European Commission

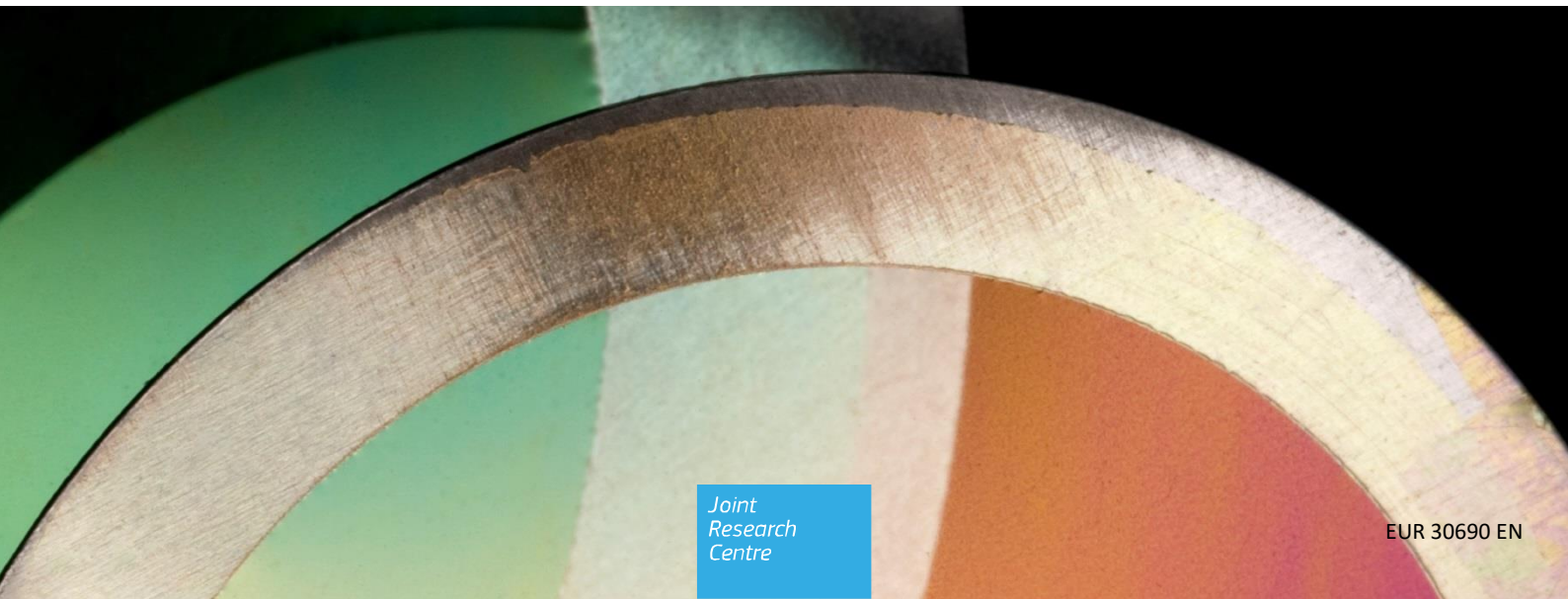
JRC SCIENCE FOR POLICY REPORT

Study on sustainable and resilient supply of medical radioisotopes in the EU

Therapeutic Radionuclides

Ligtvoet, A., Scholten, C., Davé, A., King, R., Petrosova, L., Chiti, A., Goulart De Medeiros, M., Joerger, A.

2021



Joint Research Centre

EUR 30690 EN

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Contact information
Name: Margarida Goulart
Address: European Commission
B-1049 Brussels
Email: margarida.goulart@ec.europa.eu

EU Science Hub
https://ec.europa.eu/jrc

JRC124565

EUR 30690 EN

PDF ISBN 978-92-76-37422-0 ISSN 1831-9424 doi:10.2760/642561

Luxembourg: Publications Office of the European Union, 2021

How to cite: Ligtvoet, A., Scholten, C., Davé, A., King, R., Petrosova, L. and Chiti, A., *Study on sustainable and resilient supply of medical radioisotopes in the EU*, Goulart De Medeiros, M. and Joerger, A. editor(s), EUR 30690 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-37422-0, doi:10.2760/642561, JRC124565.

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Abstracts

English

This report presents an overview of the current use of radionuclides for medical therapy in Europe as well as an estimate on the amounts being used. It also provides the expert opinion of more than 200 professionals in the field of nuclear medicine and radiopharmacy on future growth potential of the use of therapeutic radionuclides. The research signals the paucity of information, and reiterates the call for joint European efforts for more reliable data. While historical practice in radionuclide therapy has not led to major supply concerns, the imminent approval of certain treatment options (for example PSMA linked to Lutetium-177 for prostate cancer) may lead to a rise in demand for Lutetium and other radionuclides that may pose challenges to European radionuclide producers. The shutdown of European research reactors without immediate replacement capacity, as well as a general ageing of the infrastructure is an unsolved issue that also requires concerted European action.

While the market for therapeutic radionuclides is currently still small in comparison to the market for diagnostic radionuclides, the use of radiopharmaceuticals promises advances in the treatment of cancer. At the same time, technological developments for the production of these radionuclides are still uncertain and in early stages of market readiness. Supply is not fully secured, as the market is new and volatile. Future market developments are influenced by national reimbursement systems in reaction to radiopharmaceutical pricing, as well as complicated regulations that are determined by both radiation protection and pharmaceutical directives.

Français

Ce rapport présente un aperçu de l'utilisation actuelle des radionucléides en thérapie médicale en Europe, ainsi qu'une estimation des quantités utilisées. Il présente également l'avis de plus de 200 professionnels experts dans le secteur de la médecine nucléaire et de la radiopharmacie sur le potentiel de croissance de l'utilisation des radionucléides thérapeutiques. L'étude souligne le manque d'informations disponibles et renouvelle l'appel à des efforts européens communs pour collecter des données plus fiables. Si la pratique historique de la thérapie par radionucléides n'a pas soulevé de problèmes majeurs en matière d'approvisionnement, l'approbation imminente de certaines options de traitement (le PSMA lié au Lutétium 177 pour traiter le cancer de la prostate, par exemple) pourrait entraîner une hausse de la demande en Lutétium et autres radionucléides qui pourrait confronter les fabricants européens de radionucléides à des défis. L'arrêt des réacteurs de recherche européens sans capacité de remplacement immédiate, ainsi que le vieillissement général des infrastructures, est un problème qui nécessite également une action européenne concertée.

Si le marché des radionucléides thérapeutiques est actuellement encore peu développé par rapport au marché des radionucléides diagnostiques, l'utilisation des produits radiopharmaceutiques promet des avancées dans le traitement du cancer. Parallèlement, les développements technologiques pour la production desdits radionucléides sont encore incertains et se trouvent à un stade préliminaire de préparation au marché. L'approvisionnement n'est pas pleinement assuré, car ce marché est nouveau et encore volatile. L'évolution future du marché est influencée par les systèmes nationaux de remboursement en réaction à la tarification des produits radiopharmaceutiques, ainsi que par les réglementations complexes qui sont déterminées à la fois par les directives sur la radioprotection et par les directives pharmaceutiques.

Executive summary

This report was prepared on request of the European Commission's Joint Research Centre, following calls for action from the Council of the European Union, to provide insight in the use of radionuclides for medical therapy in the European Union. Radionuclides use for therapy currently is small as compared to radionuclides use for diagnosis: the market for therapeutic radionuclides is about 100 times smaller than for diagnostic radionuclides. However, in the coming decade significant growth is expected for the use of selected therapeutic radionuclides. More national level information is required to properly assess future issues of supply and demand.

Large and unexpected outages in research reactors in 2008-2010 have led to shortages in radionuclides used for medical diagnostics, which increased policy attention to the supply of notably Molybdenum/Technetium and to the search for alternatives to these radionuclides. Several European and international activities have been undertaken to (at least) increase the exchange of information regarding the supply of radionuclides for diagnostics.

In the last decade, innovations in the use of radioligands in radiopharmaceuticals have opened up potential applications in targeted radionuclide therapy – which led to the questions whether promising therapeutic innovations may face the same supply risk as the diagnostic radionuclides. Unfortunately, information to answer such questions is not publicly available and this report is a (first) attempt to provide further insight.

There are very high expectations regarding Lutetium-177 and Actinium-225 linked to PSMA (prostate-specific membrane antigen) which may result, when approved, in a soaring demand. While in this study more than 98% of the consulted experts expect growth in the demand for Lutetium-177-PSMA, 63% expect this growth to be larger than 15% over the next decade. This expectation follows from cancer incidence statistics: the target population of prostate cancer patients (incidence of ~335,000 in 2020 in the EU) is an order of magnitude larger than the population of cancer patients for which therapeutic radionuclides are currently used (for example, non-Hodgkin lymphoma incidence of ~86,000 in 2020 in the EU). Other high-potential radiopharmaceuticals that emerged from this study are several other Lutetium-177-combinations (for neuroendocrine tumours, non-Hodgkin lymphoma – more than 80% of respondents expect growth), as well as Holmium-166 (bone metastases, head and neck squamous cell carcinoma, hepatocellular carcinoma) and Thorium-227 (non-Hodgkin lymphoma, ovarian cancer and mesothelioma, prostate cancer) both for which more than 60% of respondents expect growth. In this report we focus on the radionuclides and indications for which growth is expected.

Radionuclides are produced in what could be called a quasi-market environment – production facilities for radionuclides remain in the hands of, or are financially supported by, governments while commercial organisations exploit the radiopharmaceuticals – characterised by information asymmetries.

However, the indications and therapeutic potential are not the only factors affecting whether a radiopharmaceutical is accepted in the market. There are national differences in healthcare systems and healthcare markets, including differences in reimbursement and access of radionuclides to the market, which stem from the fact that healthcare largely is a Member State competence. This means that access to radionuclide therapy is not uniform across the Union, but even within countries differences in access to facilities and trained healthcare professionals exist. Further investigation of appropriate treatment modalities through Health Technology Assessment is advised.

Furthermore, there are supply factors that need to be taken into consideration when assessing the future of radiopharmaceuticals. These factors will become more pressing as demand for radionuclides increases.

There are only few European or international production facilities that are able to provide radionuclides. Most of the available production capacity is in nuclear research reactors. Several of these mainly state-sponsored facilities are scheduled to close within the next decade without clarity on new research/production capacity. Although some information exchange regarding these facilities exists, there is no coordination on the allocation

of radionuclide production capacity. Furthermore, some of the enrichment and irradiation facilities are not available in Europe, which leads to additional worries about security of supply or self-sufficiency and dependence on foreign sources.

In spite of the current situation in radiopharmaceuticals, there seems to be little worry among healthcare professionals and other consulted experts regarding the supply of radionuclides. However, this will likely change due to the aforementioned increased demand for treatments related to cancer and ageing irradiation infrastructure in Europe. It is therefore advisable to remain observant of the developments in the radionuclides field, both for diagnostics and therapy.

Insight in the current situation regarding supply and demand is problematic, since very little information is available or disclosed at any level, save with the pharmaceutical companies. A more concerted effort to gather critical information regarding radionuclides is therefore advised, both at national and at European level. Good practices for gathering radionuclide and/or radiopharmaceutical information can be found in a number of Member States, notably Belgium, the Czech Republic, and Sweden, and could be harmonised and extended to all EU Member States. We recommend efforts to make the therapeutic market more transparent and to improve official data collection on the use (demand) of radiopharmaceuticals.

Concerted and timely European action is necessary now to ensure the continued resilient supply of therapeutic radionuclides in Europe for the future. This might include better monitoring of the progress of building new facilities, supranational attention for removing possible barriers and organising fallback options in these processes, and negotiating guaranteed levels of production of radiopharmaceuticals (for the medical market) with both existing and new facilities.

Furthermore, research and innovation actions, including health economic evaluations, could contribute to exploit the potential of therapeutic radionuclides and provide solutions to observed challenges in the radiopharmaceutical supply chain. Ultimately, the goal is to promote an equitable, efficient, and high-quality health system.

Résumé exécutif

Le présent rapport a été préparé à la demande du Centre Commun de Recherche (JRC) de la Commission Européenne suite aux appels à l'action du Conseil de l'Union Européenne, pour fournir un aperçu de l'utilisation des radionucléides pour la thérapie médicale au sein de l'Union Européenne. Actuellement, l'utilisation des radionucléides à des fins thérapeutiques est moindre par rapport à l'utilisation des radionucléides à des fins de diagnostic : le marché des radionucléides thérapeutiques est environ 100 fois moins important que celui des radionucléides à des fins de diagnostic. Toutefois, il est prévu que l'utilisation de certains radionucléides thérapeutiques augmente considérablement au cours de la prochaine décennie. De plus amples informations au niveau national sont nécessaires pour évaluer précisément les futurs problèmes de l'offre et de la demande.

Les arrêts importants et imprévus des réacteurs de recherche en 2008-2010 ont entraîné des pénuries de radionucléides destinés aux diagnostics médicaux, ce qui a renforcé l'attention politique portée à l'approvisionnement, notamment en molybdène/téchnétium, et à la recherche de solutions de substitution à ces radionucléides. Plusieurs activités européennes et internationales ont été entreprises pour intensifier (au moins) l'échange d'informations concernant l'approvisionnement en radionucléides pour les diagnostics.

Au cours de la dernière décennie, les innovations dans l'utilisation des radioligands dans les produits radiopharmaceutiques ont généré des applications potentielles dans la thérapie par radionucléides ciblée - ce qui a conduit à la question de savoir si les innovations thérapeutiques prometteuses pourraient être confrontées au même risque d'approvisionnement que les radionucléides de diagnostic. Malheureusement, les informations permettant de répondre à ces questions ne sont pas disponibles publiquement et le présent rapport est une (première) tentative pour éclaircir ces questions.

Les attentes sont très fortes en ce qui concerne le lutétium-177 et l'actinium-225 liés au PSMA (antigène membranaire spécifique de la prostate), ce qui pourrait entraîner, une fois approuvés, une forte hausse de la demande. Cette étude montre que plus de 98 % des experts consultés s'attendent à une croissance de la demande de lutétium-177-PSMA, 63 % d'entre eux prévoient que cette croissance sera supérieure à 15 % au cours de la prochaine décennie. Cette prévision découle des statistiques sur l'incidence du cancer : la population cible des patients atteints d'un cancer de la prostate (incidence d'environ 335 000 en 2020 au sein de l'UE) est plus importante que la population des patients atteints d'un cancer qui sont déjà traités avec des radionucléides thérapeutiques (par exemple, l'incidence des lymphomes non hodgkiniens est d'environ 86 000 en 2020 dans l'UE). Les autres produits radiopharmaceutiques à fort potentiel qui ont émergé de cette étude sont différentes combinaisons de Lutétium-177 (pour les tumeurs neuroendocrines, les lymphomes non hodgkiniens – plus de 80 % des répondants prévoient une croissance), ainsi que le Holmium-166 (métastases osseuses, carcinome épidermoïde de la tête et du cou, carcinome hépatocellulaire) et le Thorium-227 (lymphomes non hodgkiniens, cancer des ovaires et mésothéliome, cancer de la prostate), tous deux pour lesquels plus de 60 % des répondants prévoient une croissance. Dans ce rapport, nous nous concentrons sur les radionucléides et les indications pour lesquels une croissance est attendue.

Les radionucléides sont produits dans ce que l'on pourrait appeler un environnement quasi-marché - les installations de production de radionucléides étant aux mains des gouvernements ou soutenues financièrement par ces derniers, tandis que des organisations commerciales exploitent les produits radiopharmaceutiques - se caractérisant par des asymétries d'information.

Toutefois, les indications et le potentiel thérapeutique ne sont pas les seuls facteurs qui déterminent l'acceptation d'un produit radiopharmaceutique sur le marché. Il existe des différences nationales dans les systèmes et les marchés des soins de santé, y compris des différences dans le remboursement et l'accès au marché des radionucléides, qui découlent du fait que les soins de santé relèvent en grande partie de la compétence des États membres. Cela signifie que l'accès à la thérapie par radionucléides n'est pas uniforme dans

tous les pays de l'Union, et qu'il existe des différences au sein même des pays dans l'accès aux structures et aux professionnels de santé formés. Il est conseillé de poursuivre l'étude des modalités de traitement appropriées par le biais de l'évaluation des technologies de la santé.

En outre, certains facteurs liés à l'offre doivent être pris en considération lors de l'évaluation de l'avenir des produits radiopharmaceutiques. Ces facteurs deviendront plus astreignants à mesure que la demande de radionucléides augmentera.

Il n'existe que peu d'installations de production européennes ou internationales capables de fournir des radionucléides. Les réacteurs de recherche nucléaire sont la principale source des capacités de production. Plusieurs de ces installations, principalement parrainées par l'État, devraient fermer au cours de la prochaine décennie sans que l'on sache exactement quelles seront les nouvelles capacités de recherche/production. Bien qu'un certain échange d'informations concernant ces installations ait lieu, il n'existe aucune coordination sur la répartition de la capacité de production de radionucléides. En outre, certaines des installations d'enrichissement et d'irradiation ne sont pas disponibles en Europe, ce qui suscite de vives inquiétudes concernant la sécurité de l'approvisionnement ou l'autosuffisance et la dépendance vis-à-vis des sources étrangères.

Malgré la situation actuelle dans le domaine des produits radiopharmaceutiques, les professionnels de la santé et les autres experts consultés semblent peu préoccupés par l'approvisionnement en radionucléides. Toutefois, cela va probablement changer en raison de la hausse de la demande en traitements contre le cancer et du vieillissement des infrastructures d'irradiation en Europe. Il est donc conseillé de rester vigilants et attentifs aux évolutions dans le domaine des radionucléides, tant pour le diagnostic que pour la thérapie.

La connaissance de la situation actuelle de l'offre et de la demande est problématique, car très peu d'informations sont disponibles ou diffusées à quelque niveau que ce soit, sauf en ce qui concerne les entreprises pharmaceutiques. Il est vivement recommandé de déployer des efforts plus concertés pour recueillir des informations critiques sur les radionucléides, tant au niveau national qu'au niveau européen. Les bonnes pratiques pour la collecte d'informations sur les radionucléides et/ou les produits radiopharmaceutiques sont implantées dans un certain nombre d'États membres, notamment en Belgique, en République tchèque et en Suède, et pourraient être harmonisées et étendues à tous les États membres de l'UE. Nous recommandons des efforts pour rendre le marché thérapeutique plus transparent et pour améliorer la collecte de données officielles sur l'utilisation (la demande) des produits radiopharmaceutiques.

Une action européenne concertée et en temps utile est nécessaire pour garantir la continuité durable et future de l'approvisionnement en radionucléides thérapeutiques en Europe. Cela pourrait inclure un meilleur suivi de la progression de la construction de nouvelles installations, une attention supranationale pour éliminer les obstacles éventuels et organiser des options de repli dans ces processus, et la négociation de niveaux garantis de production de produits radiopharmaceutiques (pour le marché médical) avec les installations existantes et les nouvelles.

En outre, les actions de recherche et d'innovation pourraient contribuer à exploiter le potentiel des radionucléides thérapeutiques et apporter des solutions aux problèmes observés dans la chaîne d'approvisionnement radiopharmaceutique. En fin de compte, l'objectif est de promouvoir un système de santé équitable, efficace et de haute qualité.

1 Introduction: Supply shortages in radionuclides for medical diagnostics lead to questions about radiopharmaceuticals for therapy

The use of radionuclides for medical purposes is an important pillar of healthcare systems around the globe, including those in European member states. Nuclear (molecular) medicine involves using radionuclides injected into patients at low doses for functional imaging to detect diseases and using (usually) other radionuclides for the targeted therapy of tumours. Imaging is of primary importance to enable making correct diagnoses and providing treatments. For the purpose of imaging, the workhorse radionuclide is Technetium (^{99m}Tc, used in Single-photon emission computed tomography or SPECT), which is used in the European Union (including the UK) roughly 10 million times per year (this represents ~25% of global demand).[1]

In the last decades, the use of radionuclides for therapy has increasingly received attention in research, development and clinical trials. By binding radionuclides to other molecules or antibodies they can be guided to a target tissue, to provide local treatment of (primarily) cancers. This targeted approach, which is known as radioligand therapy, or unsealed source radiotherapy, can be combined with imaging techniques to provide theragnostics (therapy + diagnosis). Given the prevalence of cancer in Europe and worldwide, there is still much to be gained by improving diagnosis and treatment through these means.

While the importance of radionuclides for medical diagnostics and therapy is very large, there is relatively little information available on the use/demand and production/supply of the most relevant radionuclides. Until today, this branch of medicine largely depends on nuclear research infrastructures that were built in the 1950s, 1960s and 1970s to provide knowledge for nuclear energy and nuclear weaponry. The concerns on nuclear security led to some of the information being sensitive or classified (state secrets). At the same time, it should be noted that there are very large private interests at stake that are best preserved by maintaining information asymmetry (trade secrets). Both reasons may be deemed legitimate, but lead to a situation in which relatively little information is known on important medical modalities.

The European Commission as well as the Council of the European Union[2] have recognised the importance of more information on the uses of nuclear technology and nuclear medicine in particular. The responsible Commission's Directorate-General for Energy, in coordination with the DGs for Health, Research & Innovation and Economic Growth, has started a strategic initiative to assess medical, industrial and research applications of nuclear technology, called SAMIRA, in 2017.[3] This has led to a comprehensive overview report[4] as well as a range of conferences and workshops organised by the Commission. Further in-depth research has been performed on the diagnostic uses of radionuclides. However, insights in the use, demand and supply of therapeutic radionuclides has been very limited and fragmented at European level.

This report, commissioned by the European Commission's Joint Research Centre, **focuses on the supply and demand of radionuclides for therapy**. Its content is based on public or disclosed information.

Below we provide more information on the importance of the issue, the scope of this report, and the research approach.

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[1] NucAdvisor and Technopolis Group (2019). *European study on medical, industrial and research applications of nuclear and radiation technology (SAMIRA)*. Brussels: European Commission, 2019.

[2] See: https://data.consilium.europa.eu/doc/document/ST-9437-2019-INIT/en/pdf

[3] The SAMIRA agenda is expected to be published in Q1 2021.

[4] Ibid.

1.1 Reactor shutdowns at the core of supply shortages around 2008-2010

The supply of radionuclides for medicine has relied on existing research infrastructure for decades with relatively few disruptions. Research reactors[5] currently produce the majority of both diagnostic and therapeutic radioisotopes, including the most used imaging radioisotope ^{99}Mo/^{99m}Tc. European research reactors, among them HFR (The Netherlands), BR2 (Belgium), Maria (Poland) and LVR-15 (Czech Republic), are important ^{99}Mo producers, delivering more than about 60% of the global demand. Although both alternative production methods as well as alternative radionuclides for imaging and therapy are being developed, the demand for ^{99}Mo/^{99m}Tc is expected to remain significant for the next decade.[6]

The fragility of the supply chain was however demonstrated in the years 2008-2010, when planned and unplanned reactor shutdowns led to difficulties in supply and cancelled or delayed diagnostic tests around the globe. This led to the establishment of the OECD-NEA High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) as well as the European Observatory on the Supply of Medical Radioisotopes by the European Commission.[7] Focusing mainly on ^{99}Mo/^{99m}Tc, these bodies have repeatedly indicated that the small number of ageing reactors are increasing supply risks and the planned shutdown of both HFR and BR2 would lead to acute shortages of ^{99}Mo/^{99m}Tc.

1.2 With the growth in therapeutic use shortages may increase in the future

While the current use of radionuclides for therapeutic purposes remains a fraction of the radionuclide use for imaging and diagnostics, there are strong reasons to suspect that its use may increase in the near future. Especially the success of clinical trials for [^{177}Lu]Lu-PSMA for prostate cancer and its imminent (expected in 2021) EU marketing authorisation is expected to expand the market drastically. The severity and health impacts of cancers and their prevalence in the European population provide room for more targeted treatments. Large pharmaceutical companies' moves in this market (e.g. Bayer – Xofigo®, Novartis – Lutathera®) also show that commercial opportunities are identified.

The European market for therapeutic radionuclides is characterised by large uncertainty due to the relative novelty of the field, the constant innovation taking place, and the differences in nuclear medicine practice as well as differences in the healthcare system (both in terms of organisation as in terms of financing) in each separate member state. The potential growth of therapeutic radionuclides also faces many challenges. To properly assess the challenges to the deployment of therapeutic radionuclides, a clearer picture of the current status is needed, which is the purpose of this report.

1.3 A wide range of methods was used to uncover information at member state level

The research presented in this report relied on mixed methods to provide both top-down (at European level) as well as bottom-up (at Member State level but starting from individual therapy centres) data on supply and demand. Where possible, we relied on official statistical data and research reports. However, as indicated above, this information is not readily available for most member states. We further based our findings on interviews or written correspondence with international and national experts, including pharmaceutical companies, reactor operators, nuclear medicine associations, national authorities and specialists. While inviting more than 800

[5] Research reactors are nuclear reactors that are primarily used or have originally been built for research, development, education, and training activities. They are different from nuclear power reactors/plants that are purpose-built for energy production. Research reactors produce neutrons for research activities and are equipped with several instruments for research and other irradiation activities. Many research reactors also use a part of their capacity to perform industrial activities such as the production of medical radionuclides or silicon (neutron transmutation) doping.

[6] Ibid. 1

[7] See: https://ec.europa.eu/euratom/observatory_radioisotopes.html

experts directly and, with the help of nuclear medicine associations many more indirectly through newsletters and online platforms, we gathered full responses from 194 (mainly nuclear medicine) experts in a two-phased Delphi survey in the spring and summer of 2020. This has allowed us to provide a rough estimate of radionuclide use in 26 countries (while always preferring official statistics over our own estimates); this information was sent to representatives of national nuclear medicine associations and/or national health care institutes for verification. In addition, findings were put forward for validation (cross-check) to suppliers of radiopharmaceuticals. A workshop with relevant stakeholders from government, academia, and industry was held in January 2021 to discuss findings, policy implications and further recommendations. Further details on the research approach can be found in the appendices of this report.

Our research team was supported by prof. Arturo Chiti (Humanitas University, Italy) and overseen by an expert advisory board consisting of prof. Ken Herrmann (Universitätsklinikum Essen, Germany), prof. Gabriel Krestin (Erasmus University Medical Center Rotterdam, the Netherlands), and prof. Dominique Vandijck (Ghent University, Belgium).

1.4 The focus in this report is on radiopharmaceuticals

The three main medical specialties using ionising radiation are radiology, radiotherapy and nuclear medicine. In these three domains, innovation to improve healthcare is a constant driver. A weighing of the merits of each speciality goes beyond the scope of this report. Radiology uses low energy external electron beams for imaging. Radiotherapy involves higher energy external electron beams, γ-rays or ion beams, or internal (sealed) radioactive sources ("brachytherapy") for treating tumours. Nuclear medicine involves using radionuclides injected into patients at low doses for functional imaging (SPECT/PET) to detect diseases and using other isotopes at high doses for the targeted therapy of tumours. This report specifically focuses on the therapeutic use of nuclear medicine, i.e. the use of radionuclides in radiopharmaceuticals to treat patients (primarily patients with cancer) because of the promising developments taking place in this field.

In chapter 2 we provide further explanation on the topic and discuss the current use of radionuclides for therapy in Europe. Chapter 3 describes European regulations and healthcare reimbursement systems that may affect future uptake of radionuclides. Next, chapter 4 describes the supply end and the issues that may become important in the near future. Chapter 5 discusses future market developments while chapter 6 provides policy recommendations based on the previous chapters.

The annexes give additional information on methods used, the data quality per country and an overview of country factsheets that were used for the different analyses.

2 Current and emerging use of radiopharmaceuticals

Although having become widely spread relatively recently**,** nuclear medicine plays a vital role in cancer care today as it has shown to improve overall survival and quality of life for many people. As the understanding of the biology of cancer has grown, the science of nuclear medicine has evolved to deliver targeted, safe and effective diagnostics and treatments.[8] **Compared to almost all other systemic cancer treatment options, nuclear therapy has shown efficacy with minimal toxicity, and typically requires shorter cycles of therapy while showing significantly fewer (both in terms of number and severity of) side effects**. The use of nuclear medicines, however, is in early stages of development and deployment and is therefore expected to expand to yield benefits to patients.

Overview of the main conclusions of the chapter:

- Using a retrospective estimate of the annual use of radionuclides in various EU countries (and the UK) as a proxy of the demand for radionuclide use shows that ^{131}I, ^{177}Lu and ^{90}Y are the most used radionuclides in terms of activity at time of administration (TOA).
- The same data shows that [^{131}I]-NaI, [^{177}Lu]Lu-DOTATATE, [^{177}Lu]Lu-PSMA, ^{90}Y- microspheres (both glass and resin) and ^{90}Y-colloids are the most used radiopharmaceuticals (in that order) as per activity at TOA.
- The same radiopharmaceuticals account for the highest numbers of procedures delivered with the addition of [^{223}Ra]$RaCl_2$ which ranks third following [^{131}I]-NaI and [^{177}Lu]Lu-DOTATATE.
- [^{131}I]-NaI is the most commonly used radiopharmaceutical and far outstrips use of other radiopharmaceuticals in terms of both activity (two-fold compared to next most used radiopharmaceutical) and procedures (almost seven-fold compared to next most used radiopharmaceutical).
- ^{131}I and ^{223}Ra are the most ubiquitously used radionuclides in Europe, being used in almost all the countries we have data for. ^{177}Lu, ^{90}Y, ^{153}Sm and ^{186}Re are also widely used across more than 10 countries.
- Data availability and quality are major limiting factors in terms of calculating and understanding the use of and demand for therapeutic radionuclides across the EU. Only a few countries have detailed insights into the use of therapeutic radionuclides in their country. Belgium, the Czech Republic and Sweden are examples of good data collection in this regard.

Nuclear medicine encompasses both diagnostic and therapeutic applications of radioactive isotopes. This study focuses on the therapeutic application of nuclear medicine, namely use of radionuclide and radiopharmaceutical therapy, i.e. the delivery of radioactive isotopes emitting alpha (α), beta (β) and/or gamma (γ) radiation to tumour associated targets (see section 4.2). This type of radiation is called ionising radiation. Especially alpha and beta radiation are important for radionuclide therapy, as these constitute of particles that can kill cancer cells and have a short range of action. Gamma radiation, constituting of high-energy photons, is not contributing much to the (open source) therapeutic purpose, but can be used for imaging.

The beta radiations, most prevalently used in the therapeutic purposes, consist of electrons or positrons (positively charged electrons) which are derived from unstable atoms. These beta particles have a relatively long path length and lose their kinetic energies as their follow their path, eventually coming to a stop. The linear

[8] Merkel, C., Whicher, C.H., Bomanji, J. et al. (2020). *Realising the potential of radioligand therapy: policy solutions for the barriers to implementation across Europe*. Eur J Nucl Med Mol Imaging 47, 1335–1339: https://doi.org/10.1007/s00259-020-04745-7

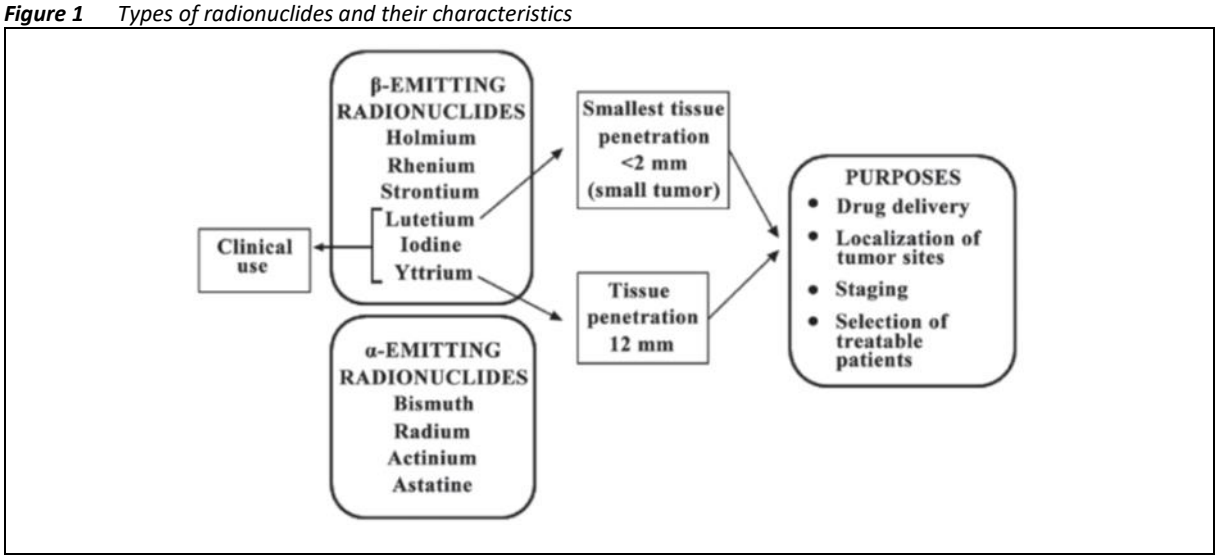
energy transfer (LET, which is the amount of energy deposited per path length) is very low, leaving little tissue damage. For beta-emitters to be effective, a high concentration of radionuclides is necessary.[9]

The alpha radiation consists of positively charged helium nuclei, which in fact are two protons and two neutrons. Alpha particles are derived from the decay of the heaviest radioactive elements, they have a relatively short path length and a high LET, meaning that they cannot travel far but lead to a more substantial amount of tissue damage along their path than beta particles. Given their path length and LET specifics, alpha-emitters are especially suitable for the treatment of small tumours, however, due to its high toxicity, administration of alpha-emitting radionuclides requires accurate dosimetry calculations, so the estimated absorbed dose is in line with toxicity considerations.[10]

Only therapeutic applications of radioactive isotopes are in the scope of this study, however, several therapeutic radionuclides are used in theragnostic (both diagnosis and treatment) as well. Several therapeutic radionuclides (e.g. ^{177}Lu, ^{153}Sm, ^{67}Cu, ^{47}Sc) emit both alpha and/or beta radiations as well as gamma radiation, which can be imageable using for instance gamma cameras. Some radiopharmaceuticals (e.g. ^{166}Ho-microspheres) also bear magnetic properties allowing for MRI imaging.

Isotopes emitting beta and/or alpha particles can be used in radiopharmaceutical therapy. Some administered radionuclides can also be visualised by nuclear imaging techniques which allows for precise targeting, substantially more advantageous as compared to other existing therapeutic approaches to cancer.[11] A recent and highly promising innovative branch of nuclear therapy, radioligand therapy is currently used in a small number of cancers, however there is evidence that a similar approach can be used in other cancer and non-cancer conditions.

Figure 1 *Types of radionuclides and their characteristics*



Source: Nitipir et al. (2017)

[9] Poty, S., Francesconi, L. C., McDevitt, M. R., Morris, M. J., & Lewis, J. S. (2018). *α-Emitters for Radiotherapy: From Basic Radiochemistry to Clinical Studies-Part 1. Journal of nuclear medicine: official publication*, Society of Nuclear Medicine, 59(6), 878–884. https://doi.org/10.2967/jnumed.116.186338

[10] Ibid Poty et al. (2018)

[11] Sgouros, G., Bodei, L., McDevitt, M.R. et al. (2020). *Radiopharmaceutical therapy in cancer: clinical advances and challenges*. Nat Rev Drug Discov 19, 589–608: https://doi.org/10.1038/s41573-020-0073-9

2.1 Radiopharmaceuticals, their indication and use

While a substantial number of radioisotopes (less than 50) are already used in clinical therapeutic applications (incl. external radiotherapy and sealed sources), many more have the potential of being successfully used for therapeutic purposes.[12] In this study we look at the use of radionuclides in the form of radiopharmaceuticals for treatment purposes – this excludes external radiotherapy and sealed sources (as used in brachytherapy). This reduced the number of radionuclides that are marketed, used in clinical trials or used for compassionate use to the 18 included in the table below. **Table 1** presents an overview of the radionuclides that are in the scope of this study, along with their main characteristics and use indications.

Table 1 *Overview of radionuclides included in the study*

Radio-nuclide	Full name	Type of emission*	Indications for use (in Europe)	Radiopharmaceutical name in Europe (if available)	Remarks
^{32}P	Phosphorous-32	β	Myeloproliferative disease Bone metastases	n/a	The first radionuclide used in therapeutic applications more than 50 years ago.
^{47}Sc	Scandium-47	β	Under investigation for liver metastases		
^{67}Cu	Copper-67	β	Under investigation for meningioma and neuroblastoma		
^{89}Sr	Strontium-89	β	Bone pain palliation arising from skeletal metastasis	Metastron®	
^{90}Y	Yttrium-90	β	^{90}Y-glass and resin microspheres (TheraSphere®/SIR-Spheres®) are used in intra-arterial treatments in the liver ^{90}Y-colloids are used in radiation synovectomy [^{90}Y]Y-ibritumomab-tiuxetan (Zevalin®) is used in B-cell lymphoma and non-Hodgkin lymphoma ^{90}Y-somatostatin is used for treatment of neuroendocrine tumours	TheraSphere® Zevalin® SIR-Spheres® Ytracis® Yttriga®	Yttrium-90 is effective in forming complexes with a variety of agents and can be broadly used in therapy for various indications.
^{131}I	Iodine-131	β	[^{131}I]-NaI is used in benign thyroid diseases, thyroid remnant ablation and thyroid cancer [^{131}I]I-mIBG (IOBENGUANE) is used in neuroblastoma	Generics and Theracap®	One of the most important and widely used radionuclides

[12] Ibid Sgouros et al. (2020)

Radio-nuclide	Full name	Type of emission*	Indications for use (in Europe)	Radiopharmaceutical name in Europe (if available)	Remarks
			and adult neuroendocrine tumours		for thyroid diseases.
^{153}Sm	Samarium-153	β	Bone metastases	Quadramet®	
^{166}Ho	Holmium-166	β	^{166}Ho-microspheres are used in intra-arterial treatment in the liver and against recurrences of head and neck squamous cell carcinoma [^{166}Ho]Ho-chitosan is used in hepatocellular carcinoma (HCC) [^{166}Ho]Ho-DOTMP is used in bone metastasis	QuiremSpheres®	
^{169}Er	Erbium-169	β	^{169}Er-colloids are used in radiation synovectomy	n/a	
^{177}Lu	Lutetium-177	β	^{177}Lu-antibodies (Betalutin®) are used in non-Hodgkin lymphoma [^{177}Lu]Lu-DOTATATE (Lutathera®) is used in gastroentero-pancreatic neuroendocrine tumours (GEP-NETs) [^{177}Lu]Lu-PSMA is used in therapy of castration resistant prostate cancer (pc) and pc-metastases [^{177}Lu]Lu-somatostatin is used in neuroendocrine tumours (NETs))	Betalutin® Lutathera® EndolucinBeta®	Lutetium-177 is a therapeutic radioisotope of rapidly increasing importance.
^{186}Re	Rhenium-186	β	Radiation synovectormy		
^{188}Re	Rhenium-188	β	Treatment of non-melanoma skin cancer [^{188}Re]Re-HEDP used in painful bone metastases	Rhenium-SCT®	
^{211}At	Astatine-211	α	Under investigation for a range of tumours		
^{212}Pb	Lead-212	β	Under investigation for a range of tumours		
^{213}Bi	Bismuth-213	α, β	Under investigation for a range of tumours		
^{223}Ra	Radium-223	α, β	Castration-resistant prostate cancer Symptomatic bone metastases and no known visceral metastases	Xofigo®	

Radio-nuclide	Full name	Type of emission*	Indications for use (in Europe)	Radiopharmaceutical name in Europe (if available)	Remarks
^{225}Ac	Actinium-225	α, β	[^{225}Ac]Ac-PSMA is used for metastatic castration resistant prostate cancer [^{225}Ac]Ac-Lintuzumab is used for acute myeloid leukemia (AML)		
^{227}Th	Thorium-227	α	^{227}Th-conjugate is used for (CD22 positive) non-Hodgkin lymphoma ^{227}Th-antibody is used for ovarian cancer and mesothelioma [^{227}Th]Th-PSMA is used for metastatic castration resistant prostate cancer		

**Y-rays are omitted from this description as they are used in imaging and are therefore not in scope of the study.*

2.2 Current use is a proxy for current demand

While there is some difference between the demand for therapeutic radionuclides and the current use of radiopharmaceuticals, we have approached the demand for radionuclides in terms of activity from the number of procedures using radiopharmaceuticals. The demand in terms of number of procedures is directly related to the deployment of the radiopharmaceutical in which the radionuclide is used. This is measured at the level of the patient/hospital. For the demand in terms of activity a reference point is needed, as activity decreases exponentially over time. We express demand in terms of activity at the patient/hospital level at time of administration (TOA). We do this, as (1) information is best available at this level (i.e. procedures), (2) activity and procedures are now expressed at the same level and (3) to avoid uncertainties/differences in time (thus affecting activity) from irradiation to application.

Measuring true demand for radionuclides in the EU is fraught with difficulty given the fragmented nature or often complete lack of data collection between countries. Additionally, suppliers of radionuclides and radiopharmaceuticals do not provide such (strategic) market information. For these reasons, a retrospective estimate of annual use of radionuclides may serve as the best proxy of the demand for radionuclides. It should be noted that true demand for radionuclides may be higher than current use, as there may be other reasons (e.g. cost, availability, knowledge) for using fewer radionuclides. It should also be noted that the demand at the irradiator is higher: due to inefficiencies, processing and transport times, higher activities need to be produced in order to meet the needed activities at the time of administration to patients.

To establish an overall estimate of current demand (using current use as proxy), annual country level demand for radionuclides was calculated first on a more granular level by radiopharmaceutical and indication. These were then summed to give a national and EU level estimate for a given radionuclide/radiopharmaceutical.

Demand at the radiopharmaceutical and indication level was estimated using two main methods. The first method makes use of national statistical data from publicly available sources or from national nuclear medicine societies, whilst the second uses Technopolis survey data to estimate demand. The first method was preferred where data were available as these were believed to be more robust than survey data. The exact methodology and important assumptions associated with current demand calculations are provided in Appendix B.2. We also asked national nuclear medicine societies and suppliers of radiopharmaceuticals to validate the final current

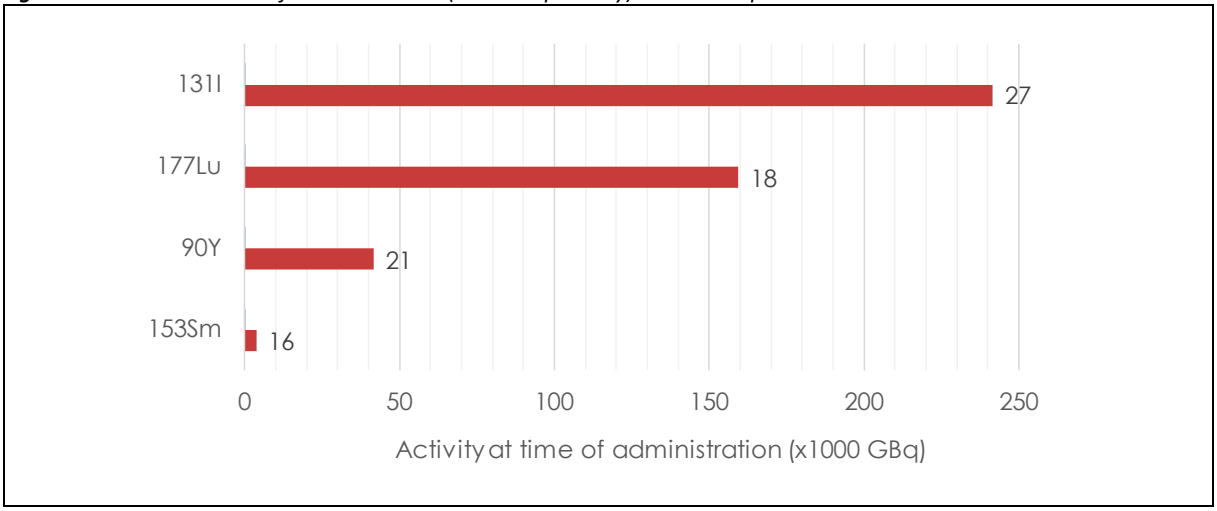
demand calculations. However, not all nuclear medicine societies and radiopharmaceutical suppliers provided responses. We indicate the countries with validated responses below and in the appendices.

The majority of the current demand calculations (14 countries) are based on our validated survey data and/or national statistics; however, a large share of countries have not validated the calculated figures. As such, the current demand calculations have to be treated with caution. Nonetheless, the figures do give **an indication of the most in demand radionuclides/radiopharmaceuticals in Europe in terms of both activity and procedures**.

