in already existing research projects (MYRRHA and the beam lines projected for that purpose, JHR, ...) whereby, in addition to carrying out scientific research, it would also be possible to produce medical radionuclides. It would then probably be possible to retain the research community present in the Netherlands for the development of new medical radiopharmaceuticals.

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# 9 Annex A: Stakeholder survey: production facilities

## 9.1 Questions for suppliers

Two different questionnaires were prepared: one for present suppliers of medical radionuclides, and one for parties who wish to become suppliers in the future.

### *9.1.1 Questions for existing irradiation facilities*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Molybdenum-99/Technetium-99m
Iodine-125
Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

Question 1: In your opinion, is this list of "nuclides of interest" complete? If not: what nuclide(s) are you missing?
Question 2: Your company is currently irradiating medical radioisotopes. Could you please indicate which one, at this moment?
Question 3: Could you please indicate whether you have plans to (1) enlarge your capacity for irradiating existing isotopes or (2) building capacity for new isotopes within the coming 5-10 years? In what year will these nuclides be available for the market, in significant amounts?
Question 4: Could you please share with us, which nuclides and which percentage of your production goes to the European hospitals?
Question 5: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable?
Question 6: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years?
Question 7: Is there anything else on this subject you would like to share with us?

### *9.1.2 Questions for future irradiation facilities*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Molybdenum-99 / Technetium-99m
Iodine-125

Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

Question 1: In your opinion, is this list of "nuclides of interest" complete?
If not: what nuclide(s) are you missing?
Question 2: Your company is currently planning to build, or building, an irradiation facility. Could you please indicate (according to present plans) which of the above nuclides your facility will be able to irradiate in the coming 5-10 years, and when (in what year) these nuclides would be available for the market, in significant amounts?
Question 3: Do you foresee that a share of your irradiated material will be available for the European market?
If yes: could you please share your expectation with us, i.e. which nuclides and which percentage of your production would be available for Europe?
Question 4: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable?
Question 5: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years?
Question 6: Is there anything else on this subject you would like to share with us?

## 9.2 Results of questionnaire

### *9.2.1 Summary*

Nine parties were approached who aim to build new production facilities:: Bruce Power (Canada), BWXT (US), Eden (US), IRE/Lighthouse (Belgium), JHR (France), NorthStar (US), Pallas (the Netherlands), SCK*CEN (Belgium), and SHINE (US). Answers were received from two parties.
Five parties who operate existing production facilities were also approached: ANSTO (Australia), FRM-II (Germany), ILL (France), LVR-15 (Czech Republic), and Maria (Poland) We received answers from three of them.

Most parties expect an increase in the turnover of molybdenum-99 (primarily due to the growth of the market in Asia, in particular India and China) and of lutetium-177.
A number of parties name terbium-161 as an interesting emerging radionuclide. The (experimental) nuclides for alpha therapy, such actinium-225 (reactor/cyclotron) and astatine-211 (cyclotron) are

named as being interesting. One respondent pointed to the potential of copper-67 (cyclotron product), which has comparable applications to lutetium.

The following factors are named as posing a threat to the supply security of medical radionuclides:

- Rising costs of keeping the older reactors operational;
- High costs of building new reactors, which means that they cannot be completely financed privately on the basis of the projected revenues from the production of medical radionuclides;
- The fact that governments do not give equal consideration to proposals for building reactors or complex accelerator installations (i.e. no level playing field);
- Not enough activity at the EU level to encourage the building of new radionuclide production facilities;
- The fact that there are almost no reactors left in the world with a very high neutron flux (i.e. more than 1015 neutrons per second per square centimetre). The disappearance of these reactors would not only endanger the scientific research that can be carried out only under these conditions but also the production of a number of "exotic" medical radionuclides that can only be produced with such a high flux, such as wolfram-188/rhenium-188 and calcium-47/scandium-47.

*9.2.2 Answers LVR-15 (Czech Republic)*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Molybdenum-99/Technetium-99m
Iodine-125
Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

| **Company Name** | **Research Centre Rez** |
|---|---|
| Contact details (e-mail) | jan.milcak@cvrez.cz |
| | |
| Question 1: In your opinion, is this list of "nuclides of interest" complete? If not: what nuclide(s) are you missing? . | As reactor operator we have been asked to participate in project for evaluation of possible utilization and production of 161Tb |

| Company Name | Research Centre Rez |
|---|---|
| Question 2: Your company is currently irradiating medical radioisotopes. Could you please indicate which one, at this moment? | Reactor serves also as radioisotope production facility but only as an irradiation without direct involvement in production medical grade. Mainly Mo-Tc is now produced but from irradiated nuclear targets also 131I is produced this way. Continuous testing of 166Ho is being done. Some project of irradiation of 192Ir and 177Lu were historically made, but currently without periodic production. |
| Question 3: Could you please indicate whether you have plans to (1) enlarge your capacity for irradiating existing isotopes or (2) building capacity for new isotopes within the coming 5-10 years? In what year will these nuclides be available for the market, in significant amounts? | As an irradiation facility we are dependent more on the demand of the final medical radioisotope processor than on the implementation of our own initiative. The capacity can be partially expanded in this area, but this limits the further use of the reactor for scientific purposes in the field of materials research, etc. Irradiation conditions and thus the necessary changes to the reactor equipment would be part of the necessary feasibility studies and would be implemented when contacted by partners. |
| Question 4: Could you please share with us, which nuclides and which percentage of your production goes to the European hospitals? | This knowledge is not known to the reactor operator, as it only performs irradiation activities and not the actual production of medical isotopes and we are thus outside the distribution channels. |
| Question 5: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable? | Until the replacement of Mo-Tc as the basis of diagnostics, demand will only grow.<br><br>After a higher examination of radiopharmaceuticals, which can be used for subsequent treatment, interest in these will also increase (Lu, Ho etc). |
| Question 6: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years? | Pressure on research reactor operators in the area of necessary adjustments to meet the new standards will increase the financial intensity of the operation and may lead to a decision to close the operation.<br><br>The increasing age of the base of irradiation infrastructure without the necessary building of a replacement leads to the risk of capacity loss - new capacities are not being built fast enough at present and the European environment is not in favour of new projects. |

| Company Name | Research Centre Rez |
|---|---|
| Question 7: Is there anything else on this subject you would like to share with us? | A joint discussion on the conditions for maintaining capacity within the EU is critical (including connections to the rest of the world) - including the necessary investments and the creation of an environment that will allow the construction of new research reactors of sufficient capacity fast enough (especially in the EU). |

*9.2.3 Answers ILL Grenoble (France)*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Molybdenum-99/Technetium-99m
Iodine-125
Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

| Company Name | Institut Laue-Langevin, Grenoble, France |
|---|---|
| Contact details (e-mail) | koester@ill.fr |
| | |
| Question 1: In your opinion, is this list of "nuclides of interest" complete? If not: what nuclide(s) are you missing? . | For the reactor-produced isotopes one should add at least W-188/Re-188, Er-169, Sm-153 and as "emerging" Tb-161<br>[Obviously there are many other "nuclides of interest" which are not reactor-produced. By the way, At-211 is cyclotron-produced and NOT reactor-produced.] |
| Question 2: Your company is currently irradiating medical radioisotopes. Could you please indicate which one, at this moment? | W-188, Lu-177, Tb-161, Ca-47/Sc-47, Er-169, Pt-195m, … |
| Question 3: Could you please indicate whether you have plans to (1) enlarge your capacity for irradiating existing isotopes or (2) | A new irradiation system for enlarged capacity is under development, to be exploited from 2024. New isotopes are being added continuously. The time scale until clinical deployment is dictated by the development of the downstream part (radiochemistry, radiopharmacy, clinical trials,…), not by the reactors. |