2.2.1 Demand in terms of activity

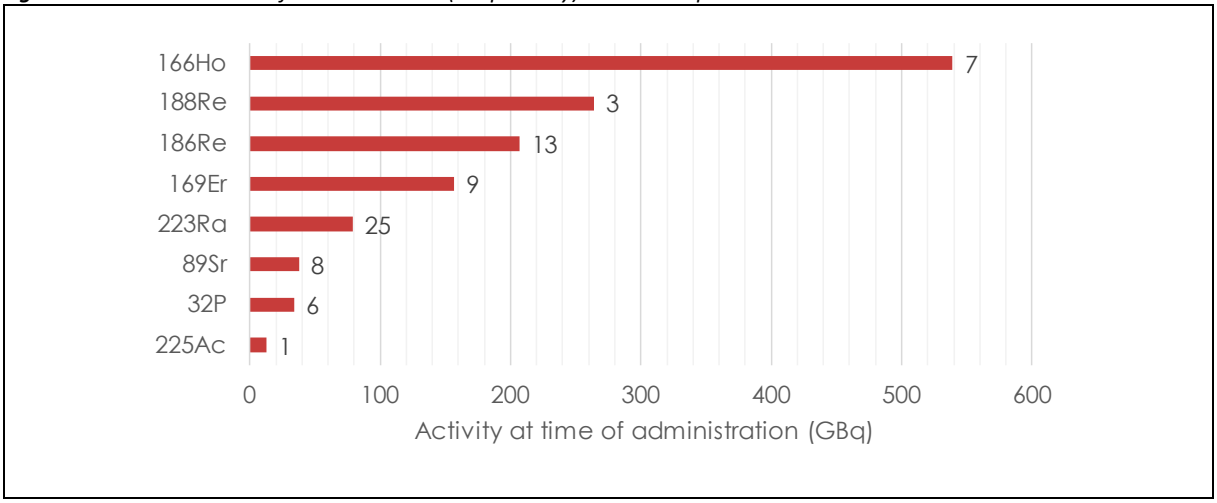
As would be expected, ^{131}I and ^{223}Ra are the most ubiquitously used radionuclides in Europe, for example, they are used in 26 and 25 countries respectively out of the 26 countries we have data for (**Figure 2** and **Figure 3** – note that the scales are different). ^{131}I and ^{223}Ra are typically used as [^{131}I]-NaI and [^{223}Ra]$RaCl_2$ in the case of various thyroid-related conditions (both benign and malignant) and bone metastases respectively. ^{177}Lu, ^{90}Y and ^{153}Sm (at high activity levels in **Figure 2**) and ^{186}Re (at lower activity levels in **Figure 3**) are also widely used across more than 10 countries.

Figure 2 *Current demand for radionuclides (1000 GBq activity) across Europe*



N.B. The data labels at the end of a bar indicate the number of countries reporting use of a particular radionuclide. Data for Denmark was not available.

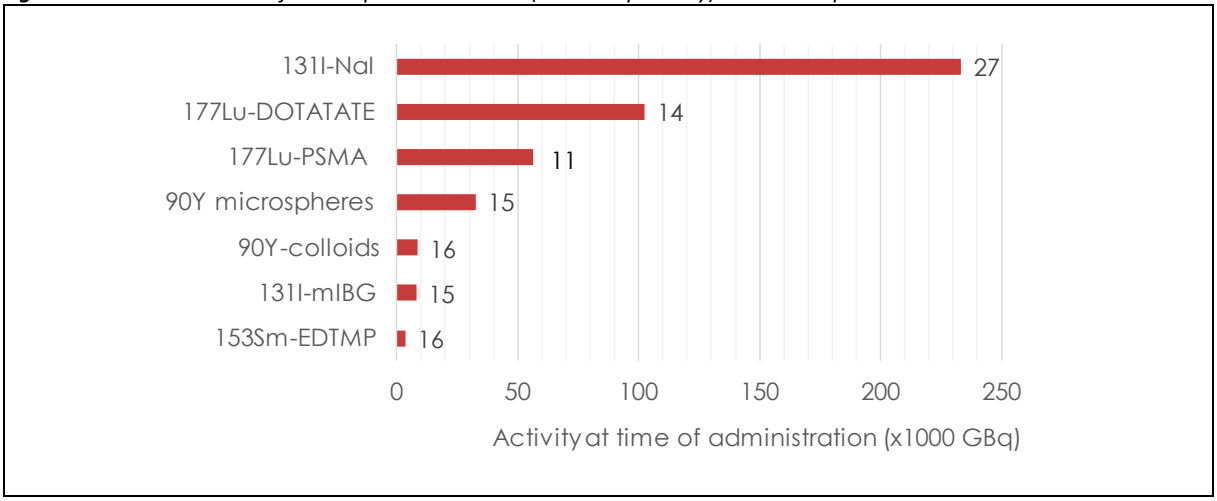
Figure 3 *Current demand for radionuclides (GBq activity) across Europe*



N.B. The data labels at the end of a bar indicate the number of countries reporting use of a particular radionuclide. Data for Denmark was not available.

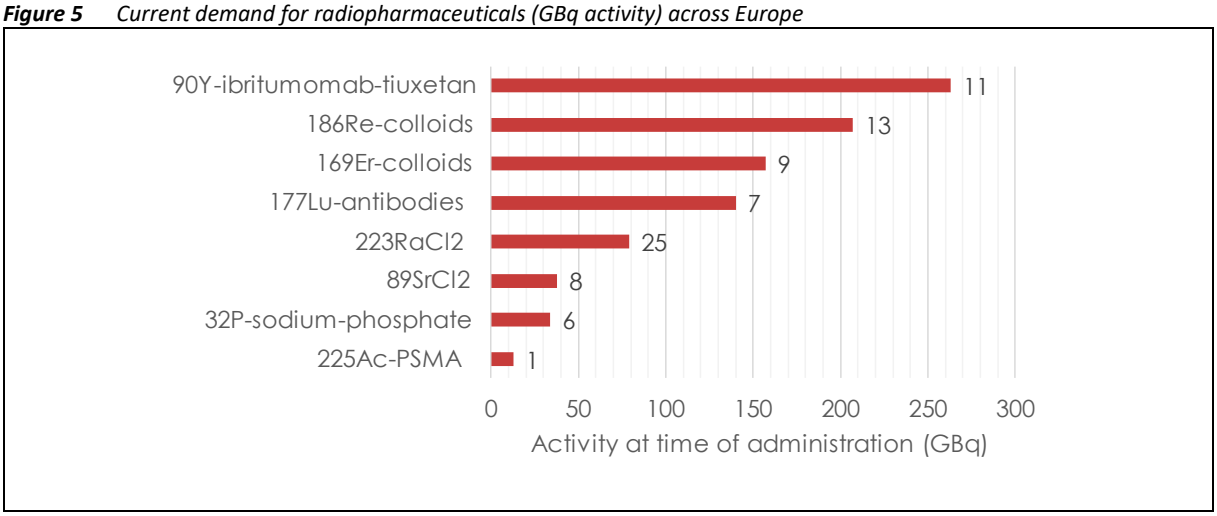
^{177}Lu and ^{90}Y are used as different radiopharmaceuticals for different indications, most prominently as ^{90}Y microspheres (both glass and resin) for intra-arterial treatments in the liver, ^{90}Y-colloids for radiation synovectomy, [^{177}Lu]Lu-DOTATATE for neuroendocrine tumours, and [^{177}Lu]Lu-PSMA for castration-resistant prostate cancer and metastases (**Figure 4**).

Figure 4 *Current demand for radiopharmaceuticals (1000 GBq activity) across Europe*



N.B. The data labels at the end of a bar indicate the number of countries reporting use of a particular radiopharmaceutical. Data for Denmark was not available.

Figure 5 *Current demand for radiopharmaceuticals (GBq activity) across Europe*



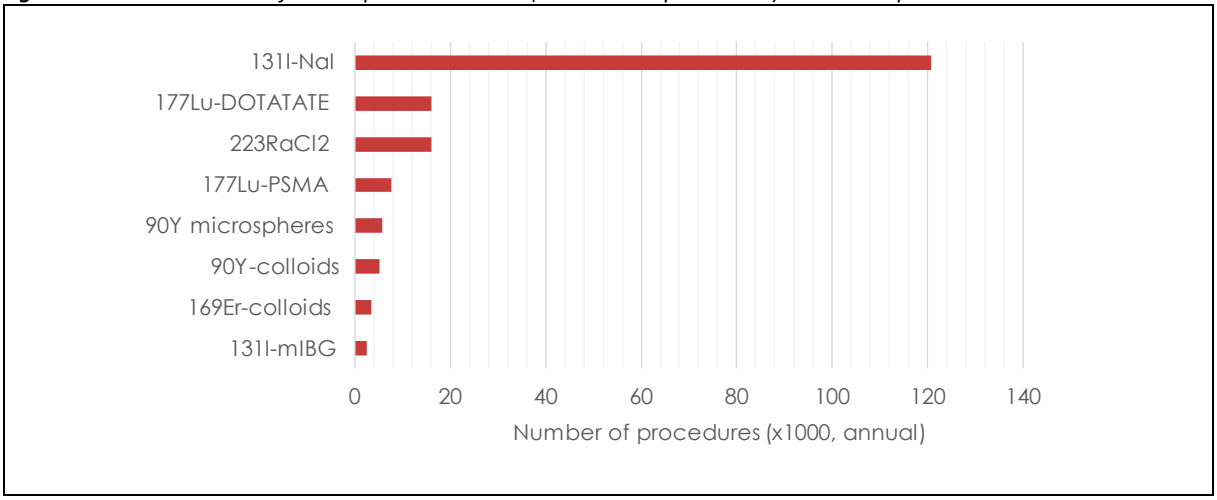
N.B. The data labels at the end of a bar indicate the number of countries reporting use of a particular radiopharmaceutical. Data for Denmark was not available.

Suppliers of radiopharmaceuticals were asked to validate the collected data for their product. From the responses received, we understand that the current demand for ^{177}Lu-antibodies is in line with the suppliers' estimate. For [^{177}Lu]Lu-PSMA suppliers estimate a 25-30% higher current European demand – which still leaves [^{177}Lu]Lu-PSMA the third radiopharmaceutical most in demand in terms of activity. For [^{177}Lu]Lu-DOTATATE the European demand is probably somewhat less, based on a crude patient number obtained during validation. Overall, this supports the conclusion that ^{177}Lu is currently high in demand, second after ^{131}I.

2.2.2 Demand in terms of procedures

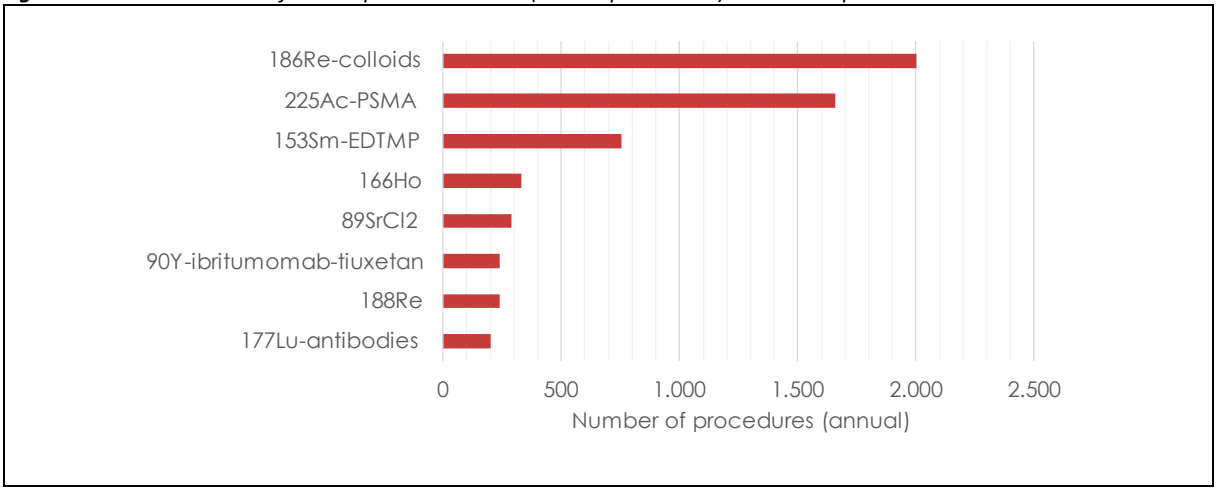
In terms of number of procedures (i.e. individual treatments or doses) delivered [^{131}I]-NaI far outstrips other radiopharmaceuticals as well. The next most popular radiopharmaceuticals in terms of procedures required are [^{177}Lu]Lu-DOTATATE and [^{223}Ra]RaCl$_2$, both of which account for about eight-fold fewer procedures compared to those delivered for [^{131}I]-NaI (16k each respectively as opposed to 120k for [^{131}I]-NaI).

Figure 6 *Current demand for radiopharmaceuticals (1000 annual procedures) across Europe*



N.B. Data for Denmark was not available.

Figure 7 *Current demand for radiopharmaceuticals (annual procedures) across Europe*



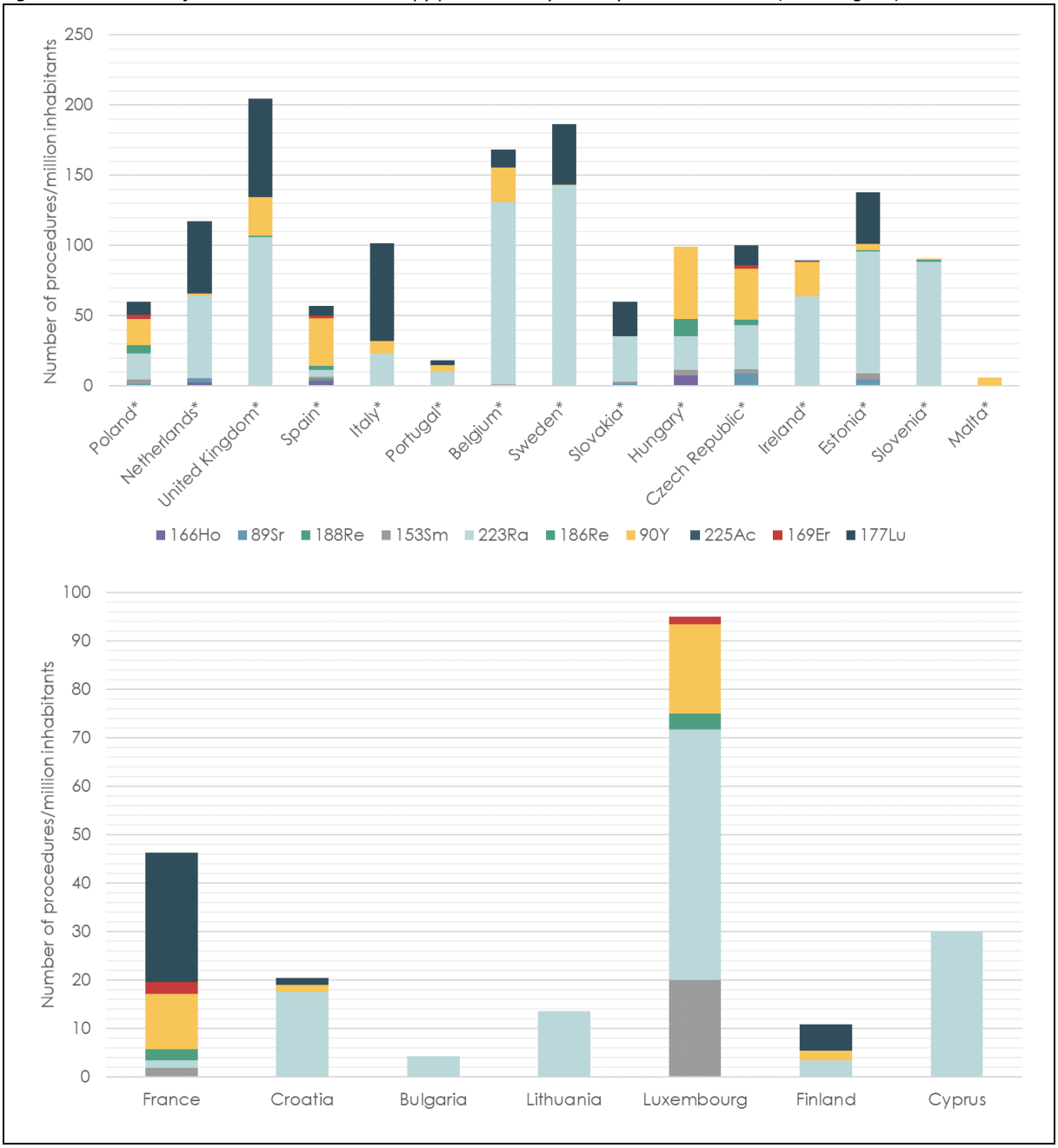
N.B. Data for Denmark was not available.

Drawing conclusions from country-level data has limitations as data for some countries was not validated by the respective national nuclear medicine society. From the countries with validated data, Estonia (781), Poland (648) and Slovakia (591) deliver the greatest number of radionuclide therapy procedures per million inhabitants, which includes ^{131}I. The UK (25k), Poland (24k), and Spain (16k) deliver the greatest number of procedures in total.

To focus on the upcoming radionuclides, we have created **Figure 8** which excludes ^{131}I (the top panel for validated data and bottom panel for indicative data that has not been validated). Here we see that per million inhabitants UK (205), Sweden (186) and Belgium (169) deliver the most radionuclide therapy procedures per million inhabitants.

Further, in per capita terms, use of ^{90}Y appears more common in Hungary, the Czech Republic and Spain than in other European countries (based on validated data; see **Figure 8** top panel). The use is largely in the form of ^{90}Y-colloids in Hungary and Czechia, while in Spain ^{90}Y-microspheres account for almost 60% of the procedures. On the other hand, the relatively higher rate of use of ^{177}Lu in the UK and Italy is down to [^{177}Lu]Lu-DOTATATE. ^{223}Ra is quite heavily used in Sweden, Belgium and the UK despite it being a more costly radionuclide. On the other hand, ^{166}Ho use is most prominent in Hungary, Spain and the Netherlands.

Figure 8 *Number of annual radionuclide therapy procedures by country and radionuclide (excluding ^{131}I)*



N.B. The top panel shows countries for which data were validated by the relevant national nuclear medicine society (as indicated by an asterisk), while the bottom panel shows indicative data for the remaining countries. Data for ^{131}I are not shown as it is used across all countries represented in the data and in very high amounts. Austria, Denmark, Germany, Greece, Latvia and Romania are not represented in the graph. Data was not available for Denmark. We received a very low number of responses from Austria, Germany and Greece. Romania only uses ^{131}I and while Latvia uses ^{131}I as well as ^{223}Ra, the procedure numbers are very low.

2.3 Incidence – population growth greatest for prostate cancer

Incidence data may be used as an indicator of the new patient population eligible for treatment with a given medicine. Here we define incidence as the number of new cases per 100,000 people in a given year, and absolute incidence gives the new cases for an entire population. A crucial caveat with the use of incidence data for this analysis is that it is the eligible, or potential, population – i.e. *not* the number of new patients that *will* be treated with radiopharmaceuticals. A proportion of these new patients will for example, receive alternative or competing treatments in practice, or in some instances die before treatment can be given.

Incidence rates for relevant cancers are calculated from the European Cancer Information System (ECIS)[13] and given in **Table 2**. Data from 2010 was used as the latest incidence data, from 2014, was not considered representative of enough countries across Europe. Using data from 2010 drew incidence information from 128 cancer registries across 27 different countries across the EU across all ages for both males and females. The average incidence per 100,000 people in 2010 was calculated for each therapeutic area from the available registries. The incidence for each therapeutic area relevant to a given radiopharmaceutical was summed to give the total new people eligible for treatment with that radiopharmaceutical in 2010. Absolute numbers were calculated assuming an EU population of 441 million in 2010.[14] Certain therapeutic areas, such as B-cell lymphoma and head and neck cancers did not have incidence data available.

Table 2 *EU incidence of cancers occurring in therapeutic areas for radiopharmaceuticals in 2010*

Radiopharmaceutical	Therapeutic area(s) relevant to a radiopharmaceutical (as given in ECIS)	Average annual incidence rate in EU countries per 100,000 people	Absolute incidence in EU countries
[^{177}Lu]Lu-PSMA	Prostate	171*	376,671
[^{225}Ac]Ac-PSMA	Prostate	171*	376,671
[^{227}Th]Th-PSMA	Prostate	171*	376,671
[^{90}Y]Y-ibritumomab-tiuxetan	Non-Hodgkin lymphoma (B-cell lymphoma n/a)	19	84,276
^{227}Th-conjugate	Non-Hodgkin lymphoma	19	84,276
^{177}Lu-antibodies	Non-Hodgkin lymphoma	19	84,276
^{90}Y-resin microspheres	Liver and intra-heptic bile ducts	15	68,121
^{90}Y-glass microspheres	Liver and intra-heptic bile ducts	15	68,121
^{166}Ho-microspheres	Liver and intra-heptic bile ducts	15	68,121
[^{166}Ho]Ho-chitosan	Liver and intra-heptic bile ducts	15	68,121
[^{225}Ac]Ac-Lintuzumab	Leukaemia	14	62,467
[^{131}I]-NaI	Thyroid gland	12	52,655

[13] ECIS - European Cancer Information System (2021). From https://ecis.jrc.ec.europa.eu, accessed on 11/01/2021. European Union.

[14] Statista data (2021). From https://www.statista.com/statistics/253372/total-population-of-the-european-union-eu/. Accessed on 11/-1/2021

Radiopharmaceutical	Therapeutic area(s) relevant to a radiopharmaceutical (as given in ECIS)	Average annual incidence rate in EU countries per 100,000 people	Absolute incidence in EU countries
[^{131}I]I-mIBG	Endocrine and Brain and other CNS	10	41,977
^{32}P-sodium-phosphate	Myeloma and Bones and Joints	9	37,565
^{227}Th-antibody	Mesothelioma	2	10,096
^{90}Y-colloids	Bones and joints	1	4,507
[^{89}Sr]$SrCl_2$	Bones and joints	1	4,507
[^{223}Ra]$RaCl_2$	Bones and joints	1	4,507
[^{188}Re]Re-HEDP	Bones and joints (non melanoma skin cancer data n/a)	1	4,507
^{186}Re-colloids	Bones and joints	1	4,507
[^{177}Lu]Lu-DOTATATE	Endocrine	1	2,588
^{169}Er-colloids	Bones and joints	1	4,507
[^{166}Ho]Ho-DOTMP	Bones and joints	1	4,507
[^{153}Sm]Sm-EDTMP	Bones and joints	1	4,507
^{166}Ho-microspheres	Head and neck	n/a	n/a

*Source: European Cancer Information System and Technopolis 2020. *calculated per 100,000 males only*

It is clear from **Table 2** that prostate cancer has by far the greatest average incidence rate (171/100,000 males) in cancers relevant to radiopharmaceuticals used in Europe. Despite being applicable to only half the population (males only), the absolute number of prostate cancers still far outweighs any absolute numbers of other relevant cancers. When combined with the expected market approval of PSMA radiopharmaceuticals[15] following on from current clinical trials in the coming months and years, it appears that use of these medicines will greatly increase over the coming decade.

Non-Hodgkin lymphoma was the therapeutic area that had the second greatest incidence rate according to ECIS data, therefore radiopharmaceuticals that treated this ([^{90}Y]Y-ibritumomab-tiuxetan, ^{227}Th-conjugate, ^{177}Lu-antibodies) ranked high in the eligible new population for treatment. Those radiopharmaceuticals that treat endocrine or bone and joint cancers ranked the lowest in terms of eligible new people for treatment.

By far, the most commonly used radiopharmaceutical, [^{131}I]-NaI, ranked relatively low in terms of incidence rates for its therapeutic areas. However, importantly ^{131}I does not have competing treatments for hyperthyroidism and thyroid cancer. We would therefore expect a large proportion of this 'potential' population to in fact receive treatment with ^{131}I – for other radiopharmaceuticals that have more competing treatments this proportion may be lower.

It should be noted that this analysis makes use of incidence data (the number of additional people in a given unit of time) rather than prevalence data (the total population of interest). Prevalence data was not available for analysis. Current incidence data in 2020/21 is also likely to be higher than the figures given here owing to the

[15] For example, the progress being made in the VISIONS study https://clinicaltrials.gov/ct2/show/NCT03511664

population demographics becoming more skewed towards older age brackets where cancer incidence is greater. Although incidence rates and absolute numbers are likely greater now for all cancers than in 2010, this data still demonstrates that prostate cancer has by far the greatest incidence rate of relevant cancers, this will hold true for 2020/21 also.

2.4 Good examples of data collection in EU-27

Data regarding the use of therapeutic radionuclides is fragmented across the EU. Only a few countries have detailed insights in the use of therapeutic radionuclides in their country and information can be obtained from official bodies. In this study we found that Belgium, the Czech Republic and Sweden are examples of good data collection in this regard. For these countries official bodies were able to provide the requested data. Here we shortly describe their approach to data collection.

- In Belgium, the federal agency for nuclear control FANC collects data on the imported activity of radiopharmaceuticals used in Belgium. This data concerns the activity per radiopharmaceutical delivered to the Belgian departments for nuclear medicine. In addition, in Belgian health insurance data, the number of units administered and invoiced of (reimbursed) radiopharmaceuticals is collected. Also, price information of reimbursable radiopharmaceuticals is monthly updated and published at the website of the national health insurance institute RIZIV. These three sources provide a reliable and fairly complete overview of radionuclides used in Belgium and their costs.
- In the Czech Republic, the State Institute for Drug Control contains databases of medicinal products and pharmacies and the comprehensive statistics it collects include the amount of radiopharmaceuticals (in Bq) used in clinical praxis. The number of patients receiving radionuclide therapy by indication is available from National Registers maintained by the Institute of Health Information and Statistics of the Czech Republic which collect the numbers of patients diagnosed each year and the type of treatment they receive. The number of procedures delivered including dose per procedure can be evaluated from statistics of health insurance companies and the Institute of Health Information and Statistics of the Czech Republic. Not all these data are publicly available, and some can be made available on request for research purposes. The Czech Society of Nuclear Medicine has access to these data.
- In Sweden, the Swedish Radiation Safety Authority (SSM) provides national data on radiopharmaceuticals. All administrations of radiopharmaceuticals are reported annually. Data collected include how many treatments each radiopharmaceutical has been used for, if the treatment is for adults or children and the average activity (MBq) of those treatments. The number of patients treated is not collected and this number may differ from the total number of treatments.

In some other countries we have seen that data on the use of radiopharmaceuticals is collected for reimbursement or radiation protection, but that the purpose and aggregation level of this information does not allow trace-back to specific radiopharmaceuticals or radionuclides. For instance, data registered at the level of indication does not discriminate between several candidate medicines or treatments. Also, radiopharmaceuticals that have not received marketing authorisation but are used in clinical trials, used compassionately, or produced in-house (magistral preparation/compounding), or that are not reimbursed, are generally not visible in official data or not specific enough to monitor (e.g. as category ‘Other nuclear medicine treatments’).

To gain better insights and to monitor European demand for therapeutic radionuclides and radiopharmaceuticals better official national data collection is needed. Current approaches for bottom-up data collection through surveys to individual healthcare professionals or nuclear medicine societies do provide some insights, but these are never complete and inherently introduced uncertainties, resulting in best estimates. Furthermore, a fatigue for such bottom-up data collection exercises is observed among nuclear medicine professionals and national associations. The examples above may provide inspiration for improving and standardising these data collection mechanisms to strengthen the European overview through national data.

3 Regulation, reimbursement, finance and guidelines

There are many different future pathways for the use of radiopharmaceuticals, and they are determined by a range of factors. The presence of radiopharmaceutical guidelines on when and how they should be used, such as those published by the EANM, do not guarantee their use. Similarly, a lack of guidelines also does not necessarily mean that a radionuclide will not be used as a part of treatment. The Technopolis survey has shown that **treatment using radionuclide therapy is done often as part of clinical trials, prior to the development of clinical guidelines. Yet even when treatments are established, there are still a number of broad factors, clinical and non-clinical, that can determine the use of radionuclide therapy**. We explore these factors in more detail throughout this chapter. These factors may also be applicable to medicine use more broadly, however; evidence specific to radiopharmaceuticals is included where available from the study.

Overview of main conclusions of this chapter:

- When being granted a licence for the European market, the Centralised procedure is the most relevant for radionuclide therapy medicines. Medicines that treat cancers must go via this procedure.
- Sharing radiopharmaceutical HTAs via the EUnetHTA may be of particular help to countries with less well-resourced healthcare bodies that lack capacity to conduct HTAs.
- Referral systems and communicative networks are necessary to help ease geographical inequalities in terms of patient access to treatment with radionuclide therapy.
- Clinical staff education can affect if alternative or competing therapies are chosen over treatment with radiopharmaceuticals.
- Radionuclide therapy may be at particular risk of shortages due to the complex supply chain required to manufacture a radiopharmaceutical and get it to the hospital bedside.
- The prices of radiopharmaceuticals are negotiated by hospitals, regions or countries (e.g. by ministries). These negotiations differ per country which can lead to a range of prices paid for the same radiopharmaceutical.

3.1 EU Regulation and licensing

Until 1989 the unique properties of radiopharmaceuticals had seen them treated differently to other medicinal products in legislative terms in the EU. However, in May 1989 the Council Directive 89/343/EEC came into action which extended the scope of Directives 65/65/EEC and 75/319/EEC on the regulation or administrative action relating to proprietary medicinal products, laying down additional provisions for radiopharmaceuticals. The result was that regulation of radiopharmaceuticals became more harmonised with more general medicines. In 2001 Directive 2001/83/EC further harmonised radiopharmaceutical legislation by stating that marketing authorisation was required for industrially manufactured radiopharmaceuticals, with exemptions in certain instances.[16]

Market authorisation may be given on the European market via a number of different routes: (1) the centralised procedure, (2) the decentralised procedure (DCP), (3) the mutual recognition procedure (MRP) and (4) national authorisation procedures.[17] The first three of these routes to market authorisation can give a company approval

[16] Verbruggen et al (2020). *Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU*. See: https://www.eanm.org/publications/guidelines/gl_radio_phct_259_853.pdf

[17] Lægemiddelstyrelsen (2016). *Marketing authorisation for a medicine*. See: https://laegemiddelstyrelsen.dk/en/licensing/licensing-of-medicines/marketing-authorisation/

to market in all or several member states at once, whilst the latter national authorisation procedure only gives authorisation to market in a single country.

Central authorisation is a key benefit to EU member states and EEA members that gives patients timely access to new and innovative medicines. **It is required that certain products, such as oncology medicines, go through the central authorisation procedure[18] making it of particular relevance to radionuclide therapy medicines**. The European Medicines Agency (EMA) evaluates centrally authorised single market authorisation applications and recommends authorisation to the European Commission who ultimately decides which medicines are granted market authorisation to EU and EEA members.[19] Xofigo® ([^{223}Ra]$RaCl_2$) is one example of a radiopharmaceutical that has gained access to the EU via a centrally authorised procedure. In 2013, Bayer was granted market authorisation for Xofigo® by the European Commission for the treatment of adults with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastases. This decision followed a positive recommendation by the EMA's Committee for Medicinal Products for Human Use (CHMP) to the EC.

The MRP is used when a product has already received national market authorisation in one member state or country and another member state wishes to use their evaluation of the product to grant market authorisation in their own country. The EU holds Mutual Recognition Agreements (MRAs) for radiopharmaceuticals with countries outside the EU including Australia, Canada, Israel, New Zealand, Switzerland and the USA.[20] The DCP is similar to this process but can be used when a product is yet to receive market authorisation in any member state. In this case a member state must act as the Reference member state (RMS) to conduct an initial evaluation of the product.[21] The product may then gain market authorisation to multiple member states through the DCP, also distinguishing it from the national authorisation procedure.

Variation in national legislation also contributes to differences in how radiopharmaceuticals can be used in different member states. France and Hungary, for example, have policies that only allow radiopharmaceuticals to be used only after authorisation has been granted or when a clinical trial has started.[22] More relaxed approaches are taken in other member states, most notably Germany. Technopolis expert interviews have suggested that Germany takes a progressive approach regarding compassionate use of radiopharmaceuticals (and other medicines in general). Compassionate use allows a promising technology that may not yet be in clinical trials to be used on a case where therapeutic need is adequate. Consequently, Germany is considered particularly innovative with a broad palette of radiopharmaceuticals in use – even though these are not yet on the market.

Other countries, like The Netherlands, Belgium, Austria and Sweden for example, also take progressive approaches. Certain radiopharmaceuticals without market authorisation can be prepared based on 'pharmacy practice' whereby hospital pharmacies take responsibility. However, scrutiny over radiation protection and Good Manufacturing Practice is required with in-house production.

New radiopharmaceuticals may also come into use in Europe as part of a clinical trial. Legislation surrounding EU clinical trials is currently undergoing a transition with the aim of simplifying the process.[23] The new Clinical Trials

[18] Medpace (2020). *The evolving landscape of therapeutic and diagnostic radiopharmaceuticals*. See: https://www.medpace.com/wp-content/uploads/2020/07/Article-The-Evolving-Landscape-of-Therapeutic-and-Diagnostic-Radiopharmaceuticals.pdf

[19] EMA (2020). *What we do*. See: https://www.ema.europa.eu/en/about-us/what-we-do

[20] EMA Mutual recognition agreements (MRA) https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra

[21] HMA Medicines Approval System. See: https://www.hma.eu/medicinesapprovalsystem.html#:~:text=The%20decentralised%20procedure%20(%20DCP%20)%20is,for%20MRP%20to%20be%20used

[22] Schwarz et al. (2019). *Harmonization of U.S., European Union, and Canadian First-in-Human Regulatory Requirements for Radiopharmaceuticals: Is This Possible?* See: http://jnm.snmjournals.org/content/60/2/158.full#ref-17

[23] Ibid.

Regulation EU 536/2014 repealed the Directive 2001/20/EC with the ambition of creating a single application and authorisation procedure via a central EU portal and database. This will replace the older Directive where each participating country must individually make a clinical trial application. Although the new regulation was due to come into force in 2016 it has been delayed; the EMA management board has proposed a new 'go-live date' of December 2021.[24] Technopolis believes the use of the central portal for clinical trials may see shorter times to approve the use of novel radiopharmaceuticals in clinical trials in Europe in the future.

3.2 Reimbursement and Finance

Although a pivotal milestone for medicine availability, licensing of radionuclides via regulators such as the EMA does not guarantee clinical use. Decision makers must still decide whether to grant reimbursement taking both clinical and financial considerations in mind. Reimbursement may occur on a national or regional level, where pharmaco-economic evaluations are used, or on an individual case-by-case basis. Factors that need to be considered are therapeutic need, if the technology is lifesaving, if an alternative technology available or not, the total number of patients that can be treated with the new technology, if only a certain sub-cohort of the eligible population will be treated and also price (which involves manufacturer negotiations).

Over recent decades **Health Technology Assessments (HTAs) have been established as important instruments for reimbursement decisions**. HTAs provide systematic literature reviews of clinical data and health economic analysis that inform if a new treatment or regimen is both more clinically and cost effective than a comparator (what is already used). These studies may typically take a national perspective, with models tailored towards a specific health system (e.g. healthcare costs). Regarding radionuclides, HTAs are more suited to interventions on the radiopharmaceutical level, whereby a specific indication can be explored.

Given the variation in healthcare systems between countries, HTAs can lead to differing reimbursement recommendations from one country to the next. Taking ^{223}Ra for the treatment of metastatic prostate cancer (mPC) for example, a HTA for the Irish National Centre for Pharmaco-economics (NCPE) did not recommend ^{223}Ra for reimbursement following findings of an incremental cost-effectiveness ratio (given by the additional cost of a treatment divided by the additional health benefit) of €79,948, which was deemed to be too costly for the additional clinical patient benefit.[25] Concurrent findings that ^{223}Ra to treat mPC was not cost-effective were found in other national HTAs (Germany, England and Wales, Scotland and Sweden)[26]. However, as demonstrated through the survey conducted in this study, despite uncertainty regarding the cost-effectiveness of ^{223}Ra it is still used in practice to treat mPC in many European countries. This may come down to individual negotiations on price at the national level between manufacturers/suppliers and purchasers. The National Institute for Healthcare Excellence (NICE) in England and Wales only recommended that ^{223}Ra is used if "company provides Radium-223 dichloride with the discount agreed in the patient access scheme".[27] Discount negotiations such as these are more often than not kept confidential, as such no further analysis on the relationship between discounting and reimbursement was possible.

In recognition of (a) the effort national health agencies need to generate HTAs and (b) that often evidence in a HTA is either generalisable or adaptable to other European countries, the EU set up the EUnetHTA (European

[24] Highlights of Management Board: June 2020 meeting: https://www.ema.europa.eu/en/documents/press-release/highlights-management-board-june-2020-meeting_en.pdf

[25] NCPE (2014). *Cost Effectiveness of Radium-223 (Xofigo®) for castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases*. See: http://www.ncpe.ie/wp-content/uploads/2013/12/Xofigo-12122014_final.pdf

[26] See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4873580/#ref18

[27] See: https://www.nice.org.uk/guidance/ta412/chapter/1-Recommendations

Network for Health Technology Assessment) as part of Directive 2011/24.[28] A Technopolis review of the EUnetHTA assessment list showed that no specific radionuclides or radiopharmaceuticals have been included. Although outside of the scope of this study, Stereotactic Body Radiation Therapy (SBRT) has been included on the EUnetHTA Prioritisation List (EPL) for "Other Technologies".[29] Given the increasing importance of HTAs in reimbursement decisions, increasing dialogue with EUnetHTA and appropriate radionuclide related bodies may help to share HTA radiopharmaceutical resources between European countries. **Supplying radiopharmaceutical HTAs via the EUnetHTA may be of particular help to countries with less well-resourced healthcare regulatory bodies that lack capacity to conduct HTAs from scratch**.

Given the high prices often attached to radiopharmaceuticals and costs to health care systems, the number of procedures reimbursed may be limited. In Hungary, for example, reimbursement of radiopharmaceuticals occurs via the National Health Insurance Fund, as is the case for other medicines. However, the decision process for reimbursement differs. The reimbursement decision is made by a special medical expert committee on a patient-by-patient basis. The effect of having a special committee taking more granular decisions works as a cost control, limiting the number of very expensive procedures,

Reimbursement and pricing strategies of radiopharmaceuticals in Europe vary significantly between member states. The variation seen is a consequence of reimbursement and pricing being decided at a national level. Generic models of reimbursement commonly used in healthcare settings are shown in **Table 3**. Reimbursement trends in secondary care have seen a shift in recent years from primarily 'unbundled' fee for service models towards 'bundled' payments where a lump sum covers a patient pathway, diagnosis or disease, for example. Bundling has previously been defined as the degree to which the components of healthcare are grouped together for payment.[30] For example, where a fee for service model is employed radiotherapy planning and rehabilitation may need to be reimbursed separately to radiotherapy treatment itself. However, these units of care could be reimbursed in one payment if a model of payment per pathway is utilised. Fee for service reimbursement has been criticised for incentivising high volume of care, perhaps at the expense of quality, whilst not encouraging integrated care.

Table 3 *Reimbursement models used in European healthcare settings*

Model	Description
Fee-for service	Payment for each unit of service and patient contact
Payment per day	Payment per day that patient stays in hospital
Payment per case / diagnosis / procedure	Payment per case based on grouping of patients with similar diagnoses /procedures or resource needs
Payment per pathway	Payment for all services required for a defined patient pathway
Budget	Global lump sum paid irrespective of the number of patients treated

Source: Nuffield Trust Reforming payment for health care in Europe to achieve better value

There is a strong lack of published literature regarding reimbursement of radiopharmaceuticals. However, some parallels may be drawn from the (also scant) literature that is published regarding other radiotherapy services and reimbursement.

[28] See: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011L0024

[29] See: https://eunethta.eu/assessments/eunethta-prioritisation-list-epl-other-technologies/

[30] See: https://www.nuffieldtrust.org.uk/research/reforming-payment-for-health-care-in-europe-to-achieve-better-value

For example, Lievens et al. (2020) found that fee-for-service radiotherapy financing is seen in nine European countries (Belgium, Estonia, France [private and public], Germany, Greece [private], Lithuania, Luxembourg, the Netherlands, and England). Only 5 countries (Bulgaria, Finland, Portugal, Romania, and Spain) used bundled payments that correspond to a payment per case, diagnosis or procedure. The study also found that where a budget is used, the budget is defined by either number of treatments delivered or investment in equipment. These findings may serve as an approximation as to the reimbursement models also used for radiopharmaceuticals.

3.3 Health systems resources and capacity

Treatment with radionuclide therapy may require considerable investment in infrastructure. For example, there may need to be dedicated radiotherapy centres that provide inpatient and outpatient facilities. The investment required for such facilities may not be covered under national reimbursement schemes. **Consequently, smaller peripheral hospitals are less likely to have such infrastructure to administer most nuclear medicine therapies**. Where patients reside closer to smaller peripheral hospitals, they may be referred to a larger hospital or specialist radiotherapy centre, or an alternative course of treatment could be prescribed. One Belgian national expert indicated that in response to the problem of geographical resource availability, nuclear medicine is run via a hub and network system that will eventually channel patients to 7 national radionuclide therapy centres. A further expert from the UK described ability to receive radionuclide therapy as a 'post code lottery' in the country, where larger cities have better equipped hospitals with highly trained staff.

As can be seen from these examples, **difficulties with resources and capacity can lead to geographical inequalities of health**. These inequalities may become particularly pronounced where expensive infrastructure is required, as is the case with radionuclide therapy. **Referral systems and communicative networks are necessary to help ease geographical inequalities**.

3.4 Staff expertise and knowledge

In practice it is usually nuclear medicine departments who perform the treatment with radiopharmaceuticals in conjunction or on referral from oncologists. Although these departments are staffed with experts in their fields, additional expertise may be required due to the clinical complexity of certain indications. Expertise and a multidisciplinary team of oncologists, radiologists, surgeons and more are all needed to revolve around patients. One Dutch expert highlighted that treating neuroendocrine tumours (NETs) with radionuclide therapy is particularly difficult due to the complications that can arise, consequently endocrinologist expertise must also be brought on board the team where not already present.

Where staff expertise and knowledge of radionuclide therapy is lacking it can be expected that alternative or competitive courses of treatment may be chosen. The majority of radiopharmaceuticals are utilised in clinical settings where multiple drugs are used. In practice the course of treatment used where competing therapies are available will be influenced by what the treating physician is able to directly manage. Therefore, the education of clinical staff has a direct effect on whether radiopharmaceuticals are used. One exception to this is the use of iodine-131 for thyroid cancer and hyperthyroidism, where there is a lack of competing therapies.

One expert in Belgium suggested that **doctors often first choose what is available in their hospital leading to inefficiencies**. Chemotherapy may be a viable alternative for many hospitals to treat certain cancers, for example. The reasons for choosing what is available to them may be to avoid referral away thus maintaining turnover in the hospital. The outcomes of staff lacking expertise in radiotherapy may be similar to those arising from a lack of resources and capacity – Increased use of alternative therapies and geographical health inequalities.

3.5 Medicine shortages

In cases where staff expertise, resources and capacity to deliver radionuclide therapy are sufficient there may still be instances where it is not possible to use it as a course of treatment. Medicine shortages, which have been a growing problem in the EU, can force triaging of patients in order to decide who gets treatment, or in the case of severe shortages force the use of alternative treatments for all patients. A 2019 survey of 400,000 community pharmacies across Europe conducted by the Pharmaceutical Group of the European Union (PGEU), found that all responding countries (24 Member States) experienced medicine shortages in the past 12 months.[31] From a patient perspective medicine shortages present a major problem as it may lead them to switch to alternative therapies, potentially resulting in increased risks of adverse effects, decreased treatment effectiveness, medication errors, non-compliance and disease progression. In addition to potentially decreasing quality of care and worsening patient outcomes, medicine shortages may represent a serious problem to the efficiency and quality of healthcare institutions.

Radionuclide therapy may be at particular risk of shortages due to the complex supply chain required to manufacture a radiopharmaceutical and get it to the hospital bedside. Unique to radiolabelled medicines, compared to other medicines, is the need to consider the half-life of the product. Radionuclides with shorter half-lives need to be produced as locally as possible to prevent decay, which renders the medicine unusable. Robust supply chains are therefore critical to prevent supply side related shortages. A specific example of supply side related shortages was reported in the Technopolis survey which occurred in Cyprus. The Cypriot example was reported as occurring due to connecting flights carrying radionuclide cargo that either arrived late or not at all. This example is demonstrative that supply chains need to be adapted and robust to the unique geographies, if any, of individual countries.

3.6 Guidelines – a preference for European level

The complexity of treatment with radiopharmaceuticals necessitates specific clinical knowledge. As such, clinical guidelines are useful to help harmonise and disseminate best practice. Information that clinicians may look to clinical guidance for assistance may be, for example, dosimetry of radiopharmaceuticals for certain sub-populations.

Guidelines can be published on varying levels from an organisation, to the national or European level. Drawing on data from the Technopolis survey and supporting interviews, **there is a clear preference among countries in Europe to make use of European level guidelines.** At this level the guidelines that tend to be used are published by the European Association of Nuclear Medicine (EANM). A total of 22 of 28 countries reported using European level guidelines for radiopharmaceutical treatment (see **Table 4**).

Additional guidelines are also requisite given that the EANM does not publish guidelines that cover all radiopharmaceuticals that are used on the European market. Slightly less (15 out of 28) countries reported using national guidelines, of these 14 reported using a combination of European and national level guidelines. Only Ireland reported using national level alone, however, this may be due to a lack of reporting through the survey, as opposed to the European level not being used (this is also the case for all instances of "Not reported" in **Table 4**). Use of guidelines at the organisational level were not well reported, with only Bulgaria, Denmark and Poland suggesting their use.

[31] PGEU (2020). *PGEU Medicine Shortages Survey 2019 Results*. Available at https://www.pgeu.eu/wp-content/uploads/2019/03/PGEU-Medicine-Shortages-Survey-Results-2019-1.pdf. Accessed 09/04/2020

There was 1 reported instance of a country – Romania – using non-European guidelines from the USA. The specific organisations were the American Thyroid Association and the National Comprehensive Cancer Network; their guidance is used for treating thyroid malignancies and hyperthyroidism with ^{131}I.