| **Company Name** | **Institut Laue-Langevin, Grenoble, France** |
|---|---|
| building capacity for new isotopes within the coming 5-10 years?<br>In what year will these nuclides be available for the market, in significant amounts? | |
| Question 4: Could you please share with us, which nuclides and which percentage of your production goes to the European hospitals? | Among the clinically used radionuclides (Lu-177, W-188/Re-188) the majority of our production (>80%) goes to European hospitals. In addition we produce radionuclides for basic research or preclinical research which go to European research labs. |
| Question 5: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable? | Demand for Lu-177, Ac-225 and for emerging radionuclides (Tb-161, etc.) will rise.<br><br>Demand for Y-90 + Ho-166 for SIRT will rise, but the development of the relative market share of both competing nuclides is difficult to predict as it mainly depends on the commercial success of the different actors in the SIRT field.<br><br>Demand for Mo-99/Tc-99m will slowly decline in the developed countries (due to partial replacement by PET procedures and due to reduction of injected activity with more efficient SPECT cameras respectively). |
| Question 6: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years? | Worldwide there is a lack of reactors with very high neutron flux (> 1E15 cm-2s-1), at present only HFIR (Oak Ridge, USA), SM3 (Dimitrovgrad, Russia) and RHF (the reactor exploited by ILL Grenoble, France). This could be a threat for sustainability of reaction paths requiring the highest possible flux such as double-neutron capture for W-188 (generator of Re-188), high conversion yield for Ca-47 (generator of Sc-47) and other "rare" enriched targets, long term breeding of Ra-226 targets to Th-229 (as generator of Ac-225), etc. |
| Question 7: Is there anything else on this subject you would like to share with us? | |

*9.2.4 Answers NorthStar (United States of America)*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Molybdenum-99/Technetium-99m
Iodine-125
Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

| **Company Name** | **NorthStar Medical Technologies, LLC** |
|---|---|
| Contact details (e-mail) | jharvey@northstarnm.com |
| | |
| Question 1: In your opinion, is this list of "nuclides of interest" complete? If not: what nuclide(s) are you missing? . | No, "upcoming" should have Cu-67. Cu-67 is neither an alpha emitter nor is it produced via a reactor. Similar to Lu-177 in therapeutic potential and use. It is accelerator produced. |
| Question 2: Your company is currently irradiating medical radioisotopes. Could you please indicate which one, at this moment? | Mo-99 on market now<br>Ac-225 & Cu-67 commercially available starting in 2023 |
| Question 3: Could you please indicate whether you have plans to (1) enlarge your capacity for irradiating existing isotopes or (2) building capacity for new isotopes within the coming 5-10 years?<br>In what year will these nuclides be available for the market, in significant amounts? | Mo-99 is US only at this time; ROW within 5 years<br>Ac-225 & Cu-67 will be available worldwide within 3 years<br>Percentages are business sensitive |

| **Company Name** | **NorthStar Medical Technologies, LLC** |
|---|---|
| Question 4: Could you please share with us, which nuclides and which percentage of your production goes to the European hospitals? | Mo-99 we except to show slight growth in US and Europe next 5-10 years. Asia/Pacific + India expected to show modest growth next 5-10 years fuelled mostly by China and possibly India. |
| Question 5: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable? | Aging reactor infrastructure; challenging supply chain currently in place; use of fission uranium to produce medical isotopes will only get more difficult and more expensive – not sustainable currently and worse at full cost recovery; reimbursement of costs by insurers/governments. |
| Question 6: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years? | New technologies, not dependent on the aging reactor fleet around world and the uranium fission process, which are less costly per unit volume produced, are the future of medical radioisotope production. |
| Question 7: Is there anything else on this subject you would like to share with us? | |

### *9.2.5 Answers SHINE (Unites States of America)*


MEMORANDUM

TO: Lars Roobol (RIVM)

FROM: Harrie Buurlage

DATE: Friday August 14, 2020

SUBJECT: SHINE reply to your questions (in blue)

Your RIVM Text in black:

To our knowledge, the most commonly used reactor-produced medical radionuclides are:

- Yttrium-90
- Molybdenum-99/Technetium-99m
- Iodine-125
- Iodine-131
- Iridium-192
- Holmium-166
- Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.

- Astatine-211
- Radium-223
- Actinium-225

| | |
|---|---|
| Company Name | **SHINE MEDICAL TECHNOLOGIES, LLC** |
| Contact details (e-mail) | **harrie.buurlage@shinemed.com** |
| | |
| Question 1: In your opinion, is this list of "nuclides of interest" complete?<br><br>If not: what nuclide(s) are you missing? | **The nuclides of interest are nuclides that are being used, or are being projected to be used, in clinically relevant studies, clinical treatments, or both. The number of patients, the projected volume trends and the availability of nuclear or non-nuclear alternatives determine the level of interest and the economic value of the nuclides of interest. The projected economic value is a good way of categorizing these nuclides of interest.**<br><br>**According to SHINE, the best way of categorizing these nuclides is:**<br><br>• **High level of interest:**<br>• **Mo-99, Lu-177, Ac-225**<br>• **Medium level of interest:**<br>• **I-131, Y-90, Ir-192, Xe-133 and possibly Ho- 166.**<br><br>**SHINE is monitoring the R&D in theranostics and TAT for other promising nuclides and this could result in adjustment of the above-mentioned categorization.**<br><br>**Note 1:**<br><br>**We believe that I-125 should be categorized as a nuclide with a low level of interest given the available non-nuclear alternatives. I-125 cannot be considered a standard of care given the very limited number of hospitals that decide to use I-125 for patients with early stage prostate cancer, for instance.** |

| | |
|---|---|
| | **Note 2:**<br><br>**Most of the promising nuclides for TAT (including As-211 and Ac-225) are being produced by making use of accelerators instead of research reactors.** |
| Question 2: Your company is currently planning to build, or building, an irradiation facility. Could you please indicate (according to present plans) which of the above nuclides your facility will be able to irradiate in the coming 5-10 years, and when (in what year) these nuclides would be available for the market, in significant amounts? | **SHINE plans to have its U.S. accelerator-driven, uranium- fission plant commercially operational in 2022. This facility will be able to produce at least one-third of the global demand for Mo-99. Mo-99 produced in this plant will be available for export to the EU from the start. This facility also will produce I-131 soon after. The facility also will produce other fission isotopes like Y-90 (as daughter of Sr-90) and Xe- 133, conditioned on a solid business case. In fact, SHINE's technology can be used for all U-235 fission products and most of the trans-mutational neutron activation products.**<br><br>**SHINE also is in the process of selecting a site in Europe for its European production facility. The site selection will be concluded this year. Construction of the EU plant is planned to start in 2023. This facility will be a copy of the USA facility and could be serving European patients as early as 2025.**<br><br>**Both the USA and the EU facilities will be equipped with additional irradiation ports, allowing for the production of a broad range of neutron activation products including Lu-177, Ho-166 and, if needed, I-125.**<br><br>**SHINE is also focusing on Ac-225 from a therapeutics perspective, but at this stage time-to-market is unclear.**<br><br>**Note on Lu-177:**<br><br>**The production of Lu-177 does not only require a neutron source (like a reactor or the SHINE accelerator), it also needs enriched target material and a very complex radiochemistry process, post-irradiation. SHINE is active in all of these three** |

| | |
|---|---|
| | **critical steps in this supply chain and is likely to become the first and only vertically integrated Lu-177 supplier soon. First Lu-177 sales are expected early next year.** |
| Question 3: Do you foresee that a share of your irradiated material will be available for the European market?<br><br>If yes: could you please share your expectation with us, i.e. which nuclides and which percentage of your production would be available for Europe? | **SHINE's USA facility will be exporting significant quantities of Mo-99 and (soon thereafter) other key nuclides to Europe as of the start of commercial operations in the USA. This will last until the SHINE EU plant takes over.**<br><br>**SHINE has firm plans to install more than sufficient production capacity in Europe for European patients.**<br><br>**Our planned EU infrastructure will be more than sufficient to supply all EU patients with Mo-99, I-131, and Lu-177. Y-90 and, if needed, Ho-166 and I-125 also will be produced in Europe, if a solid business case justifies it.**<br><br>**Note 1:**<br><br>**SHINE intends to utilize reactors initially for Lu-177 irradiations and to transition using our own accelerator system over time.**<br><br>**Note 2:**<br><br>**Most medical isotopes with a medium to low level of interest (like Ir-192) are eligible for centralized production. As an example, Ir-192 can be produced all over the world with enough time for transportation (decay time of Ir-192 is 74 days). Furthermore, the production of these isotopes benefits from the freed-up European and global reactor capacity caused by the introduction of SHINE Mo-99.**<br><br>**Note 3:**<br><br>**SHINE will not limit her product portfolio to utilization of its current innovative technology but will invest in other non-** |