Table 4 *Level of radiopharmaceutical guidelines used by country*

Country	European clinical guidelines (e.g. from the EANM)	National clinical guidelines	Organisation clinical guidelines
Austria	Yes	Yes	Not reported
Belgium	Yes	Not reported	Not reported
Bulgaria	Not reported	Not reported	Yes
Croatia	Yes	Yes	Not reported
Cyprus	Yes	Not reported	Not reported
Czech Republic	Yes	Not reported	Not reported
Denmark	Yes	Not reported	Yes
Estonia	Yes	Yes	Not reported
Finland	Yes	Yes	Not reported
France	Yes	Yes	Not reported
Germany	Yes	Yes	Not reported
Greece	Yes	Yes	Not reported
Hungary	Yes	Yes	Not reported
Ireland	Not reported	Yes	Not reported
Italy	Yes	Yes	Not reported
Latvia	Not reported	Not reported	Not reported
Lithuania	Not reported	Not reported	Not reported
Luxembourg	Yes	Yes	Not reported
Malta	Yes	Not reported	Not reported
Netherlands	Yes	Yes	Not reported
Poland	Not reported	Not reported	Yes
Portugal	Yes	Not reported	Not reported
Romania	Yes*	Not reported	Not reported
Slovakia	Yes	Not reported	Not reported
Slovenia	Yes	Not reported	Not reported
Spain	Yes	Yes	Not reported
Sweden	Yes	Yes	Not reported
United Kingdom	Yes	Yes	Not reported
Total (Yes)	23	15	3

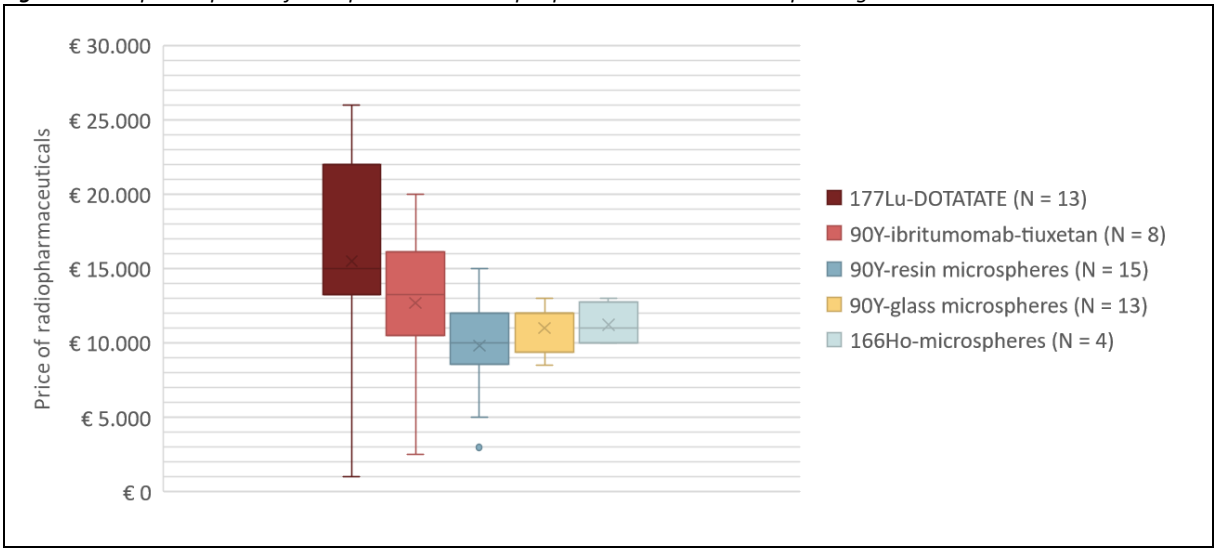
*Source: Technopolis survey and interviews. *also reported using US guidelines*

3.7 Radiopharmaceuticals prices vary, especially "high potentials"

Prices for therapeutic radiopharmaceuticals are generally not publicly available and not shared by suppliers. Only in Belgium detailed price data for radiopharmaceuticals were found online.[32] To obtain insights in the prices of radiopharmaceuticals nuclear medicine experts and professionals have been asked in the Technopolis survey to provide ranges of prices: minimum and maximum prices of the radiopharmaceutical in their countries. Based on an analysis of this data we have obtained some relevant price information on most of the radiopharmaceuticals included in this study, although not for all.

The prices of radiopharmaceuticals are negotiated by hospitals, regions or countries (e.g. by ministries). These negotiations differ per country and the outcomes are therefore different. In addition, for some countries the transport of radiopharmaceuticals is more costly due to further distance from suppliers or more expensive transporting (e.g. air transport instead of road transport). As a result, **prices of radiopharmaceuticals are different among countries for most radiopharmaceuticals**. The minimum and maximum prices that have been provided by respondents to the survey are therefore spread over a certain range (depending on the number of respondents). The results of the survey are provided in **Figure 9** and **Figure 10**.

Figure 9 *Reported prices of radiopharmaceuticals per patient dose across Europe – high end*



Source: Technopolis survey, figures are based on estimates and data, N is number of respondents

The figures show that the **among the most expensive radiopharmaceuticals are some of the highest growing radiopharmaceuticals in terms of demand**. The average price per patient dose is highest for [^{177}Lu]Lu-DOTATATE, around €18k (if only responses based on data are considered). This radiopharmaceutical, also commercially known as Lutathera®, is expected to rise in demand in the next ten years. The price of this radiopharmaceutical spans a wide range, as **some hospitals in Europe (esp. in the Netherlands) produce this medicine in-house, which results in a considerably lower price than paid to the supplying pharmaceutical company** (€4k per patient dose versus ~€23k per patient dose excl. €2.5k transport costs in the Netherlands)[33]. In the Netherlands, where [^{177}Lu]Lu-DOTATATE was developed, the Dutch minister has stimulated to continue in-hospital (magistral)

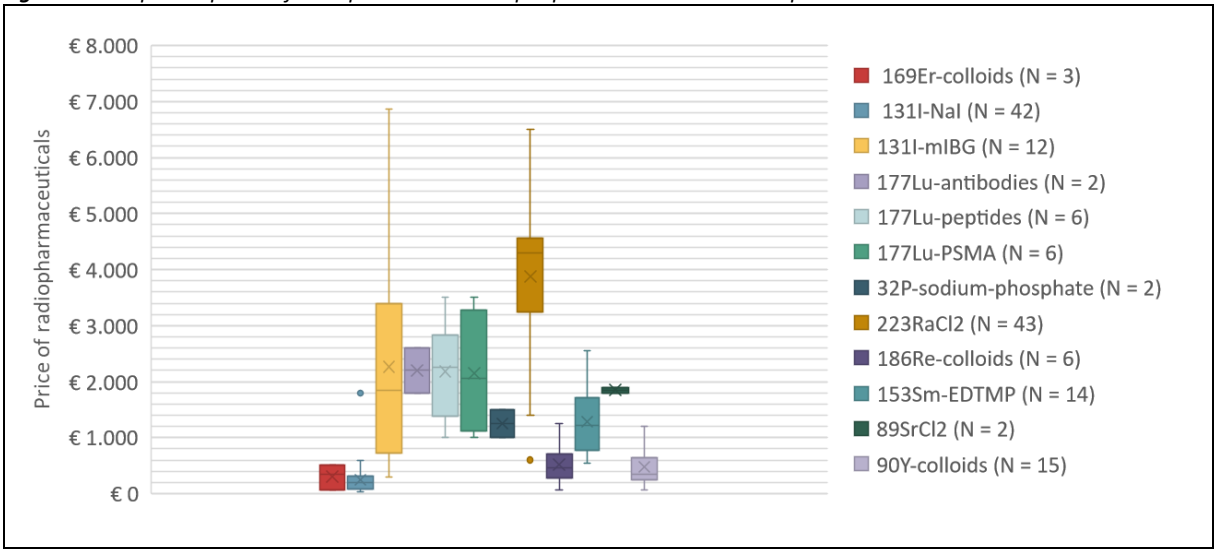
[32] Public data from RIZIV (2020), the Belgian institute for health and disability insurance. See: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/radiopharma/Paginas/vergoedbare-radiofarmaceutische-referentielijsten-referentiebestanden.aspx

[33] Lucien Hordijk (2019). *Reconstructie lutetium-octreotaat*. NTVG, 09-01-2019. See: https://www.ntvg.nl/artikelen/reconstructie-lutetium-octreotaat/volledig

preparation in response to the price difference for this radiopharmaceutical after marketing approval and orphan drug designation[34] by the EMA.[35]

Radiopharmaceuticals based on ^{90}Y- and ^{166}Ho-microspheres are also among the most expensive radiopharmaceuticals and are expected to grow in demand. The average price for these products per patient dose is between €9k-€12k. The spread in prices is lower for these medicines, though in Germany a low minimum price for [^{90}Y]Y-ibritumomab-tiuxetan was reported – which is likely due to in-hospital preparation.

Figure 10 *Reported prices of radiopharmaceuticals per patient dose across Europe – low end*



Source: Technopolis survey, figures are based on estimates and data, N is number of respondents

Most other radiopharmaceuticals are considerably lower priced, with average prices ranging between €250-€4.000 per patient dose. The radiopharmaceutical [^{131}I]-NaI is one of the oldest and cheapest radiopharmaceuticals, being a side product from the production of the commonly used diagnostic ^{99}Mo/^{99m}Tc. Prices in the same range are paid for ^{169}Er-colloids, ^{90}Y-colloids and ^{186}Re-colloids, with prices being closer to the cost of the radionuclide.

Several ^{177}Lu radiopharmaceuticals are currently priced in the mid-range, but these are not commercially on the market and still used in clinical trials (esp. [^{177}Lu]Lu-PSMA) or used compassionately. Preparation of these radiopharmaceuticals is mainly in-house, resulting in varying prices per hospital in the order of several thousand euros per patient dose. Once these products receive marketing authorisation an increase in price is to be expected. The price of the commercially available and marketed [^{223}Ra]$RaCl_2$ is on average €4k per patient dose and is thus more expensive than in-hospital prepared medicine, although priced in a somewhat similar mid-price range.

The price for the radionuclides used in these radiopharmaceuticals was hard to obtain due to confidentiality and little information was found. From the information we received, **the prices of radionuclides are in the order of several hundreds of euros per patient dose, with lower prices for ^{131}I and higher prices for the more novel therapeutic radionuclides such as ^{90}Y and ^{177}Lu**. Generally, interviewees state that the **prices for most therapeutic radionuclides are higher than prices for diagnostic radionuclides** (esp. ^{99}Mo/^{99m}Tc). Origins lie in

[34] Meaning 10 years of market exclusivity in the EU.

[35] See: https://www.tweedekamer.nl/kamerstukken/moties/detail?id=2019D17566

different production volumes, as well as in legacy prices: irradiators have become more commercial/business minded and there has been a stronger focus on full cost recovery for novel radionuclides.

In interviews, some insights have been provided in the cost structure of radiopharmaceuticals. The price of more novel radiopharmaceuticals is for roughly 10-15% related to the price of the radionuclide: irradiation, processing and margin for irradiator and processor. Which indeed suggests prices of several hundreds of euros per patient dose, but also higher. Another rough 20-25% of the price is related to the radionuclide labelling to produce the final radiopharmaceutical including margin. The remaining 70-60% of the price is related to transport, recovery of investments (incl. R&D costs), marketing of the products and margin of the radiopharmaceutical company. Radiopharmaceuticals produced in-hospital and for experimental or compassionate use are generally cheaper and have a different cost structure. For in-hospital production, expert estimates are that 50-60% of the price is attributable to the price of the radionuclide and about 20-30% to the price of the vector and the rest to other costs, such as labour costs for in-hospital preparation.

Table 5 *Average prices of radiopharmaceuticals per patient dose in Europe*

Radiopharmaceuticals	Average price per patient dose in Europe	Number of respondents from which average is calculated
[^{177}Lu]Lu-DOTATATE	€ 18.056	7
[^{90}Y]Y-ibritumomab-tiuxetan	€ 11.923	6
^{90}Y-glass microspheres	€ 11.500	5
^{90}Y-resin microspheres	€ 9.214	7
[^{223}Ra]$RaCl_2$	€ 4.041	26
[^{177}Lu]Lu-PSMA	€ 3.050	2
^{177}Lu-peptides	€ 3.050	2
^{177}Lu-antibodies	€ 2.200	2
[^{131}I]I-mIBG	€ 2.150	10
[^{153}Sm]Sm-EDTMP	€ 1.426	9
^{186}Re-colloids	€ 661	4
^{90}Y-colloids	€ 562	10
^{169}Er-colloids	€ 431	2
[^{131}I]-NaI	€ 255	27

Source: Technopolis survey, calculated from responses that were based on data (estimates excluded)

4 Supply chain capacity is becoming a pressing issue

Therapeutic radiopharmaceuticals consist of radionuclides often labelled with a carrier molecule that target specific cells (often cancer cells). Only a few radionuclides target the right cells directly, such as ^{131}I, and do not have to be labelled with a carrier molecule for the specific therapy. The production of these radiopharmaceuticals contains of several steps, which we describe in this chapter. In our description we focus on the time-sensitive ingredient of the radiopharmaceutical: the radionuclide. We first provide an overview of the general production process of the carrier molecule before we delve into specific supply chains.

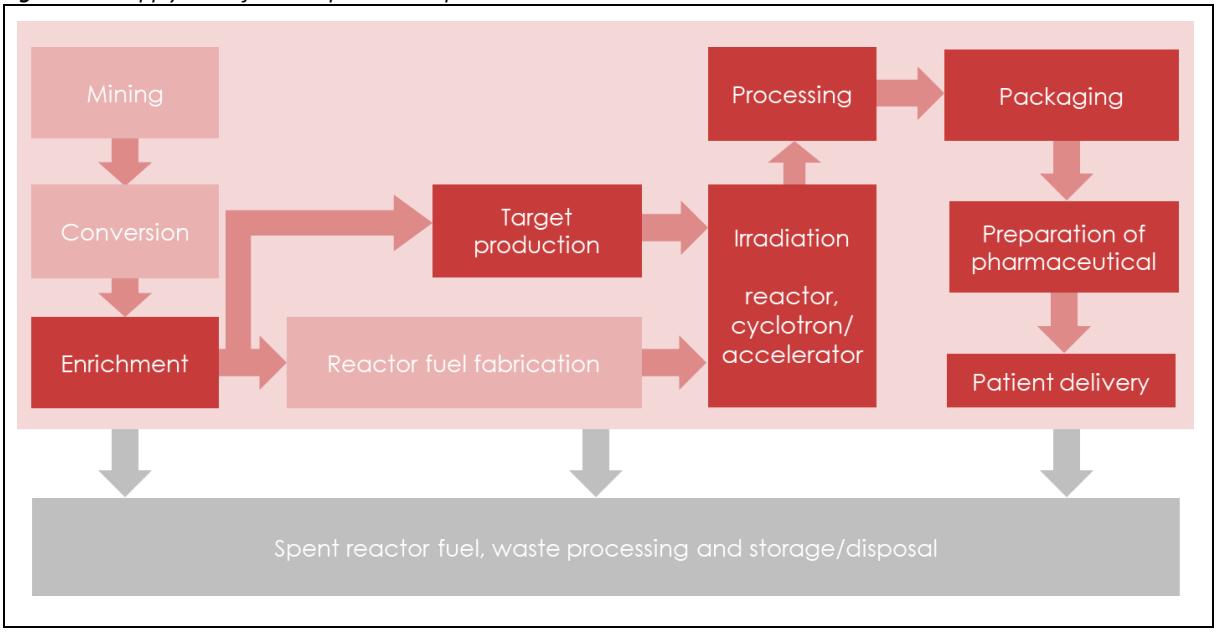
Overview of main conclusions of this chapter:

- Most therapeutic radionuclides are most effectively produced in nuclear reactors, only a few are most effectively produced in accelerators (e.g. cyclotrons).
- Currently, Europe has multiple local suppliers for most therapeutic radionuclides often used to date, an exception seems ^{223}Ra. For most long-lived therapeutic radionuclides foreign suppliers exist as well.
- Cyclotron-produced therapeutic radionuclides (e.g. ^{67}Cu and ^{211}At) have limited supply and very few suppliers in Europe, limiting research and adoption. Also, the current supply of ^{225}Ac (which could be produced in cyclotrons, but now obtained from US stockpiles) is a concern for its further development.
- For the supply of radiopharmaceuticals about 20 different suppliers have been identified, for some (generic) radiopharmaceuticals multiple suppliers exist. Radiopharmaceutical companies, especially those with a (novel) patented product, manage and protect their supply chain actively and tend to vertically integrate their supply chain to secure supply.
- In Europe, seven research reactors currently produce most therapeutic radionuclides. Their capacity to produce therapeutic radionuclides competes with capacity for their other (irradiation/research) activities.
- Most of these European research reactors that produce therapeutic radionuclides are over 50 years old. Many of them are planned to stop operations within the next 10-20 years, while there is limited potential to increase production capacity of younger installations
- Several plans for new build capacity to replace these research reactors exist, but it is uncertain whether these will be realised (in time) and can provide sufficient capacity for the variety of therapeutic radionuclides to match demand expectations. This poses a risk for the future security of supply of therapeutic radionuclides in Europe.
- Overall, the supply of therapeutic radionuclides has been reasonably stable in the past five years, although disruptions of supply do occur, mainly caused during external production or transport. This directly impacts the treatment of patients, causing delays in their treatment.
- Several critical issues and foreign dependencies exist in the supply chain. These include foreign dependencies for the supply of raw material and enrichment of LEU and stable isotopes, and issues such as ageing European irradiation capacity and uncertain future irradiation capacity.

4.1 Overview of the international radiopharmaceutical supply chain

An overview of the general supply chain for therapeutic radiopharmaceuticals is provided in **Figure 11**. This supply chain starts at the mining of the raw material for the radionuclide and ends at patient delivery in the hospital. The most important steps in the supply chain are highlighted. Between each step transport occurs. The exact processes that are performed in each step differs per radiopharmaceutical – here we describe the more general or common processes.

Figure 11 *Supply chain for therapeutic radiopharmaceuticals*



Technopolis Group, 2020

The first step is **mining** the raw material to produce the desired radionuclide. Although we do not describe this step in great detail, it is important to note that not all isotopes needed for the production of therapeutic radiopharmaceuticals are naturally abundant. For instance, rhenium is one of the scarcest materials in the earth's crust. Also, the isotopes needed for targets are sometimes only a fraction of the natural occurring material: ^{176}Lu is <3% abundant and only traces of ^{226}Ra and ^{229}Th can be found in nature as these elements have no stable isotopes[36]. Many of these materials are not mined in Europe, but imported from abroad, including uranium.

The second step is **conversion**. This process is relevant for radionuclides that are produced from enriched targets (instead of targets from materials that have sufficiently high isotopic abundance in nature). In this step the raw material is prepared for enrichment. The conversion depends on the enrichment process. For instance, for uranium, used to produce ^{131}I (among others), the uranium ore is converted to uranium hexafluoride gas that can be used for gaseous enrichment.

In the **enrichment** step, the concentration of a certain isotope is increased. Methods to separate undesired isotopes from the source material are used. These methods are based on the mass difference between isotopes, such as centrifugal separation, diffusion separation or electromagnetic separation (applied in calutrons – a type of mass spectrometers). Enrichment facilities exist in Europe (e.g. Urenco applying centrifugal separation for stable isotopes), but enrichment is also done outside Europe (e.g. Russian calutrons for ^{176}Yb enrichment).

Enrichment delivers materials that can be used for both the **fabrication of targets and reactor fuel**. The reactor fuel is generally fabricated from low enriched uranium (LEU) powder, pressed into pallets that are stacked into rods. This is only relevant for the production of radionuclides through a reactor. The target production is key to produce virtually all therapeutic radionuclides, as it is also used in accelerators (such as cyclotrons). The target is bombarded with elementary particles (electrons, protons or neutrons) or alpha particles to establish a nuclear reaction of which the product is the desired radionuclide (as the only or one of the products). This process occurs during **irradiation**. In a nuclear reactor irradiation of the target is done with neutrons (generated with the reactor fuel). In an accelerator, which can be a linear accelerator or a cyclotron, charged particles are used for irradiation

[36] CIAAW (2020). *Isotopic compositions of the elements 2019*. Available online at www.ciaaw.org.

of the target. For example, to produce ^{211}At alpha particles (positively charged) are used, while for the production of ^{67}Cu protons (positively charged) are used for irradiation. The desired product of the nuclear reactions, that are thus established in the target, remains within the target. These radionuclides need to be extracted from the target material and other (undesired) reaction products that reside within the target.

Processing is the activity in which the desired radionuclide is extracted from the target. Different methods have been established for this extraction, of which most are chemical processes. Processing can be difficult and costly. For example, the extraction of ^{177}Lu from ^{176}Yb is notoriously difficult as both have very similar chemical properties.[37] During processing the radionuclide is converted into a chemical form that allows transport and further preparation of the radiopharmaceutical. For radionuclides such as ^{212}Pb and ^{213}Bi, a generator is used: a device from which users can locally elute the desired radionuclide from a longer-lived parent radionuclide. This allows for longer transport times for short lived radionuclides.

The **radiopharmaceutical is prepared** by pharmaceutical companies or in hospital and/or commercial radiopharmacies. In this preparation the radionuclide can be chemically bound to a carrier molecule that acts as a targeting agent to specific cells in the human body. These carrier molecules are often called vectors and can – for instance – be peptides, proteins, antibodies or particles.[38] The radiopharmaceutical can be delivered in multiple forms (e.g. solution for injection, powder for in capsules) to the hospital. Radiopharmacies may use precursors, generators or kits to prepare in-house the final radiopharmaceutical.

When the radiopharmaceutical is prepared for therapy, it can be **delivered to the patient** in the hospital. This might require specific beds and facilities to safely administer radiopharmaceuticals and to deal with the radioactive waste associated with the procedure (both leftover radiopharmaceutical as well as body excretions). Routine radiopharmaceuticals, such as [^{131}I]-NaI can be administered in a wide range of hospitals, while more recent radiopharmaceuticals such as [^{177}Lu]Lu-DOTATATE, require more advanced facilities and expertise (e.g. related to waste and regulation). Treatment may require multiple injections at the hospital, spread over several weeks, such as with [^{223}Ra]$RaCl_2$ and [^{177}Lu]Lu-DOTATATE.

4.2 Production of therapeutic radionuclides

Therapeutic radionuclides are unstable isotopes that emit radiation while decaying into a stable isotope (eventually). The radiation is used for therapeutic purposes, e.g. for damaging cancerous tissue. The radiation type is often β-radiation – electrons or positrons – and sometimes α-radiation – helium nuclei, 2 protons and 2 neutrons – that consists of larger particles. In addition, γ-radiation – high energy photons – can also be produced, although these are not contributing much to the therapeutic purpose but may be used for imaging. These radionuclides generally decay within several hours or several days.

The production of these therapeutic radionuclides occurs in the irradiation phase of the supply chain after which (chemical) processing occurs to extract the radionuclide. Here we first describe the production routes of therapeutic radionuclides in the irradiation phase, which determines the technology/infrastructure needed for irradiation. Next, we describe the international context in which production occurs, highlighting the position of Europe in this part of the supply chain.

[37] A. Dash, R. Chakravarty, F.F. Knapp and A.M.R. Pillai (2015). *Indirect Production of No Carrier Added (NCA) 177Lu from Irradiation of Enriched 176Yb: Options for Ytterbium/Lutetium Separation*. Current Radiopharmaceuticals 8: 107.

[38] F.F. Knapp and A. Dash (2016). *Radiopharmaceuticals for Therapy*. New Delhi: Springer.

4.2.1 Production routes for therapeutic radionuclides

To produce these unstable therapeutic radionuclides, nuclear reactions are needed. Stable nuclides react with an elementary particle (neutrons, protons, electrons, or photons) to create the desired unstable radionuclide (as one of the reaction products). Such reactions can be created by irradiating the stable nuclide with neutrons, resulting in unstable neutron-rich radionuclides, or by irradiating with charged particles (electrons or protons), resulting in neutron-poor radionuclides. The first is typically done in nuclear reactors – but can also be achieved using spallation in accelerators – while the latter is done with linear accelerators or cyclotrons.

Sometimes no nuclear reactor or accelerator is needed. Some therapeutic radionuclides are a product of spontaneous nuclear reactions, such as ^{225}Ac. The radionuclide is then a result of the decay of another (long-living) radionuclide. An extraction method is then needed to separate the useful decay product from its parent nuclide. When the therapeutic radionuclide is chemically different from its parent, generators can be used for this separation. The therapeutic radionuclide can then be eluted from the generator.

Most therapeutic radionuclides are most effectively produced using nuclear reactors. In most cases the common/commercial production route is through the irradiation of prepared targets with neutrons in a nuclear reactor. This holds for the most widely used therapeutic radionuclides. Some of these radionuclides are indirectly produced in nuclear reactors, as they are eluted from generators. Examples are ^{212}Pb and ^{213}Bi. Sometimes also alternative production routes exist using accelerators or cyclotrons, for instance to produce ^{186}Re, ^{223}Ra or ^{225}Ac – although these are often not widely applied or still being tested.

A few therapeutic radionuclides are most effectively produced using accelerators or cyclotrons. These are ^{67}Cu and ^{211}At, which are currently not widely used.

Table 6 provides an overview of the production routes all therapeutic radionuclides that are included in this study. It indicates whether the production method leads to a carrier added (CA) product or a no-carrier-added (NCA) product, which is generally easier to process. NCA means that precautions are taken to minimise contamination with stable isotopes[39] of the element in question, resulting in a higher specific activity.[40] The table also provides some basis properties of these radionuclides, including half-life and emission.

Table 6 *Radionuclides, their properties and production routes*

Radionuclide	Production	Half-life	Emission	Remarks
^{32}P	Nuclear reactor (inefficient through cyclotron): Irradiation of ^{32}S targets	14.26d	Single β- (pure emission)	
^{47}Sc	Nuclear reactor: NCA: irradiation of enriched ^{47}Ti target (high flux, lower cost process) NCA: irradiation of enriched ^{46}Ca target (expensive process, possibility of ^{47}Ca/^{47}Sc generator)	3.35d	Multiple β- and multiple γ (imageable)	Theragnostic

[39] The difference between NCA and CA is especially relevant in the case of ^{177}Lu where the direct production route results in ^{177}Lu CA with the coproduction of ^{177m}Lu (160.1d half-life) which causes significant waste issues at hospitals (laboratory waste and waste from excretions) and additional radiation dose.

[40] A. Dash, M.R.A. Pillai and F.F. Knapp (2015). *Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options*. Nucl. Med. Mol. Imaging, 49(2). See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4463871/

Radionuclide	Production	Half-life	Emission	Remarks
^{67}Cu	Accelerator/cyclotron (most effective route): High-energy proton irradiation of natural Zn targets (typical route)	2.6d	Single β- and multiple γ (imageable)	Theragnostic
^{89}Sr	Nuclear reactor: Irradiation of highly enriched ^{88}Sr target (high flux)	50.5d	Single β- (pure emission)	
^{90}Y	Nuclear reactor: CA: irradiation of stable/natural ^{89}Y (100% abundant) target (high flux) NCA: decay of ^{90}Sr (fission product of ^{235}U in reactors) to ^{90}Y following separation from ^{90}Sr (elution from industrial generator)	64.1h	Single β- (pure emission)	
^{131}I	Nuclear reactor: CA: extraction of ^{131}I from ^{235}U fission product (by-product from ^{99}Mo production, similar processing) CA: irradiation of (enriched) ^{130}Te target	8.02d	Multiple β- and multiple γ (imageable)	Theragnostic By-product from ^{99}Mo production, the workhorse for SPECT diagnostics with ^{99m}Tc
^{153}Sm	Nuclear reactor: CA: irradiation of enriched ^{152}Sm targets	46.27h	Multiple β- and γ (imageable)	Theragnostic
^{166}Ho	Nuclear reactor: CA: Irradiation of ^{165}Ho (100% abundant) target (common route) NCA: elution of ^{166}Dy/^{166}Ho generator, with ^{166}Dy produced by irradiation of enriched ^{164}Dy with high flux (experimental, not yet available)	26.83h	Multiple β- and multiple γ (imageable)	
^{169}Er	Nuclear reactor: CA: irradiation of (enriched) ^{168}Er target (fairly scarce)	9.4d	Multiple β-	
^{177}Lu	Nuclear reactor: CA: irradiation of highly enriched ^{176}Lu targets (direct route, efficient, but contains long-lived ^{177m}Lu impurity) NCA: irradiation of ^{176}Yb targets (indirect route, requires elaborate processing)	6.65d	Multiple β- and multiple γ (imageable)	Theragnostic Direct route through 176Lu has issue of separating ^{177}Lu from ^{176}Lu: as this is difficult carrier (^{176}Lu) is still present in the final product, incl. ^{177m}Lu. This results in lower specific activity and ^{177m}Lu causes waste issues at hospitals.[41]

[41] The ^{177m}Lu impurity has a half-life of 160.1 days and will be excreted by patients. It results in an additional dose to patients and excretions that need to be stored and processed as radioactive waste. Concerns are that this waste exceeds activity limits in European radiation

Radionuclide	Production	Half-life	Emission	Remarks
				NCA will also be produced in Canadian CANDU nuclear power plants for German ITM supplier.
^{186}Re	Nuclear reactor (commonly used): CA: Irradiation of metallic enriched ^{185}Re target Accelerator/cyclotron: NCA: proton or deuteron irradiation of ^{186}W target (arising)	90.64h	Multiple β- and γ (imageable)	Theragnostic
^{188}Re	Nuclear reactor: CA: irradiation of (highly) enriched ^{187}Re target NCA: elution of ^{188}W/^{188}Re generator, with ^{188}W produced by irradiation of enriched ^{186}W in (very) high flux reactors	16.9h	Multiple β- and multiple γ (imageable)	
^{211}At	Accelerator/cyclotron: Alpha particle irradiation of natural ^{209}Bi (100% abundant) targets	7.2h	Multiple α (during therapy)	Theragnostic
^{212}Pb	Generator: Elution from ^{224}Ra/^{212}Pb generator	10.4h	Multiple β- and single γ emission of parent for ^{212}Bi (decaying in α, β- and imageable γ)	Scalable production, easier to transport due to generator, receives strong research interest in NL and FR
^{213}Bi	Generator: Elution from ^{225}Ac/^{213}Bi generator (limited availability, high costs, see also ^{225}Ac production)	45.6m	Single α, multiple β- and single γ (imageable)	Theragnostic Short half-life requires very short time-to patient Requires ^{225}Ac which has limited supply/availability
^{223}Ra	Nuclear reactor: NCA: Irradiation (high flux) of ^{226}Ra target, resulting in ^{227}Ac which days into ^{223}Ra (industrial generator) Accelerator/cyclotron: Proton irradiation of ^{232}Th (naturally abundant) target (not yet industrialised)	11.43d	Multiple α, multiple β- and multiple γ (imageable)	
^{225}Ac	Nuclear reactor: Extraction from natural decay of ^{229}Th, obtained from fissile ^{233}U, originally	10.0d	Multiple α and multiple β-	Limited supply and difficult to make, only from aged sources

safety regulations and that many regular hospitals cannot deal with this waste properly. See for instance: A. Dash, M.R.A. Pillai and F.F. Knapp (2015). *Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options*. Nucl. Med. Mol. Imaging, 49(2).

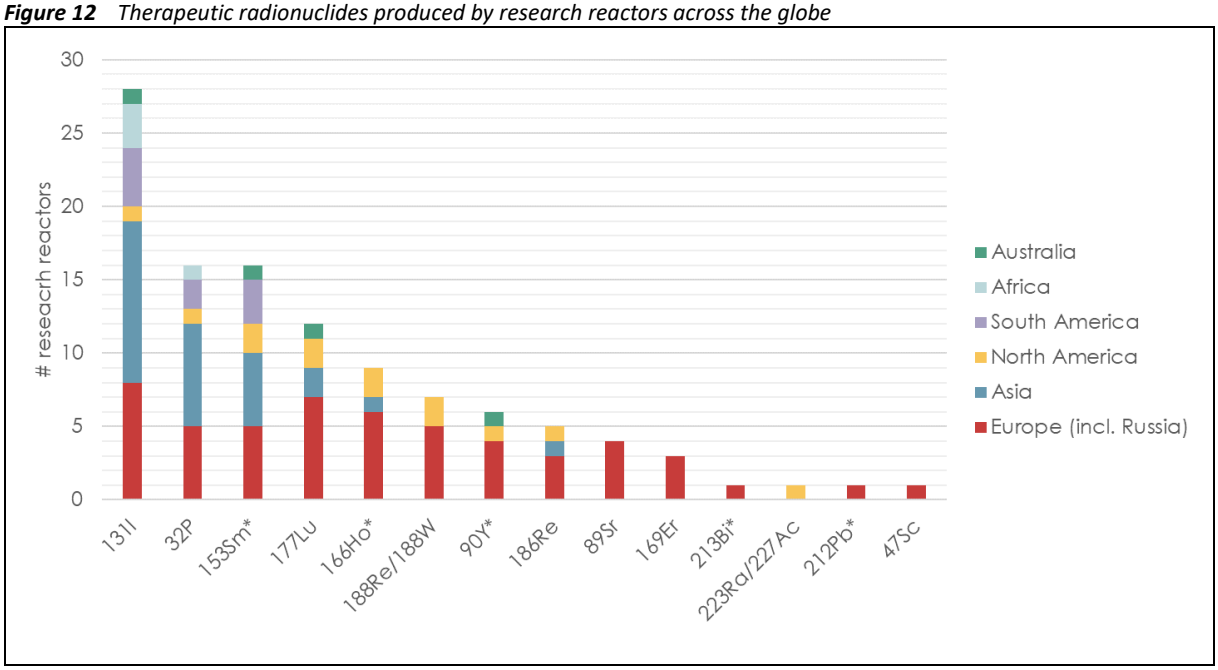
Radionuclide	Production	Half-life	Emission	Remarks
	reactor produced by irradiation of natural ^{232}Th targets (limited, too small amounts to serve market) Extraction from natural decay of ^{229}Th, obtained from ^{233}U legacy waste from US weapon programme (limited, inefficient, costly, long half-life) Accelerator/cyclotron: Proton irradiation of ^{226}Ra target (few producers)			Currently provided at no/low costs for medical research Very radiotoxic due to long half-life and multiple α's – main challenge in use
^{227}Th	Nuclear reactor: Irradiation of ^{226}Ra target	17.72d	Single α and multiple γ (imageable)	Not much produced yet, but experts say production is scalable

Source: F.F. Knapp and A. Dash (2016). Radiopharmaceuticals for Therapy. New Delhi: Springer.

4.2.2 European production of radionuclides in an international supply chain

Therapeutic radionuclides are used across the globe. The production of therapeutic radionuclides is therefore not limited to Europe but occurs in reactors and accelerators in many countries. **Figure 12** provides an overview of the number of research reactors across the globe producing specific therapeutic radionuclides. Although based on several sources, this picture is likely not fully complete, but provides some relevant insights.

Figure 12 *Therapeutic radionuclides produced by research reactors across the globe*



*Sources: IAEA RRDB (2016-2020), C.D. Ferguson, T. Kazi and J. Perera (2003), RIVM (2020) and interviewees. (*half-life less than 72h)*

First, it shows that **Europe (in contrast to other continents) has multiple local suppliers for most therapeutic radionuclides** that are commonly used, including the short-lived therapeutic radionuclides (marked in the figure with an asterisk). The latter group is not (well) suited for transport across continents. The fact that there are multiple reactors producing these radionuclides in Europe would in principle allow for diversification of supply

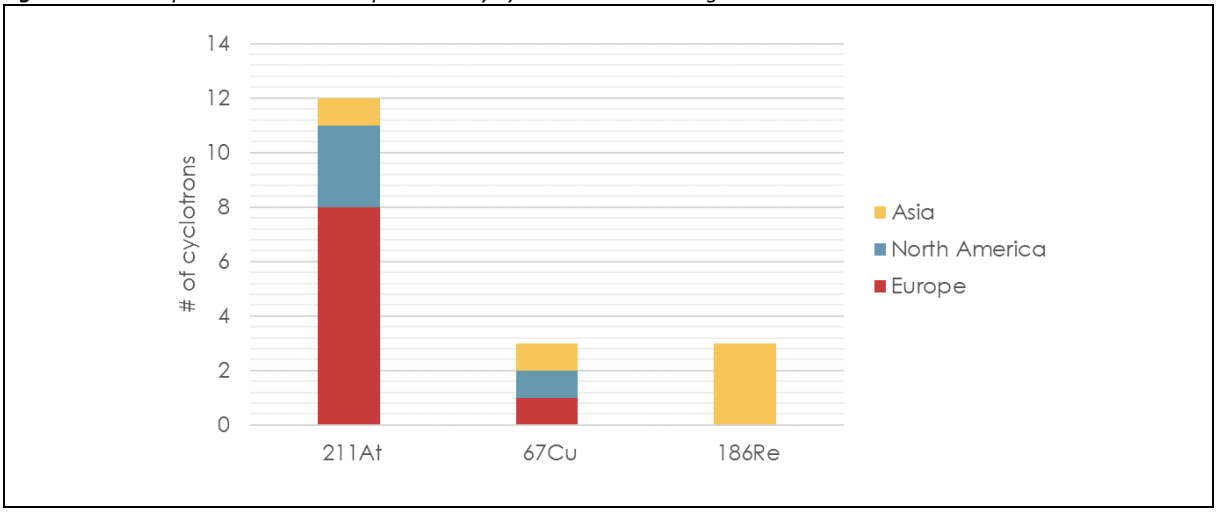
and makes the supply chain more robust. However, figures on the amount of a radionuclide supply by each of the reactors, and to whom they supply for what use, is not clear.

Second, **for most long-lived therapeutic radionuclides foreign (non-European) suppliers exist**. This would in principle allow for international transport of therapeutic radionuclides to Europe. For some therapeutic radionuclides, specifically ^{177}Lu and ^{223}Ra, we know such international transport exists. For the latter, no European source was disclosed. Whether transport of other long-lived therapeutic radionuclides to Europe would occur, depends on contracts with pharmaceutical companies, excess of supply for local use – on which we do not have data – and economic factors such as price and demand.

Lastly, we note that **the most produced therapeutic radionuclide worldwide is** ^{131}I, which is one of the most established radionuclides in medicine. It is produced in research reactors in every continent and generally linked to the production of the diagnostic ^{99}Mo/^{99m}Tc pair – of which supply is actively monitored and coordinated (e.g., through the OECD NEA and the EU Observatory). Currently **not so widely produced therapeutic radionuclides are** ^{89}Sr**,** ^{169}Er**,** ^{213}Bi **(experimental use),** ^{223}Ra **and** ^{212}Pb **(experimental use)**. For some we could only identify one or two suppliers worldwide, which may in practice be more, but nonetheless signals a weaker supply chain in terms of diversity of supply.

For the therapeutic radionuclides produced in accelerators no up-to-date information was available. These radionuclides are novel and not routinely applied in clinical practice. Based on the IAEA's 2006 Directory of Cyclotrons used for Radionuclide Production in Member States[42], some insights are available, although outdated. Nevertheless, **Figure 13** provides an overview of the number of cyclotrons listed by the IAEA as producer of ^{67}Cu, ^{211}At, and ^{186}Re.

Figure 13 *Therapeutic radionuclides produced by cyclotrons across the globe*



Source: IAEA (2006). Directory of Cyclotrons used for Radionuclide Production in Member States: 2006 Update. IAEA: Vienna. Report number: IAEA-DCRP/2006.

For ^{211}At, there are likely multiple sources available in Europe, while for ^{67}Cu and ^{186}Re no current sources are available in Europe. Still, ^{211}At **is reported as being only limited available, which is considered as the most important barrier to the clinical use of** ^{211}At**.** Several cyclotrons installed are capable of producing ^{211}At, also in Europe. Copenhagen University Hospital and Arronax in France have been reported as pursuing production of

[42] IAEA (2006). *Directory of Cyclotrons used for Radionuclide Production in Member States: 2006 Update*. IAEA: Vienna. Report number: IAEA-DCRP/2006. See: https://www-pub.iaea.org/MTCD/Publications/PDF/dcrp2006-cd/start.pdf

^{211}At at a regular basis in Europe, several sites in Japan and two in the USA are reported as having similar ambitions.[43]

The availability of ^{67}Cu is very limited, with only a few producers outside Europe, and has been reported as limiting its potential use.[44] There have been issues with steady supply, acquiring sufficient amounts for clinical studies and high costs.[45] No current source for ^{67}Cu could be identified in Europe, although the Paul Scherrer Institute (Swiss) previously produced ^{67}Cu for research purposes. This activity has however halted over a decade ago and cannot be scaled for commercial use, as the IP2 Irradiation station is only used for about 9 months/year.[46]

The therapeutic radionuclide ^{186}Re is produced with cyclotrons in Asia. In Europe several reactors produce this radionuclide, as well as in Asia and North America.

4.3 Specific European supply chains

The supply chain for each therapeutic radiopharmaceutical is completely different. On a conceptual level, as discussed in section 4.1, the components of the supply chain are identical, but the organisations involved, the resources, processes and equipment needed are different. Therefore, in fact, we have to consider multiple supply chains: one for each therapeutic radionuclide.

Here we consider the radionuclide specific supply chains in Europe, zooming in on the most relevant and time-sensitive phases of the supply chain: irradiation, processing and preparation of the radiopharmaceutical. We identify the producers and processors of therapeutic radionuclides in Europe and the radiopharmaceutical producers and suppliers.

4.3.1 Suppliers for radionuclides and radiopharmaceuticals

The supply chain for the therapeutic radionuclides included in this study is further detailed in **Table 7**. For each radionuclide and associated radiopharmaceutical(s) we have indicated the main organisations in Europe that produce (irradiate) and/or process the radionuclide and that produce/supply the radiopharmaceutical.

For the most used radiopharmaceuticals suppliers across Europe were identified, resulting in a list of **almost 20 different suppliers of radiopharmaceuticals**. For the more recent therapeutic radiopharmaceuticals only the patent holder supplies the radiopharmaceutical. Examples are AAA/Novartis supplying [^{177}Lu]Lu-DOTATATE, Bayer supplying [^{223}Ra]$RaCl_2$ and Boston Scientific supplying ^{90}Y-glass microspheres. **For most other (generic) therapeutic radiopharmaceuticals multiple suppliers exist in Europe**. Especially for ^{131}I pharmaceuticals there is a diversity of suppliers available. Suppliers for novel or still experimental radiopharmaceuticals, such as ^{213}Bi and ^{211}At, could not be identified. We expect that these radionuclides are generally prepared/labelled within the hospital.

On the level of radionuclide producers and processors about 20 different suppliers of radionuclides were identified across the continent. For each radionuclide multiple producers and processors exist in Europe. The

[43] S. Lindegren et al. (2020). *Realizing Clinical Trials with Astatine-211: The Chemistry Infrastructure*. Cancer Biotherapy & Radiopharmaceuticals, 35 (6). See: https://doi.org/10.1089/cbr.2019.3055

[44] T. Ohya et al. (2018). *Small-scale production of ^{67}Cu for a preclinical study via the ^{64}Ni(α,p)^{67}Cu channel*. Nucl. Med. Biol, 59. See: https://pubmed.ncbi.nlm.nih.gov/29475187/

[45] N.A. Smith, D.L. Bowers and D.A. Ehst (2012). *The production, separation, and use of ^{67}Cu for radioimmunotherapy: A review*. Applied Radiation and Isotopes, 70. See: http://dx.doi.org/10.1016/j.apradiso.2012.07.009

[46] N.P. Van der Meulen et al. (2019). *The use of PSI's IP2 beam line towards exotic radionuclide development and its application towards proof-of-principle preclinical and clinical studies*. 22nd Int. Conf. on Cyclotrons and their Applications. See: http://accelconf.web.cern.ch/cyclotrons2019/papers/tua03.pdf

only exception is ^{223}Ra where no European supplier could be identified/disclosed. Bayer is the only supplier of the ^{223}Ra-based radiopharmaceutical and has secured supply for 10 years from the USA. The irradiators among this list are all research reactors. Processors are often the same organisations as the radiopharmaceutical producer/supplier or are affiliated with them or the irradiator.

Interviews reveal that radiopharmaceutical companies have vertically integrated supply chains in Europe to secure the supply of radionuclides for their products as much as possible. They have long-term contracts with suppliers ensuring delivery of radionuclides matching their demand projections. Where possible, radionuclides are produced as close as possible to the customer, to reduce transport and thus loss of product (activity). Supply is diversified to limit risks and backups are created in the supply chain, the specifics of which are not disclosed.