| | |
|---|---|
| | **reactor key technologies like cyclotrons if a solid business case justifies such an investment.** |
| Question 4: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable? | **The growing development of theranostics will not only drive significant growth in Lu-177 and other potential therapeutics such as Ac-225, but also their companion diagnostic radionuclides. Mo-99 usage also will grow, mostly driven by increased Asia-Pacific (APAC) needs. While some TAT applications are promising, it is too early to make reliable growth assumptions.** |
| Question 5: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years? | **The opportunities are clearly the therapy applications (Lu- 177 and TAT) and the increased use of Mo-99.**<br><br>**The main threat is the non-existence of a level playing field caused by the continuation of national governments financially supporting research reactor technology only. This continues despite clear direction from international organizations like the OECD stating that the supply of nuclear medicine can only become stable if national governments decide to withdraw their subsidies so that privately funded innovation can take over.**<br><br>**The introduction and expansion of non-research reactor- based innovations like SHINE is hindered strongly because of this lack of a level playing field. The Dutch government should publicly state that they will withdraw its financial support for research reactors used for the production of nuclear medicine. As an alternative, national governments could decide to equalize public financial support over all promising initiatives fairly.** |

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| Question 6: Is there anything else on this subject you would like to share with us? | **The production of medical isotopes asks for much more than just the availability of a neutron source. In fact, four critical steps must be taken care of and SHINE is managing all these steps internally with its two plants (USA and EU).** |


| | |
|---|---|
| | 1. **Availability of enriched target material**<br>2. **Irradiation with a neutron source (like SHINE or PALLAS)**<br>3. **The radiochemical separation process post- irradiation**<br>4. **The radiopharmaceutical process assuring the elimination of unwanted impurities and the assurance that the final product meets all other quality specifications**<br><br>**The reliability of supply is dictated by all four steps and simply having a neutron source does not guarantee the supply of medical isotopes, especially when steps three or four, or both, are taken care of by other organizations than the neutron source providers.**<br><br>**SHINE advises RIVM and the Dutch ministries to review the supply of medical isotopes holistically, meaning taking all four steps into their considerations.** |

*9.2.6 Answers Pallas (the Netherlands)*

To our knowledge, the most commonly used reactor-produced medical radionuclides are:
Yttrium-90
Iodine-125
Iodine-131
Iridium-192
Holmium-166
Lutetium-177

In the medical world, there is much attention for "upcoming" radionuclides, suitable for cancer therapy by alpha irradiation. To our understanding, the following three nuclides are the main ones under investigation now.
Astatine-211
Radium-223
Actinium-225

| **Company Name** | **PALLAS (Stichting Voorbereiding PALLAS-reactor)** |
|---|---|
| Contact details (e-mail) | Titus Tielens, Director Strategy |
| | |
| Question 1: In your opinion, is this list of "nuclides of interest" complete? If not: what nuclide(s) are you missing? . | Most commonly used reactor isotopes is accurate, with a few comments:<br>Molybdenum-99 must be added of course<br>I believe the list is pretty accurate, except Ho-166 is still early phase, and not yet used very much, with perhaps a few hundred treatments per year<br>(There are some more traditional isotopes that are being phased out: Sr-89, Er-169, Sm-153, Pd-103, Au-198 – these are now of lesser interest, so good to exclude from the list.)<br><br>As for upcoming isotopes, terbium-161 should definitely be added, a potential successor to Lu-177, as it seems to have better medical properties and the terbium family includes also alpha and auger electron emitters – allowing for a single chemistry across a range of nuclides.<br><br>Other upcoming radionuclides, currently of slightly lesser interest, include:<br>Phosphor-32, see Oncosil<br>Lead-212 (alpha), see Orano Med<br>Rhenium-186 and 188 (e.g., the focus of the Meander hospital)<br>Stannum-117m |
| Question 2: Your company is currently irradiating medical radioisotopes. | The PALLAS reactor is being designed to mass produce a wide range of isotopes. As long as there is demand for any of the isotopes on the list (or yet other ones), it is the intention that PALLAS will produce them. There are only a few |