Table 7 *Suppliers of radionuclides and radiopharmaceuticals in Europe*

Radionuclide	Radiopharmaceutical	Radionuclide producer/ processor	Radiopharmaceutical producer/ supplier	Comments
^{32}P	^{32}P-sodium-phosphate ([^{32}P]-Na_3PO_4)	POLATOM (PL) BRR (HU)	Curium Pharma GE Healthcare	
^{47}Sc	^{47}Sc	Institut Laue-Langevin (FR)	Unknown: likely hospital preparation as still experimental	
^{67}Cu	^{67}Cu	unknown	Unknown: likely hospital preparation as still experimental	Accelerator produced Has in the past been produced by the Paul Scherrer Institute (Swiss)
^{89}Sr	[^{89}Sr]$SrCl_2$	POLATOM (PL) SCK-CEN (BE)	GE Healthcare MGP POLATOM	Commercial name: Metastron®
^{90}Y	^{90}Y-colloids	POLATOM (PL) - precursor NRG (NL) SCK-CEN (BE) BRR/IZOTOP (HU)	Curium Pharma/CIS Bio GE Healthcare	CIS Bio also supplies ^{90}Y-precursor under the commercial name Ytracis®
	^{90}Y-glass microspheres		Boston Scientific	NRG irradiator for Boston Scientifc Commercial name: TheraSphere®
	[^{90}Y]Y-ibritumomab-tiuxetan		Bayer Curium Pharma Eckert & Ziegler IBA	Commercial name: Zevalin® Eckert & Ziegler also supplies ^{90}Y-precursor under the commercial name Yttriga®
	^{90}Y-resin microspheres		Sirtex Medical Curium Pharma	Commercial name: SIR-Spheres® (SIRT)
^{131}I	[^{131}I]I-mIBG	POLATOM (PL)	GE Healthcare	

Radionuclide	Radiopharmaceutical	Radionuclide producer/ processor	Radiopharmaceutical producer/ supplier	Comments
		SCK-CEN (BE) IRE (BE)	Curium Pharma POLATOM	
	[^{131}I]-NaI	BRR/IZOTOP (HU) CVŘ Řež (CZ)	GE Healthcare Curium Pharma IZOTOP POLATOM Monrol Europe	
^{153}Sm	[^{153}Sm]Sm-EDTMP	POLATOM (PL) SCK-CEN (BE) BBR/IZOTOP (HU) CVŘ Řež (CZ)	Curium Pharma/CIS Bio GE Healthcare	Commercial name: Quadramet®
^{166}Ho	[^{166}Ho]Ho-chitosan	NRG (NL) ITM/FRMII (DE) POLATOM (PL) BRR/IZOTOP (HU) CVŘ Řež (CZ)	Unknown	
	[^{166}Ho]Ho-DOTMP		Unknown	
	^{166}Ho-microspheres (HoMS)		Quirem Medical/Terumo Europe	NRG irradiator for Quirem Medical Commercial name: QuiremSpheres®
^{169}Er	^{169}Er-colloids	NRG (NL) CVŘ Řež (CZ) Institut Laue-Langevin (FR)	Curium Pharma	
^{177}Lu	^{177}Lu-antibodies	POLATOM (PL) – CA, precursor NRG (NL) SCK-CEN (BE) FRMII/ITM (DE) – NCA BRR/IZOTOP (HU) Eckert & Ziegler (DE, GMP in 2021) CVŘ Řež Institut Laue-Langevin (FR)	ITM Nordic Nanovector	NRG largest producer of ^{177}Lu in Europe ITM and Monrol Europe also provide the precursor ^{177}Lu-Cl_3 for hospitals Commercial names: Betalutin® (antibodies), EndolucinBeta® and Luthatera® (DOTATATE)
	[^{177}Lu]Lu-DOTATATE		AAA/Novartis	
	^{177}Lu-peptides		ITM	
	[^{177}Lu]Lu-PSMA		ITM in collaboration with Edocyte/Novartis	
^{186}Re	^{186}Re-colloids	POLATOM (PL) SCK-CEN (BE) CVŘ Řež (CZ) NRG (NL)	Curium Pharma/CIS BIO	
^{188}Re	^{188}Re	POLATOM (generator) (PL) SCK-CEN (generator) (BE)	Curium Pharma	Commercial name: Rhenium-SCT® Requires very high flux, therefore few
	[^{188}Re]Re-HEDP		Curium Pharma	

Radionuclide	Radiopharmaceutical	Radionuclide producer/ processor	Radiopharmaceutical producer/ supplier	Comments
		CVŘ Řež (generator) (CZ)		irradiators available
^{211}At	^{211}At	NPI Řež cyclotron (CZ) University Hospital Copenhagen (DK) CNRS/CERI (FR) Forschungszentrum Karlsruhe cyclotron (DE) Medizinische Hochschule Hannover cyclotron (DE) JRC IHCP Ispra cyclotron (IT) HNIP cyclotron Krakow (PL)	Unknown: likely hospital preparation as still experimental	Accelerator produced Production seems limited, not only produced for medical applications Only some have limited routine production Radionuclide producer information from 2006 (IAEA), no recent information available
^{212}Pb	^{212}Pb	NRG (NL) – production Orano Med (FR)	Orano Med/Roche	In development, not clinical practice Easy transport as can be sold as generator
^{213}Bi	^{213}Bi	JRC Karlsruhe (DE)	Unknown: likely hospital preparation as still experimental and very short half-life	Supply limited due to limited ^{225}Ac supply, currently not possible to enlarge supply
^{223}Ra	[^{223}Ra]$RaCl_2$	IFE (NO) Supply from abroad, only disclosed source: Oakridge National Laboratory, part of US DOE	Bayer (NO)	IFE in Kjeller prepares product for Bayer Bayer has 10-year supply contract of ^{227}Ac for production with US DOE Commercial name: Xofigo®
^{225}Ac	[^{225}Ac]Ac-Lintuzumab	JRC Karlsruhe (DE) Eckert&Ziegler (DE) Rest of suppliers abroad in US and Russia	Unknown: likely hospital preparation as still experimental	Not used in EU
	[^{225}Ac]Ac-PSMA		Unknown: likely hospital preparation as still experimental	Only supply for several hundred patients Limited supply worldwide, strong interest from producers, several studies for alternative

Radionuclide	Radiopharmaceutical	Radionuclide producer/ processor	Radiopharmaceutical producer/ supplier	Comments
				production routes, supply less than demand, expected to grow, currently only compassionate use in EU
^{227}Th	^{227}Th-antibody	Irradiator unknown	Bayer (NO)	^{227}Th is obtained from the same source as ^{223}Ra
	^{227}Th-conjugate	Eckert&Ziegler (DE)		
	[^{227}Th]Th-PSMA			

Based on multiples sources: websites and documents of producers, information received for country factsheets, IAEA databases for research reactors and cyclotrons, reports and this study's survey

4.3.2 Characteristics of the supply chain before irradiation and during transport

The supply chain before irradiation is less time-critical, as the activity of the desired product is not yet decaying in this phase. In many cases the used raw material is a stable isotope, so that time is no longer a limiting factor. Therefore, usually the supply chain is analysed from irradiation and beyond. The supply chain before irradiation is very international.

As part of their vertically integrated supply chain, **pharmaceutical companies manage the supply chain actively**. Irradiators are in many cases service providers, who get their targets for radionuclide production delivered from the radiopharmaceutical company**. Strategic reserves of the enriched target material are created to ensure production continuity, but also to set competition aside**. As an example of the latter, 99% enriched ^{176}Yb has been bought from the market for several years by one of the pharmaceutical companies delivering ^{177}Lu radiopharmaceuticals to strengthen its competitive position.

Enrichment and fabrication of the target material and the nuclear fuel is in part done in Europe. Orano enriches uranium (reactor fuel and target material for ^{131}I) in France and Urenco in the Netherlands and UK. Urenco also enriches several stable isotopes for medical applications. The latter is done in the Netherlands by the Urenco Stable Isotopes subsidiary, producing for instance ^{186}W (for ^{188}Re production) and ^{47}Ti (for ^{47}Sc production).[47] However, about 40% of the world's production of stable isotopes is from Russia, using old calutrons.[48] **Russia is the go-to supplier for "difficult-to-source" stable isotopes and the only producer of enriched** ^{176}Yb (by the Electrokhimprebor and Kurchatov Institute, sold by JSC Isotope from ROSATOM). These calutrons are built during and shortly after the Second World War and need to be replaced within one or two decades.[49] Information on initiatives for replacements of such equipment, e.g. ROSATOM's and US Oak Ridge Laboratory's plans to use gas centrifuge to produce such stable isotopes, is scarce and not up to date.[50]

In addition to enrichment for stable isotopes, Europe also relies on the US and Russia for high-assay low-enriched uranium (HALEU) that is used as fuel in research reactors. HALEU is obtained from Russia or from down-blending

[47] Urenco (2019). *Urenco Stable Isotopes Brochure*. See: https://www.urenco.com/cdn/uploads/supporting-files/Urenco_Stable_Isotopes_brochure_2019.pdf

[48] NSAC Isotopes Subcommittee (2015). *Meeting Isotope Needs and Capturing Opportunities for the Future: The 2015 Long Range Plan for the DOE-NP Isotope Program*. See: https://www.asc.ohio-state.edu/physics/ntg/6805/readings/2015_NSACI_Report_to_NSAC_Final.pdf

[49] L.P. Roobol and I.R. de Waard (2019). *Marktontwikkeling en leveringszekerheid voor medische radionucliden*. RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2019-0101.pdf

[50] NIDC (2019). *ORNL's Enriching Isotopes Again*. See: https://www.isotopes.gov/node/335

US' highly-enriched uranium stocks. A recent ESA-report[51] highlights the risk that foreign supply of HALEU cannot be guaranteed beyond 2030-2040, impacting medical radionuclide production.

The French Orano is involved in the fuel mining and conversion. **Mining activities are not done within Europe**, but in North America, Middle East and Africa.[52] For most raw materials used for fuel and targets Europe relies on mining in other continents. The conversion of Uranium is done by Orano in France.[53]

The produced radionuclides in Europe are transported by specialised companies. Transport needs to be efficient and is bound by regulations. **Europe has at least 16 specialised transporters across Europe to timely distribute radionuclides to hospitals in Europe and beyond.**[54] Transport requires just in time delivery and therefore uses both road transport as well as air transport. Special regulations and administration exists to regulate safe and timely transport and to prioritise medical radionuclides in air transport (using mainly cargo flights but also passenger fights).[55,56]

4.4 Production capacity for therapeutic radionuclides in Europe

4.4.1 Installed production and processing capacity

Although most therapeutic radionuclides are produced in nuclear reactors, **only a limited number of nuclear reactors produce therapeutic radionuclides**. Unlike nuclear power plants for energy, there are currently no single-purpose nuclear reactors to produce radionuclides. Commercial production of radionuclides occurs in research reactors, which are also used for several other research or industrial applications.[57] **The capacity to produce therapeutic radionuclides in these research reactors thus competes with capacity for other (irradiation/research) activities**, including the production of diagnostic radionuclides (larger market). However, depending on the production route and irradiation cycle, different instruments within the reactor are needed – this determines in practice the current production capacity. Increasing production capacity for a specific radionuclide thus not only requires changing production schedules, but also instruments (i.e. reactor set-up) – the latter can be a major process taking several years.[58]

The radioactive decay of therapeutic radionuclides results in a short shelf-life of the radionuclide and the radiopharmaceutical. The time to patient should therefore be optimised. Distance and transport are crucial factors in optimising the time to patient. Therefore, only radionuclides with a half-life of several days, or that can be eluted from generators, are suitable for transport across continents. **Production in Europe for European patients is thus clearly beneficial**.

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[51] Euratom Supply Agency (2019). *Securing the European Supply of 19.75% enriched Uranium Fuel. A revised Assessment*. May 2019. See: https://ec.europa.eu/euratom/docs/ESA_HALEU_report_2019.pdf

[52] Orano Website (2020). See: https://www.orano.group/en/nuclear-expertise/orano's-sites-around-the-world/uranium-mines

[53] Orano Website (2020). See: https://www.orano.group/en/nuclear-expertise/orano's-sites-around-the-world/uranium-transformation

[54] European Isotopes Transport Association (2020). See: http://www.eita.org/members

[55] J.S. Hughes and S.J. Watson (2004). *A survey of the transport of radioactive materials by air to, from and within the UK*. PATRAM 2004, Berlin. See: https://inis.iaea.org/collection/NCLCollectionStore/_Public/37/088/37088554.pdf?r=1&r=1

[56] EITA (2016). *The transport of radiopharmaceuticals – a race against the clock*. See: https://www.youtube.com/watch?v=qUoSA0WSJZw&t

[57] A recent and notable exception (October 2020) are the CANDU reactors of Bruce Power in Canada that will have an Isotope Production System installed during ongoing life-extension works of the reactors. After installation, these reactors will produce ^{177}Lu NCA for ITM (worldwide distribution) starting 2022. According to experts interviewed, only this type of CANDU reactors would be suitable for radionuclide production. See: https://www.brucepower.com/2020/10/29/agreement-signed-to-advance-lutetium-177-isotope-production-to-meet-global-demand-for-critical-cancer-fighting-therapies/

[58] As indicated by interviewees and as the case of Bruce Power in footnote 57 shows (addition of instruments during life-extension works, planned already several years before).

In Europe seven research reactors currently produce most therapeutic radionuclides[59]. These are:

- The MARIA (1974) reactor in Poland, operated by POLATOM
- The HFR (1961) in the Netherlands, owned by the EC/JRC and operated by NRG
- The BR2 (1961) in Belgium, operated by SCK-CEN
- The FRMII (2004) in Germany, operated by the Technical University of Munich
- The ILL (1971) reactor in France, operated by Institute Laue-Langevin
- The LVR-15 (1957) in the Czech Republic, operated by CVŘ Řež
- The BRR (1959) in Hungary, operated by BNC/AEKI

In addition, the JRC in Karlsruhe (Germany) supplies some alpha emitters for (pre-)clinical trials and research use.

Figure 14 provides an overview of the therapeutic radionuclides[60] that are produced by these research reactors in Europe. The figure contains information collected from several sources but may not be fully complete. Also, some reactors may not routinely produce a therapeutic radionuclide, as is for instance the case with the production of ^{177}Lu in the LVR-15. Also, these reactors are only a limited number of days (between 100-270) each year available for irradiation services.[61]

The figure shows that **many of the therapeutic radionuclides considered in this study are produced in Europe**, especially those that are commonly applied in clinical practice. The only exception is ^{223}Ra for which no European source was found in available data. For the more novel therapeutic radionuclide ^{227}Th also no European supplier could be identified, while for the novel/experimental therapeutic radionuclides ^{47}Sc, ^{212}Pb, ^{213}Bi and ^{225}Ac only one supplier could be identified among these reactors. For the other therapeutic radionuclides multiple suppliers seem to exist in Europe, although it is unclear what their production capacity is for each radionuclide.

Figure 14 *Radionuclides produced by current research reactors in Europe*

MS	RN Supplier	32P	47Sc	89Sr	90Y	131I	153Sm	166Ho	169Er	177Lu	186Re	188Re	212Pb	213Bi	223Ra	225Ac	227Th	
BE	BR-2 Reactor			■	■	■	■			■	■	■						7
CZ	LVR-15 Reactor					■	■	■	■	■	■	■						7
FR	ILL Reactor		■						■	■		■						4
DE	FRM II Reactor							■		■								2
	JRC													■		■		2
HU	BRR Reactor	■			■	■	■	■		■								6
IT	TRIGA RC-1							■										1
NL	HFR			■	■			■	■	■			■					6
PO	MARIA	■		■	■	■	■	■		■	■	■						9
RO	TRIGA II Pitesti					■												1
		2	1	3	4	5	4	6	3	7	3	4	1	1	0	1	0	

IAEA RRDB (2016/2020), C.D. Ferguson, T. Kazi and J. Perera (2003), RIVM (2020) and interviewees.

Most of the research reactors that produce therapeutic radionuclides in Europe are over 50 years old. The only exception is the FRMII reactor, which only produces a limited amount of therapeutic radionuclides (^{177}Lu and ^{166}Ho). The other reactors – including the largest radioisotope producers MARIA, BR2 and HFR – reach their end of lifetime within the next 10-20 years. The expected end of operation for the BRR is 2023, for the HFR 2026, for the LVR-15 2028, for MARIA 2040 and the BR2 will at least be operational until 2026 but is investigating the

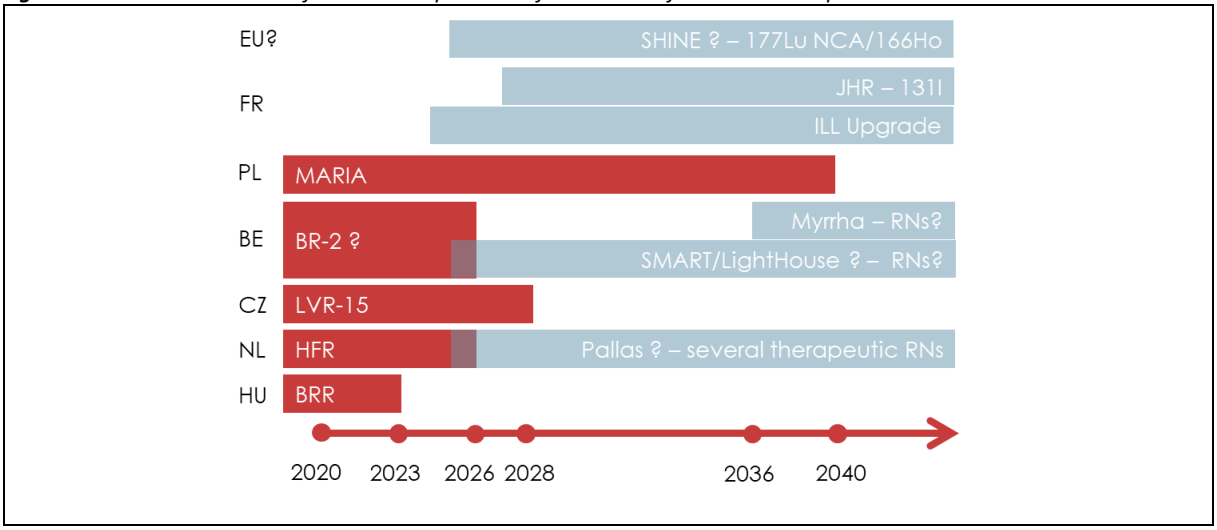
[59] IAEA (2020). *Research Reactor Database*. See: https://nucleus.iaea.org/RRDB/RR/ReactorSearch.aspx

[60] The radionuclides ^{67}Cu and ^{211}At, which are not produced with reactors, are not included in the figure.

[61] For example, the HFR has 270 days or operation, FRMII 240 days, MARIA 200 days, BR2 147 and ILL 100 days. Source: L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020*. RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

possibility to operate until 2036.[62] This means that **most of the radionuclide producers in Europe will stop operations, even within the next 10 years** (cf. **Figure 15**), if the lifetime of these facilities will not be extended or when these facilities will not be replaced.

Figure 15 *Timelines of current and planned infrastructures for radionuclide production in the EU*



Based on websites of infrastructures, information from representatives and OECD NEA (2019)

4.4.2 Planned production and processing capacity

As most European research reactors producing therapeutic radionuclides are ageing, new production facilities are being planned. Most of these facilities are intended to take over the activities of current research reactors. Apart from new facilities, replacing the current fleet, existing facilities can to some extent increase the supply of some therapeutic radionuclides.

Currently, **three new research reactors are being planned in Europe** (cf. **Figure 15**)**.** These are the MYRRHA reactor (scheduled to be operational in 2036)[63] to replace the BR2 in Belgium and the Pallas reactor (scheduled to be operational in 2025)[64] to replace the HFR in the Netherlands. Both plan to produce therapeutic radionuclides – for Pallas this is even a major part of its business case – but construction has not yet started. The only research reactor that is currently being built in Europe, and that plans to produce medical radionuclides, is the Jules Horowitz Reactor (JHR/RJH) in France. However, the JHR is planning to produce ^{131}I only – there are no concrete plans to produce other therapeutic radionuclides (although this is possible and not explicitly excluded).[65] The focus of the JHR will be on research.

In addition, **some novel concepts are planned – and currently being piloted – to produce therapeutic radionuclides**. One of these is ASML's and IRE's SMART/LightHouse project in Belgium, where a high-power superconducting linear electron accelerator is used to produce radionuclides. Another is SHINE, a US initiative that is planning to build a plant in Europe, where an accelerator-based neutron source is used to produce

[62] Several sources, including OECD NEA (2019). *The supply of Medical Radioisotopes. 2019 Medical Isotope Demand and Capacity Projection for the 2019-2024 Period*. See: https://www.oecd-nea.org/jcms/pl_19912/2019-medical-isotope-demand-and-capacity-projection-for-the-2019-2024-period

[63] Website MYRRHA (2020): https://www.myrrha.be/myrrha-project/myrrha-phased-implementation/

[64] Website Pallas (2020): https://www.pallasreactor.com/en/en-pallas-van-levensbelang-voor-miljoenen/

[65] L.P. Roobol and I.R. de Waard (2019). *Marktontwikkeling en leveringszekerheid voor medische radionucliden. RIVM*. DOI: 10.21945/RIVM-2019-0101.

radionuclides. Both are focussed on the production of the diagnostic radionuclide ^{99}Mo but explore or plan the production of therapeutic radionuclides.

Foreseen new production capacity or extension of current production capacity (cf. **Figure 15**)**:**

- **Pallas reactor in the Netherlands (Petten)**: a research reactor that is planned to replace the current HFR, with a strong focus on the production of diagnostic and therapeutic radionuclides. The key radionuclide that will be produced is the diagnostic ^{99}Mo/^{99m}Tc. Other radionuclides planned, include the therapeutic ^{177}Lu, ^{131}I, ^{166}Ho, ^{153}Sm and ^{89}Sr. Pallas is still evaluating the potential production of ^{188}Re and ^{186}Re.[66] Pallas is still in a preparatory phase and should be the first privately financed research reactor. Recently the Dutch government has indicated that this ambition is not realistic, and that public financing may be needed or even extension of the lifetime of the HFR.[67] There has been no final decision on the build of Pallas, but officially Pallas is scheduled for operations in 2025.
- **Myrrha reactor in Belgium (Mol)**: is an innovative research reactor that consists of a subcritical nuclear reactor driven by a high-power linear accelerator as external neutron source. It thus consists of a nuclear reactor and a linear accelerator. Myrrha will be used to produce ^{99}Mo, taking over the role of the BR2. In addition, the reactor and accelerator will be used to produce other radionuclides as well, including therapeutic radionuclides – although which ones are not specified.[68] Myrrha is planned to start operations in 2036.
- **Jules Horowitz Reactor in France (Cadarache)**: The JHR is currently being built by an international consortium mainly for research purposes, but also plans to produce Uranium-based medical radionuclides.[69] This will be primarily the diagnostic pair ^{99}Mo/^{99m}Tc, but also the therapeutic radionuclide ^{131}I will be produced. There are no concrete plans to produce other radionuclides, although this option is reported to be not excluded.[70] JHR is planned to start operations between 2026 and 2028.
- **SMART/LightHouse in Belgium (Fleurus)**: Based on technology that spun-off from ASML, a novel accelerator-based facility to produce radionuclides is developed in Belgium. A high-power superconductive linear electron accelerator is used to produce primarily ^{99}Mo. Lighthouse is however investigating the possibility to produce therapeutic radioisotopes; it is unclear which exactly.[71] Commercial production of ^{99}Mo should start in 2025.[72]
- **SHINE in US/Europe**: Shine is currently testing and preparing a novel accelerator-based concept to produce medical radionuclides in the US and plans to build a plant in Europe (Groningen, The Netherlands is named as a potential location). The focus is on the production of ^{99}Mo through a low-energy accelerator-based neutron source using a liquid lowly enriched uranium target. SHINE is also producing ^{177}Lu NCA, where they claim to control the whole supply chain, including own enrichment of ^{176}Yb and processing of the targets.[73] SHINE does this in cooperation with GE Healthcare and the Czech Institute of Organic Chemistry and Biochemistry. Supply started in 2020. Additionally, SHINE plans to produce ^{131}I and ^{90}Y using the ^{99}Mo facility

[66] PWC (2018). *PALLAS/LightHouse Review*. Extract of final report.

[67] Dutch Ministry of Health, Welfare and Sport (2020). *Kamerbrief over stand van zaken Pallas-reactor. 9 December 2020*. See: https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2020/12/09/kamerbrief-over-stand-van-zaken-pallas-reactor/kamerbrief-over-stand-van-zaken-pallas-reactor.pdf

[68] Website MYRRHA (2020): https://www.myrrha.be/science-and-myrrha/nuclear-medicine/

[69] JHR/CEA website (2020): http://www-rjh.cea.fr/radio-isotopes.html

[70] L.P. Roobol and I.R. de Waard (2019). *Marktontwikkeling en leveringszekerheid voor medische radionucliden. RIVM*. DOI: 10.21945/RIVM-2019-0101.

[71] PWC (2018). PALLAS/LightHouse Review. Extract of final report.

[72] IRE (2019). *The SMART project: accelerator based production of Mo-99*. Presentation. See: https://ec.europa.eu/energy/sites/ener/files/documents/s1-3_ekollegger_ire.pdf

[73] SHINE website (2020): https://shinemed.com/177Lu/

and intends to install additional irradiation ports for neutron activation, planning to produce ^{177}Lu and ^{166}Ho.[74] SHINE also claims to investigate ^{225}Ac production. The commercial operation of the shine plant in the US is planned for 2022, while construction of the European plant is planned for 2023 with operations starting 2025.[75]

- **Institut Laue-Langevin in France (Grenoble)**: At the ILL reactor a new irradiation system is developed that should be operational in 2024.[76] This would enlarge the capacity to produce therapeutic radionuclides at the ILL reactor.
- **Bruce Power CANDU reactors in Canada**: the German ITM is currently working with Bruce Power to produce ^{177}Lu in their CANDU nuclear power plants. These reactors will be upgraded and receive an Isotope Production System to produce ^{177}Lu NCA that will be supplied to ITM for global distribution. With this upgrade the production of ^{177}Lu should start in 2022.[77]

In addition, the **European Spallation Source (ESS) in Sweden (Lund)** has started a project to explore the potential of the ESS to produce medical radionuclides. [78] The ESS is an accelerator producing high-flux neutrons through spallation. This could potentially be used to produce medical radionuclides, although the current focus of the ESS is very much on research. In the project the diagnostic radionuclide ^{99}Mo/^{99m}Tc and the therapeutic radionuclides ^{131}I, ^{177}Lu, ^{225}Ac are considered.[79] It is unclear whether or when the ESS will indeed produce therapeutic radionuclides and whether prices will be competitive. As indicated before, decision criteria for production are not available; the priority use of facilities for research or medical purposes is a political decision.

There are no official plans to replace the MARIA reactor in Poland or the LVR-15 in the Czech Republic. It is unclear whether their lifetime will be extended with upgrades. Both produce a variety of radionuclides. If the listed foreseen production capacities will not be realised or take over the supply from these reactors, supply in Europe will likely be reduced. In that situation, there will also be fewer suppliers, reducing the redundancy in supply and thus weakening the supply chain.

4.4.3 Potential to increase production and processing capacity

Building new facilities for radionuclide production and processing is expensive and has so far not successfully been taken up by the market. Pharmaceutical companies interviewed rely on existing research reactor infrastructure to produce therapeutic radionuclides. Although some new production capacity is planned, there are also options to extend the current production capacity – which may also take time but is less expensive than building new facilities. With the ageing of current research reactors, this seems to be only a solution on the short or medium term (next decade).

Interviews with suppliers of therapeutic radionuclides reveal that **there is some potential to increase current production capacity**. Some reactor cores do have space for additional instruments for the irradiation or therapeutic radionuclides. This would however require changing and optimising the reactor setup, which will take easily five years and is a costly project – which would require timely decision making and investments.

[74] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020. RIVM*. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

[75] Ibid.

[76] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020.* RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

[77] Bruce Power website (2020): https://www.brucepower.com/2020/10/29/agreement-signed-to-advance-lutetium-177-isotope-production-to-meet-global-demand-for-critical-cancer-fighting-therapies/

[78] The ESS is since 2015 officially a European Research Infrastructure Consortium (ERIC) and a landmark research infrastructure in the ESFRI Roadmap 2018. In this European roadmap for research infrastructures also the JHR and the Myrrha are listed as projects.

[79] Y.J. Lee and M. Jensen (2019). *Isotope Production at European Spallation Source. A potential new access to neutrons*. 30 April 2019. See: https://indico.cern.ch/event/782482/contributions/3413625/attachments/1836380/3009684/INFRAIA_kickoff_ESS.pdf

Therefore, this would only be an option for younger research reactors, such as the FRMII. At the FRMII production capacity for ^{177}Lu production could technically be increased with factor 4 and for ^{166}Ho with factor 5 using current instruments. Personnel is a limiting factor in this. At the LVR-15 irradiation capacity could be further expanded as well, but this would limit the use of the reactor for scientific purposes.[80] At the HFR there is also some capacity left to increase the production of ^{177}Lu. However, the expected demand growth for ^{177}Lu is higher than the potential increase of available production capacity in these installations.

The **production of certain radionuclides could be prioritised within the available reactor capacity and instruments**. This would mean that, in order to avoid supply shortages of important medical radionuclides, other radionuclides would be produced less or less reactor capacity will be available for scientific research. From a commercial perspective, an irradiator would prioritise radionuclides that are more profitable. From a scientific perspective, a research reactor would prioritise the research activities for which it was build and funded. Therefore, such prioritisation requires openness, coordination and collaboration, and a framework to make such prioritisation decisions.

Additional **increase of supply can be realised by further increasing the efficiency of the post-irradiation supply chain**.[81] Especially shortening transport times would be beneficial. Due to radioactive decay the activity of the product decreases over time, meaning that less product remains for clinical use if the time between production and administration to patients is longer. The effective supply can thus be increased if the supply chain is optimised and the distance between producer and user is shortened. This is one of the benefits of having a European supply. It is however unclear how much further efficiency increase is still possible within the current supply chain; more openness and coordination could contribute to insight in further efficiency potential.

Overall, the expectation is that **meeting the projected demand for specifically ^{177}Lu will be difficult in the longer term with current (ageing) installations**. In the next decade it is expected to be possible to double the current production capacity for ^{177}Lu, especially through optimising processes and prioritising ^{177}Lu production. This would only be sufficient to sustain a 3% demand growth[82], while the projected demand for ^{177}Lu is in fact higher (see section 5.2)

4.5 Stability of supply in Europe

4.5.1 Supply disruptions to European hospitals

As therapeutic radionuclides cannot be stocked due to their short shelf lives (because of radioactive decay), a continuous and undisrupted supply is essential for patient treatments. Across the supply chain disruptions may occur that affect the supply to patients, but especially the steps from irradiation to pharmaceutical preparation, with transport in between, are time sensitive and disruptions there affect the supply. The Moly-crises, during which several reactors were (temporarily) shut-down, has shown the vulnerability of the medical radionuclide supply chain.

Overall, the supply of therapeutic radionuclides has been reasonably stable in the past five years, although unplanned disruptions of supply do occur. Such disruptions are fairly limited, based on Technopolis' survey among relevant clinical experts. Most respondents indicated no disruption of supply in five years' time for most therapeutic radionuclides considered in this study. Exceptions are ^{131}I, ^{166}Ho, ^{169}Er and ^{186}Re, for which a majority

[80] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020.* RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

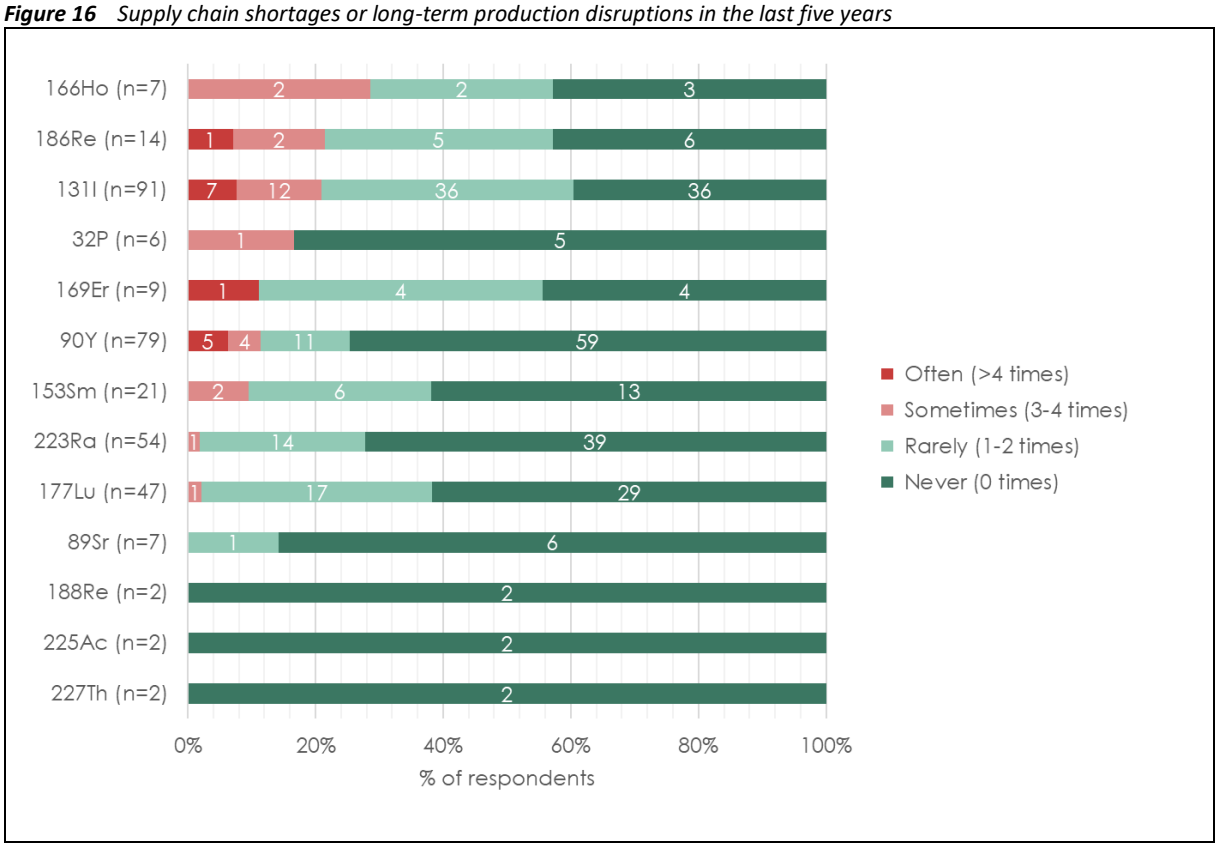
[81] Ibid.

[82] Ibid.

of respondents indicate at least some disruptions in the last five years. Interestingly, ^{131}I is one of these radionuclides, being one of the most widely used therapeutic radionuclides.

The commonly used therapeutic radionuclides ^{131}I and ^{90}Y have been most reported by surveyed experts as being often short in supply – meaning that there have been supply shortages more than four times in five years. These shortages were reported from across Europe, but as these are widely used, the absolute numbers give a distorted view. Relative numbers (percentages) show that ^{169}Er – relative to the amount of users of this radionuclide among the survey respondents – is most mentioned as being often short in supply, followed by ^{131}I, ^{186}Re and ^{90}Y. Still, for any of the radionuclides included in this study less than 12% of the respondents indicate that often (>4 times in 5 years) supply issues occur, while less than 30% of the respondents indicate that they are sometimes (3-4 times in 5 years) faced with supply issues.

Figure 16 *Supply chain shortages or long-term production disruptions in the last five years*



Source: survey among experts across Europe (numbers in bars are # of respondents)

4.5.2 Impact of disruption on patient treatments

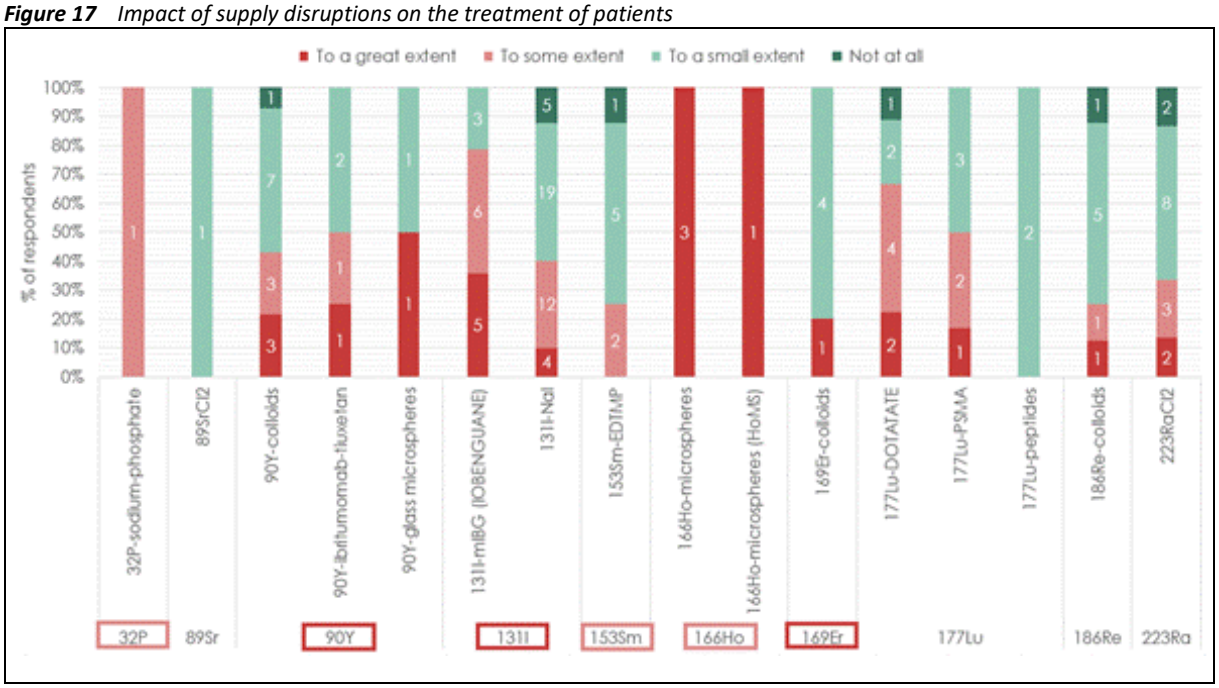
Supply shortages always have impacts on the treatment of patients, resulting in delayed treatments. As the treatment is with a radiopharmaceutical, we have explored the impact of shortages of specific radionuclides per radiopharmaceutical. However, we asked experts participating in the survey to indicate the severity of supply disruptions for the treatment of patients. The result is displayed in **Figure 17**.

The impact of supply shortages on treatments strongly differs per radiopharmaceutical. For ^{166}Ho-microspheres respondents indicate that supply shortages impact the treatment of patients to a great extent. In contrast, for [^{89}Sr]$SrCl_2$, ^{177}Lu-petides, ^{169}Er-colloids, [^{153}Sm]Sm-EDTMP and ^{186}Re-colloids most respondents believe disruptions have only impact on treatments to a small extent or not at all. The difference in impact of supply shortages on treatment per radiopharmaceutical is also clear for ^{131}I, where respondents indicate that a shortage of [^{131}I]I-mIBG has a stronger impact on treatments than a shortage in [^{131}I]-NaI.

A few radionuclides have the unfavourable combination of being reported by experts as being often or sometimes short in supply and having a great or some impact on the treatment of patients. Among these are the widely used ^{131}I and ^{90}Y radionuclides, for which ~30% of respondents indicate >3 shortages in 5 years' time and ~50% of respondents indicate a great or some impact on the treatment of patients. The less applied ^{166}Ho is also important to note, for this radionuclide about 24% of respondents indicate >3 shortages in 5 years' time and all respondents indicate a great impact on the treatment of patients.

We emphasise that this is a first estimate of the severity of impacts on treatment; further details on treatment specifics would have to be investigated to provide more detailed findings.

Figure 17 *Impact of supply disruptions on the treatment of patients*

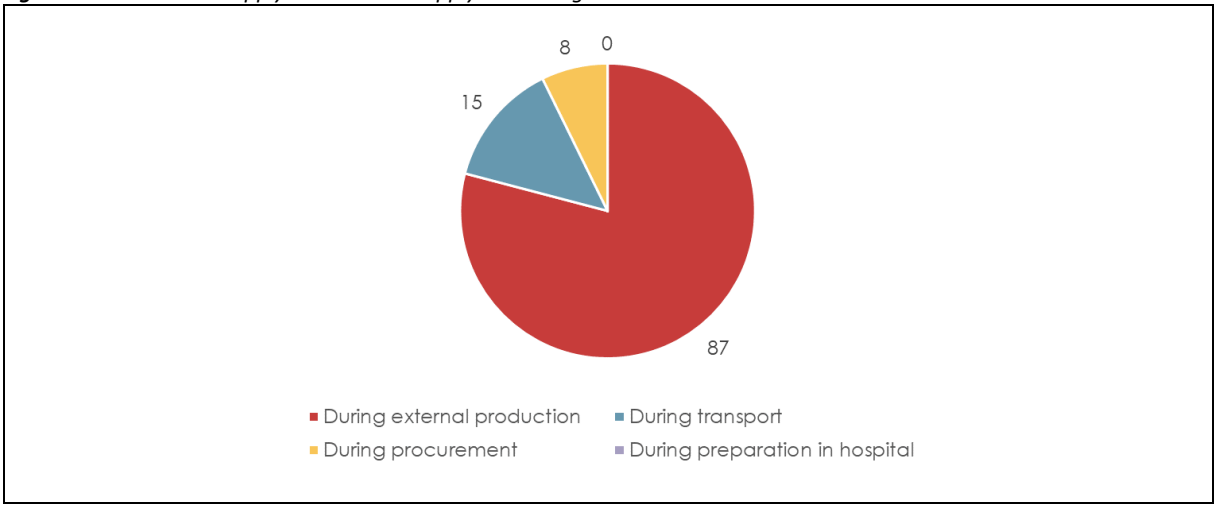


Source: survey among experts across Europe (numbers in bars are # of respondents). NB: the boxes indicate whether a radionuclide has been indicated as often or sometimes short in supply in ***Figure 16***

4.5.3 Causes of supply disruptions

Most of the reported supply chain disruptions (79%) occur during external production. These are the phases of irradiation, processing and preparation of the radiopharmaceutical by pharmaceutical companies. Another 14% of all disruptions occur during transport after irradiation and 7% of all disruptions occur during procurement in the hospital.

Figure 18 *Position in supply chain where supply issues originate*



Source: survey among experts across Europe (numbers are # of respondents)

The **causes of supply disruptions are often related to quality control issues, maintenance/outage of reactors or delayed shipping**, although causes are not always reported to hospitals. **Table 8** specifies the causes of experienced supply issues per radionuclide based on responses to the survey.

Table 8 *Reported supply causes of supply issues per radionuclide*

Radionuclide	Causes of experienced supply issues	Solutions suggested for supply issues
^{131}I	• Product failed quality control • Reactor maintenance or outage • Shipping delayed (esp. air travel)	• Improve quality control throughout value chain • Better anticipation of demand/orders
^{153}Sm	• Reactor maintenance or outage	
^{166}Ho	• Reactor maintenance or outage • Product failed quality control	• Increase the number of suppliers/sources for the radionuclide
^{169}Er	• Reactor maintenance or outage • Product failed quality control	• As demand is low, supply is less (frequent), which makes supply chain weaker. Higher demand could solve these issues, but depends on needs.
^{177}Lu	• Problems with labelling (PSMA/DOTATATE) • Reactor maintenance or outage • Shipping delayed (esp. air travel – flight activity limit reached) • Miscommunication with supplier	• Expand the network of suppliers/sources for the radionuclide • Optimising transport/flight bookings by better monitoring flight activity limits
^{186}Re	• Changes in production schedule • Product failed quality control	• Better coordination within supply chain • Increase number of suppliers/sources for the radionuclide
^{223}Ra	• Long delivery times • Reactor maintenance or outage (for parent radionuclide) • Shipping delayed (esp. air travel)	• Increase number of suppliers/sources for the radionuclide (capacity has increased after long delivery times)
^{32}P	• Product no longer offered	
^{89}Sr	• Product no longer offered	

Radionuclide	Causes of experienced supply issues	Solutions suggested for supply issues
^{90}Y	• Product failed quality control • Vector for labelling unavailable (ibritumomab-tiuxetan)	

Source: survey among experts across Europe

Especially during the COVID pandemic, transport has been an important cause of disruptions and turned out to be the weakest link in the current supply chain. Cross-border transport, especially using (commercial) flights, had been severely disrupted. Countries that rely on flight transport for radionuclides often mentioned flight issues in the past five years: Cyprus, UK, Portugal and Italy reported flight issues. Flights did not arrive, were delayed (resulting in less activity delivered or delay of procedure) or flights reached their activity limit. To better coordinate this during the COVID pandemic, a corona response team was set-up during the pandemic.[83] The pandemic has shown that road transport is less vulnerable to disruptions than flight transports. Countries that rely on cross-continental flights experienced more (complex) supply disruptions than countries that could be supplied by road transport. As Europe has irradiation facilities, processing facilities and pharmaceutical companies located within its continent, road transport is for many countries feasible and disruptions have been relatively mild.[84] This shows that having such irradiation and post-irradiation facilities within Europe adds to the robustness of the European supply chain.

4.6 Critical issues and foreign dependencies in the supply chain

The supply chain for therapeutic radionuclides is international by nature and has some critical issues. Non-European, foreign, supply is part of this supply chain, especially before irradiation. Generally, this is not a critical issue, but some weak links/dependencies are identified. Below we describe the critical issues and foreign dependencies in general, but we first provide an overview of identified critical issues and foreign dependencies per radionuclides. This is given in **Table 9**.