| **Company Name** | **PALLAS (Stichting Voorbereiding PALLAS-reactor)** |
|---|---|
| Could you please indicate which one, at this moment? | exceptions based on technical limitations: At-211, Ra-223, P-32. |
| Question 3: Could you please indicate whether you have plans to (1) enlarge your capacity for irradiating existing isotopes or (2) building capacity for new isotopes within the coming 5-10 years?<br>In what year will these nuclides be available for the market, in significant amounts? | The PALLAS reactor will be able to supply a large percentage (20-40%) of global demand. It is expected that the majority of output will be supplied to radiopharmaceutical production sites in Europe, for the purpose of mass production of registered medicines (such as Lutathera), as well as to European University Medical Centres (UMCs, academische ziekenhuizen), for the purpose of clinical trials and small scale use (in manu medici, compassionate use, 'magistrale bereiding'). It is difficult to foresee exactly what volumes and percentages will be available for Europe, but you may assume anywhere between 50 and 80%. PALLAS will be able to supply 50-80% of European demand. These are ballpark numbers.<br><br>Looking at current trends in the supply chain, a likely end state will be that each major pharma company will have 2 or 3 production sites globally, e.g., one in North America, one in Europe and one in Asia. Likewise, each region will have a few production hubs. It is expected that the PALLAS-reactor will sit at the heart of the main hub for Europe, perhaps together with the Belgian infrastructure (BR2, IRE, …). |
| Question 4: Could you please share with us, which nuclides and which percentage of your production goes to the European hospitals? | We expect that Lu-177 will indeed prove to be the main workhorse for the coming 10-20 years for beta emitting medicines, while the other isotopes fulfil niche positions. Over time, Tb-161 could replace Lu-177 thanks to more convenient medical and chemical properties.<br><br>Y-90 will likely remain popular, Ho-166 will probably be used more widely (with the acquisition of Quirem by Terumo), I-131 will probably grow in use (with 3 new medicines in the pipeline, e.g., by Actinium Pharmaceuticals and Cellectar)<br><br>At the same time, Targeted Alpha Therapy is attracting a lot of research attention for its close-range tumour search-and-destroy power. But alpha based medicines are not as advanced yet, as they have significant challenges (e.g., on how to handle recoil and daughter decay effects), and production routes have not been settled. So it is well possible that alpha therapies will become popular say ten years from now. It is not clear |

| **Company Name** | **PALLAS (Stichting Voorbereiding PALLAS-reactor)** |
|---|---|
| | what the winning alpha isotope will be. Currently most attention is paid to Ac-225, but Pb-212 or another one could be more attractive in the long run. |
| Question 5: looking at the list of nuclides of interest, what trends do you see for the coming years? Will demand for these nuclides grow, decline, or remain stable? | Setting up robust supply chains for medical radionuclides will be key in order to support expected demand for the very promising new nuclear medicines that are now in the pipeline. As you can see from a recent PALLAS presentation at an IAEA conference, there are two or three critical elements that need to be in place:<br>Sufficient irradiation capacity, both from reactors and cyclotrons. PALLAS will significantly improve the robustness of global production capacity, but other research reactors remain needed, also in Europe.<br>Efficient post-irradiation processing supply chains – these are needed to increase capacity, and reduce the time between irradiation and administration to a patient. If the supply chain can be reduced by a few days, then capacity grows by tens of percentage points, while waste per unit is reduced.<br>Supply of target material, particularly of ytterbium-176 for Lu-177. |
| Question 6: When thinking about the sustainability of supply of medical radionuclides, what are the opportunities and threats you see for the coming 5 years? | Feel free to come by to discuss any topic further. |
| Question 7: Is there anything else on this subject you would like to share with us? | |

# 10 Appendix B: Questions for stakeholders - hospitals

## 10.1 Questions for users (nuclear medicine departments)

Explanation
RIVM was asked to describe the current situation with regard to the supply security of medical radionuclides and the role that the Pallas reactor can play in that area. RIVM published a report on this topic in 2019 [3]. This report concluded that, if the HFR in Petten were to shut down without the Pallas reactor being built, the Netherlands would lose its position within the supply chain. The employment market as well as the nuclear knowledge infrastructure would be negatively impacted as a result.

| Radionuclide | Utilisation (much, little, none) | Quantity ordered in 2019 | Number of patients treated in 2019 | Projected trend for coming years (growth, no change, decrease) |
|---|---|---|---|---|
| Tc-99m | | | | |
| I-131 | | | | |
| I-125 | | | | |
| Lu-177 | | | | |
| Y-90 | | | | |
| Ho-166 | | | | |
| Ra-223 | | | | |
| … | | | | |