Supply chains are specific to each therapeutic radionuclide. For the currently most used therapeutic radionuclides no significant critical issues exist, but there are some foreign dependencies. For ^{223}Ra supply seems to rely for a significant part on the US and the NCA production of ^{177}Lu relies on enrichment in Russia. In the long-term, the expected demand for ^{177}Lu seems difficult to be met. For several novel or experimental radionuclides, that are not much used in clinical practice, dependencies and supply issues exist. Once demand for these radionuclides increases, some of these dependencies are likely to be solved, but these take time and may delay clinical uptake. For ^{225}Ac and ^{213}Bi, supply issues are more fundamental, as new industrial production processes need to be developed – for ^{213}Bi also close to the patient.

Table 9 *Overview of identified critical issues and foreign dependencies per radionuclide*

Radionuclide	Critical issues and foreign dependencies
^{32}P	-
^{47}Sc	Experimental, limited sources available. Only one irradiator in Europe identified.
^{67}Cu	Currently limited supply for medical use, experimental only, but small quantities. No European source was identified. Short lifetime for foreign supply.

[83] World Nuclear news (2020). *Air transport improves for medical radioisotopes*. 28 April 2020. See: https://world-nuclear-news.org/Articles/Air-transport-bottleneck-easing-for-medical-radioi

[84] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020*. RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

^{89}Sr	Phased out: limited use and reduced supply. Reported to be not available anymore.
^{90}Y	- (short lifetime for foreign supply)
^{131}I	-
^{153}Sm	- (short lifetime for foreign supply)
^{166}Ho	- (short lifetime for foreign supply)
^{169}Er	-
^{177}Lu	Sufficient supply in Europe for short term, although very limited supply of NCA. Shortage on long-term expected. Several initiatives to improve supply, mainly in North America (SHINE & Bruce Power). When ageing European reactors decommission, stronger foreign dependency is likely. Relies on ageing Russian calutrons for enrichment of non-carrier added ^{177}Lu. Current business continuity plans from pharmaceutical companies rely on US.
^{186}Re	-
^{188}Re	Requires very high flux reactors for production, not many available and most of these are ageing in Europe.
^{211}At	Very limited supply for medical use, experimental only, but small quantities. There are cyclotrons in Europe that could technically produce ^{211}At in the future. Short lifetime for foreign supply.
^{212}Pb	Experimental, currently limited supply for medical use. Short lifetime for foreign supply.
^{213}Bi	Relies on availability of ^{225}Ac, which has limited supply, currently reliant on US DOE.
^{223}Ra	No European supply disclosed (if available). Likely strong dependency on US. Only one pharmaceutical company has a radiopharmaceutical using ^{223}Ra on the market, which has supply secured for projected demand in next 10 years. This holds risk of monopolised supply of ^{223}Ra.
^{225}Ac	Very hard to obtain. Limited supply, currently largely reliant on US DOE. Other production routes need to be developed. When clinical trials successful, additional (European) sources are needed for clinical application.
^{227}Th	Experimental, not much produced yet. No European irradiation source identified but has potential to be scaled.

Source: synthesis of information in this report.

4.6.1 Before irradiation phase

Before the irradiation phase there are some inherent foreign dependencies. First of all, the **raw material for reactor fuel (mostly Uranium) and most targets are mined outside Europe**. The French Orano is involved in mining activities for reactor fuel. Sources are in multiple countries; there is no dependency on a single non-European country. Most Uranium is mined in Kazakhstan, Canada and Australia, although there is a relatively small amount mined in Ukraine. Some raw material for targets are mined in Europe, such as Sulphur (for ^{32}P production), Strontium (for ^{89}Sr production) and Tungsten (for ^{186}Re and ^{188}Re production).[85] Some raw material for targets is however very scarce limiting its availability, such as Rhenium. Similarly, for some isotopes, such as ^{176}Lu, the natural abundance is low.

Europe has limited facilities for enrichment. Most of these facilities are used for the enrichment of uranium as reactor fuel (power plants). These include the enrichment facilities of Urenco (NL, DE, UK) and Orano (FR). However, **for the fuel of research reactors (high-assay low-enriched uranium – HALEU) Europe relies on the US**

[85] Minerals Education Coalition website (202): https://mineralseducationcoalition.org/mining-minerals-information/periodic-table-of-the-elements/

and Russia. This is a clear foreign dependency, for which ESA suggested several actions and explored potential business cases for European supply with Orano and Urenco.[86]

Urenco has also facilities for the enrichment of stable isotopes that can be used in targets. For the enrichment of lanthanides, including lutetium and ytterbium, foreign enrichment facilities are needed. Especially Russian calutrons are used, which are old and need replacement in the next decades. **This is a critical element in the supply chain and a clear foreign dependency**. As demand for enriched isotopes for therapeutic radionuclides will remain, it is likely that such facilities will be replaced or that innovative alternatives will appear.

4.6.2 In irradiation phase

Irradiation capacity in Europe seems currently sufficient, although future capacity issues depend on new irradiation facilities replacing the ageing fleet of current research reactors. In Europe a wide range of radionuclides are produced, limiting foreign dependencies. The HFR, BR2, MARIA and LVR-15 reactors are currently the largest suppliers of radionuclides, but all are planned to be decommissioned in the next 10-20 years.

Most therapeutic radionuclides are most efficiently produced using such research reactors. **Replacement capacity is needed in order to sustain supply in Europe and to avoid foreign dependencies** – which are possible for longer-lived radionuclides. Outage of research reactors have been reported in many European countries as causes of supply disruptions of therapeutic radionuclides.

To that end several replacement irradiation facilities are planned in Europe. These are planned to become operational in the next decade – although planned dates have in the past been delayed. Not all of these facilities will be built with 100% certainty: there is no final decision on the build of Pallas and SHINE in Europe seems also not certain. For most planned facilities it is unclear what therapeutic radionuclides they will produce, for example for Myrrha and SMART/LightHouse this is not specified. The JHR that is currently being built, currently has only the production of ^{131}I in scope. As building new facilities takes time and are prone to delays, this uncertainty is a risk for securing European supply.

Interviewees indicate that there is a role for governments in building new reactors. Risks and investments in such facilities are high and – in a young and volatile market such as for therapeutic radionuclides – the market is not likely to take such risks and make the required investments themselves. Pallas has embarked on a mission to be fully privately funded, but has recently seized this pursue. European could play a role in coordinating future capacity needs and initiatives.

Across Europe several cyclotrons and accelerators could produce the therapeutic radionuclides ^{67}Cu and ^{211}At[87], but supply is currently low. As these are currently experimental and not widely used in clinical practice, demand is also low. The lack of supply is however reported to hold back the development and uptake of these radionuclides. As the half-life of these radionuclides is rather short a network of cyclotrons across Europe that produce these radionuclides seems to be important should these become widely adopted in clinical use.

4.6.3 After irradiation phase

The current irradiators of radionuclides are associated with processors that are located near irradiation facilities. **In Europe, no imminent lack of current processing capacity for therapeutic radionuclides** was reported or conveyed during the study. Yet, the demand for such facilities, especially for labelling, is expected to increase significantly should [^{177}Lu]Lu-PSMA receive marketing authorisation following a successful VISION clinical trial.

[86] Euratom Supply Agency (2019). *Securing the European Supply of 19.75% enriched Uranium Fuel. A revised Assessment*. May 2019. See: https://ec.europa.eu/euratom/docs/ESA_HALEU_report_2019.pdf

[87] M.R. Zalutsky and M. Pruszynski (2011). *Astatine-211: Production and Availability*. Curr. Radipharm. 4(3). See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503149/#R39

Interviewees indicate that – although this will involve significant investments and planning several years ahead – this will likely be picked up by the market to follow demand. New processing capabilities are for instance planned in the Netherlands (the Nuclear Health Centre) on the site of the HFR and the planned Pallas reactor.[88] There is no significant foreign dependency in this phase.

4.6.4 During transport

Transport post-irradiation is very time-sensitive: the longer transport takes; the more activity is lost. **Flight transport has proven to be the weakest link in the current supply chain during the COVID pandemic**.[89] Interviewees indicate that during the pandemic a lot of effort was put in place to ensure the international transport of radionuclides, establishing a special working group to coordinate this.[90] European countries that are dependent on cross-country or cross-continental flights for their radionuclide supply have reported most disruption of supply. Overall, Europe has had limited disruptions compared to Asia and North America, as many irradiators and processors are based in Europe. **For many European countries road transport of therapeutic radionuclides is possible, which has been less sensitive for disruptions than air travel**.[91] This is a clear benefit of having important parts of the supply chain in Europe, with multiple suppliers across Europe.

[88] Pallas (2020). *Focus on Pallas*. Edition 3. See: https://www.pallasreactor.com/focus-on-pallas/3/22/

[89] World Nuclear News (2020). *Air transport improves for medical radioisotopes*. 25 April 2020. See: https://world-nuclear-news.org/Articles/Air-transport-bottleneck-easing-for-medical-radioi

[90] Nuclear Medicine Europe (2020). *How the COVID crisis has affected the transport of radiopharmaceuticals*. See: http://nuclearmedicineeurope.eu/wp-content/uploads/2020/11/Transport_WG.pdf

[91] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020*. RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

5 Future demand may rise, depending on market developments

The market for therapeutic radionuclides is in development. Current demand is likely to change in the next decade. In this chapter we describe the characteristics of the therapeutic radionuclide and radiopharmaceutical market, including expected developments of demand. We also discuss the drives and challenges for the development of this market.

Overview of main conclusions of this chapter:

- The market for therapeutic radionuclides is much more volatile than the market for diagnostic radionuclides with new products that entered the market in the last five years and that are on the brink of entering the market.
- Driven by its therapeutic potential and the promise of growth in demand, the therapeutic radiopharmaceutical market has caught the interest of big pharmaceutical companies.
- The demand for ^{177}Lu, ^{225}Ac, ^{227}Th and ^{166}Ho is expected to increase in the next ten years. Especially the demand for ^{177}Lu is expected to rise strongly, outgrowing current demand capacity.
- The demand for PSMA pharmaceuticals is expected to increase strongly. An increase or even strong increase is also expected for several targeted alpha therapies.
- The demand for ^{90}Y, ^{131}I and ^{169}Er is expected to remain stable in the next ten years, while the expected demand trend for ^{223}Ra is inconsistent among experts.
- The demand for ^{89}Sr, ^{32}P, ^{153}Sm and ^{188}Re and related radiopharmaceuticals is expected to decrease in the next ten years.
- Challenges for the development of the therapeutic radionuclide/radiopharmaceutical market revolve around competition with alternative treatments, supply capacity not sustaining demand growth, regulatory barriers, market intransparency and asymmetry, and political decisions.
- As the market for therapeutic radionuclides/radiopharmaceuticals is volatile and intransparent, matching supply and demand is difficult. It is not likely that in such a market supply and demand will be optimally met.
- The current European supply chain for radiopharmaceuticals currently used in clinical practice seems adequate, but fragile, and not resilient. The development of several new radionuclides is hindered by insufficient current supply.

5.1 Characteristics of the therapeutic radiopharmaceutical market

The current size of the market for therapeutic radionuclides (in terms of volume) is much smaller than the market for diagnostic radionuclides. Factors of 100 have been reported, meaning that the market for therapeutic radionuclides is 100 times smaller than that of diagnostic radionuclides.[92] As an example, in the Netherlands roughly 1% (3,800) of all radionuclide procedures in nuclear medicine (370,000) are therapeutic.[93]

The therapeutic market is younger and less established than the diagnostic market, showing more growth than the diagnostic market.[94] In terms of revenue, an expected annual growth of 5-8% has been reported for the therapeutic market.[95] Much larger growth numbers are expected when PSMA-617 will receive marketing

[92] PWC (2018). PALLAS/LightHouse Review. Extract of final report.

[93] L.P. Roobol, C.E.N.M. Rosenbaum and I.R. de Waard (2020). *Leveringszekerheid voor medische radionucliden – aanvullingen 2020.* RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2020-0153.pdf

[94] L.P. Roobol and I.R. de Waard (2019). *Marktontwikkeling en leveringszekerheid voor medische radionucliden. RIVM*. See: https://www.rivm.nl/bibliotheek/rapporten/2019-0101.pdf.

[95] Ibid.

approval – depending on the outcomes of the currently ongoing VISION clinical trial. Two distinct interviewees suggest that in ten years' time the market for radionuclides will have grown, and the share of therapeutic radionuclides (in terms of expenditures) will outnumber the share of diagnostic radionuclides in this market. The demand for diagnostic radionuclides will not decrease, but the demand for therapeutic radionuclides will be significantly higher. This will also depend on successful outcomes of ongoing clinical trials (e.g. for [^{177}Lu]Lu-PSMA -617).

The market for therapeutic radionuclides is much more volatile with new products that entered the market in the last five years (e.g. Lutathera®) and that are on the brink of entering (e.g. [^{177}Lu]Lu-PSMA). Several new therapeutic radiopharmaceuticals are used compassionately or being tested in clinical trials.[96] Due to the time-complexity of the product and supply and regulations regarding both pharmaceuticals as well as radiation protection, these products take more time to bring to the market and are associated with higher risks.

In 10 years' time the interest in radionuclide therapies has increased. Although a small market, **radionuclide therapies caught the interest of big pharmaceutical companies**. BAYER, Novartis and AstraZeneca have been taking over (or have been partnering with) smaller radiopharmaceutical companies and their product pipelines in recent years. Through these mechanisms they are entering the market of therapeutic radiopharmaceuticals. Expectations for the development of these markets are at the basis of these decisions of non-specialised big pharmaceutical companies.

Europe is traditionally the hotspot for medical radionuclides, with several research reactors producing a large part of the world's demand for medical radionuclides (especially diagnostics). The US and Canada rely more on foreign sources than Europe does, especially for the diagnostic ^{99}Mo/^{99m}Tc, and have been supporting (innovative) local initiatives to produce medical radionuclides. North American entrants, such as SHINE and Bruce Power, supplying also ^{177}Lu, are in part a result of these efforts and politics. Such **new entrants can change the dynamics of the market and the position of European players into this market**. New initiatives still have to prove their promises, and some are focusing on specific radionuclides (due to technical limitations), leaving the supply side of some radionuclides unaffected – at least in the short term.

5.2 Expected development of demand in Europe

5.2.1 Therapeutic radionuclides

Experts in nuclear medicine, clinical practitioners and producers of therapeutic radionuclides across Europe have been surveyed to understand their expectation for the development of demand for specific radionuclides in the next 10 years. Their response is displayed in **Figure 19**.

Most surveyed experts believe that the demand for ^{177}Lu, ^{225}Ac, ^{227}Th and ^{166}Ho will increase in the next ten years. In terms of our study, increase means a growth of demand between 1-15% in 10 years' time. The growth of ^{166}Ho is also signalled by the acquisition of Quirem Medical by the Japanese Terumo mid-2020, after clinical trails showed the safety and efficacy of ^{166}Ho-microspheres for treatment in liver cancer.[97]

Many respondents believe that for ^{177}Lu and ^{225}Ac demand will strongly increase, even well beyond 15% growth in 10 years' time. Indeed, ^{177}Lu is considered the workhorse for nuclear medicine in the next decades. Interviewees support these projections for ^{177}Lu, which are also confirmed by other studies: reporting even

[96] See Appendix A.

[97] Quirem Medical (2020). *Terumo acquires Quirem medical to enhance its interventional oncology field*. See: https://www.quirem.com/terumo-acquires-quirem-medical-to-enhance-its-interventional-oncology-field/

growths of 7% or more per annum (which would almost double current demand in 10 years' time).[98] For ^{225}Ac similar demand growth expectations of 5-8% per annum have been reported.[99] However, interviewees express different views regarding ^{225}Ac, with some being more sceptical, noting its long half-life, strong radiotoxicity with four α-particles in its decay chain (potentially causing side effects of the treatment) and current severe supply issues requiring significant investments to be solved. Similar notions have been made for ^{227}Th, with an even longer half-life, one additional α-particle in its decay chain and currently limited supply – although better scalable than ^{225}Ac. Both ^{225}Ac and ^{227}Th are subject of clinical studies[100] and still need to be proven effective for application in targeted alpha therapy – which is quite novel, with ^{223}Ra being the only radionuclide for alpha therapy on the market. Respondents in the survey are however mostly positive regarding the clinical potential of targeted alpha therapy.

Most surveyed experts believe that the demand for ^{90}Y, ^{131}I and ^{169}Er will remain stable in the next 10 years. Both ^{90}Y and ^{131}I are currently widely applied in clinics across Europe. Some experts expect a decrease of the use of these radionuclides in the next 10 years, while roughly a similar number of experts expect an increase, suggesting that the number of centres performing treatments is currently the limiting factor. Experts indicate that in the treatment of primary liver cancer or liver metastases, ^{166}Ho-microspheres is an alternative for ^{90}Y-microspheres, with the advantage that ^{166}Ho can also be used for imaging. For the treatment of synovitis, ^{186}Er and ^{90}Y have been mentioned as alternatives for ^{169}Er. However, for ^{131}I several clinical trials are in phases 2/3 in the US, labelling ^{131}I to novel conjugates (CLR131/PDC), for the treatment of multiple myeloma and lymphoma (Cellectar Biosciences)[101], and antibodies (Iomab-B/BC8), for the treatment of leukaemia and lymphoma (Actinium Pharmaceuticals)[102]. If these products enter the market, demand for ^{131}I may indeed increase.

Most surveyed experts expect a decrease in demand for ^{89}Sr, ^{32}P and ^{153}Sm, while many experts also foresee a decrease of demand for ^{188}Re in the next 10 years. More than one third of responding experts even expect a strong decrease of demand for ^{89}Sr and ^{32}P. Therapy with ^{89}Sr is phased out, as well as its production, because alternative shorter-lived radiopharmaceutical therapies are preferred over the use of ^{89}Sr, e.g. [^{153}Sm]Sm-EDTMP, [^{188}Re]Re-EDTMP and [^{223}Ra]$RaCl_2$, and [^{177}Lu]Lu-PSMA will likely be used for its main indication prostate cancer. For ^{153}Sm the argument was given that impurities/low specific activity of this radionuclide, and the lack of new applications beyond [^{153}Sm]Sm-EDTMP , will potentially lead to decreased use. The first therapeutic radionuclide on the market was ^{32}P in 1936, but currently it has limited applications. Still, these trends can be influenced by innovations: novel radiopharmaceuticals that are tested, such as [^{188}Re]Re-HER2-Sd, could change demand trends when outcomes of clinical trials are positive.

The expectation on the development of demand for ^{223}Ra is ambiguous: roughly an equal amount or respondents assess a decrease, stable and increase demand in 10 years' time. Some respondents list the positive aspects of alpha therapy and its replacement of other therapies as a reason for growing demand. Several other respondents indicate that the demand for [^{223}Ra]$RaCl_2$ will be reduced once PSMA pharmaceuticals (esp. [^{177}Lu]Lu-PSMA) are authorised on the market and because of side effects of ^{223}Ra.

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[98] L.P. Roobol and I.R. de Waard (2019). *Marktontwikkeling en leveringszekerheid voor medische radionucliden*. RIVM. See: https://www.rivm.nl/bibliotheek/rapporten/2019-0101.pdf.

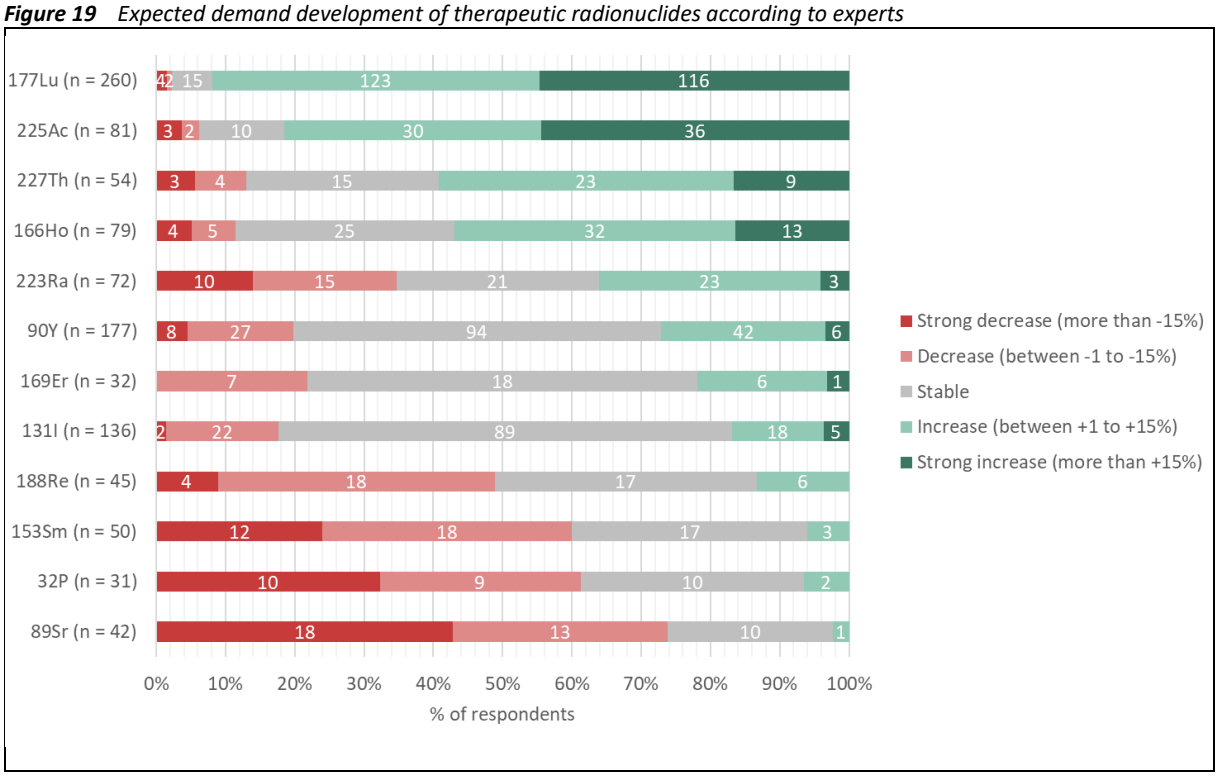
[99] Ibid.

[100] Phase 1 clinical trials, which indicates still long-term development before entering the market. Our clinical trial analysis in appendix B.1 has excluded such Phase 1 trials because of their uncertain trajectories and long-term development.

[101] Celectar Biosciences website: https://www.cellectar.com/product-pipeline/clr-131

[102] Actinium Pharmaceuticals website (2021): https://www.actiniumpharma.com/product-pipeline/iomab-b

Figure 19 *Expected demand development of therapeutic radionuclides according to experts*



Source: Technopolis Group, survey among experts

5.2.2 Therapeutic radiopharmaceuticals

The market for therapeutic radionuclides has strongly developed in the last few decades. The introduction of Lutathera® ([^{177}Lu]Lu-DOTATATE) and Xofigo® ([^{223}Ra]$RaCl_2$) to the market in respectively 2017[103] and 2013[104] has further driven developments in the market and in R&D. It has also increased the interest of pharmaceutical companies into the market of radiopharmaceuticals, leading to investments by Bayer and Novartis. Several clinical trials are ongoing of which those on [^{177}Lu]Lu-PSMA (for the treatment of prostate cancer) are far developed and considered very promising by experts. New products are therefore expected to enter the market in the next 5-10 years.

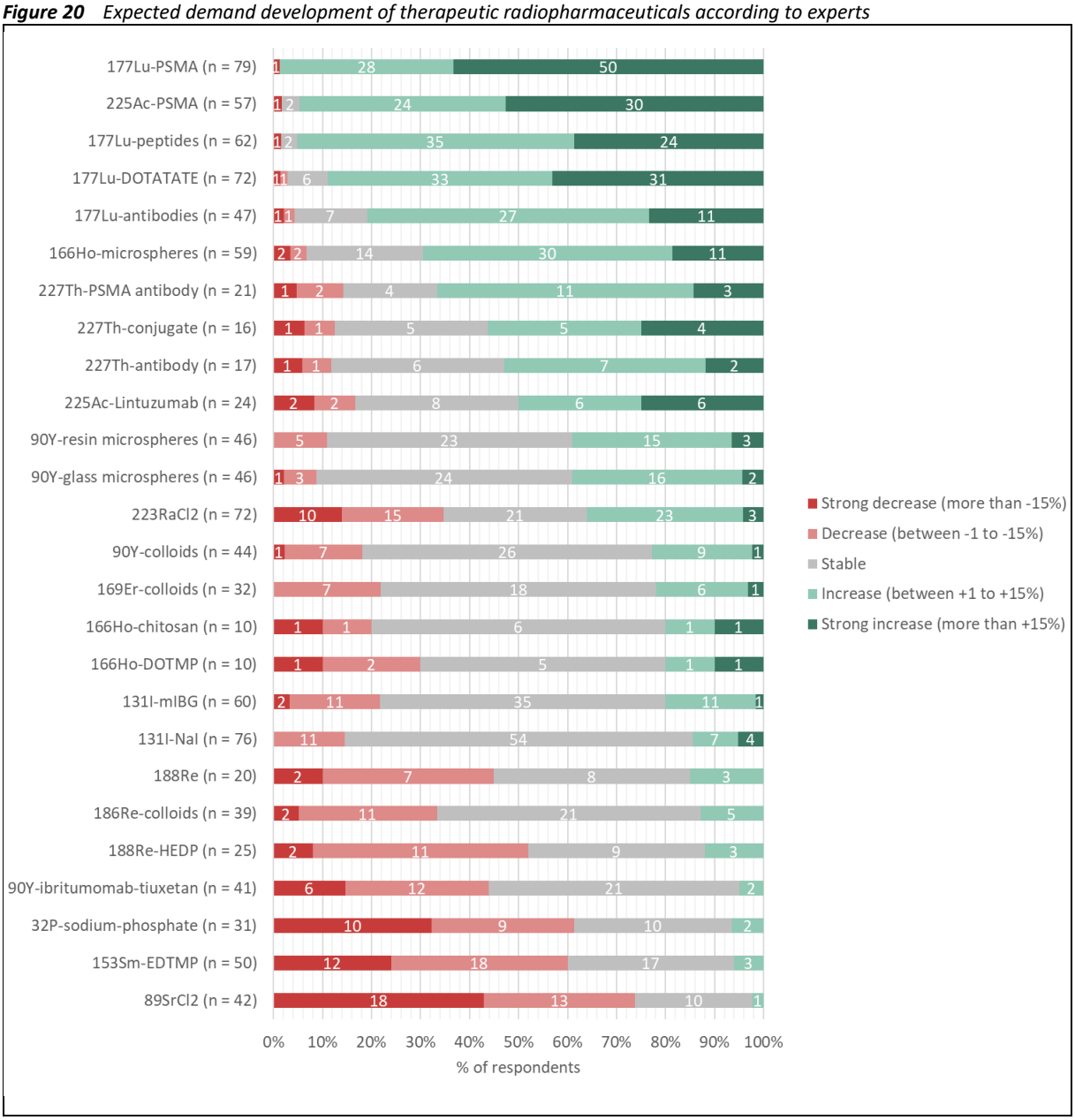
These developments show that the market is developing but quite volatile. A new success product on this market can change the market characteristics significantly (market size, investments, dominance of players, number of players etc.) and could further boost R&D as well as the use of radionuclide therapies in clinical practice. The uptake of these products in clinical practice is also determined by investments and knowledge of these products in hospitals (e.g. prescriptions by oncologists, facilities for nuclear medicine) as well as the supply capacity.

The characteristics of the market for radionuclide therapy makes it hard to foresee how this market is developing in the next 10 years. We therefore relied on expert assessments, mainly from the medical field, across Europe. Through our survey we asked experts to share their expectations for the development of demand for therapeutic radiopharmaceuticals. Their response is displayed in **Figure 20**.

[103] See: https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera

[104] See: https://www.ema.europa.eu/en/medicines/human/EPAR/xofigo

Figure 20 *Expected demand development of therapeutic radiopharmaceuticals according to experts*



Source: Technopolis Group, survey among experts

Most surveyed experts expect a strong increase in the demand/use of PSMA[105] based radiopharmaceuticals for prostate cancer therapy, specifically [^{177}Lu]Lu-PSMA and [^{225}Ac]Ac-PSMA, and to a lesser extent [^{227}Th]Th-PSMA. An effective radionuclide therapy for prostate cancer has indeed strong potential for increased demand/use as prostate cancer is the most frequent diagnosed cancer among men in Europe, resulting in 10% of total cancer deaths in the EU.[106] As European populations are ageing the incidence of prostate cancer is likely to increase. So far, experts are positive of the results obtained with the use of PSMA based radiopharmaceuticals.

Most respondents expect an increase or even strong increase of several targeted alpha therapies, including ^{225}Ac and ^{227}Th pharmaceuticals. The only exception is [^{223}Ra]$RaCl_2$, where responses are ambiguous.

[105] PSMA = Prostate-Specific Membrane Antigen

[106] See: https://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe

Respondents name alpha therapies as promising, although availability of ^{225}Ac and ^{225}Th may be an issue. Although not addressed in the survey, several experts mention ^{212}Pb as a promising candidate for targeted alpha therapy, that is currently being studied and in early development by Orano Med[107].

In general, **for ^{177}Lu-based radiopharmaceuticals an increase in demand/use is expected by most experts**. Respondents name the positive experiences with [^{177}Lu]Lu-DOTATATE, which is currently the only accessible therapy for NETs, and the fact that ^{177}Lu is widely available and easy to handle. Furthermore, more hospitals are expected to prepare ^{177}Lu pharmaceuticals in-house. [^{177}Lu]Lu-PSMA is also considered very promising, being most developed of all PSMA-radiopharmaceuticals, and expected to be entering the market in short term. Competing PSMA-radiopharmaceuticals are being less available in terms of supply and less far in clinical development.

A majority of surveyed experts also believe that we will see an in increase in the demand/use of ^{166}Ho-microspheres. Expectations for the latter are based on its multimodality purpose: apart from being a therapy for liver tumours, it is also imageable in SPECT and MRI (due to magnetic properties). The latter makes ^{166}Ho-microspheres more favourable for demand growth than ^{90}Y-microspheres – for which most respondents expect stable demand.

On the other hand, **most surveyed experts expect a decrease in the demand/use of [^{89}Sr]$SrCl_2$, [^{153}Sm]Sm-EDTMP, [^{188}Re]Re-HEDP and ^{32}P-sodium-phosphate**. These radiopharmaceuticals are currently less used, not much in development and being replaced by more favourable alternatives (e.g., shorter half-lives, fewer side effects).

5.3 Developments in the therapeutic radiopharmaceutical market

5.3.1 Drivers

First and foremost, **the market for therapeutic radionuclides is driven by the promise of growth in demand**. The outcomes of the survey reflect a shared belief among healthcare professionals, as well as among large pharmaceutical companies, that the importance of several radionuclides (^{177}Lu and ^{225}Ac, followed by ^{227}Th, ^{166}Ho) will increase. This belief is strengthened by R&D activities: good clinical results in the past decades and an ongoing portfolio of clinical trials using radionuclides. The expected approval of PSMA-617-based therapies by the European Medicines Agency will be a further boost for radiopharmaceuticals. Positive results of the [^{177}Lu]Lu-PSMA clinical trial (VISION) will likely drive increased investments of new radiopharmaceuticals, negative results may cause a set-back in investments.

Not only the quantity of demanded treatments is driving the market, also the expected higher margins for therapeutical radionuclides increases the interest of producers. This holds especially when compared to radionuclides for diagnostics. The prices of commercially available radiopharmaceuticals reflect the expected return by market players for risks taken. As we will elaborate below, this is countered by some consumers' and national medicine authorities' opinion on fairness.

All in all, the market for therapeutic radiopharmaceuticals is still young, volatile, and uncertain: there is room for new entrants and subsequent acquisitions, market positions are still to be found, and the overall lack of coordination among European member states allows for risks and associated rewards.

[107] All candidate ^{212}Pb radiopharmaceuticals are currently in Phase 1 or pre-clinical phases of development. See: https://www.oranomed.com/en/pipeline

5.3.2 Challenges: production, regulation, market asymmetries, and political decisions

Whereas the drivers seem to push the business case in a favourable direction, there remain many uncertainties and hence risks for the further development of the radiopharmaceutical market.

Competition with non-radioactive drugs and/or treatments acting on the same disease

Therapeutic radiopharmaceuticals, with the only exception of ^{131}I for thyroid cancer and hyperthyroidism, are employed in clinical settings where multiple drugs are used. In reality the competition with drugs that can be directly managed by the treating physician has an influence, on top of the other issues mentioned below, on the willingness to invest in this field from pharmaceutical companies.

Production capacity

Like with diagnostic radionuclides, the production capacity for therapeutic radionuclides remains limited to a relatively small set of ageing production facilities and infrastructures both within and outside Europe. **Currently, production capacity seems adequate for meeting demand, but overall projected growth cannot be sustained**.

Within Europe, most research reactors are planned to be decommissioned this decade. The follow-up is largely uncertain and often focussed on a limited set of radionuclides. Although replacement of BR2 and HFR are planned, no final decision has been taken. No replacements for MARIA and LVR-15 are planned, further weakening production capacity within Europe.

All in all, Europe remains dependent on the US and Russia for the enrichment of several stable isotopes for targets used in the production of therapeutic radionuclides, such as ^{177}Lu NCA, which currently is one of radionuclides with the largest growth potential. In addition, Europe relies on the US and Russia for research reactor fuel (high-assay low-enriched uranium – HALEU), which is obtained from Russia or from down-blending US highly-enriched uranium stocks. A recent ESA-report[108] highlights the risk that foreign supply of HALEU cannot be guaranteed beyond 2030-2040, impacting medical radionuclide production.

While reactors constitute proven technology, several alternative routes for production are being tested and/or only recently proven viable (SMART/Lighthouse and SHINE). These alternatives weaken the business case for private or even public reactors providing medical radionuclides: they provide an innovative, but hardly proven option that requires time to scale up to global demand.

New European production capacity for therapeutic radionuclides is needed to sustain Europe's position in this market and to meet expected demand, especially for ^{177}Lu. This requires significant investments in infrastructure in the next few years.

Regulatory barriers

In the global context, there are fewer barriers for producing radionuclides in the US and Russia as compared to the European Union. In the EU, legislative frameworks for handling radionuclides and radioactive waste are not consistent among countries or even within countries (e.g. in Germany this is a state (Länder) rather than a federal issue).

Furthermore, regulation for pharmaceuticals and radiation protection do not always align, delaying the development and market entry of new radiopharmaceuticals.

Market asymmetries

[108] Euratom Supply Agency (2019). *Securing the European Supply of 19.75% enriched Uranium Fuel. A revised Assessment*. May 2019. See: https://ec.europa.eu/euratom/docs/ESA_HALEU_report_2019.pdf

The market for radiopharmaceuticals is largely intransparent and maintains information asymmetries among players. Such conditions can lead to market failure: mismatches of supply and demand. The lack of information makes it extremely difficult to coordinate supply and to tackle supply issues timely. This makes it difficult to gather market information for policy decisions, such as investments in new irradiation facilities, the appointment of reactor time or supply to specific parties.

Political decisions

The special character of nuclear technology and the associated infrastructures puts radiopharmaceuticals (for therapy) in a realm that is in essence one of political decisions.

As indicated above, there is no framework or coordination mechanism to prioritise production of certain radionuclides over others to avoid shortages or to address medical/societal needs. In our interviews, the decision logic in the supply chain was characterised as "first come, first serve" and long-term relationship driven.

The long-term security of supply requires timely investment discussions and discussions regarding new capacity at European level. Building new capacity or even extending current capacity takes five to ten years and requires significant investments that will not be fully carried by commercial investors.

As currently the market does not want to bear the costs and risks of major investments – given the case of the Pallas reactor – a coordinated European view on the need, importance and conditions for future capacity for therapeutic radionuclides is needed.

5.3.3 Matching supply and (expected) demand is difficult under current situation

Matching supply and demand in an intransparent, volatile market is difficult. Due to the short shelf lives of their products, pharmaceutical companies wish to control their supply chain, making long-term agreements with radionuclide suppliers, enrichers and target producers. They also tend to protect supply for their product and limit access to their suppliers and the market of other, competing businesses. Lack of transparency is then beneficial and sustained.

Under such conditions, **it is not likely that on a system level supply and demand for therapeutic radionuclides will be optimally met**. A resilient and sustainable supply first of all requires more openness in terms of information, to which this report is contributing. There is little quantitative information available on this fairly novel and small therapeutic market. There is no international coordination of supply (European and beyond) and countries do not (consistently) record information on the use of therapeutic radionuclides (providing insight in current demand on system/market level instead of product level). Also, there are no frameworks for radionuclide suppliers to prioritise production capacity to match supply/demand other than client relations/contracts and price. Therefore, international coordination similar to that for ^{99}Mo/^{99m}Tc is advisable.

5.3.4 Adequacy and resilience of the supply chain cannot be maintained

The current European supply chain for radiopharmaceuticals that are currently used in clinical practice seems to be adequate, but fragile. Sometimes supply shortages occur, but these occur not often for most therapeutic radionuclides. However, this is likely not sustained in the medium to long-term (10+ years) due to the following:

- The overall demand for radiopharmaceuticals is expected to grow in the next decades, with especially a strong increase in demand for ^{177}Lu.
- At the same time existing irradiation facilities (reactors) in Europe are planned for decommissioning in the next decades. Replacement is only foreseen for some of these reactors and the replacement plans are shrouded in unclarity. Some of the reactors only focus on specific radionuclides. Therefore, uncertainty remains on several levels: whether/when planned capacity is truly built in Europe, which/how much radionuclides they can/will produce, and whether they will meet proclaimed expectations.

- Enrichment of targets for some of the most promising therapeutic radionuclides (for which strong demand growth is expected), relies on old facilities in Russia that need replacement in the coming decades.
- Europe has limited capacities for the enrichment of stable isotopes for the production of therapeutic radionuclides.

Additionally, the **development of several new radiopharmaceuticals is hindered by insufficient current supply of radionuclides**, requiring the development of new industrial processes and the uptake by producers once radiopharmaceuticals pass clinical trials and market authorisation. Here some foreign dependencies exist (mainly US) that need to be overcome. Once demand increases, it is likely that these problems can be absorbed by the market. Coordination of supply capacity, as is done for ^{99}Mo/^{99m}Tc, is relevant to organise.

6 Policy recommendations

Based on the findings from this study, there are clear opportunities for action at EU level. In this chapter we present the main policy recommendations along the main topics of this report.

6.1 Recommendations on monitoring demand

In order to be able to better monitor the market for therapeutic radionuclides, **official (annual) data collection on the use of radiopharmaceuticals has to be improved**. Data collection should be at the level of radiopharmaceuticals in terms of number of treatments as well as activity used (at time of administration). This needs to be organised first and foremost at national level in a standardised way – the standard is to be agreed upon at European level. This report has shown good examples of data gathering in e.g. Belgium, Czech Republic and Sweden. However, coordination of such efforts lies with the European Commission. Eurostat could be tasked with this data collection in collaboration with national statistical offices, but this would require a mandate from EU Member States and is thus a matter to discuss with the EU Council.

The European Commission should consider supporting (translational) research, innovation and training in novel radionuclide therapies and pharmaceuticals to accelerate innovation and translation of knowledge to clinical practice. Given the European cancer incidence (and the development thereof), the demand expectations and the promises of this fairly novel targeted therapy, public interest for better healthcare in the field of oncology could be served through such research, innovation and training actions. Activities in this field should be aligned with the new Horizon Europe Mission against cancer.[109]

6.2 Recommendations on securing future supply

Concerted and timely action at European level is required to secure sufficient irradiation capacity for therapeutic radionuclides in Europe for the future. This urges for a more active role at European level, including a vision on the need, importance, role of governments, and conditions/requirements for (future) irradiation (and processing) capacity for medical radionuclides in Europe. Current plans for new facilities to replace or add to current irradiation capacity for therapeutic radionuclides are uncertain in terms of realisation date, state of innovation, start of operations, the therapeutic radionuclides produced, and production volumes. To reduce these uncertainties information sharing (monitoring), coordinated planning, and identifying and removing barriers for new build (incl. public/private investments) are essential *now* to secure the public interest of a secured supply of therapeutic radionuclides in the future.

Europe relies for enrichment of some important target materials (stable isotopes, such as ^{176}Yb) on Russia, and for the supply of (enriched) research reactor fuel (LEU) on Russia and the US. As both supply chains are associated with risks, either due to old foreign facilities, reducing stockpiles or possible political instabilities, **a political decision should be made on whether Europe wants to be self-sufficient for these products to secure the (therapeutic) radionuclide supply chain (for the future)**. Being self-sufficient would require (co)investments in enrichment facilities, and perhaps innovation in enrichment technology, in Europe.

The European Commission should consider supporting applied research and innovation to strengthen the future supply chain for therapeutic radionuclides. This can be best implemented in the form of a public-private partnership (e.g. in the shape of an Institutionalised European Partnership)[110] between the European Commission, Member States, industry and research organisations, as changes to or innovation in the supply chain require collaborative involvement and investments. It should focus on applied research (at high Technology

[109] See: https://ec.europa.eu/info/horizon-europe/missions-horizon-europe/cancer_en

[110] See https://ec.europa.eu/info/horizon-europe/european-partnerships-horizon-europe_en

Readiness Levels) and innovation regarding irradiation concepts, processing methods, enrichment of stable isotopes and accelerator-based production of radionuclides (such as with the European Spallation Source). It is advisable to keep several technology options open rather than "choosing" a preferred technology.

6.3 Recommendations on the factors influencing demand and supply

Given the volatility and future expectations of the therapeutic radiopharmaceutical market, and the concerns regarding future supply, similar international mechanisms as for the security of supply ^{99}Mo/^{99m}Tc should be developed. Such efforts should be undertaken with industry to make this market more transparent. Historically, both the OECD-NEA High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) and the European Observatory on the Supply of Medical Radioisotopes focus on the main diagnostic radionuclide. As this is still the most used radionuclide this makes sense, but **more information-sharing regarding supply capacities, new builds, demand expectations and outages for key therapeutic radionuclides is important to secure supply for these medicines**. For starters, the focus should be on ^{131}I (the most used therapeutic radionuclide and the one with most reported supply disruptions) and ^{177}Lu (the therapeutic radionuclide that is expected to grow most and has substantial concerns for future supply). This could be incorporated in existing mechanisms, such as the European Observatory, with involvement of the industry.

6.4 Recommendations on regulation, reimbursement, finance and guidelines

Differences in prices for radiopharmaceuticals between European Members States exists, that cannot be fully explained by inherent regional differences such as in transport. Negotiations with suppliers are considered a significant factor in price differences between hospitals, regions or countries, depending on the level at which prices and contractual conditions are negotiated. **In discussion with Member States, the European Commission could explore the possibilities for and desirability of EU-level negotiations on price and contractual conditions, opening up possibilities to also negotiate supply issues, such as guaranteed levels of production, (co)investment in supply infrastructure and fallback capacity**. Lessons from the centralised procurement and negotiation for COVID-19 vaccines could be of use here.

In Europe legislative frameworks for handling radionuclides and radioactive waste is not consistent among (or even within) Member States. In addition, regulations for pharmaceuticals and radiation protection do not always align, delaying the development and market entry of new radiopharmaceuticals. **It is recommended to review current EU and national legislative frameworks that deal with transport, waste, use and R&D of radiopharmaceuticals to identify opportunities for harmonisation and removing regulatory barriers, whilst safeguarding high levels of safety and security.**

Heath Technology Assessment (HTAs) inform decision-making in order to promote an equitable, efficient, and high-quality health system. Thus, they are highly relevant in national reimbursement decisions for new, especially expensive, medicines and treatments. HTAs are generalisable and adaptable to specific national contexts (e.g. specific healthcare systems) and therefore the European Network for Health Technology Assessment (EUnetHTA) was established to help Member States collaborate on Joint Assessments and share HTA resources. However, EUnetHTA does not include radiopharmaceuticals in their assessment list. **It is therefore recommended to include radiopharmaceuticals within EUnetHTA activities to facilitate HTA-based reimbursement decisions for radiopharmaceuticals at Member States.** This will be of particular help to Member States' healthcare bodies that lack capacity to conduct HTAs.

Appendix A Reimbursement models

A.1 Financing healthcare in Europe

Medicines must be approved for use by gaining marketing authorisation before they can be used for the patient population. In the context of the EU marketing authorisation may occur through a centrally based procedure via the European Medicines Agency, or a. The traditional process by which medicines are reimbursed in Europe may follow a number of different routes. A key stakeholder in this process is the European Medicines Agency (EMA).

Although healthcare coverage in Europe is varied between member states, two main types are observed: social health insurance systems (SHI) and national health services (NHS).[111] In SHI systems health risks of the population are pooled through insurance contributions by, for example, the workforce and their employers. Thus, revenues to cover the costs of healthcare are sourced from earnings-based contributions to funds and further subsidised by the national governments. SHI systems also vary themselves where subsets of the population may be covered by different funds through different means, such as by region or employment type, for example.

By contrast NHS type healthcare systems gather money to cover the costs of healthcare through general taxation.

There are typical differences between SHI and NHS type healthcare delivery. SHI systems are more likely to contract healthcare providers to deliver healthcare to patients, thus setting up a competitive contract-based environment. Those member states with competitive and non-competitive SHI systems are shown in **Table 10**.

Table 10 *European member state healthcare systems*

Country	NHS/SHI	Single (S) or Multi payer (M)	Competitive SHI	Proportion of population covered by public health insurance
Austria	SHI	M	No	100%
Belgium	SHI	M	Yes	99%
Bulgaria	SHI	S	No	88.2% (2013)
Croatia	SHI	S	No	100%
Cyprus	NHS	S	Not applicable	83% (2013)
Czechia	SHI	M	Yes	100%
Denmark	NHS	S	Not applicable	100%
Estonia	SHI	S	No	94%
Finland	NHS	S	Not applicable	100%
France	SHI	M	No	100%
Germany	SHI	M	Yes	88.9% (public) 10.9% (private)
Greece	Mixed SHI/NHS	S	No	86% (2015)
Hungary	SHI	S	n/a	95%
Ireland	NHS	S	Not applicable	100%
Italy	NHS	S	Not applicable	100%

[111] The management of health systems in the EU Member States - The role of local and regional authorities, 2012. See: https://cor.europa.eu/en/engage/studies/Documents/health-systems/health-systems-en.pdf

Country	NHS/SHI	Single (S) or Multi payer (M)	Competitive SHI	Proportion of population covered by public health insurance
Latvia	NHS	S	Not applicable	100%
Lithuania	SHI	S	No	100%
Luxembourg	SHI	M	No	96%
Malta	NHS	S	Not applicable	100%
Netherlands	SHI	M	Yes	100%
Norway	NHS	S	Not applicable	100%
Poland	SHI	S	No	91%
Portugal	NHS	S	Not applicable	100%
Romania	SHI	S	No	86%
Serbia	SHI	S	No	100%
Slovakia	SHI	M	Yes	94%
Slovenia	SHI	S	No	100%
Spain	NHS	S	Not applicable	99.1% (public) 0.8% (private)c
Sweden	NHS	S	Not applicable	100%
Switzerland	SHI	M	Yes	100%
United Kingdom	NHS	S	Not applicable	100%

Adapted from WHO

Table 11 *Reimbursement models used in EU member states for radiotherapy*

Country	**Budget**		**Bundled payment**			**Fee for service**
	Per hospital	**Per department**	**Per disease**	**Per treatment**	**Per day**	
Austria	Yes					
Belgium	Yes					Yes
Bulgaria		Yes		Yes		
Czechia		Yes				
Denmark		Yes				
Estonia						Yes
Finland	Yes				Yes	
France						Yes
Germany						Yes
Greece						Yes (private)
Hungary	Yes	Yes				
Ireland	Yes					
Italy	Yes (public)	Yes (private)				
Lithuania						Yes
Luxemburg	Yes					Yes
Netherlands						Yes
Poland	Yes	Yes				
Portugal				Yes (in patient)	Yes (outpatient)	
Romania	Yes		Yes (inpatient)		Yes (outpatient)	
Spain		Yes		Yes		
UK	Yes (Scotland and Wales)					Yes (England)

Source: Lievens et al. (2020)

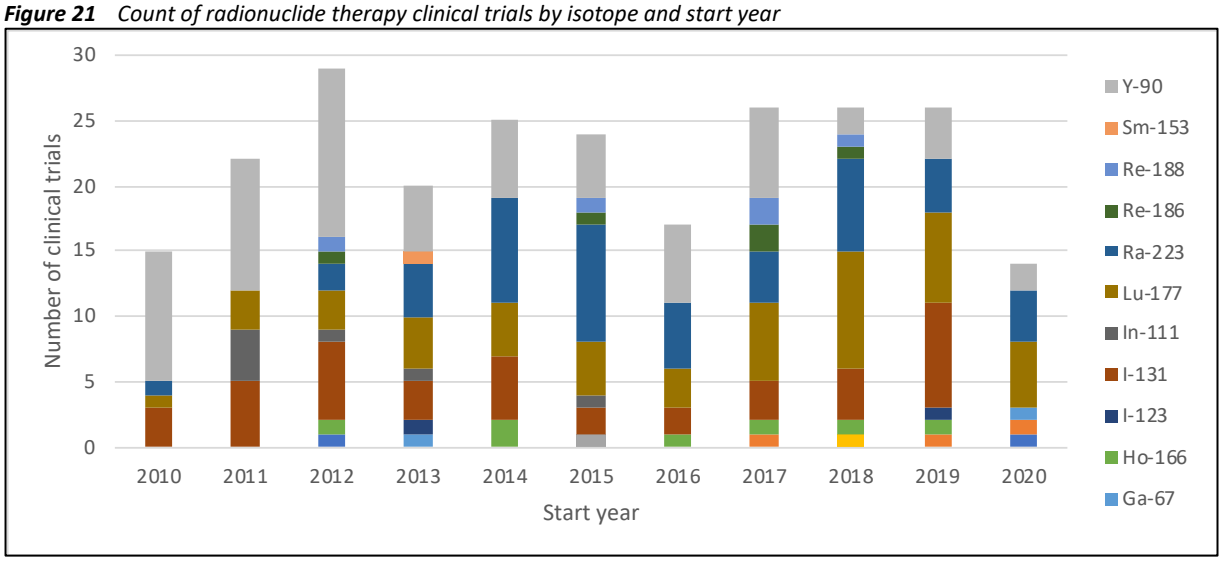
Appendix B Methodological notes and caveats

In order to fill in the lack of information concerning the use of radionuclides for therapy, we have taken a mixed method approach to gather as much reliable information as possible. This appendix describes methodological approaches, caveats and sources of information.

B.1 Analysis of radionuclide therapy clinical trials

To establish the prominence of radionuclides, we analysed a database of global clinical trials. The analysis only includes treatment trials of Phase 1/2 and higher, and which started between 1 April 2010 and 31 March 2020 were included in the analysis. As such, a total of 244 trials were included in the analysis. However, data for all variables were not available for each trial.

Figure 21 *Count of radionuclide therapy clinical trials by isotope and start year*



Based on data from ClinicalTrials.Gov (2020)

Table 12 *Clinical trials per radionuclide over years 2010-2020*

Start Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Grand Total
^{225}Ac			1								1	2
^{211}At								1		1	1	3
^{213}Bi						1						1
^{67}Cu									1			1
^{67}Ga				1							1	2
^{166}Ho			1		2		1	1	1	1		7
^{123}I				1						1		2

Start Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Grand Total
^{131}I	3	5	6	3	5	2	2	3	4	8		41
^{111}In		4	1	1		1						7
^{177}Lu	1	3	3	4	4	4	3	6	9	7	5	49
^{223}Ra	1		2	4	8	9	5	4	7	4	4	48
^{186}Re			1			1		2	1			5
^{188}Re			1			1		2	1			5
^{153}Sm				1								1
^{90}Y	10	10	13	5	6	5	6	7	2	4	2	70
Grand Total	**15**	**22**	**29**	**20**	**25**	**24**	**17**	**26**	**26**	**26**	**14**	**244**

Based on data from ClinicalTrials.Gov (2020)

^{90}Y, ^{177}Lu, ^{223}Ra and ^{131}I account for the most clinical trials in the last 10 years. The total number of radionuclide therapy clinical trials has not changed greatly year on year except for a dip in 2016.

Out of the 234 clinical trials for which location of the trial sites was available, over half had at least one trial site in the USA. ^{90}Y and ^{223}Ra accounted for the most clinical trials in the US (58%, 69 out of 120). Interestingly, ^{166}Ho radionuclide therapy clinical trials have been solely conducted in the Netherlands. Overall, ^{90}Y, ^{223}Ra and ^{177}Lu are the isotopes that feature most prominently in clinical trials in most countries.

It should be noted that although ^{227}Th is listed in other parts of this report, it was not found in the clinical trials analysis as most these trials are in early stages.[112]

Table 13 *Distribution of radionuclide therapy clinical trials by country*

Country	^{166}Ho	^{131}I	^{111}In	^{177}Lu	^{223}Ra	^{186}Re	^{188}Re	^{90}Y	TOTAL
United States	0	23	4	20	27	2	2	42	120
France	0	5	3	8	9	0	0	11	36
Netherlands	7	1	2	8	5	1	1	5	30
Canada	0	4	1	7	8	1	1	6	28
Italy	0	2	1	7	9	0	0	7	26

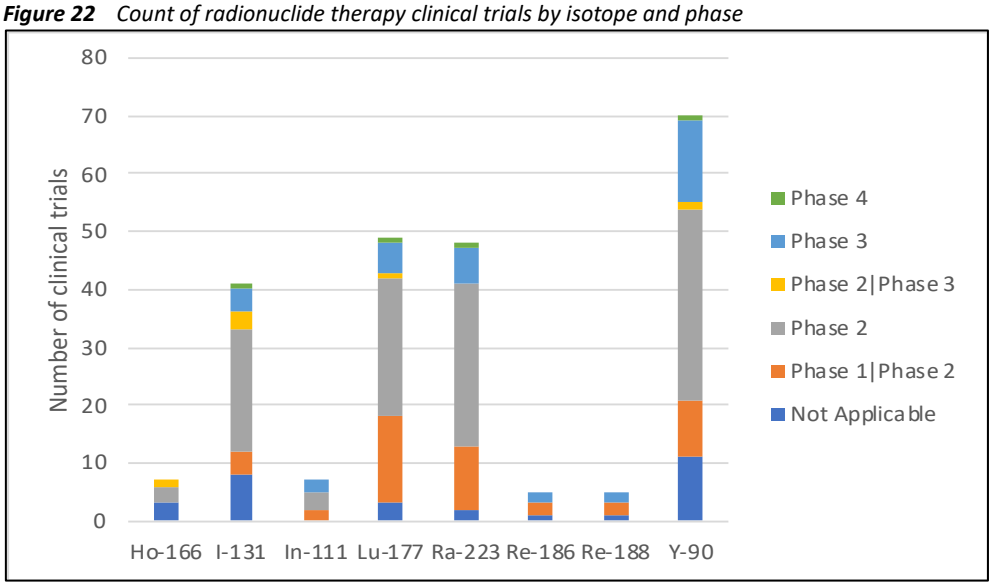
[112] See: https://clinicaltrials.gov/ct2/results?cond=&term=Thorium&cntry=&state=&city=&dist=

Spain	0	3	1	3	12	0	0	7	26
Belgium	0	3	1	6	6	0	0	9	25
United Kingdom	0	3	1	4	8	0	0	5	21
Germany	0	3	0	2	8	0	0	5	18
Australia	0	3	1	7	3	0	0	2	16
South Korea	0	6	0	1	6	0	0	3	16
China	0	6	0	2	1	1	1	4	15
Israel	0	1	1	1	8	0	0	2	13
Austria	0	2	1	4	2	0	0	3	12
Poland	0	2	0	3	5	0	0	2	12
Total	**7**	**67**	**17**	**83**	**117**	**5**	**5**	**113**	**414**

Note: only countries with 10 or more clinical trials and radionuclides with 5 or more clinical trials are shown. Based on data from ClinicalTrials.Gov (2020)

Just under half (47%, 115 out of 244) of the radionuclide therapy clinical trials were Phase 2 trials. Consequently, Phase 2 trials accounted for the highest number of clinical trials for most isotopes.

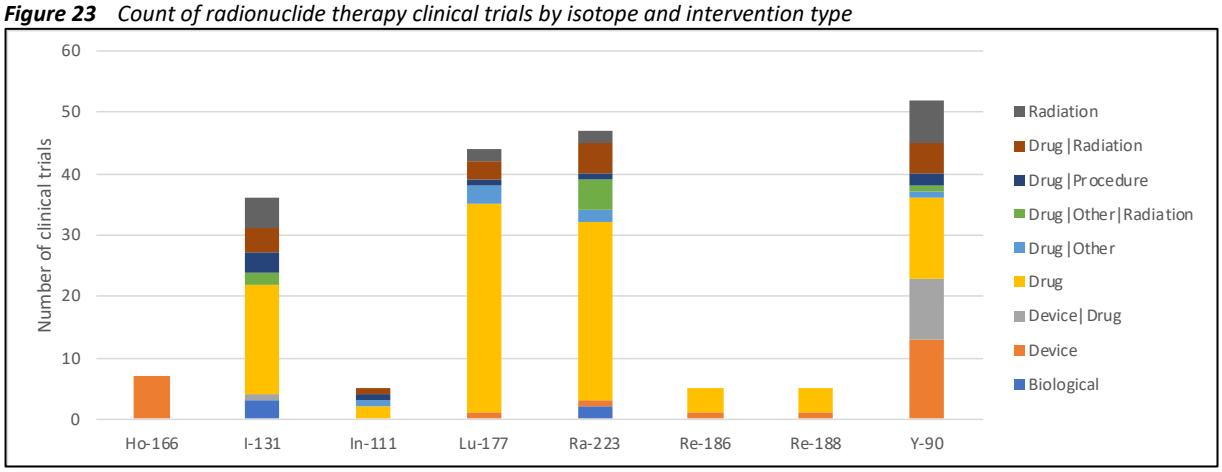
Figure 22 *Count of radionuclide therapy clinical trials by isotope and phase*



Note: isotopes with fewer than 5 trials are not shown. Based on data from ClinicalTrials.Gov (2020)

The therapeutic interventions being tested in clinical trials were largely drugs (45%, 109 out of 244 trials) or drugs in combination with a biological, device, diagnostic, procedure, radiation or other intervention (32%, 77 out of 244), followed by devices (10%, 24 out of 244). A large number of the ^{90}Y trials (33%, 23 out of 70) concerned devices or devices in combination with a drug.

Figure 23 *Count of radionuclide therapy clinical trials by isotope and intervention type*



Note: isotopes and interventions with fewer than 5 trials are not shown. Based on data from ClinicalTrials.Gov (2020)

In terms of indications, almost all ^{90}Y trials (67 out of 70) were looking at cancer treatments with more than one-third (39%, 27 out of 70) focussing on liver cancers. All ^{177}Lu, ^{223}Ra and ^{131}I trials were related to cancer with over half ^{177}Lu trials (57%, 28 out of 49) concerning neuroendocrine tumours, almost two-thirds of ^{223}Ra trials (71%, 34 out of 48) concerning prostate cancer treatment and just under half of ^{131}I trials (41%, 17 out of 41) concerning thyroid cancers.

B.2 Methodology to calculate current demand

B.2.1 From national statistical data

National statistical data was collected from interviews or e-mail exchange with key national contacts from national public health agencies and national nuclear medicine societies. Data requested included:

- number of procedures per radiopharmaceutical and indication
- number of patients per radiopharmaceutical and indication
- total annual activity administered per radiopharmaceutical and indication

Availability of data was highly variable from country to country. Country-level data on total annual activity administered per radiopharmaceutical and indication was preferred. However, few countries collect data at this level, Sweden, Belgium and Czechia being three of the best examples. Failing the availability of activity data, the annual number of procedures or patients per radiopharmaceutical and indication were multiplied with the prescribed activity per procedure.

Assumptions:

- Activity – This number was derived primarily from EANM guidelines. Where guidelines provided a range for the optimal activity, we assumed that the mid-point of the range was the activity given. For example, EANM guidelines suggest[113] "optimal" activity of 1-5 GBq for [^{131}I]-NaI thyroid remnant ablation of adults, in this case 3GBq was be used for further calculation. Where activity was described in terms of MBq or Gbq per kilogram (kg) of bodyweight, activity per procedure was calculated assuming typical bodyweights of 70.8kg[114] and 30kg[115] for adults and children respectively. Where EANM guidelines were not available, country-specific guidelines were used and where these were also not available a brief literature search was conducted to determine typical activity amounts.
- Where only data on numbers of patients were available, guidelines were used to determine the number of procedures per patient.
- Radionuclide level – In some instances, the data regarding the number of annual procedures were supplied at the radionuclide level rather than the radiopharmaceutical level. Hence, procedures could not be matched to indication.

B.2.2 From survey data

Survey participants were invited to fill out the total number of procedures administered in their organisation by radiopharmaceutical and indication. For each country, the average number of procedures administered per indication per radiotherapy centre was then calculated. This number was then multiplied by a) the typical activity per procedure (as outlined in the previous section) and b) the total number of radionuclide therapy centres in a given country.

Assumptions:

The main assumptions were as follows.

- Radionuclide therapy centres – Our calculations assume that in a given country, all radionuclide therapy centres offer the same services and administer the same number of procedures. This is of course unlikely to be the case, particularly in countries with many radionuclide therapy centres. Moreover, it was not possible to find a reliable figure for radionuclide therapy centres for all countries. In such cases, we had to rely on figures provided in interview responses or from published literature. The latter includes centres offering external radiotherapy as well. Thus, current demand estimates needs to be treated with caution.
- Representativeness of responses: We assume that the survey responses received are representative i.e. our responses cover the different sizes of and therapies delivered in radionuclide therapy centres, and consequently averages are a good overall representation of procedures being delivered. This is especially a concern for estimations for countries where survey participation was low: the calculation may be based on responses from very few participants, much lower than the actual number of national radionuclide therapy centres. In these instances, there is a danger that estimates of demand are very skewed.

B.3 Validation of acquired information and calculated data

The information in this study is obtained from several sources. Most is collected bottom-up from experts participating in our survey, interviews or responding to our country factsheets. This information is used in calculations, such as explained in Appendix B.2.

[113] See: https://eanm.org/publications/guidelines/gl_radio_ther_259_883.pdf

[114] See: https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-12-439/tables/3

[115] Technopolis' estimate

Based on our calculations and the information collected, we have completed the country factsheets and asked for validation at various national contacts. These included national authorities and national nuclear medicine associations (see Appendix B.4). For each country we have approached several contacts and – when needed – reminded them of our validation request. Not all contacts responded, resulting in some country data not being validated, which is indicated.

For most countries we received a validation response. Respondents sometimes provided additional information or alternative figures when data were considered incorrect. In most cases respondents indicated that – although no other data available – figures are in line with their expectation or understanding of the nuclear medicine practice in their country. Only for one country the respondent indicated that figures are not correct, but no alternative data could be provided.

Country factsheets were updated based on new information received or comments made. The final country factsheets are presented in Appendix C. The information in these country factsheets have been used throughout the report and for our calculations.

In January 2021, a workshop was held in which over 40 experts participated and the main results of the study were presented. The goal of the workshop was to validate these main results and to test the study's recommendations. During the workshop some comments were made regarding the data presented. These comments were followed-up and resulted in additional and improved data for two countries. The data, calculations and factsheets were adapted accordingly.

An additional round of validation was undertaken by contacting the main suppliers of therapeutic radiopharmaceuticals in Europe. They were provided with our data and calculations on national and European level for their products, requesting validation of those figures (and, if possible due to the commercially sensitive nature of this information, providing alternative internal data). When requested a call was set up to explain our request. One reminder was sent when no response was received. In the end, three responses were received with data at a high aggregate level. For one country this led to alterations to data, factsheet and calculations.

Information received from distinct suppliers of ^{177}Lu radiopharmaceuticals showed that for ^{177}Lu-antibodies our figures were in line with their estimates, [^{177}Lu]Lu-PSMA was said to be underestimated with 20-30% and [177Lu]Lu-DOTATATE seems overestimated. For the overestimation, a crude estimated figure for the number of patients treated across Europe was provided, indicating that our calculations are in the same order of magnitude and certainly less than a factor 2.5 off. Strong conclusions regarding validity of our figures could not be drawn based on the provided level of detail, also considering that these medicines are in some countries produced in-hospital.

Overall, we conclude that most of the data presented in this report is validated to the study team’s best efforts. When not validated, this is explicitly indicated. The data in this report presents the best publicly available information at the time of publishing. Calculated data (mainly those for the use of radionuclides and radiopharmaceuticals) are indicative figures but provide the best insights available to the study team.

B.4 Involved stakeholders and experts in interviews, workshop and national data requests

As part of the data collection and validation of our findings, we have interacted extensively with individual stakeholders and experts in the wider field of therapeutic radionuclides. We have approached many knowledgeable individuals and organisations (stakeholders) across Europe throughout our study, but not all responded to our (repeated) requests or were able to cooperate. Here we provide information on the characteristics of those that did respond and cooperated, providing us with information that was used in this

study. These stakeholders and experts either participated in an interview, provided information on their country or their business' products, participated in our workshop or validated our findings.

In this study we have consulted/involved 84 stakeholders and/or experts across Europe, distributed over 25 European countries, in our data collection – meaning that they provided us with insights in any of our data collection methods (excl. the survey). Of these, 52 provided information on their country or organisation in an online interview or via e-mail (e.g. in the country fact sheets or for validation). In total 41 stakeholders and/or experts (also) participated in the workshop that was organised to present and validate the main findings and recommendations of the study. In **Table 14** and **Table 15** we provide statistics on the number of stakeholders and experts involved.

Table 14 *Type of organisations involved in or consulted for data collection (excl. survey)*

Type of organisation	**Number of stakeholders/experts**
National nuclear medicine association	19
National authority	19
Supplier	14
European authority	14
Nuclear medicine professional/expert	10
Research consultancy	4
International organisation	2
European nuclear medicine association	2
Total	**84**

Source: Technopolis Group

Table 15 *Number of stakeholders per country involved in or consulted for data collection through interview, e-mail or workshop.*

Country	**Number of stakeholders/experts involved in data collection**		
	Unique total	**Involved via interview or e-mail**	**Involved in workshop**
Belgium	5	4	1
Bulgaria	1		1
Croatia	2	1	1
Cyprus	1	1	
Czech Republic	2	2	

Country	Number of stakeholders/experts involved in data collection		
	Unique total	**Involved via interview or e-mail**	**Involved in workshop**
Denmark	1	1	
Estonia	1	1	1
France	5	1	4
Germany	6	5	1
Greece	2	2	
Hungary	1	1	1
Ireland	2	2	
Italy	2	1	1
Malta	1	1	
Netherlands	12	9	5
Norway	2	2	
Poland	3	3	
Portugal	3	1	3
Romania	1	1	1
Slovakia	1		1
Slovenia	1	1	
Spain	2	2	1
Sweden	1	1	
Switzerland	4	4	
United Kingdom	1	1	
European Commission	14		14
International	7	4	5

Country	Number of stakeholders/experts involved in data collection		
	Unique total	Involved via interview or e-mail	Involved in workshop
Total	**84**	**52**	**41**

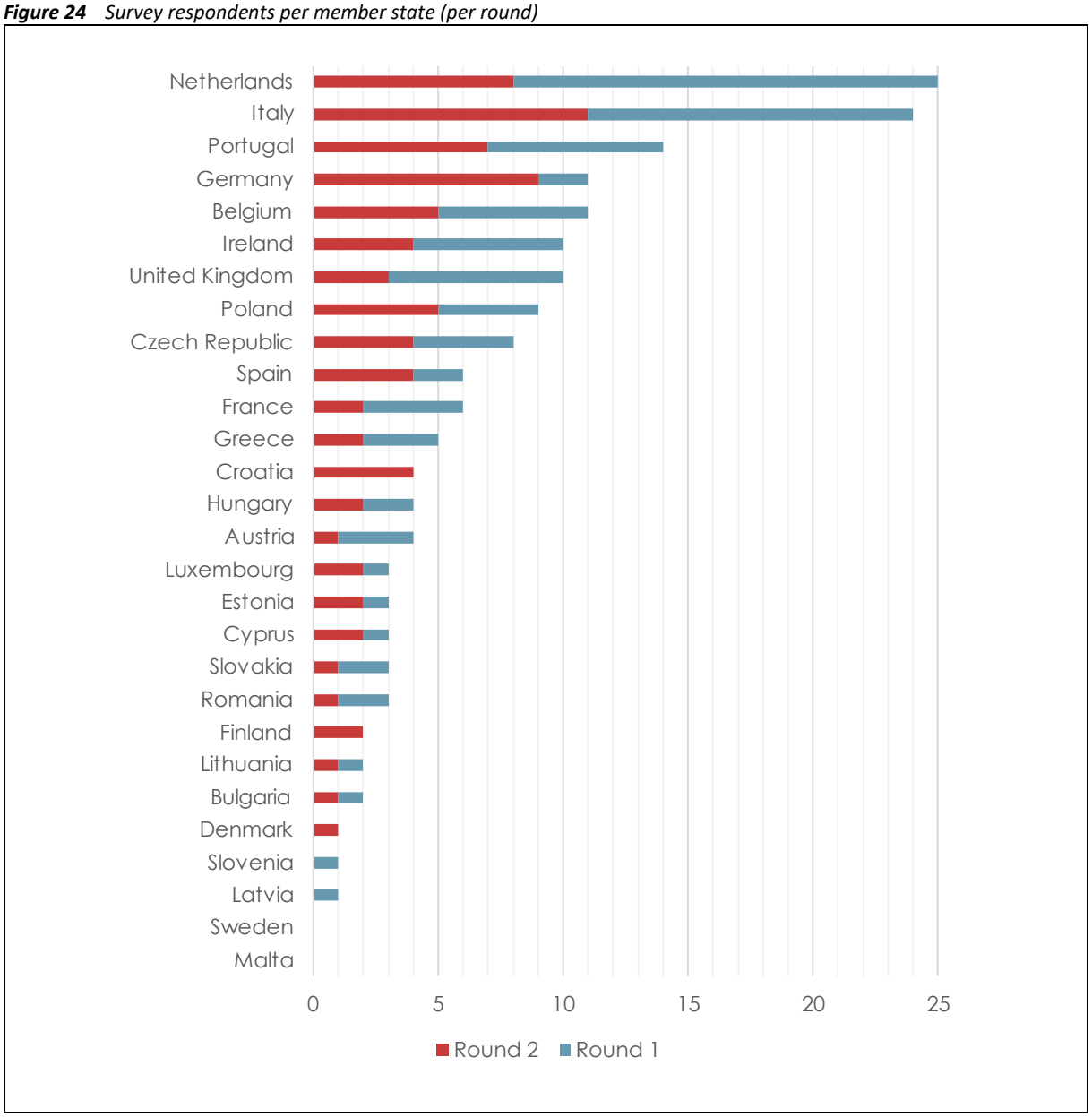
Source: Technopolis Group

B.5 Delphi survey respondents

Taking a bottom-up approach to gather more detailed information on Member States as well as the European Union in general, we sent out a Delphi survey to experts in the field of nuclear medicine. The survey took place in two rounds during the summer of 2020. The first round was deployed to 800+ named individuals, which yielded a response rate of ~16% (125). With the help of EANM, DGN and several other national nuclear medicine societies, as well as several professional LinkedIn groups, a wide invitation was sent out, which yielded 69 responses, a fraction of a percent of the targeted population. In total, 194 full responses were received in the first round – including from non-EU countries Norway, USA, Israel, Switzerland, and even Kazakhstan. Round two was only sent to the 175 EU-respondents of the first round and yielded a 48% response rate with 84 full responses.

Figure 24 shows the responses per EU member state. At a national level, the response rate was not very high except for the first 7 countries (NL, IT, PT, BE DE, IE, UK). In terms of representativity, the responses for these countries seem sufficient. Also, in smaller member states, such as Luxembourg, Estonia and Cyprus, we have reached a representative sample of respondents (as was indicated by some of our contacts). Nevertheless, at the European level, this group of respondents provides a sufficient sample of professionals to represent larger developments in supply and demand.

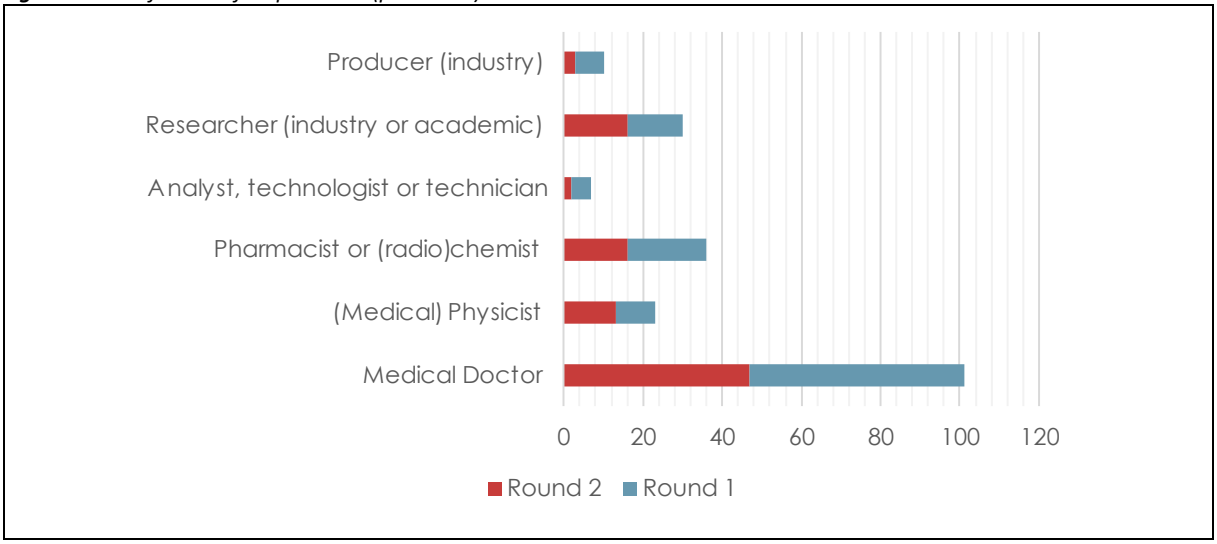
Figure 24 *Survey respondents per member state (per round)*



Note: only respondents to round 1 were invited to round 2

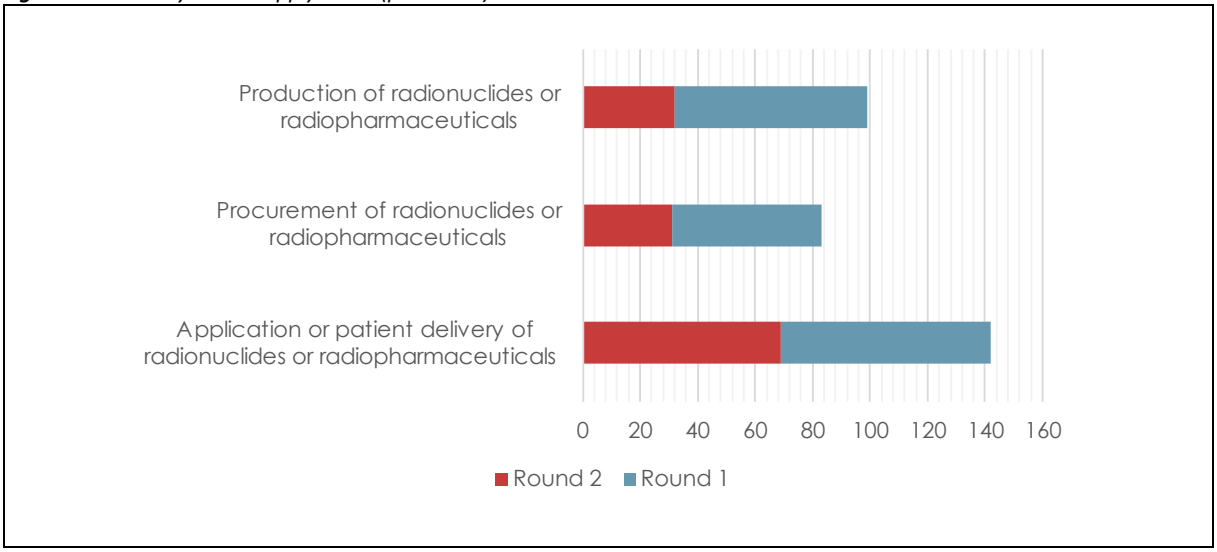
In terms of the profession of the respondents, **Figure 25** shows the main respondents were medical doctors (predominantly nuclear medicine), with as sizeable group of pharmacists, researchers, and physicists.

Figure 25 *Profession of respondents (per round)*



Most of the respondents were active in the application or patient delivery (see **Figure 26**), however there were quite some respondents from other parts of the supply chain. It needs to be noted that respondents were allowed to select several supply chain positions.

Figure 26 *Activity in the supply chain (per round)*



Appendix C Country factsheets

The following appendices present the country factsheets that have been filled based on the available information in our survey, and (where relevant) interviews, email exchanges, and other sources of information.

Note that the provided information differs per country. In the overview below we provide insight in the completeness of the information and the robustness per section of the factsheet.

Completeness is our assessment of the amount of information we received from our sources, taking into consideration that different sources may have complemented each other. This is indicated with the colour: dark green is more complete information from several sources, light green indicates some sources, and light red indicates no sources or no information available.

Robustness relates to the types of sources used to gather the information. Letters indicate sources and in case more than one source is mentioned, this allowed for triangulation of the data. D=official (statistical) data; I=interviews and email exchanges; S=survey; L=supporting literature; C=database of clinical trials (own analysis).

Whereas this information is based on the different data gathering methods at our disposal, we have encountered both positive support from national representatives as well as what could be called "fatigue" at being asked the same questions again (note that both HERCA and UNSCEAR had recently deployed surveys with similar questions). All communication explicitly mentioned the openness of the report, which we believe should be a positive incentive to most respondents involved.

Country	1 - RP used	2 - emerging RP	3 - therapies	4 - prices	5 - medical guidelines	6 - future	7 - supply	8 - access
Austria	S	C		S	S	S	S	L
Belgium	DS	C	D	DS	DS	S	IS	DI
Bulgaria	IS	C	IS	S	IS	S	S	I
Croatia	IS	C	SL	S	S	S	S	I
Cyprus	IS	C	IS	D	S	S	IS	s
Czechia	DI	DI	DI	DIL	D	I	I	IL
Denmark	ID	C			I	S		
Estonia	SI		SI	I	I	S	I	I
Finland	S	C	S	S	S	S	L	L
France	SI	C	S	L	D	S		L
Germany	IS	C	S	S	S	S	S	DS
Greece	S	C	L	IS	IS	S	IS	L
Hungary	S	C	IS	S	S	S	S	L
Ireland	IS	I	IS		I	IS	I	IL
Italy	IS	C	S	S	S	S	S	IL
Latvia	S	C	S					
Lithuania	S		S	L		S		S
Luxembourg	S	C	SL	S	S	S	S	L

Malta								
Netherlands	DIS	C	DL	IS	ISL	S	IS	DI
Poland	IS	C	IS	IL	D	S	I	I
Portugal	IS	C	IS	S	S	S	S	I
Romania	S	C	IS	I	I		S	L
Slovakia	DI	C	I	I	I	S		DIL
Slovenia	DS	C	DL	IS	I	I	I	DI
Spain	S	C	S	ISL	I	IS	IS	IL
Sweden	DI	C	D		I	I	I	I
UK	IS	IC	I	I	DI	I	I	IL

C.1 Austria – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{153}Sm, ^{169}Er, ^{177}Lu, ^{186}Re, ^{223}Ra, ^{225}Ac, ^{90}Y

The above listed RNs have been indicated in the survey.

2. Emerging radionuclides / radiopharmaceuticals

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	^{177}Lu-OPS201, Satoreotide tetraxetan (Phase 1/2)	Neuroendocrine Tumours	Ipsen: Study to Evaluate the Safety and Preliminary Efficacy of ^{177}Lu-OPS201 in NETs
	^{177}Lu-edotreotide PRRT, Everolimu, Amino-Acid Solution (Phase 3)	Neuroendocrine Tumours	ITM Solucin GmbH: Efficacy and Safety of ^{177}Lu-edotreotide PRRT in GEP-NET Patients
	^{177}Lu-lilitomab (Betalutin®) (Phase 1/2)	Non-Hodgkin Lymphoma, Follicular Lymphoma	Nordic Nanovector: A Phase I/II Study of Betalutin® for Treatment of Relapsed Non-Hodgkin Lymphoma
^{177}Lu / ^{68}Ga	[^{177}Lu]-NeoB|[^{68}Ga]-NeoB (Phase 1/2)	Neoplasms	AAA: [^{177}Lu]-NeoB in Patients With Advanced Solid Tumours and With [68Ga]-NeoB Lesion Uptake

3. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 6250 therapeutic treatments in nuclear medicine are performed in Austria.

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-colloids used in radiation synovectomy	360	Survey	203	73
^{90}Y	[^{90}Y]Y-ibritumomab-tiuxetan used in b-cell lymphoma and non-hodgkin lymphoma (EMA authorised)	2	Survey	1000	2
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	2	Survey	3000	6
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	5	Survey	7450	37
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	14	Survey	7450	104
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	1366	Survey	500	683
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	697	Survey	5500	3834
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	119	Survey	1942	231
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	1540	Survey	3000	4620
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	189	Survey	1942	367
^{177}Lu	^{177}Lu-antibodies used in non-hodgkin lymphoma	7	Survey	1062	7
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (EMA authorised)	756	Survey	6475	4895
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	1232	Survey	7400	9117

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	237	Survey	3,85	1
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	21	Survey	3133	66
^{169}Er	^{169}Er-colloids used in radiation synovectomy	1050	Survey	25	26
^{186}Re	^{186}Re-colloids used in radiation synovectomy	36	Survey	111	4

4. Prices and reimbursement

Radio-pharmaceutical	Price (€)	Other information / reflection on distributors
[^{131}I]-NaI	€41-€400 per GBq (from survey)	From survey: Curium Pharma/THP and GE
[^{131}I]I-mIBG		From survey: GE and Polatom
[^{223}Ra]$RaCl_2$	€4300-€4400 (from survey)	From survey: BAYER
[^{90}Y]Y-ibritumomab-tiuxetan		From survey: Curium Pharma/THP and IBA
^{90}Y-resin microspheres		From survey: IBA/ Curium Pharma
^{186}Re		From survey: Curium Pharma/THP and IBA
^{169}Er		From survey: Curium Pharma/THP
^{90}Y-colloids		From survey: Curium Pharma/THP and IBA
[^{177}Lu]Lu-PSMA		From survey: FZ Sibersdorf/BSM and ITG
^{177}Lu-colloids		From survey: ITG
^{153}Sm		From survey: Curium Pharma/THP

5. Medical guidelines

According to the survey responses Austria uses both European and national clinical guidelines for all relevant radiopharmaceuticals.

6. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
^{177}Lu-peptides	Respondent believes RP will strongly increase (+15%) in 10 years	Survey
^{177}Lu-antibodies	Respondent believes RP will strongly increase (+15%) in 10 years	Survey
[^{225}Ac]Ac-PSMA	Respondent believes RP will strongly increase (+15%) in 10 years	Survey
^{166}Ho-microspheres	Respondent believes RP will strongly increase (+15%) in 10 years	Survey
[^{177}Lu]Lu-PSMA	Respondent believes RP will strongly increase (+15%) in 10 years	Survey
[^{223}Ra]$RaCl_2$	Respondent believes RP will strongly decrease (-15%) in 10 years	Survey
[^{153}Sm]Sm-EDTMP	Respondent believes RP will strongly decrease (-15%) in 10 years	Survey

The expected strong decrease of the demand for [^{223}Ra]$RaCl_2$ is due to replacement of the radiopharmaceutical with either [^{177}Lu]Lu-PSMA or [^{225}Ac]Ac-PSMA as soon as these radiopharmaceuticals receive market authorisation and their use described in clinical guidelines. For ^{177}Lu, a strong increase is expected for labelled antibodies and peptides once they enter the clinic or receive marketing authorisation.

7. Supply situation

In Austria supply issues only happened rarely (1-2 times in five years) for [^{131}I]-NaI, which had to a great extent impact on patients. The supply issue was caused by technical issues during external production. No other supply issues have been reported in the survey.

8. Patient access to radionuclide therapy (e.g. regional differences)

- Number of radiopharmacies:

  Unknown, but likely similar to number of radionuclide therapy practicing centres.

- Number of radionuclide therapy practicing centres:

  According to Gleisner (2017) Austria has 7 (inpatient) practicing centres for radionuclide therapy in 2015-2016.

9. Sources of information / References

[1] Both surveys (N = 4 in Round 1 and N = 1 in Round 2) of this study (2020)

[2] Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[3] ClinicalTrials.Gov database (2020)

C.2 Belgium – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: **^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{223}Ra**, ^{213}Bi

Radionuclides in bold have been listed by FANC and were confirmed by the survey. Underlined RNs have been indicated in the survey, but are likely only rare RNs in experimental use.

2. Emerging radionuclides / radiopharmaceuticals

[^{177}Lu]Lu-DOTATATE is currently only supplied under magistral preparation as it is not officially registered yet.

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	^{177}Lu-3BP-227 (also called ^{177}Lu-IPN01087) (Phase 1/2)	Pancreatic Ductal Adenocarcinoma, Colorectal Cancer, Gastric Cancer, Squamous Cell Carcinoma of the Head and Neck, Bone Cancer, Metastatic Tumours	Ipsen: Study to Evaluate the Safety and Activity (Including Distribution) of ^{177}Lu-3BP-227 in Subjects With Solid Tumours Expressing Neurotensin Receptor Type 1.
	[^{177}Lu]Lu-DOTATATE (Phase 3)	Gastroenteropancreatic Neuroendocrine Tumours, Neuroendocrine Tumours	Jules Bordet Institute: ^{177}Lutetium-octreotate Treatment Prediction Using Multimodality Imaging in Refractory NETs
	[^{177}Lu]Lu-PSMA (Phase 3)	Prostate Cancer	Endocyte: Study of [^{177}Lu]Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer
	[^{177}Lu]Lu-DOTATATE (Phase 3)	Carcinoid Tumour of the Small Bowel, Neuroendocrine Tumour	AAA: A Study Comparing Treatment With ^{177}Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours
	^{177}Lu-lilitomab (Betalutin®) (Phase 1/2)	Non-Hodgkin Lymphoma, Follicular Lymphoma	Nordic Nanovector: A Phase I/II Study of Betalutin® for Treatment of Relapsed Non-Hodgkin Lymphoma
^{90}Y	^{90}Y SIRT + chemotherapy (Phase 2/3)	Intrahepatic Cholangiocarcinoma	Sirtex Medical: SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{90}Y / ^{131}I	^{131}I/^{90}Y radioembolisation + TACE-DEB) (Phase 2)	Hepatocellular Carcinoma (HCC)	Ghent University Hospital: Transarterial RAdioembolisation Versus ChemoEmbolization for the Treatment of Hepatocellular Carcinoma
^{223}Ra	^{223}Ra, Enzalutamide (Phase 3)	Prostate Cancer	European Organisation for Research and Treatment of Cancer – EORTC: Comparing Enzalutamide vs. a Combination of Ra223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Castration Resistant Prostate Cancer Patients Metastatic to Bone.
	[^{223}Ra]$RaCl_2$, Pembrolizumab (Phase 1/2)	Carcinoma, Non-Small-Cell Lung, Non-small Cell Lung Cancer	BAYER: An Open-label, Multicenter, Phase 1/2 Study of Radium-223 Dichloride in Combination With Pembrolizumab in Participants With Stage IV Non-small Cell Lung Cancer

3. Therapies and procedures

Radio-pharmaceutical	Number of Patients receiving therapy per year	Number of procedures per year (2018)	Activity (2019)	Source of data
[^{131}I]-NaI	2729	2729	4204.49 GBq	FANC
[^{131}I]I-mIBG	19	19	45.56 GBq	FANC
^{90}Y-Cl (precursor for [^{90}Y]Y-ibritumomab-tiuxetan)	-	-	10.63 GBq	FANC
^{90}Y-colloid (citrate)	28	28	7606.81 GBq	FANC
^{90}Y-microspheres	251	251	1426.95 GBq	FANC
[^{177}Lu]Lu-PSMA	25 (calculated: 2 injections per patient)	50 (calculated from average patient dose of 7400 MBq)	371.37 GBq	FANC
[^{177}Lu]Lu-DOTATATE	25 (calculated: 4 injections per patient)	100 (calculated from average patient dose of 6475 MBq)	651.24 GBq	FANC
[^{153}Sm]Sm-EDTMP	-	11	27.45 GBq	FANC
^{166}Ho-microspheres	-	-	5.2 GBq	FANC
^{186}Re-sulphide	-	2 (calculated from average patient dose of 111 MBq)	208 MBq	FANC

Radio-pharmaceutical	Number of Patients receiving therapy per year	Number of procedures per year (2018)	Activity (2019)	Source of data
[^{223}Ra]$RaCl_2$	250	1498	26.52 GBq	FANC

4. Prices and reimbursement

Information on prices, producers and reimbursement in Belgium is monthly updated and published on the website of the national health insurance institute of Belgium: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/radiopharma/Paginas/vergoedbare-radiofarmaceutische-referentielijsten-referentiebestanden.aspx

Radio-pharmaceutical	Price (€)	Type of procedure	Total budget spent per year	Calculation method	Other information / reflection on distributors
[^{131}I]-NaI	€166-€960 (depending on supplier and activity)	Capsule	€453k-€2.62M (calculated estimate)	No. of procedures x price	Producers: CIS BIO International (CAPSION), Mallinckrodt/ Curium Pharma (CAPSULE T), GE Healthcare (THERACAP®)
[^{131}I]I-mIBG	€3060-€7242 (depending on activity)	Injection	€58k-€138k (calculated estimate)	No. of procedures x price	Producer: CIS BIO International
^{90}Y-Cl (precursor for [^{90}Y]Y-ibritumomab-tiuxetan)	€2290	Precursor	-		Producer: CIS BIO International Additional reimbursement condition: Reimbursable for the radiolabeling of ibritumomabtiuxetan, for the treatment, in third line or later, of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL) stage III and IV. Ibritumomabtiuxetan is reimbursable only once in patient's life time.
[^{90}Y]Y-ibritumomab-tiuxetan (Zevalin®)	€8255	Injection	-		Producer: SPECTRUM Pharmaceuticals BV

Radio-pharmaceutical	Price (€)	Type of procedure	Total budget spent per year	Calculation method	Other information / reflection on distributors
					Same additional reimbursement condition as ^{90}Y-Cl (this RPs precursor)
^{90}Y-colloid (citrate)	€264-€437 (depending on activity)	Injection	€7.39k-€12.2k (calculated estimate)	No. of procedures x price	Producer: CIS BIO International
^{90}Y-microspheres	€12.000 - €15.000 (depending onsupplier, independent on activity)		€3.01M-€3.77M (calculated estimate)	No. of procedures x price	Producers: SIRTEX Medical Europe, BIOCOMPATIBLES UK Ltd
[^{177}Lu]Lu-PSMA	-	Injection	-		Not reimbursed
[^{177}Lu]Lu-DOTATATE	Costs about €4.000 to produce in-house, commercial price is expected to be around €12.000	Injection	€400k-€1.20M (calculated estimate)	No. of procedures x price	Not reimbursed, but request has been submitted to add to list of reimbursable RPs. Until then, only produced in-house by some hospitals using ^{177}Lu from ITG.
[^{153}Sm]Sm-EDTMP (samarium lexidronaat, QUARDAMET®)	€1300	Injection	€14.3k (calculated estimate)	No. of procedures x price	Supplier: CIS BIO International
^{166}Ho-microspheres (Quirem spheres®)	€15000	Microspheres	-		Supplier: TERUMO Europe NV
^{186}Re-sulphide	-		-		Not reimbursed
[^{223}Ra]$RaCl_2$ (Xofigo®)	€4400 (per injection)	Injection	€6.59M (calculated estimate)	No. of units administered (no. of injections) x price	Producer: BAYER Additional reimbursement conditions: a) Reimbursable for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone

Radio-pharmaceutical	Price (€)	Type of procedure	Total budget spent per year	Calculation method	Other information / reflection on distributors
					metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment b) maximum 6 vials reimbursable per patient (max 1 vial every 4 weeks). Per administration maximum 1 vial is reimbursable, if needed the second vial is delivered for free by the company.