**Question 1**
The above table presents a summary of reactor-produced radionuclides. Are these the most frequently used reactor-produced radionuclides in your centre? If frequently used radionuclides are missing in the table, would you please add them to the table?
For the radionuclides listed, would you please fill out the following information:
How often it is utilised (much, little, never)
The quantity ordered in 2019 (e.g. in doses or vials or Bq)
How many patients were treated with it in 2019
What your expectation is for the coming years with respect to utilisation (growth, decrease, no change)

**Question 2**
Did your centre experience any delivery problems with respect to reactor-produced radionuclides in 2019?

If so, how often? What were the two most common causes of any such problems?

**Question 3**
Which opportunities, risks, or threats do you see in the coming years with respect to supply security?

## 10.2 Results of questionnaire

There are a total of 64 hospitals in the Netherlands with a department of nuclear medicine [https://www.nvng.nl/praktijk/afdelingen-nucleaire-geneeskunde]. Unfortunately, there was not enough time to obtain information from all the departments via the relevant professional association. In collaboration with several medical specialists, 12 hospitals were selected to be contacted for the questionnaire. These hospitals were selected based on the type of procedures that they perform (diagnostic and therapeutic) as well as the number of procedures per year. The hospitals selected include all eight university hospitals and four hospitals from the periphery.
The questionnaire was filled out and returned by seven of the university hospitals and three hospitals from the periphery. The results are presented in tables 1 and 2. The respondents (hospitals) have been assigned numbers from 1 to 10.

Table B.1 shows the numbers given for the number of patients treated in 2019 with the most frequently used radionuclides. As expected, the largest share of examinations was carried out using technetium-99m. Two hospitals expect a modest increase in its use, and the other eight expect an unchanged or modestly decreasing use. Treatments with radioactive iodine are also not expected to increase much, although this could be a distorted picture with regard to iodide-125, as this radionuclide can also be used in the form of a radioactive iodine seed implant in departments other than nuclear medicine departments. These could, for example, include surgery, radiology, or radiotherapy, and no data has been collected from these departments. Lutetium therapy is expected to show the biggest growth.
Table B.2 shows a summary of the answers provided to questions 2 and 3 of the questionnaire. This makes it clear that 9 of the 10 responding hospitals experienced problems in 2019 with regard to the delivery of radionuclides, in particular technetium. A few respondents even experienced problems more than once during the year. The respondents also reported that patient programmes had to be modified as a result. Causes that were mentioned several times were a shortage of available molybdenum-99 in Petten and insufficient backup by other reactors. Almost all the respondents named the closure of the HFR without any structural alternative as a risk for supply security and therefore for patient care. They are already currently experiencing delivery problems a few times per year and actually expect an increase in the demand for radionuclides.

*Table B.1 Numbers of patients in 2019 and prognosis for the future of the most commonly used reactor-produced radionuclides. The responding hospitals have been assigned numbers from 1 to 10.*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total number of patients |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Technetium-99m** | | | | | | | | | | | |
| Number of patients in 2019 | 1,417 | 3,072 | 2,995 | 2,471 | 3,000 | 2,272 | 2,190 | 5,200 | 2,500 | >5000 | >30117 |
| Prognosis for the future | Unchan-ged | Unchan-ged | Modest decrease | Modest growth | Unchan-ged | Unchan ged | Decrease | Unchan-ged | 3 - 5% annual increase | Slight decrease | |
| **Iodine-131** | | | | | | | | | | | |
| Number of patients in 2019 | 95 | 178 | 195 | 89 | 200 | 108 | 56 | 103 | 20 | 112 | 1,156 |
| Prognosis for the future | Unchan-ged | Unchan-ged | Modest decrease | Unchan-ged | Unchan-ged | NR | Growth | Unchan-ged | Unchanged | Stable / slight decrease | |
| **Iodine-125** | | | | | | | | | | | |
| Number of patients in 2019 | 0 | Unknown, processed via surgery | 0 | 35 | 70 | 0 | 171 | 365 | 900 radiology, 120 radiotherapy | 0 | 1,661 |
| Prognosis for the future | Unchan-ged | | Unchan-ged | Increase | Unchan-ged | NR | Growth | Unchan-ged | 3 - 5% annual increase | NR | |
| **Lutetium-177** | | | | | | | | | | | |
| Number of patients in 2019 | 0 | 451 | 6 | 120 | 5 | 0 | 0 | 0 | 45 | 4 | 631 |
| Prognosis for the future | Growth | Strong growth | Growth | Increase | Increase | Growth | Growth | Growth | Robust growth | Strong increase | |
| **Yttrium-90** | | | | | | | | | | | |
| Number of patients in 2019 | 7 | 29 | 10 | 23 | 20 | 38 | 0 | 7 | 20 | 1 | 155 |