5. Medical guidelines

In Belgium the EANM guidelines and SNMMI guidelines are used. There are several advices from the Belgian Higher Health Council (advisory body of the Federal Public Service Health) which can be found on the FANC website (https://fanc.fgov.be/nl/studies-en-projecten):

- https://fanc.fgov.be/system/files/aanbeveling_inzake_therapie_door_middel_van_radionucliden_onder_niet-ingekapselde_vorm.pdf
- https://fanc.fgov.be/system/files/radionuclide_therapy_for_symptomatic_prostate_cancer_in_castration-resistant_prostate_cancer_patients_with_raci.pdf
- https://fanc.fgov.be/system/files/peptide_receptor_radionuclide_therapy.pdf
- https://fanc.fgov.be/system/files/advies_betreffende_de_problematiek_van_de_crematie_van_overleden_dragers_van_radioactieve_bronnen.pdf

6. Future demand

^{90}Y microspheres currently used are expected to be in-part replaced by ^{166}Ho microspheres, as these are magnetic and therefore can be traced in MRI scanners.

[^{177}Lu]Lu-DOTATATE is expected to be used a lot in the future, depending on approval for use on several indications. Use requires however significant infrastructural investments by hospitals (see supply situation), which may spread growth over several years.

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{177}Lu]Lu-PSMA	80% of respondents believes RP will strongly increase (>15%), while 20% believes RP will increase (1-15%) in 10 years	Survey (N=5)
[^{177}Lu]Lu-DOTATATE	60% of respondents believes RP will strongly increase (>15%), while 40% believes RP will increase (1-15%) in 10 years	Survey (N=5)
[^{225}Ac]Ac-PSMA	67% of respondents believes RP will strongly increase (>15%), while 33% believes RP will increase (1-15%) in 10 years	Survey (N=3)
^{177}Lu-antibodies	67% of respondents believes RP will strongly increase (>15%), while 33% believes RP will increase (1-15%) in 10 years	Survey (N=3)
^{177}Lu-peptides	67% of respondents believes RP will strongly increase (>15%), while 33% believes RP will increase (1-15%) in 10 years	Survey (N=3)
^{166}Ho-microspheres (HoMS)	50% of respondents believes RP will strongly increase (>15%), while 50% believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{32}P-sodium-phosphate	Respondent believes RP will decrease (-1% - -15%) in 10 years	Survey (N=1)
^{227}Th-conjugate	Respondent believes RP will strongly increase (>15%) in 10 years	Survey (N=1)
^{227}Th-antibody	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=1)
[^{89}Sr]$SrCl_2$	Respondent believes RP will decrease (-1% - -15%) in 10 years	Survey (N=1)
[^{153}Sm]Sm-EDTMP	67% of respondents believe RP will decrease (-1% - -15%), while 33% believes RP will remain stable in 10 years	Survey (N=3)
[^{223}Ra]$RaCl_2$	50% of respondents believe RP will remain stable, while 50% believes RP will decrease (-1% - -15%) in 10 years	Survey (N=4)

7. Supply situation

In Belgium supply issues only happened rarely (1-2 times in five years) for [^{131}I]-NaI, which had to a small extent impact on patients. The supply issue was caused by reactor issues during external production of the radionuclide. No other supply issues have been reported in the survey.

[^{177}Lu]Lu-DOTATATE is currently produced in-house in some centres in Belgium, using supply of ^{177}Lu by ITG. Only these hospitals use this RP, roughly 2 treatments/week fulfilling current demand (each patient will receive 4 treatments with 2-3 months interval). Requires special beds and infrastructure: 24h stay is needed and urine and faeces need to be collected and disposed as radioactive waste. Some hospitals are investing in this infrastructure so that they can use this RP once it is licenced for the treatment of multiple cancers. This determines future demand.

SCK-Mol and IRE are collaborating to produce ^{225}Ac with linear accelerators. They are currently investing to produce this RN for world supply. This is an alpha emitter that is expected to be growing in clinical use over 10 years.

8. Patient access to radionuclide therapy (e.g. regional differences)

In Belgium hospitals work in hubs and spokes, with central hospitals performing most RN therapy, while peripheral hospitals refer their patients to these hospitals. This results in a good access and coverage of RN therapy across the country.

- Number of radiopharmacies:

  Unknown, but likely similar to number of radionuclide therapy practicing centres.

- Number of radionuclide therapy practicing centres:

  According to the Belgian competent authority FANC, 136 centres are performing any form of radionuclide therapy in Belgium. Roughly 7 of these centres perform a wider scala of (more complex) RN therapies.

9. Sources of information / References

[1] Information based on interview (2020) with Dr. Patrick Flamen (chair of BELNUC workgroup regarding development of therapeutic radionuclides) from the Jules Bordet Institute of the Université Libre de Bruxelles (ULB).

[2] Information based on extensive national data provided by FANC, resulting from communications with Annie Vanderlinck from FANC (2020)

[3] Information based on public data from RIZIV (2020), the Belgian institute for health and disability insurance, see: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/radiopharma/Paginas/vergoedbare-radiofarmaceutische-referentielijsten-referentiebestanden.aspx

[4] Both surveys (N = 11 in Round 1 and N = 5 in Round 2) of this study (2020)

[5] Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[6] ClinicalTrials.Gov database (2020)

C.3 Bulgaria – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{223}Ra, ^{153}Sm

Radiopharmaceuticals in compassionate use: none reported

2. Emerging radionuclides/radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials): none reported in Technopolis clinical trials analysis

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year	Source of data	Activity per procedure (MBq)	Total annual activity (MBq)
[^{131}I]-NaI	Benign thyroid diseases	2000	Survey	500	1,000,000
[^{223}Ra]$RaCl_2$	Bone metastases	30	Survey	3.8	114
^{153}Sm	Bone metastases	n/a	n/a	n/a	n/a

4. Prices and reimbursement

Information based on survey

Radio-pharmaceutical	Price per patient dose in € [mean (min, max)]	Number of procedures per year	Total budget spent per year
^{131}I	325 (200, 450)	2000	€650,000
[^{223}Ra]$RaCl_2$	5,000, (5,000, 5,000)	30	€150,000

5. Medical guidelines

National and organisational guidelines are used [1], [2]

6. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{153}Sm]Sm-EDTMP	100% of Bulgarian respondents expect there to be a weak decrease (-1% to -15%) in demand	[1]
^{177}Lu-peptides	100% of Bulgarian respondents expect there to be a weak increase (+1% to +15%) in demand	[1]
[^{177}Lu]Lu-PSMA	100% of Bulgarian respondents expect there to be a weak increase (+1% to +15%) in demand	[1]
[^{223}Ra]$RaCl_2$	100% of Bulgarian respondents expect there to be a strong decrease (<-15%) in demand	[1]

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
$[^{89}Sr]SrCl_2$	100% of Bulgarian respondents expect there to be a strong decrease (<-15%) in demand	[1]

7. Supply situation

- $[^{131}I]$-NaI - 100% of relevant respondents suggested that $[^{131}I]$-NaI had been shortage sometimes (3-4 times) over the last 5 years. These shortages were reported to have happened due to procurement issues.

8. Patient access to radionuclide therapy (e.g. regional differences)

- Number of radiotherapy practicing centres:

  There are 10 radiotherapy practicing centres in Bulgaria [2]

9. Other information

Radiopharmaceuticals are imported to Bulgaria as there are no small-scale facilities for preparation of radiopharmaceuticals for therapeutic purposes.

10. Sources of information / References

[1] Technopolis survey (N = 2)

[2] E-mail exchange with Professor Valeria Hadzhiyska, Head of Clinic of Nuclear medicine, University Hospital Alexandrovska

C.4 Croatia – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{177}Lu, ^{223}Ra, ^{90}Y

Radiopharmaceuticals in compassionate use: none reported

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials):

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	^{177}Lu-antibodies	Relapsed Non-Hodgkin Lymphoma	Yes - Phase I/II

3. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 1274 therapeutic treatments in nuclear medicine are performed in Croatia, however, our current estimates place this number much higher.

Radiopharmaceutical	Indication and type of procedure	Estimates number of annual procedures	Source of data	Average activity per procedure	Activity (MBq)
[^{131}I]-NaI	Benign thyroid diseases	4176	Survey	500	2,088,000
[^{131}I]-NaI	Thyroid remnant ablation of adults	2940	Survey	3000	8,820,000
[^{131}I]-NaI	Thyroid cancer therapy for adults	1320	Survey	5550	7,326,000
[^{223}Ra]$RaCl_2$	Bone metastases	72	Survey	3.8	274
[^{131}I]-NaI	Thyroid remnant ablation of children and young adults	408	Survey	1942	792,540
[^{131}I]-NaI	Thyroid cancer therapy for children and young adults	138	Survey	1942	268,065
[^{131}I]I-mIBG (IOBENGUANE)	Neuroendocrine tumours	42	Survey	7450	312,900
[^{131}I]I-mIBG (IOBENGUANE)	Neuroblastoma	102	Survey	7450	759,900
[^{90}Y]Y-ibritumomab-tiuxetan	B-cell lymphoma and non-hodgkin lymphoma	6	Survey	1000	6,000
^{177}Lu-antibodies	Non-hodgkin lymphoma	6	Survey	1062	6,372

4. Prices and reimbursement

Information based on survey

Radiopharmaceutical	Price per patient dose in € mean (min, max)
[^{131}I]-NaI	100 (50, 150)

Radiopharmaceutical	Price per patient dose in € mean (min, max)
[^{131}I]I-mIBG (IOBENGUANE)	1976 (1976, 1976)
[^{223}Ra]$RaCl_2$	4300 (4300, 4300)

5. Medical guidelines

Croatia uses both European (e.g. the EANM) and national medical guidelines for radiotherapy according to survey respondents.

6. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{225}Ac]Ac-PSMA	75% of Croatian respondents expect there to be a **weak increase** (+1 to +15%) in demand. Another 25% expect there to be **strong increase** in demand (> +15%)	[1]
[^{177}Lu]Lu-DOTATATE	100% of Croatian respondents expect there to be a **weak increase** (+1 to +15%) in demand.	[1]
^{177}Lu-peptides	75% of Croatian respondents expect there to be a **weak increase** (+1 to +15%) in demand.	[1]
[^{177}Lu]Lu-PSMA	100% of Croatian respondents expect there to be a **weak increase** (+1 to +15%) in demand.	[1]

7. Supply situation

No significant issues have been reported

8. Patient access to radionuclide therapy

Number of radiotherapy practicing centres: 12 [2]

9. Sources of information / References

[1] Technopolis survey (N = 4)

[2] E-mail exchange with Zdravka Tečić, Head of Radiological and Nuclear Safety, Ministry of the Interior Civil Protection Department and Boris Ilijas Head of Environment and Radioactive Waste Unit

C.5 Cyprus – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: $I^{131}I$, ^{153}Sm, ^{177}Lu, ^{223}Ra, ^{225}Ac

Radiopharmaceuticals in compassionate use: ^{153}Sm

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials):

Clinical trials analysis suggested that Cyprus is not involved with any radionuclides or radiopharmaceuticals in clinical trials

3. Therapies and procedures

Radiopharmaceutical	Indication and type of procedure	Number of procedures per year	Source of data	Average dose per procedure (MBq)	Activity (MBq)
[^{223}Ra]$RaCl_2$ (Xofigo®)	Bone metastases	27	National statistics	3.8	103
131-NaI	Thyroid remnant ablation (adults)	110[116]	National statistics	3,000	330,000
131-NaI	Thyroid remnant ablation (young adults and children)	110	National statistics	327.5	36,020

4. Prices and reimbursement

Radiopharmaceutical	Price (€)	Number of annual procedures	Total budget spent per year
[^{131}I]-NaI	€160-€320 per patient dose	210	€33,600 - €67,200
[^{131}I]I-mIBG	€253/vial	n/a	-
[^{223}Ra]$RaCl_2$	€5000 per patient dose	27	€135,000

5. Medical guidelines

Information from survey

[116] Data did not specify distribution of treatments between adults, young adults and children, so a 50/50 split was assumed

Radio-pharmaceutical	Indication	Guideline making organisation	Title of/link to guideline
^{131}I	Thyroid remnant ablation (adults, young adults and children)	EANM	Guidelines for radioiodine therapy of differentiated thyroid cancer
[^{223}Ra]$RaCl_2$	Bone metastases	EANM	EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer

6. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{131}I]-NaI	Estimates range between stable an and strong increase (>15%)	[3]
[^{131}I]I-mIBG	Decrease (-1% to -15%	[3]
[^{177}Lu]Lu-DOTATATE	Increase (+1% to +15%)	[3]
^{177}Lu-peptides	Increase (+1% to +15%)	[3]
[^{177}Lu]Lu-PSMA	Increase (+1% to +15%)	[3]
[^{225}Ac]Ac-PSMA	Increase (+1% to +15%)	[3]
[^{223}Ra]$RaCl_2$	Stay stable or increase (+1% to +15%)	[3]
[^{153}Sm]Sm-EDTMP	Decrease (-1% to -15%	[3]

7. Supply situation

Cyprus have had several issues due to problems with connected flights to Cyprus. Radionuclides have arrived late or not at all [1].

Shortages or supply disruption has been reported in Cyprus over the last 5 years for [3]:

- [^{131}I]-NaI - Reported as being due to transportation issues where flights did not arrive, or flight activity limit was reached. This was reported as occurring between 1-2 times and more than 4 times). These shortages were reported to have had to some extent, and in one case to a great extent had a disruptive effect on the treatment of patients.
- [^{177}Lu]Lu-PSMA - Reported as being due to transportation issues where flights did not arrive, or flight activity limit was reached. This was reported as occurring between 1-2 times. These shortages have had a disruptive effect on the treatment of patients to a small extent.
- [^{177}Lu]Lu-DOTATATE - Reported as being due to transportation issues where flights did not arrive, or flight activity limit was reached and also due to production stopping due to COVID-19. This was reported as occurring between 1-2 times. These shortages have had a disruptive effect on the treatment of patients to some extent.

- [^{223}Ra]$RaCl_2$ - Reported as being due to transportation issues and logistics issues. This was reported as occurring between 1-2 times. These shortages have had a disruptive effect on the treatment of patients to a small extent.

One survey respondent suggested that in order to help these issues of shortages specific to Cyprus that "flight companies should have a process to monitor in advance the activity limits booked for the specific flight and let the involved people know in advance to make other transport arrangements".

8. Patient access to radionuclide therapy (e.g. regional differences)

- Number of radiotherapy practicing centres:

  7 +2 hospitals with therapy rooms, Therapy in 2+2 Hospitals [1]

9. Other information

Cyprus do not produce any radiopharmaceuticals. They have reported one request for compassionate use of Sm-153.

10. Sources of information / References

[1] Email exchange with Demetris Sakkas, Radiation Inspection and Control Service, Cyprus

[2] Nicosia Hospital price data

[3] Technopolis survey (survey respondents N = 3)

C.6 Czech Republic – validated

1. Radiopharmaceuticals currently in use [1]

Radionuclides in use: ^{131}I, ^{90}Y, ^{153}Sm, ^{89}Sr, ^{223}Ra, ^{186}Re,^{169}Er, ^{177}Lu

Radiopharmaceuticals in compassionate use: While allowed, not really used

2. Emerging radionuclides

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{225}Ac	PSMA-PRRT	mCRPC	N/A
^{227}Th	N/A	N/A	N/A
149Tb	N/A	N/A	N/A

3. Therapies and procedures

Information based on data supplied by Czech Society of Nuclear Medicine (CSNM) for 2018 (data selected from comprehensive statistics of State institute for Drug Control and the Institute of Health Information and Statistics of the Czech Republic)

Radiopharmaceutical	Indication and type of procedure	Number of Patients Receiving therapy per year	Source of data	Number of procedures per year	National annual demand (GBq)
^{89}Sr Metastron®	Bone painful metastases	96	CSNM	96	12.8
[^{153}Sm]Sm-EDTMP	Bone painful metastases	32	CSNM	34	53.5
^{223}Ra	CR prostate cancer	60	CSNM	335	0.0013
^{90}Y-colloid	Synoviorthesis	385	CSNM	390	93.2
^{186}Re-colloid	Synoviorthesis	39	CSNM	39	3.4
^{169}Er-colloid	Synoviorthesis	25	CSNM	25	0.24
^{131}I	Hyperthyroidism	199	CSNM	199	4859
[^{131}I]I-mIBG	Thyroid carcinoma	1093	CSNM	1292	123.2
[^{131}I]I-mIBG	Pheochromocytoma, neuroblastoma		CSNM	16	
[^{90}Y]Y-ibritumomab	Lymphoma	1	CSNM	2	2
^{177}Lu-oxodotreotid (Lutathera®)	Neuroendocrine Tumours (NET G1 and G2) and Neuroendocrine Carcinomas	30-45	CSNM	120-180	1000 (estimate from incidence data)

4. Prices and reimbursement

In 2015, the equivalent of €75.4 million (based on 2014 purchasing power parity) was spent on radiotherapy i.e. a per capita expenditure of €7.2. Radiotherapy accounted for 0.37% of the total healthcare spending and 8.5% of total cancer care expenditure (Lievens et al. (2020)).

Radiopharmaceutical	Price (€)	Total budget spent per year (€, 2018)	Calculation method	Other information / reflection on distributors
^{89}Sr Metastron®	13.28/MBq	169 984.00	Price x no. of MBq used	

[^{153}Sm]Sm-EDTMP	0.5/MBq	26 750.00	As above	
^{223}Ra	4824.30 /injection	1 616 140.50	As above	
^{90}Y-colloid	1.07/MBq	99 724.00	As above	
^{186}Re-colloid	2.72/MBq	9 248.00	As above	
^{169}Er-colloid	6.67/MBq	1 600.80	As above	
^{131}I	0.067/MBq	325 553.00	As above	
[^{131}I]I-mIBG	0.44/MBq	54 208.00	As above	
[^{90}Y]Y-ibritumomab	19533.34 /injection	39 066.68	Price x no. of procedures	
^{177}Lu-oxodotreotide (Lutathera®)	22320.12 /injection	3 348 018.00	Price x no. of avg estimated procedures	registered by State institute for Drug Control and reimbursed by Health Insurance Companies since 2020
Total		5 690 292.98		

5. Medical guidelines

Radionuclide therapies are covered by

a) EANM guidelines

b) National standards for Clinical Audits in Nuclear Medicine[117]

c) Summaries of Product characteristics (manufacturer documents)

Radiopharmaceutical	**Indication**	**Guideline making organisation**
^{89}Sr Metastron®	Bone painful metastases	European
[^{153}Sm]Sm-EDTMP	Bone painful metastases	European
^{223}Ra	CR prostate cancer	European
^{90}Y-colloid	Synoviorthesis	European
^{186}Re-colloid	Synoviorthesis	European

[117] In Czech at http://www.mzcr.cz/Legislativa/dokumenty/vestnik-c2/2016_11347_3442_11.html

Radiopharmaceutical	Indication	Guideline making organisation
^{169}Er-colloid	Synoviorthesis	European
^{131}I	Hyperthyroidism	European
[^{131}I]I-mIBG	Thyroid carcinoma	European
[^{131}I]I-mIBG	Pheochromocytoma, neuroblastoma	European
[^{90}Y]Y-ibritumomab	Lymphoma	European
^{177}Lu- oxodotreotide	Neuroendocrine Tumours and Carcinomas	European

6. Future demand

Radionuclide	Indication	Number of Patients expected to receive therapy in future	Procedures and dosage	Source of data
^{177}Lu	metastatic castration-resistant prostate cancer (mCRPC)	200-400/year	3 doses of 6 GBq/patient	CSNM
^{225}Ac (as ^{177}Lu alternative)	mCRPC	200-400/year	3 doses of 7 MBq/patient	CSNM

Radiopharmaceutical	Number of Patients Expected to receive therapy in future	Source of data
[^{177}Lu]Lu-PSMA	Strong increase or increase expected by majority of respondents	Survey(n=4)
[^{225}Ac]Ac-PSMA	Strong increase expected by half of all respondents	Survey(n=4)
[^{177}Lu]Lu-DOTATATE	Strong increase or increase expected by majority of respondents	Survey(n=4)
^{177}Lu-peptides	Increase expected by half of all respondents	Survey(n=4)
^{177}Lu-antibodies	Increase expected by half of all respondents	Survey(n=4)
^{90}Y-colloids	Stable expected by half of all respondents; Increase by a minority	Survey(n=4)
^{90}Y-glass microspheres	Stable expected by half of all respondents	Survey(n=4)
[^{153}Sm]Sm-EDTMP	Stable expected by majority of respondents	Survey(n=4)
131-mIBG	Stable expected by half of all respondents	Survey(n=4)

Radiopharmaceutical	Number of Patients Expected to receive therapy in future	Source of data
131-NaI	Stable expected by half of all respondents; Increase by a minority	Survey(n=4)
^{169}Er-colloids	Stable expected by majority of respondents	Survey(n=4)

7. Supply situation

Only registered radionuclides may be imported for human use with the exception of commercial clinical trials [1]. Transportation of these radiopharmaceuticals is without any problem.

There is no production of radiotherapeutic pharmaceuticals in the Czech Republic [1]. So called all "in-house" production of diagnostic or therapeutic radiopharmaceuticals (at Universities etc.) is strictly prohibited in the Czech Republic. Therefore, in clinical practice (except clinical trials) only the use of radiopharmaceuticals authorised by State Institute for Drug Control is permitted – process of registration copies usually previous EMA registration or other international European registration. Exceptional cases are transient (2 years) permissions to use F-choline in patients with hyperparathyroidism and imaging of hypoxia using F-MISO.

Therapeutic PRRT radiopharmaceuticals are not commercially produced in the Czech Republic. Currently there is no official information on the upcoming marketing authorisation of the PRRT product manufactured in the Czech Republic.

8. Patient access to radionuclide therapy

According to Gleisner et al. (2017), there are 4.4 radiotherapy centres per million inhabitants, 47 in total [3]. Among these, according to the CSNM, there are 6 Inpatient radionuclide therapy practicing centres and 4 outpatient radionuclide therapy practicing departments [1]

9. Sources of information / References

[1] Email exchange with Dr Pavel Koranda, Czech Society of Nuclear Medicine (CSNM)

[2] Email exchange with Mr Petr Papírník, State Office for Nuclear Safety, Czech Republic

[3] Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[4] Lievens, Y., Borras, J. M., & Grau, C. (2020). Provision and use of radiotherapy in Europe. *Molecular Oncology*.

[5] Technopolis survey (N = 4)

C.7 Denmark – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{90}Y, ^{131}I, ^{177}Lu, ^{223}Ra

Radiopharmaceutical	Trade Name	Supplier/Distributor
^{177}Lu oxodotreotide	Lutathera®	Advanced Accelerator Application

Radiopharmaceutical	Trade Name	Supplier/Distributor
^{223}Ra dichloride	Xofigo®	Bayer Pharma AG
^{153}Sm-ethylenediaminetetramethylene phosphonic acid	Quadramet®	Cis Bio International Oris Ind.
^{90}Y compounds	Ytracis®	Cis Bio International Oris Ind.
^{131}I sodium iodide	Sodium iodide (I131) capsules T	Curium Netherlands B.V.
Other therapeutic radiopharmaceuticals	Yttriga®	Eckert & Ziegler
[^{131}I]-iobenguane	(131-I)Meta-iodobenzylguanidine therap. GE Health.	GE Healthcare Buchler GmbH .
[^{131}I]-sodium-iodide	Sodium Iodide (^{131}I) Injection GE Healthcare Limited	GE Healthcare Buchler GmbH .
[^{131}I]-sodium iodide	Theracap®	GE Healthcare Buchler GmbH .
Other therapeutic radiopharmaceuticals	EndolucinBeta®	ITG Isotope Technologies Garchin
^{131}I sodium iodide	Moniyot-131 Capsule T	Monrol Europe S.R.L.
^{131}I sodium iodide	Moniyot-131 Oral Solution	Monrol Europe S.R.L.
^{90}Y Ibritumomab tiuxetan	Zevalin®	Schering AG

2. Medical guidelines

Overall, EANM guidelines are used with a few local guidelines. Source: [1]

3. Future demand

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
[^{131}I]-NaI	Respondent expects increase in the next 10 years	Survey (n=1)
^{177}Lu-peptides	Respondent expects increase in the next 10 years	Survey (n=1)

4. Patient access to radionuclide therapy (e.g. regional differences)

- Number of radiotherapy practicing centres:

  5 large centres (benign and malign) and 9 small centres (benign). Source: [1]

5. Sources of information / References

[1] Information received from Dr. Peter Hovind, Danish Society of Clinical Physiology and Nuclear Medicine

[2] Technopolis survey (N = 1)

C.8 Estonia – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{32}P, ^{223}Ra, ^{186}Re, ^{169}Er,^{153}Sm, 89, ^{90}Y, ^{177}Lu

Radiopharmaceuticals in compassionate use: [^{177}Lu]Lu-DOTATATE

2. Therapies and procedures

Radiopharmaceutical	Indication and type of procedure	Number of Patients Receiving therapy per year	Source of data
^{131}I, 131-MIBG	Differentiated thyroid cancer (adults)	137 (2019)	Estonian Nuclear Medicine Society
^{131}I, 131-MIBG	Differentiated thyroid cancer (children)	137 (2019)	Estonian Nuclear Medicine Society
^{131}I	Benign thyroid disease	363 (2019)	Estonian Nuclear Medicine Society
^{223}Ra-dichloride (Xofigo®)	Bone lesions in prostate cancer	95 (2019)	Estonian Nuclear Medicine Society
[^{177}Lu]Lu-PSMA	Prostate cancer	31 (2019)	Estonian Nuclear Medicine Society
^{90}Y-colloid	Radiosynovectomy	6 (2019)	Estonian Nuclear Medicine Society
^{186}Re-colloid	Radiosynovectomy	1 (2019)	Estonian Nuclear Medicine Society

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-colloids used in radiation synovectomy	11	Survey	203	2

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	2	Survey	7450	15
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	2	Survey	7450	15
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	660	Survey	500	330
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	143	Survey	5500	787
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	12	Survey	1942	23
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	308	Survey	3000	923
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	9	Survey	1942	17
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (EMA authorised)	3	Survey	6475	19
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	45	Survey	7400	333
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	108	Survey	3.85	0.4
^{32}P	^{32}P-sodium-phosphate used in myeloproliferative disease	3	Survey	185	1
^{89}Sr	[^{89}Sr]$SrCl_2$ used in bone metastases (EMA authorised)	6	Survey	150	1
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	6	Survey	3133	19
^{186}Re	^{186}Re-colloids used in radiation synovectomy	2	Survey	111	0.2

3. Prices and reimbursement

Source: [1]

Radiopharmaceutical	**Price (€)** **All reimbursement sums; price per procedure**	**Type of procedure**	**Supplier/Distributor**
[^{131}I]-NaI	1066 EUR	treatment of Thyroid cancer with^{131}I	Curium; GE
[^{131}I]-NaI	588 EUR	treatment of Thyrotoxicosis with ^{131}I	Curium; GE
[^{131}I]I-mIBG	7355 EUR	treatment of NET with [^{131}I]I-mIBG	
153 Sm-EDTMP	1959 EUR	palliative treatment of bone metastasis with [^{153}Sm]Sm-EDTMP	CisBio, Curium Pharma
^{89}Sr -chloride	1643 EUR	palliative treatment of bone metastasis with ^{89}Sr -chloride	GE; Polatom
^{223}Ra-dichloride	27 EUR + radiopharmaceutical 4803 EUR (limited to 1st, 2nd, 3rd and 6th dose, each)	treatment of bone metastasis with ^{223}Ra-dichloride	Bayer
^{169}Er	3404 EUR (reimbursement for one procedure, which can include the treatment of several joints at one time)	radiosynovectomy with ^{169}Er for small joints	
^{90}Y	938 EUR (per procedure per joint)	radiosynovectomy with ^{90}Y for medium and large joints	CisBio, Curium Pharma
^{186}Re	938 EUR (per procedure per joint)	radiosynovectomy with ^{169}Er for medium and large joints	
[^{177}Lu]Lu-PSMA-ligand	currently no reimbursement, however the hospital may perform treatment without reimbursement	treatment of prostate cancer with [^{177}Lu]Lu-PSMA-ligand	
[^{177}Lu]Lu-DOTATATE	-	-	AAA Novartis

4. Medical guidelines

Mainly EANM/SNMMI guidelines are used. Institutional guidelines in Estonian are in place. Thyroid cancer treatments are also covered by ATA (American Thyroid Association)/ETA (European Thyroid Association) guidelines, bone pain palliation by ESMO (European Society for Medical Oncology) and NCCN guidelines (National Comprehensive Cancer Network).

5. Future demand

Radiopharmaceutical	Demand expectation	Source of data
[^{177}Lu]Lu-DOTATATE	Strong increase (more than +15%)	Survey
[^{177}Lu]Lu-PSMA	Strong increase (more than +15%)	Survey
[^{89}Sr]$SrCl_2$	Strong decrease (more than -15%)	Survey

6. Supply situation

As radiopharmacies with only operational level 2 are in operation in the country, all therapeutic radiopharmaceuticals are imported. [1]

7. Patient access to radionuclide therapy (e.g. regional differences)

There are three hospitals in the country that practice nuclear medicine, incl. therapy with radionuclides. All of them have a radiopharmacy with operational level 2 (according to IAEA classification). There are two hospitals in the country that practice external beam radiotherapy and HDR therapy. And finally, there is one hospital that uses brachytherapy in ophthalmology. [1]

8. Sources of information / References

[1] Information received from Dr. Sergej Nazarenko, Estonian Nuclear Medicine Society

[2] Survey responses (N = 3), Technopolis Group

C.9 Finland – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: [^{131}I]-NaI, [^{177}Lu]Lu-DOTATATE, ^{90}Y-glass microspheres, [^{131}I]I-mIBG, ^{186}Re-colloids. [1]

2. Therapies and procedures

Radiopharmaceutical	Indication and type of procedure	Number of procedures per year	Activity (GBq)	Source of data
[^{131}I]-NaI	benign thyroid diseases	155	77	[1]
[^{131}I]-NaI	thyroid remnant ablation of adults	99	297	[1]
[^{131}I]-NaI	thyroid remnant ablation of children and young adults	3	6	[1]

Radiopharmaceutical	Indication and type of procedure	Number of procedures per year	Activity (GBq)	Source of data
[^{131}I]-NaI	thyroid cancer therapy for adults	3	17	[1]
[^{131}I]-NaI	thyroid cancer therapy for children and young adults	8	15	[1]
[^{131}I]I-mIBG	neuroblastoma	2	11	[1]
[^{131}I]I-mIBG (IOBENGUANE)	adult neuroendocrine tumours	2	11	[1]
[^{177}Lu]Lu-PSMA	therapy of castration resistant prostate cancer and pc-metastases	30	222	[1]
^{32}P-sodium-phosphate	myeloproliferative disease	29	5	[1]
[^{223}Ra]$RaCl_2$	bone metastases	20	74	[1]

3. Prices and reimbursement

Radiopharmaceutical	Price (€) per patient dose
[^{131}I]-NaI	360
[^{223}Ra]$RaCl_2$	5000
^{90}Y-resin microspheres	12000
^{90}Y-colloids	1200

4. Medical guidelines

Radiopharmaceutical	Guideline making organisation
[^{131}I]-NaI	Both European and national clinical guidelines
[^{131}I]I-mIBG	European clinical guidelines (e.g. from the EANM)

5. Future demand

Radiopharmaceutical	Growth expected in future	Source of data
[^{177}Lu]Lu-DOTATATE	Up to 15%	[1]

Radiopharmaceutical	Growth expected in future	Source of data
^{177}Lu-peptides	More than 15%	[1]
^{90}Y-resin microspheres	Up to 15%	[1]

6. Patient access to radionuclide therapy (e.g. regional differences)

In Finland there are **five** university hospitals with full nuclear medicine services, all of which are equipped with PET/CT. One of the leading European radiopharmaceutical companies, MAP Medical Technologies Oy, has three production sites in Finland, so the access to the radiopharmaceuticals is good in spite of long distances within the country. There is nuclear medicine activity in approximately 40 laboratories in Finland. The cyclotron facilities for radiopharmaceutical production are located in Turku and Helsinki. Nuclear medicine research has been active throughout the years in Finland, but it has been focusing to Turku, Kuopio and Helsinki. [2]

7. Sources of information / References

[1] Technopolis Survey data (N = 6)

[2] Kairemo K. (2012). Nuclear medicine in Finland. World journal of nuclear medicine, 11(3), 101–102. https://doi.org/10.4103/1450-1147.103406

C.10 France – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{169}Er, ^{177}Lu, ^{186}Re, ^{223}Ra

Radiopharmaceuticals in compassionate use: not used

2. Emerging radionuclides / radiopharmaceuticals

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	Betalutin®	Non-Hodgkin Lymphoma, Follicular Lymphoma	No
^{90}Y	^{90}Y-Epratuzumab	Acute Lymphoblastic Leukemia	Yes – Phase I/II
^{166}Ho	^{166}Ho-microspheres	intra-arterial treatment in the liver	Don't know

3. Therapies and procedures

Radiopharmaceutical	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
[^{131}I]I-mIBG (IOBENGUANE)	adult neuroendocrine tumours	15	[5]	7450	114
[^{131}I]I-mIBG	neuroblastoma	15	[5]	7450	114
[^{131}I]-NaI	benign thyroid diseases	3925	[5]	500	1963
[^{131}I]-NaI	thyroid cancer (adults)	1840	[5]	5550	10120
[^{131}I]-NaI	thyroid cancer (children and young adults)	230	[5]	1942.5	447
[^{131}I]-NaI	thyroid remnant ablation (adults)	3688	[5]	3000	11063
[^{131}I]-NaI	thyroid remnant ablation (children and young adults)	383	[5]	1942.5	744
[^{153}Sm]Sm-EDTMP	bone metastases	130	[5]	3133	408
^{169}Er-colloids	radiation synovectomy	161	[5]	25	4
[^{177}Lu]Lu-DOTATATE	gastroenteropancreatic neuroendocrine tumours	1100	[1]	6475	7123
[^{177}Lu]Lu-PSMA	castration resistant prostate cancer and metastases	690	[5]	7400	5106
^{186}Re-colloids	radiation synovectomy	161	[5]	111	18
[^{223}Ra]$RaCl_2$	bone metastases	101	[4]	3.85	0.384
^{90}Y-colloids	radiation synovectomy	276	[5]	203.5	56
^{90}Y-glass microspheres	intra-arterial treatment (liver)	196	[4]	11500	2254
^{90}Y-resin microspheres	intra-arterial treatment (liver)	230	[4]	3000	690
[^{90}Y]Y-ibritumomab-tiuxetan	b-cell lymphoma and non-hodgkin lymphoma	61	[5]	1000	61

According to a survey conducted in 2017, about 14 000 patients annually receive radiotherapy. About half of these (6 580) are treated as outpatients for hyperthyroidism, synoviorthesis (treated with synovectomy) etc. [4]

4. Prices and reimbursement

In 2015, the equivalent of €921 million (based on 2014 purchasing power parity) was spent on radiotherapy i.e. a per capita expenditure of €13.9. Radiotherapy accounted for 0.39% of the total healthcare spending and 6.9% of total cancer care expenditure (Lievens et al. (2020)).

Radiopharmaceutical	Price (€, mean) per treatment	Other information / reflection on distributors
^{169}Er-colloids	430.50	[5,6]
[^{131}I]-NaI	80.00	[5,6]
[^{153}Sm]Sm-EDTMP	1321.50	[5, 6]
^{186}Re-colloids	443.00	[5,6]
[^{223}Ra]$RaCl_2$	3575.00	[5,6]
^{90}Y-colloids	296.00	[5, 6]

5. Medical guidelines

Radiopharmaceutical	Indication	Guideline making organisation	*Source of data*
[^{131}I]-NaI	Thyroid conditions	National	[6]
[^{153}Sm]Sm-EDTMP	bone metastases	National	[6]
[^{223}Ra]$RaCl_2$	bone metastases	National	[6]
^{90}Y-colloids	radiation synovectomy	European and National	[6]

All other radiopharmaceuticals are covered under EANM guidelines.

6. Future demand

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
^{177}Lu-peptides	Strong increase for majority of respondents	[6], n=3
[^{177}Lu]Lu-PSMA	Strong increase for majority of respondents	[6], n=3

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
[^{177}Lu]Lu-DOTATATE	Increase for majority of respondents	[6], n=3
^{177}Lu-antibodies	Increase for all respondents	[6], n=3
[^{223}Ra]$RaCl_2$	Decrease for majority of respondents	[6], n=3
^{169}Er-colloids	Increase for all respondents	[6], n=3
[^{131}I]I-mIBG	Unclear	[6], n=3
[^{131}I]-NaI	Stable for majority of respondents	[6], n=3
^{90}Y-colloids	Decrease for majority of respondents	[6], n=3
^{90}Y-glass and resin microspheres	Unclear	[6], n=3
[^{90}Y]Y-ibritumomab-tiuxetan	Decrease for all respondents	[6], n=3
^{186}Re-colloids	Decrease for all respondents	[6], n=3
[^{153}Sm]Sm-EDTMP	Decrease for majority of respondents	[6], n=3

7. Supply situation

Shortages were reported rarely (1–2 times for [^{131}I]-NaI, [^{153}Sm]Sm-EDTMP and [^{223}Ra]$RaCl_2$) or sometimes (3-4 times) for ^{90}Y-colloids by one individual [6]. This was caused by external production issues and affected patients to a small ([^{131}I]-NaI, [^{153}Sm]Sm-EDTMP) or some extent ([^{223}Ra]$RaCl_2$, ^{90}Y-colloids).

8. Patient access to radionuclide therapy (e.g. regional differences)

0.9 radiotherapy centres per million inhabitants (based on Gleisner et al. (2017))

In France, radiopharmacies are directly included in NM departments. They are mandatory in public hospitals but not in private hospitals

According to the 2017 ASN survey, about 46 nuclear medicine departments that carry out internal radiation therapy procedures. [4]

9. Other information

The production capacity of 177 Lu has (and could) to increase to meet the clinical demand [6]. Moreover, if high efficacy is confirmed for [^{177}Lu]Lu-PSMA in prostate cancer, the number of patients treated will be much higher [6].

10. Sources of information / References

[1] Email and interview exchange with IRSN – Institute for Radiological Protection and Nuclear Safety

[2] Gleisner, K. S., Spezi, E., Solny, P., Gabina, P. M., Cicone, F., Stokke, C., ... & Tipping, J. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[3] Lievens, Y., Borras, J. M., & Grau, C. (2020). Provision and use of radiotherapy in Europe. *Molecular Oncology*

[4] Autorité de sûreté nucléaire (2019) Médecine nucléaire en France: État du parc, des moyens humains et des activités en 2017. Available at: https://www.asn.fr/Professionnels/Activites-medicales/Medecine-nucleaire/Bilan-des-inspections-en-medecine-nucleaire/Medecine-nucleaire-en-France-Etat-du-parc-des-moyens-humains-et-des-activites-en-2017

[5] Technopolis survey Round 1, N = 22 respondents

[6] Technopolis survey Round 2, N = 3 respondents

C.11 Germany – not validated

Please note: the German Society of Nuclear Medicine (DGN) has carefully examined the country factsheet for Germany. It strongly recommends that the data must not be used to determine the radionuclide use for therapy in Germany. In its assessment, the data presented in no way reflects the real need for therapeutic radionuclides and are not representative (i.e. based on a survey including only 8 centres).

The research team acknowledges this caveat and refers to this in the report.

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{32}P, ^{67}Cu, ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{169}Er, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, ^{213}Bi, ^{223}Ra, ^{225}Ac, ^{227}Th

Clinics/centres try to expand compassionate use if legislation is very strict. The compassionate use route is used relatively much in Germany: some centres have done more than 1000 PSMA treatments.[2]

2. Emerging radionuclides

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{227}Th	[^{227}Th]Th-HER2 antibody		N/A [3]
^{177}Lu	[^{177}Lu]Lu-DOTA0-Tyr3-Octreotate	Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours	Y
^{177}Lu	^{177}Lu-edotreotide PRRT	GEP-Net patients	Y
^{90}Y		Transarterial Radioembolisation in Uveal Melanoma Liver Metastasis	Y
^{90}Y	Y-90 SIRT	Advanced Stage Intrahepatic Biliary Tract Cancer	Y

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{90}Y	TheraSphere®	Inoperable Liver Cancer	Y
^{90}Y	TheraSphere®	Metastatic Colorectal Cancer	Y
^{131}I	Lenvatinib (E7080)	Differentiated Thyroid Cancer	Y
^{223}Ra	Radium-223 Dichloride	Castration-resistant Prostate Cancer Metastatic to the Bone	Y
^{223}Ra	Radium-223 Dichloride	Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases	Y
^{223}Ra	Radium-223 Dichloride	Bone Predominant HER2 (Human Epidermal Growth Factor Receptor 2) Negative Hormone Receptor Positive Metastatic Breast Cancer	Y
^{223}Ra	Radium-223 Dichloride	Stage IV Non-small Cell Lung Cancer With Bone Metastases	Y

3. Therapies and procedures

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-colloids used in radiation synovectomy	995	Survey	203	202
^{90}Y	^{90}Y-glass microspheres used in intra-arterial treatments in the liver	77	Survey	11500	880
^{90}Y	[^{90}Y]Y-ibritumomab-tiuxetan used in b-cell lymphoma and non-hodgkin lymphoma (EMA authorised)	64	Survey	1000	64
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	1403	Survey	3000	4209
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	77	Survey	7450	574
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	38	Survey	7450	283
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	9435	Survey	500	4718
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	510	Survey	5500	2805
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	38	Survey	1942	74

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	4845	Survey	3000	14535
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	102	Survey	1942	198
^{177}Lu	^{177}Lu-antibodies used in non-Hodgkin's lymphoma	13	Survey	1062	14
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (EMA authorised)	4718	Survey	6475	30549
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	3570	Survey	7400	26418
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	230	Survey	3,85	0.9
^{225}Ac	[^{225}Ac]Ac-PSMA used in metastatic castration resistant prostate cancer	1658	Survey	8	13,3
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	163	Survey	3133	511
^{169}Er	^{169}Er-colloids used in radiation synovectomy	1875	Survey	25	47
^{186}Re	^{186}Re-colloids used in radiation synovectomy	1063	Survey	111	118
^{188}Re	[^{188}Re]Re-HEDP used in painful bone metastases	25	Survey	3079	77

4. Prices and reimbursement

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
[^{131}I]-NaI	300-1800	Survey
[^{131}I]I-mIBG	1700	Survey
^{177}Lu-antibodies	1800-2600	Survey
^{177}Lu-peptides	2600-3500	Survey
[^{177}Lu]Lu-PSMA	2600-3500	Survey
[^{177}Lu]Lu-DOTATATE	24000-26000	Survey
[^{223}Ra]$RaCl_2$	6500	Survey

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
^{153}Sm-EDTP	600-1500	Survey
[^{90}Y]Y-ibritumomab-tiuxetan	2500-17000	Survey
^{90}Y-resin microspheres	12500	Survey
^{90}Y-glass microspheres	12000-13000	Survey
^{90}Y-colloids	300-600	Survey

5. Medical guidelines

Radiopharmaceutical	Guideline making organisation
^{90}Y-colloids	Both European and national
[^{90}Y]Y-ibritumomab-tiuxetan	Both European and national
[^{131}I]I-mIBG (IOBENGUANE)	Both European and national
[^{131}I]-NaI	Both European and national
[^{153}Sm]Sm-EDTMP	European
^{169}Er-colloids	National
[^{177}Lu]Lu-DOTATATE	Both European and national
^{177}Lu-peptides	Both European and national
[^{177}Lu]Lu-PSMA	Both European and national
^{186}Re-colloids	Both European and national
[^{223}Ra]$RaCl_2$	Both European and national

6. Future demand

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
[^{177}Lu]Lu-PSMA	Strong increase expected by large majority of respondents	Survey
[^{225}Ac]Ac-PSMA	Strong increase expected by large majority of respondents	Survey
[^{177}Lu]Lu-DOTATATE	Strong increase expected by majority of respondents	Survey

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
^{177}Lu-peptides	Strong increase expected by majority of respondents	Survey
^{177}Lu-antibodies	Strong increase expected by majority of respondents	Survey
^{32}P-sodium-phosphate	Decrease expected by majority of respondents	Survey
[^{89}Sr]$SrCl_2$	Decrease expected by majority of respondents	Survey
[^{153}Sm]Sm-EDTMP	Decrease expected by majority of respondents	Survey

7. Supply situation

Survey respondents indicate there are often shortages in ^{212}Pb, less so in ^{131}I and ^{186}Re. They indicate that shortages in ^{131}I may have some effects on patients. However, most respondents indicate that supply is not a large problem. The commonly used reactor produced radionuclides are generally available. The deficit is in novel radionuclides. Shortages are sometimes related to reactor maintenance, which could be solved with better information and coordination. One respondent suggests the regulations regarding the production process are overly complicated. [4]

8. Patient access to radionuclide therapy (e.g. regional differences)

There are 102 centres offering therapy (in 2020). [1] The following graph shows the number of therapeutic centres in Germany from 2009-2015, showing a slight decline in centres, and a more significant decline in number of beds, cases and patient-days. [4]

Tab. 11 Nuklearmedizinische Fachabteilungen mit Therapiestation in Krankenhäusern und ihre Nutzung. Quelle: Krankenhausstatistik – Grunddaten, Statistisches Bundesamt, Zweigstelle Bonn. Abfrage von www.gbe-bund.de am 10.12.2016.