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total number of patients |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Prognosis for the future | Unchan-ged | Growth | Unchan-ged | increase | Unchan-ged | Unchan-ged or modest growth | Unchan-ged | Unchan-ged | Slow growth | Stable | |
| **Holmium-166** | | | | | | | | | | | |
| Number of patients in 2019 | 0 | 6 | 0 | 35 | 0 | 2 | 0 | 0 | 0 | 0 | 43 |
| Prognosis for the future | Unchan-ged | Growth | Unchan-ged | increase | Unchan-ged | Unchan-ged | Unchan-ged | Unchan-ged | Modest growth after introduction in 2020 | NR | |
| **Radium-223** | | | | | | | | | | | |
| Number of patients in 2019 | 6 | 55 | 23 | 37 | 60 | 18 | 4 | 11 | 10 | 16 | 240 |
| Prognosis for the future | Unchan-ged | Unchan-ged | Unchan-ged | Unchan-ged | Unchan-ged | Unchan-ged or modest decrease | Unchan-ged | Unchan-ged | Unchanged | Stable | |
| **Other** | | | | | | | | | | | |
| Number of patients in 2019 | Not repor-ted | In-111: 8 | I-123: 231 Sm-153: 2 | I-123: 238 | Not reported | Not reported | I-123: 63 | Not reported | Ir-192: 200 | Not reported | 742 |
| Prognosis for the future | | Modest decrease | Growth | Increase | | | Growth | | Unchanged | | |

*Tabel B.2 Delivery problems regarding radionuclides The responding hospitals have been assigned numbers from 1 to 10 as in Table 1.*

| | **Delivery problems in 2019** | **If so, which** | **Causes** | **Risks and opportunities for the future** |
|---|---|---|---|---|
| 1 | Yes | Mo-99/Tc-99m generators were delivered with insufficient activity four different times, as a result of which patient programmes had to be adjusted. | Shortage of available Mo-99 in Petten | * Reduced delivery capacity poses a threat to patient examinations<br>* In view of the expected increase in demand for radionuclides for therapeutic purposes, a situation in which such radionuclides remain available will provide opportunities |
| 2 | Yes | Not specified | Two scram (emergency stop) situations in the reactor for Lu-177 | * In view of the age of the HFR and other medical reactors (experiencing associated defects in past years), I would expect major threats to supply security if no action is taken<br>* A new reactor for (e.g.) the production of medical isotopes would give the Netherlands a leading global role in the production of and research into medical isotopes. |
| 3 | Yes | * Sr-89 no longer available at all since the beginning of 2019<br>* In March, May, June, and September: no Tc-99m or reduced supply | Not reported | * Closure of the reactor in Petten will have major negative consequences for the availability of medical isotopes<br>* A new reactor in Petten provides opportunities for research into new treatment modalities and also secures the availability of Mo-99 |
| 4 | Yes | Not specified | Due to maintenance on the reactor (more frequent due to age of the HFR), foreseen or unforeseen | * Without Petten or a replacement reactor, supply security would immediately be endangered, and this would pose a threat to the diagnostic procedures and treatments of thousands of (mostly cancer) patients<br>* Opportunities involve the large increase in the number of lutetium-177 based treatments and related economic activity! |
| 5 | No | Not applicable | Not applicable | * We foresee a strong increase in radionuclide-based therapy, which is often a treatment of last resort for patients<br>* Supply security of medical radionuclides is a requirement for the Dutch care sector |

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