Jahr	Anzahl Fachabteilungen	Betten	Fälle	Belegungstage	durchschnittliche Verweildauer in Tagen
2009	112	941	51 391	196 196	3,8
2010	112	921	48 855	181 653	3,7
2011	113	898	48 519	179 548	3,7
2012	110	893	46 376	168 299	3,6
2013	110	877	44 486	158 680	3,6
2014	110	863	43 158	152 316	3,5
2015	107	842	43 112	147 398	3,4

Source: [4]

9. Other information

Germany has a federal system: states handle permits, which means there are different offices for radiology and radioisotopes. Also, there are different surveillance authorities in different states.

10. Sources of information / References

[1] Interview with Bernd Krause, German Society of Nuclear Medicine (DGN)

[2] Interview with Sabine Klingele, Bundesamt für Strahlenschutz (BfS - German Federal Office for Radiation Protection)

[3] Technopolis survey (N = 8)

[4] Dirk Hellwig; Jörg Marienhagen; Karin Menhart; Jirka Grosse, Nuklearmkedizin in Deutschland, Nuklearmedizin, 2, 2017

C.12 Greece – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{169}Er, ^{177}Lu, ^{186}Re, ^{188}Re, ^{223}Ra

Radiopharmaceuticals in compassionate use: compassionate use is generally not possible in Greece. However, the use of [^{177}Lu]Lu-PSMA is allowed for only very specific patients, as this RP is not yet commercially licensed in Greece.

2. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 1315 therapeutic treatments in nuclear medicine are performed in Greece.

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-colloids used in radiation synovectomy	975	Survey	203	198
^{90}Y	^{90}Y-glass microspheres used in intra-arterial treatments in the liver	15	Survey	11500	173
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	465	Survey	3000	1395
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	12	Survey	7450	89
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	9	Survey	7450	67
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	1050	Survey	500	525
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	2175	Survey	5500	11963

Radio-nuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	150	Survey	1942	291
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	4050	Survey	3000	12150
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	525	Survey	1942	1020
^{177}Lu	^{177}Lu-antibodies used in non-Hodgkin's lymphoma	18	Survey	1062	19
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (EMA authorised)	36	Survey	6475	233
^{177}Lu	^{177}Lu-peptides (other than somatostatin analogues and PSMA)	15	Survey	?	?
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	15	Survey	7400	111
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	330	Survey	3,85	1
^{89}Sr	[^{89}Sr]$SrCl_2$ used in bone metastases (EMA authorised)	6	Survey	150	1
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	24	Survey	3133	75
^{169}Er	^{169}Er-colloids used in radiation synovectomy	30	Survey	25	1
^{186}Re	^{186}Re-colloids used in radiation synovectomy	30	Survey	111	3
^{188}Re	[^{188}Re]Re-HEDP used in painful bone metastases	33	Survey	3079	102

3. Prices and reimbursement

Greece has a public healthcare insurance which reimburses low-cost radiopharmaceuticals and therapies, e.g. for ^{131}I RPs. For high-costs radiopharmaceuticals and therapies patients need to receive permission for reimbursement. These expensive treatments are not officially (or generally) reimbursed and require permission to make exemptions.

Interviewees indicated that the price of (many) RPs in Greece is higher than in some (neighbouring) countries. Prices can be five times higher, which is not likely explained by transport costs when it concerns neighbouring

countries. Another issue is the fact that in-house prepared medicine cannot be reimbursed, while costs are significantly lower (roughly factor 3 for [^{177}Lu]Lu-DOTATATE). This is mainly an issue for patients.

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
^{90}Y-resin microspheres		From survey: Mediray
^{90}Y-colloids	€650 (estimate from survey)	From survey: Curium
^{223}RaCl	€4000 (estimate from survey)	From survey: Bayer
[^{131}I]-NaI	€120-€200 (from survey)	From survey: Polatom
[^{153}Sm]Sm-EDTMP	€3800 (from survey)	From survey: Curium

4. Medical guidelines

Greece has no national guidelines but uses the EANM guidelines.

5. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{225}Ac]Ac-PSMA	Respondents believe RP will strongly increase (>15%)	Survey (N=2)
[^{177}Lu]Lu-PSMA	Respondents believe RP will strongly increase (>15%)	Survey (N=2)
[^{177}Lu]Lu-DOTATATE	50% of respondents believes RP will strongly increase (>15%), while 50% believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{223}RaCl	50% of respondents believes RP will strongly increase (>15%), while 50% believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{177}Lu-peptides	50% of respondents believes RP will strongly increase (>15%), while 50% believes RP will increase (1-15%) in 10 years	Survey (N=2)
[^{153}Sm]Sm-EDTMP	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=2)
[^{188}Re]Re-HEDP	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{90}Y-glass microspheres	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{90}Y-colloids	Respondent believes RP will remain stable in 10 years	Survey (N=2)
^{90}Y-resin microspheres	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=2)
^{177}Lu-antibodies	Respondent believes RP will increase (1-15%) in 10 years	Survey (N=2)

The expected increases for [^{225}Ac]Ac-PSMA and [^{177}Lu]Lu-PSMA is due to the current success stories for prostate cancer therapy with PSMA radiopharmaceuticals. In addition, some hospitals have started to produce ^{177}Lu radiopharmaceuticals in-house.

6. Supply situation

In Greece quite some supply issues have been reported in the survey.

- Often (>4 times in five years) shortages have occurred for ^{169}Er-colloids, ^{186}Re-colloids, ^{90}Y-colloids, all had to a great extent impact on patients. These supply issues were caused during external production.
- Sometimes (3-4 times in five years) shortages have occurred for [^{153}Sm]Sm-EDTMP , which had to some extent impact on patients. The supply issue was caused during external production.
- Rarely (1-2 times in five years) shortages gave occurred for [^{131}I]-NaI and [^{223}Ra]$RaCl_2$, which had resp. to some extent and to a small extent impact on patients. The supply issue for [^{131}I]-NaI was caused due to transport, while the cause for [^{223}Ra]$RaCl_2$ is unknown.

Radiopharmaceuticals and radionuclides used in radionuclide therapy are imported. Greece has no RP or RN production facilities, only for diagnostics or industrial applications. However, one hospital in Greece is currently in the process acquiring a license for producing [^{177}Lu]Lu-DOTATATE in-house. All equipment is already available and licensing is expected soon.

The supply from abroad has been quite stable, without any significant disruptions for radionuclide therapy (these were only for diagnostics).

7. Patient access to radionuclide therapy (e.g. regional differences)

Number of radiopharmacies is unknown, but likely similar to number of radionuclide therapy practicing centres.

There are many centres in Greece who apply radionuclide therapy, especially for ^{131}I radiopharmaceuticals. According to Gleisner (2017) there were 33 radionuclide therapy practicing centres in 2015-2016 in Greece. Interviewees estimate this number a bit lower, with 10-15 centres using ^{131}I RPs and 3 centres using radionuclide microspheres and ^{177}Lu RPs.

8. Sources of information / References

[1] Information based on interview (2020) with Dr. Prassopoulos (former delegate of the Hellenic Society of Nuclear Medicine and Molecular Imaging to the EANM) and Dr. Ntalianis (medical physicist), both working at the Hygeia Hospital.

[2] Technopolis survey (N = 5)

C.13 Hungary – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{223}Ra

2. Emerging radionuclides

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	Betalutin®	Relapsed Non-Hodgkin Lymphoma	Y

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y-colloids	radiosynovectomy	approx. 500	Estimation based on national statistics	200	86.5
^{90}Y resin microspheres	SIRT of primary and secondary hepatic malignancies	4	National statistics	2500	10
[^{90}Y]Y-ibritumomab tiuxetan	relapsed/refractory CD20+ follicular non-Hodgkin lymphoma	2	National statistics	1500	3
^{131}I	benign thyroid diseases	1366	National statistics	500	683
^{131}I	thyroid cancer	697	National statistics	2500	1743
[^{131}I]I-mIBG (Iobenguane)	metastatic neuro-crest tumours (pheochromocytomas and paragangliomas)	5	National statistics	3700	18.5
^{166}Ho-colloids	radiosynovectomy	75	National statistics	600	45
^{223}Ra-dichloride	metastatic castration-resistant prostate cancer (mCRPC)	237	National statistics	3.85	2
[^{153}Sm]Sm-EDTMP	palliative treatment of multiple painful osteosclerotic bone metastases	36	National statistics	2500	9
^{186}Re-colloids	radiosynovectomy	approx.120	Estimation based on national statistics	100 (37-185)	12

Source: Szilvasi, based on national data

All of these therapies were reimbursed (with negligible few exceptions) by the National Health Insurance Fund.

The calculated "average" costs of each radiopharmaceuticals are included in the total reimbursement of the given type of (inpatient or outpatient) treatment (except ^{223}Ra-dichlorid). The number of therapeutic procedures may sometimes limited by the underestimated cost of treatment.

Due to the high cost of ^{223}Ra-dichloride – compared to other therapeutic radiopharmaceuticals currently used in Hungary – it has a "special" financing procedure. Its real cost is separately reimbursed from a special budget of the National Health Insurance Fund after approval of the given patient's treatment by a medical committee of the Fund [1].

Some patients (estimated 30-35 per year) are treated with [^{177}Lu]Lu-DOTATATE abroad (e.g. in Basel), even financed by the National Health Insurance Fund [1].

4. Medical guidelines

For all radiopharmaceuticals, the European (EANM) guidelines are followed.

For radiosynovectomy using ^{166}Ho-colloid the Hungarian guideline is an adaptation of the European one.

Radiopharmaceutical	**Guideline making organisation**
^{90}Y-colloids	European
[^{131}I]I-mIBG (IOBENGUANE)	European
[^{131}I]-NaI	European
[^{153}Sm]Sm-EDTMP	European
^{186}Re-colloids	European
[^{223}Ra]$RaCl_2$	European

5. Future demand

Remark: medical demand is high, but reimbursement is limited(1).

Radionuclide	**Number of Patients Expected to receive therapy in future**	**Source of data**
[^{177}Lu]Lu-PSMA	Strong increase expected by large majority of respondents	Survey
[^{225}Ac]Ac-PSMA	Strong increase expected by large majority of respondents	Survey (although in validation this was deemed too high – suggest "increase')
[^{177}Lu]Lu-DOTATATE	Strong increase expected by majority of respondents	Survey

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
^{177}Lu-peptides	Strong increase expected by majority of respondents	Survey (although in validation this was deemed too high – suggest "increase')
[^{227}Th]Th-PSMA antibody ^{227}Th-conjugate	Increase expected by majority of respondents	Survey
^{32}P-sodium-phosphate	Strong decrease expected by majority of respondents	Survey
[^{90}Y]Y-ibritumomab-tiuxetan	Strong decrease expected by majority of respondents	Survey
[^{89}Sr]$SrCl_2$	Decrease expected by majority of respondents	Survey (validation suggests: never used)
^{90}Y-glass microspheres ^{90}Y-colloids	Decrease expected by majority of respondents	Survey (validation suggests: never used)
[^{153}Sm]Sm-EDTMP	Decrease expected by majority of respondents	Survey

6. Supply situation

One respondent indicates there are often shortages of ^{90}Y-colloids, whereas others indicate sometimes shortages in ^{131}I (mIBG and NaI), ^{186}Re-colloids, [^{153}Sm]Sm-EDTMP , which may to some extent impact patients (^{131}I and ^{153}Sm). These shortages lie in external production, no further explanation is given. [2]

7. Patient access to radionuclide therapy (e.g. regional differences)

With 13 centres [3], Hungary has 1.3 centres per million inhabitants.

8. Sources of information / References

[1] Istvan Szilvasi, President, National College of Nuclear Medicine

[2] Technopolis survey (N=4)

[3] Gleisner et al. 2017

C.14 Ireland – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{90}Y, ^{131}I, ^{177}Lu, ^{186}Re, ^{223}Ra, ^{153}Sm, ^{169}Er, ^{32}P [1, 3]

Radiopharmaceuticals in compassionate use: [^{177}Lu]Lu-PSMA-617 (in discussion); Lutathera® i.e. [^{177}Lu]Lu-DOTATATE (planned use in one hospital)

2. Emerging radionuclides / radiopharmaceuticals

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	Betalutin®	Lymphoma	Yes

3. Therapies and procedures

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases	310	[1, 3]	3.85	1
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	336	[1, 3]	500	168
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	69	[1, 3]	3000	240
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	2	[1, 3]	1942	4
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	171	[1, 3]	5500	1110
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	2	[1, 3]	1942	4
^{186}Re	^{186}Re-colloids used in radiation synovectomy	2	[1, 3]	111	0.22
^{90}Y	^{90}Y-colloids used in radiation synovectomy	55	[1, 3]	203.5	11
^{90}Y	^{90}Y-glass microspheres (TheraSpheres®) used in intra-arterial treatments in the liver	31	[1, 3]	11500	414
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver (^{90}Y-SIRT)	34	[3]	3000	102

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{169}Er	^{169}Er-colloids used in radiation synovectomy	2	[3]	25	0.05
^{177}Lu	^{177}Lu-antibodies used in non-Hodgkin lymphoma	2	[3]	1062	2
^{32}P	^{32}P-sodium-phosphate used in bone metastases	2	[3]	450	1
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases	2	[3]	3133	6

4. Prices and reimbursement

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
^{223}Ra	Not available	Bayer [3]
^{177}Lu	Not available	Business plan for reimbursement created [1]

5. Medical guidelines

Radio-pharmaceutical	Indication	Guideline making organisation	Title of/link to guideline
^{223}Ra	castration-resistant metastatic prostate cancer (mCRPC)	National Cancer Control Program	https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/genitourinary/257-radium-223-therapy1.pdf

All other radiopharmaceuticals are covered under EANM guidelines.

6. Future demand

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
^{177}Lu PSMA	Significant demand increase	[1]
[^{225}Ac]Ac-PSMA	Increase for majority of respondents	[4]
[^{131}I]I-mIBG	Stable for majority of respondents	[4]
[^{131}I]-NaI	Stable for majority of respondents	[4]
^{90}Y-glass microspheres	Stable for majority of respondents	[4]

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
^{90}Y-colloids	Stable for majority of respondents	[4]
[^{90}Y]Y-ibritumomab-tiuxetan	Stable for majority of respondents	[4]
^{177}Lu-peptides	Strong increase for majority of respondents	[4]

7. Supply situation

No local production of any therapeutic isotope.

Brexit has potential implications for supply of radionuclides. This has been discussed at length at EU level and with industry. Plans are adequate.

8. Patient access to radionuclide therapy (e.g. regional differences)

2.8 radiotherapy centres per million inhabitants [2]

- One independent Radiopharmacy Company, M2i: https://www.m2i.ie/
- 21 Radiopharmacies in teaching hospitals, general hospitals and private hospitals. [1] These are not for therapeutic radioligand production.
- Number of radionuclide therapy practicing centres: 12 [1]

9. Other information

There is very poor awareness about radionuclide therapy in regulatory authorities despite interactions over 10 years.

10. Sources of information / References

[1] Email exchange with Dr Martin O'Connell and Ronan Killeen, Irish Nuclear Medicine Association

[2] Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[3] Technopolis survey (Round 1), N = 14

[4] Technopolis survey (Round 2), N = 5

C.15 Italy – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{166}Ho, ^{177}Lu, ^{169}Er, ^{188}Re, ^{223}Ra, ^{89}Sr, ^{90}Y,

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials):

Radio-nuclide	Radio-pharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTATATE	Neuroendocrine Tumours	Yes – Phase II
^{177}Lu	[^{177}Lu]Lu-PSMA	Castration Resistant Prostate Cancer (CRPC)	Yes – Phase II
^{177}Lu	^{177}Lu-edotreotide PRRT	Neuroendocrine Tumours	Yes – Phase III
^{177}Lu	^{177}Lu-edotreotide PRRT	Neuroendocrine Tumours	Yes – Phase II
^{177}Lu	^{177}Lu-antibodies	Non-Hodgkin Lymphoma	Yes – Phase I and Phase II
^{90}Y	^{90}Y- resin microspheres	Intrahepatic Cholangiocarcinoma	Yes – Phase II and Phase III

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year	Data source	Average activity per procedure(MBq)	Activity (GBq)
[^{131}I]I-mIBG (IOBENGUANE)	Adult neuroendocrine tumours	24	Survey	7450	176
[^{131}I]I-mIBG (IOBENGUANE)	Neuroblastoma	41	Survey	7450	303
[^{131}I]-NaI	Benign thyroid diseases	1646	Survey	500	8223
[^{131}I]-NaI	Thyroid cancer therapy for adults	2704	Survey	5500	15009
[^{131}I]-NaI	Thyroid cancer therapy for children and young adults	135	Survey	1942.5	262
[^{131}I]-NaI	Thyroid remnant ablation of adults	1982	Survey	3000	5946
[^{131}I]-NaI	Thyroid remnant ablation of children and young adults	96	Survey	1942.5	187
[^{153}Sm]Sm-EDTMP	Bone metastases	17	Survey	3133	54

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year	Data source	Average activity per procedure(MBq)	Activity (GBq)
^{166}Ho-microspheres	Intra-arterial treatment in the liver	6	Survey	1890	12
^{177}Lu-antibodies	Non-hodgkin lymphoma	21	Survey	1062	23
[^{177}Lu]Lu-DOTATATE	Gastroenteropancreatic neuroendocrine tumours	3525	Survey	6475	22824
[^{177}Lu]Lu-PSMA	Prostate cancer and pc-metastases	647	Survey	7400	4789
[^{223}Ra]$RaCl_2$	Bone metastases	1361	Survey	3.8	5
[^{89}Sr]$SrCl_2$	Bone metastases	19	Survey	150	3
^{90}Y-colloids	Radiation synovectomy	11	Survey	203.5	2
^{90}Y-glass microspheres	Intra-arterial treatments in the liver	257	Survey	11500	2957
[^{90}Y]Y-ibritumomab-tiuxetan	b-cell lymphoma and non-hodgkin lymphoma	9	Survey	1000	9
^{90}Y-resin microspheres	Intra-arterial treatments in the liver	255	Survey	3000	765

4. Prices and reimbursement

Radio-pharmaceutical	Price per patient treatment in € (mean (min, max)) [1]	Type of procedure	Total budget spent per year
[^{131}I]-NaI	157.5 (65, 250)	Benign thyroid diseases	€259,245
[^{131}I]-NaI	157.5 (65, 250)	Thyroid cancer therapy for adults	€425,880
[^{131}I]-NaI	157.5 (65, 250)	Thyroid cancer therapy for children and young adults	€21,262.5
[^{131}I]-NaI	157.5 (65, 250)	Thyroid remnant ablation of adults	€312,165
[^{131}I]-NaI	157.5 (65, 250)	Thyroid remnant ablation of children and young adults	€21,262.5
[^{131}I]I-mIBG (IOBENGUANE)	750 (700, 800)	Adult neuroendocrine tumours	€18,000

Radio-pharmaceutical	Price per patient treatment in € (mean (min, max)) [1]	Type of procedure	Total budget spent per year
[^{177}Lu]Lu-PSMA (not licensed)	20,000 (20,000, 20,000)	Neuroblastoma	€12,940,000
[^{177}Lu]Lu-DOTATATE	17500 (15000, 20000)	Gastroenteropancreatic neuroendocrine tumours	€61,687,500
[^{223}Ra]$RaCl_2$	2,870 (2,500, 3,240)	Bone metastases	€3,906,070
[^{90}Y]Y-ibritumomab-tiuxetan	15,000 (10,000, 20,000)	b-cell lymphoma and non-Hodgkin lymphoma	€135,000
^{90}Y-resin microspheres	*1,000 (1,000, 1,000)*	Intra-arterial treatments in the liver	€255,000
^{90}Y-glass microspheres	*1,000 (1,000, 1,000)*	Intra-arterial treatments in the liver	€257,000

5. Medical guidelines

Italy uses both European (e.g. the EANM) and national medical guidelines for radiotherapy according to survey respondents [1]

6. Future demand

Radionuclide	Growth in the next 10 years	Source of data
[^{177}Lu]Lu-PSMA	61.5% of Italian respondents expect there to be a strong increase (>15%) in demand. Another 30.8% expect there to be weak increase in demand (+1 to +15%)	[1]
[^{225}Ac]Ac-PSMA	46.2% of Italian respondents expect there to be a strong increase (>15%) in demand. Another 30.8% expect there to be weak increase in demand (+1 to +15%)	[1]
[^{177}Lu]Lu-DOTATATE	53.9% of Italian respondents expect there to be a weak increase (+1 to +15%) in demand. Another 23.1% expect there to be strong increase in demand (> +15%)	[1]
^{177}Lu-peptides	69.2% of Italian respondents expect there to be a weak increase (+1 to +15%) in demand. Another 23.1% expected there to be strong increase in demand (> +15%)	[1]
[^{89}Sr]$SrCl_2$	38.5% of Italian respondents expect there to be a strong decrease (<-15%) in demand. Another 15.4% expect there to be weaker decrease in demand (-15% to -1%)	[1]
[^{153}Sm]Sm-EDTMP	38.5% of Italian respondents expect there to be a strong decrease (<-15%) in demand. Another 23.1% expect there to be weaker decrease in demand (-15% to -1%)	[1]

Radionuclide	Growth in the next 10 years	Source of data
[^{90}Y]Y-ibritumomab-tiuxetan	30.8% of Italian respondents expect there to be a weak decrease in demand (-15% to -1%. Another 23.1% of respondents expect there to be a strong decrease (<-15%) in demand.	[1]

7. Supply situation

Italy have had few reported issues with supply of radionuclides. However, shortages or supply disruption have been reported in Italy over the last 5 years for [3]:

- [^{223}Ra]$RaCl_2$ - 50% of relevant respondents suggested that [^{223}Ra]$RaCl_2$ had been shortage rarely (1-2 times) over the last 5 years. A variety of reasons were suggested for these shortages occurring: during external production, during transport and during procurement. These shortages were reported to have had a small disruptive effect on the treatment of patients.
- ^{177}Lu-antibodies - 50% of relevant respondents suggested that ^{177}Lu-antibodies had been shortage rarely (1-2 times) over the last 5 years. These shortages were reported to have happened during transport.

8. Patient access to radionuclide therapy (e.g. regional differences)

There are an estimated 0.50 radionuclide therapy centres per million inhabitants in Italy. This has been calculated from:

- There being 30 radiotherapy centres in Italy [2]
- The Italian population being 60,462,000 in 2020 (United Nations Population Division)[118]

It has been reported that regional governance structures can create differences in reimbursement fees. For example, in the Lombardia region healthcare services are reimbursed much less than healthcare services in the Romania region. However, these differences in reimbursement do not affect patient access [2]

There are 4 to 5 radiopharmacies in Italy equipped for radionuclide therapy (academic studies) [2].

9. Other information

Italy was reported to have had a radiotherapy expenditure of 508 million euros in 2016, this was 0.36% of total health care expenditure [4].

10. Sources of information / References

[1] Technopolis survey (survey respondents N = 24)

[2] Interview with Professor Giovanni Paganelli, Director at School of Specialisation in Nuclear Medicine University of Ferrara

[3] Gleisner et al. (2017)

[118] See: https://population.un.org/wpp/Download/Standard/Population/

[4] Lievens et al. (2020)

C.16 Latvia – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{90}Y, ^{131}I, ^{223}Ra

2. Therapies and procedures

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	1	Survey	7450	7
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	2	Survey	7450	15
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	250	Survey	500	125
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	60	Survey	5550	333
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	15	Survey	1942	29
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	160	Survey	3000	480
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	15	Survey	1942	29
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	1	Survey	3.85	0

3. Patient access to radionuclide therapy

Number of radiotherapy practicing centres: 1 centre (based on survey data).

4. Sources of information / References

[1] Technopolis survey (N = 1)

[2] Gleisner et al. (2017)

C.17 Lithuania – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{90}Y, ^{131}I, ^{166}Ho, ^{223}Ra

Radiopharmaceuticals in compassionate use: N/A

2. Therapies and procedures

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	500	Survey (n=2)	500	250.00
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	1	Survey (n=2)	3000	3.00
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases	38	Survey (n=2)	3.85	0.15

3. Prices and reimbursement

In 2016, the equivalent of €9.7 million (based on 2014 purchasing power parity) was spent on radiotherapy i.e. a per capita expenditure of €3.3. Radiotherapy accounted for 0.24% of the total healthcare spending and 4.3% of total cancer care expenditure (Lievens et al. (2020)).

Radiopharmaceutical	Reflection on distributors
[^{131}I]-NaI	GE, Polatom/Elins
[^{223}Ra]$RaCl_2$	Bayer

4. Future demand

Radiopharmaceutical	Number of Patients Expected to receive therapy in future	Source of data
[^{131}I]I-mIBG	Strong increase expected by respondent	Survey (n=1)
[^{131}I]-NaI	Strong increase expected by respondent	Survey (n=1)
[^{177}Lu]Lu-DOTATATE	Strong increase expected by respondent	Survey (n=1)
[^{223}Ra]$RaCl_2$	Increase expected by respondent	Survey (n=1)

5. Patient access to radionuclide therapy

Number of radionuclide therapy practicing centres: two

6. Sources of information / References

[1] Lievens, Y., Borras, J. M., & Grau, C. (2020). Provision and use of radiotherapy in Europe. Molecular Oncology.

[2] Survey data (Round 1), N = 2

[3] Survey data (Round 2), N = 1

C.18 Luxembourg – not validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{169}Er, ^{186}Re, ^{211}At, ^{213}Bi, ^{223}Ra, ^{225}Ac, ^{227}Th

2. Emerging radionuclides

Trials with ^{177}Lu and ^{225}Ac are reported by one respondent.

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-glass microspheres used in intra-arterial treatments in the liver	1	Survey	11500	12
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	10	Survey	3000	30
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	1	Survey	7450	7
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	110	Survey	500	55
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	35	Survey	5550	194
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	3	Survey	1942	6

Radio-pharmaceutical	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	180	Survey	3000	540
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	2	Survey	1942	4
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	31	Survey	3.85	0.12
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	12	Survey	3133	38
^{169}Er	^{169}Er-colloids used in radiation synovectomy	1	Survey	25	0.02
^{186}Re	^{186}Re-colloids used in radiation synovectomy	2	Survey	111	0.22

4. Prices and reimbursement

Radiopharmaceutical	Price (€)	Other information
[^{131}I]-NaI	100-300	estimate
[^{223}Ra]$RaCl_2$	4400	
^{153}Sm-EDTP	700-1000	estimate
^{90}Y-resin microspheres	3000-5000	estimate

5. Medical guidelines

Radiopharmaceutical	Guideline making organisation
[^{131}I]-NaI	Both European and national
[^{153}Sm]Sm-EDTMP	National
[^{223}Ra]$RaCl_2$	Both European and national

6. Future demand

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
[^{225}Ac]Ac-PSMA [^{225}Ac]Ac-Lintuzumab	Strong increase expected by respondents	Survey
^{177}Lu-peptides ^{177}Lu-antibodies	Strong increase expected by majority of respondents	Survey
[^{227}Th]Th-PSMA ^{227}Th-conjugate	Increase expected by majority of respondents	Survey
^{166}Ho-microspheres (HoMS)	Increase expected by majority of respondents	Survey
^{90}Y-glass microspheres ^{90}Y-resin microspheres	Increase expected by majority of respondents	Survey
^{32}P-sodium-phosphate	Strong decrease expected by majority of respondents	Survey
[^{223}Ra]$RaCl_2$	Strong decrease expected by majority of respondents	Survey
[^{90}Y]Y-ibritumomab-tiuxetan	Strong decrease expected by majority of respondents	Survey
[^{153}Sm]Sm-EDTMP	Strong decrease expected by majority of respondents	Survey
[^{89}Sr]$SrCl_2$	Decrease expected by majority of respondents	Survey
^{90}Y-glass microspheres ^{90}Y-colloids	Decrease expected by majority of respondents	Survey

7. Supply situation

Only sometimes shortages in ^{131}I occur, which may have some impact on patients. Reasons are given as production issues and/or nuclear reactor issues. [1]

8. Patient access to radionuclide therapy (e.g. regional differences)

With 3 centres, Luxembourg has 4.8 centres per million inhabitants. [2]

9. Sources of information / References

[1] Technopolis survey (N = 3)

[2] Gleisner et al. (2017)

C.19 Malta – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: **^{131}I, ^{90}Y**

Radiopharmaceuticals in compassionate use: N/A

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials): None found according to clinicaltrials.gov.

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
N/A			

3. Therapies and procedures

Radiopharmaceutical	Indication and type of procedure	Number of Patients Receiving therapy per year	Number of procedures per year	Activity	Source of data
[^{131}I]-NaI	Thyroid Ca	52	52	211.84 GBq	
[^{131}I]-NaI	Thyrotoxicosis	45	45	16.65 GBq	
^{90}Y-microspheres	SIRT	3	3	6.52GBq	

4. Prices and reimbursement

NM therapy procedures are all performed at the main general hospital of the island. The campus encompasses Mater Dei Hospital and the Sir Anthony Mamo Oncology Centre. The health care model in Malta (public) is similar to the UK model i.e. free at the point of use, funded through taxes. No departmental re-imbursement procedures are in place.

5. Medical guidelines

Guidelines generally followed are those issued by EANM and SNMMI.

6. Future demand

In May 2020, ^{68}Ga PSMA and DOTATATE PET imaging was started.

The next step that would follow would be ^{177}Lu therapy (both PSMA and DOTATATE) though there are no plans for this in the immediate future.

7. Supply situation

2020 has been fraught with logistical problems for all radiopharmecuticals due to a heavily curtailed flight schedule. Being an island, all radiopharmaceuticals are imported via commercial flights. Freight costs have also increased substantially since the start of the COVID pandemic though this has not resulted in any curtailing of services.

8. Patient access to radionuclide therapy (e.g. regional differences)

Number of radiotherapy practicing centres: 1, as country has only one hospital

9. Other information

N/A

10. Sources of information / Reference

Email correspondence with Anthony Samuel, Consultant Nuclear Medicine Physician, Mater Dei Hospital

C.20 Netherlands – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: **^{32}P,** ^{89}Sr**, ^{90}Y**, 103Pd, ^{125}I, **^{131}I**, 152Eu, 154Eu, **^{153}Sm, ^{166}Ho, ^{169}Er**, **^{177}Lu, ^{186}Re, ^{188}Re**, ^{213}Bi, **^{223}Ra, ^{225}Ac**, 227Ac, **^{227}Th**

Based on NVS report from 2017, but underlined RNs have not been mentioned in other sources – likely only incidental use – while those in bold have been confirmed by this study's survey.

Radiopharmaceuticals in compassionate use:

Only "magistral preparation" is allowed in certain cases and in clinical trials. Due to high price, it is allowed to produce [^{177}Lu]Lu-DOTATATE in-house. [^{225}Ac]Ac-PSMA is prepared in-house as well for clinical trials.

2. Emerging radionuclides (RNs) / radiopharmaceuticals (RPs)

Based on an analysis of registered clinical trials (Clinicaltrials.gov), several emerging RNs are studied in the Netherlands: ^{177}Lu, ^{90}Y, ^{223}Ra, ^{188}Re. Some of these are already used in clinic as different RP or for different indications. In interviews we understood that ^{225}Ac (PSMA for prostate cancer, phase 1), ^{227}Th and ^{212}Pb are also studied, but no details have been found on Dutch involvement.

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTATATE	Neuroendocrine Tumours, Liver Metastases	Utrecht University: Intra-arterial [^{177}Lu]Lu-DOTATATE for Treatment of Patients With Neuro-endocrine Tumour Liver Metastases

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
	^{177}Lu-3BP-227 (also called ^{177}Lu-IPN01087) (Phase 1/2)	Pancreatic Ductal Adenocarcinoma, Colorectal Cancer, Gastric Cancer, Squamous Cell Carcinoma of the Head and Neck, Bone Cancer, Metastatic Tumours	Ipsen: Study to Evaluate the Safety and Activity (Including Distribution) of ^{177}Lu-3BP-227 in Subjects With Solid Tumours Expressing Neurotensin Receptor Type 1.
	[^{177}Lu]Lu-PSMA (Phase 3)	Prostate Cancer	Endocyte: Study of [^{177}Lu]Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer
	^{177}Lu-edotreotide PRRT, Everolimu, Amino-Acid Solution (Phase 3)	Neuroendocrine Tumours	ITM Solucin GmbH: Efficacy and Safety of ^{177}Lu-edotreotide PRRT in GEP-NET Patients
	^{177}Lu-lilitomab (Betalutin®) (Phase 1/2)	Non-Hodgkin Lymphoma, Follicular Lymphoma	Nordic Nanovector: A Phase I/II Study of Betalutin® for Treatment of Relapsed Non-Hodgkin Lymphoma
^{90}Y	^{90}Y SIRT + chemotherapy (Phase 2/3)	Intrahepatic Cholangiocarcinoma	Sirtex Medical: SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma
^{223}Ra	Docetaxel 75 mg/m2, Docetaxel 60 mg/m2, Radium-223 (Phase 3)	Prostate Cancer	Memorial Sloan Kettering Cancer Center: A Study to Test Radium-223 With Docetaxel in Patients With Prostate Cancer
^{223}Ra / ^{188}Re	[^{223}Ra]$RaCl_2$, [^{188}Re]Re-HEDP (Phase 3)	Prostate Cancer Metastatic to Bone, Prostate Cancer	VU University Medical Center: Rhenium-188-HEDP vs. Radium-223-chloride in Patients With Advanced Prostate Cancer Refractory to Hormonal Therapy

3. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 5000 therapeutic treatments in nuclear medicine are performed in the Netherlands.

Information based on analysis of national insurance codes for specific treatments, not always retraceable to specific RPs, but some to RNs. Analysis provided by RIVM, based on 2017 data.

Radionuclide	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{90}Y	25	Health Authority	-	121*
^{131}I	1394	Health Authority	-	3934*
^{166}Ho	50	Health Authority	1890	95
^{177}Lu	900	Health Authority	-	5855*
^{223}Ra	1021	*DBC, 2017*	3.85	4
^{32}P	15	*DBC, 2017*	185	3
^{89}Sr	44	Survey	150	7
^{153}Sm	6	Survey	3133	19

**Spread of procedures across different indications based on proportions indicated from survey data*

4. Prices and reimbursement

In this study's survey we have received estimates for the price of RPs. Full data was not available or not possible to disclose.

Radiopharmaceutical	Price (€)	Est. Total budget spent per year	Calculation method
[^{131}I]-NaI	Est. 50-200 per patient dose		
^{177}Lu-peptides	Est. 1000-1500 per patient dose		
[^{177}Lu]Lu-PSMA	Est. 1000-1500 per patient dose		
[^{177}Lu]Lu-DOTATATE	Est. 1000-1500 per patient dose		
^{32}P-sodium-phosphate ($Na_3{}^{32}PO_4$)	Est. 1000-1500 per patient dose		
[^{223}Ra]$RaCl_2$	Est. 1500-2500 per patient dose	1.5M-2.5M	Est. Price x no. Procedures/year (DBC data)

5. Medical guidelines

Based on interviews and link to national guidelines. National guidelines are all based on European guidelines (EANM) or international guidelines (SNMMI). National medical guidelines are used, which have been developed by the Dutch Society for Nuclear Medicine (NVNG) and can be found online at:

https://richtlijnendatabase.nl/richtlijn/nucleaire_geneeskunde/part_ii_-_radionuclide_therapy.html

This study's survey suggests that in practice national and European clinical guidelines are used, some even use only European guidelines.

Radiopharmaceutical	**Indication**	**Guideline making organisation**	**Link to guideline**
[^{131}I]-NaI	Graves' hyperthyroidism	NVNG	Link
[^{131}I]-NaI	Non-toxic goitre-reduction	NVNG	Link
[^{131}I]-NaI	Toxic adenoma	NVNG	Link
[^{131}I]-NaI	Toxic multinodular goitre	NVNG	Link
[^{131}I]-NaI	Thyroid Carcinoma	NVNG	
^{89}Sr Chloride (Metastron®)	Pain reduction skeletal metastasis	NVNG	Link
^{153}Sm Lexidronam (Quadramet ®)	Pain reduction in (osteoblastic) skeletal metastases	NVNG	Link
^{188}Re HEDP Etidronate	Pain reduction skeletal metastasis	NVNG	Link
[^{223}Ra]$RaCl_2$ (Xofigo ®)	pain relief in symptomatic bone metastases due to castration-resistant prostate cancer	NVNG	Link
^{90}Y Ibritumomab tiuxetan (Zevalin®)	Treatment of follicular non-Hodgkin's lymphoma	NVNG	Link
^{90}Y radioembolisation (microspheres)	Treatment of hepatic malignancies	NVNG	Link
^{32}P	Treatment Polycythaemia vera and Essential T hrombocythaemia	NVNG	Link
[^{177}Lu]Lu-DOTATATE (octreotate)	Treatment of advanced and metastasized neuroendocrine tumours (NET) (and neuroblastoma or medullary thyroid carcinoma)	NVNG	Link

6. Future demand

Base on this study's survey we have some indication on the expected growth in future demand in the Netherlands. These concern expectations, we have listed the majority response.

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
[^{177}Lu]Lu-PSMA	Strong increase (>15%)	Survey
[^{225}Ac]Ac-PSMA	Increase (+1-15%)	Survey
^{166}Ho-microspheres (HoMS)	Increase (+1-15%)	Survey
^{166}Ho-microspheres	Increase (+1-15%)	Survey
[^{177}Lu]Lu-DOTATATE	Increase (+1-15%)	Survey
[^{223}Ra]$RaCl_2$	Increase (+1-15%)	Survey
^{177}Lu-antibodies	Increase (+1-15%)	Survey
[^{153}Sm]Sm-EDTMP	Increase (+1-15%)	Survey
^{169}Er-colloids	Decrease (-1-15%)	Survey
^{177}Lu-peptides	Increase (+1-15%)	Survey
[^{89}Sr]$SrCl_2$	Strong decrease (<-15%)/ Decrease (-1-15%)	Survey
^{90}Y-colloids	Increase (+1-15%)	Survey
^{90}Y-glass microspheres	Increase (+1-15%)	Survey
^{188}Re	Decrease (-1-15%)	Survey
[^{188}Re]Re-HEDP	Decrease (-1-15%)	Survey

7. Supply situation

In the Netherlands shortages in the supply of RPs is generally not a big problem, but supply issues have been mentioned for [^{131}I]I-mIBG and [^{131}I]-NaI. In the survey respondents answered often or sometimes for these RPs, meaning that the supply was disrupted at least more than three times in the past five years. Also, for ^{166}Ho-microspheres, sometimes shortages have been experienced (3-4 times/5 years). The impact of these disruptions has a great impact on patients, especially disruptions for ^{177}Lu and ^{166}Ho have. The origin of these disruptions is all with external production, so reside at the side of the supplier/producer. The causes have been linked to reactor downtime, so is already caused at the stage of RN production.

8. Patient access to radionuclide therapy (e.g. regional differences)

Patients across the country have good access to radionuclide therapy. Hospitals have different specialisations and facilities, but patients can go to other hospital for specific therapies.

2017 data on reimbursement (non-specific aggregation level for radiotherapy), suggest that 18 centres have been practicing radionuclide therapy in the Netherlands. The main providers of radionuclide therapy are the 7 Academic hospitals in the Netherlands. Largest capacity is 6 therapy beds in special radionuclide therapy facility of Erasmus MC.

9. Sources of information / References

[1] Interviews (2020) with RIVM, ErasmusMC and NRG.

[2] Data provided by RIVM and NVNG through e-mail exchange.

[3] Technopolis surveys (2020) (N = 25 in Round 1 and N = 8 in Round 2)

[4] Data from national insurance (DBC)

C.21 Poland – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{153}Sm, ^{89}Sr, ^{223}Ra, ^{90}Y, ^{169}Er, ^{186}Re, ^{131}I, ^{177}Lu [1, 3, 5]

2. Emerging radionuclides

Radiopharmaceuticals in experimental use (clinical trials): [1,5]

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{225}Ac	[^{225}Ac]Ac-PSMA	Prostate cancer	Yes
^{225}Ac	[^{225}Ac]Ac-DOTA-SP	glioblastoma	Yes
^{211}At	PSMA, DOTATATE	Cancer	No

3. Therapies and procedures

Radionuclide	Radiopharmaceutical	Number of doses in 2019	Average dose (MBq)	Total Activity (GBq)	Source of data
^{153}Sm	[^{153}Sm]Sm-EDTMP	112	3133	351	[6]
^{89}Sr	[^{89}Sr]$SrCl_2$	60	150	9	[6]
^{90}Y	^{90}Y-colloids*	664	203.5	135	[6]

Radionuclide	Radiopharmaceutical	Number of doses in 2019	Average dose (MBq)	Total Activity (GBq)	Source of data
^{90}Y	^{90}Y-glass spheres	53			[6]
^{90}Y ^{177}Lu	DOTATATE (30% ^{90}Y/^{177}Lu and 70% ^{177}Lu)	350	6475	2266	[6]
^{131}I	[^{131}I]-NaI	22097	(5500 for 12%; 500 for 88%)	24439	[6]
^{131}I	[^{131}I]I-mIBG	45	7450	335	[6]
^{223}Ra	[^{223}Ra]$RaCl_2$	714	3.85	3	[6]
^{186}Re	^{186}Re-colloids*	210	111	23	[6]
^{169}Er	^{169}Er-colloids	101	25	3	[6]

*vial could be divided Re-colloids 4-6, Y-colloids to 4-8 patients so number of procedures could be higher

4. Prices and reimbursement

In 2016, the equivalent of €328.2 million (based on purchasing power parity) was spent on radiotherapy i.e. a per capita expenditure of €8.6. Radiotherapy accounted for 0.67% of the total healthcare spending and 10.8% of total cancer care expenditure [2].

The prices of individual reimbursed radionuclides/radiopharmaceuticals are not publicly available. Radionuclide therapies are typically reimbursed under the general regulation of National Health Fund and separate pricing is not available. Below is a list of estimated prices (excluding transportation costs) provided by the national supplier - The National Centre For Nuclear Research – POLATOM.

Radiopharmaceutical	Price (€ per MBq)	Other information / reflection on distributors
IODOPOL® - Sodium iodide (^{131}I) for therapy	1.00	
Gelatin capsules ^{131}I	20.00	
Strontium (^{89}Sr) chloride for injection	3.73	
Quadramet® [^{153}Sm]Sm-EDTMP	0.55	Manufactured and distributed by the National Centre for Nuclear Research – POLATOM
Colloidal erbium citrate (^{169}Er) (Radiosynovectomy)	15.00	
Colloidal Rhenium sulphide (^{186}Re) (Radiosynovectomy)	12.00	
Colloidal Yttrium (^{90}Y) citrate (Radiosynovectomy)	8.00	

5. Medical guidelines

Radio-pharmaceutical	Indication	Guideline making organisation	Title of/link to guideline
^{131}I	Hyperthyroidism (in Graves' disease)	National and European recommendation	Published in Journal of Laws of the Ministry of Health of 2014, item 82 (based on national and European guidelines [6])
^{131}I	Hyperthyroidism (goitre)		
^{131}I	Struma neutralis		
^{131}I	Hyperthyroidism in children I-131		
^{89}Sr	Bone metastases (pain therapy)		
^{153}Sm	Bone metastases (pain therapy)		
^{223}Ra	Bone metastases (pain therapy)		
^{186}Re	Bone metastases (pain therapy)		
^{90}Y	Joint diseases		
^{186}Re	Joint diseases		
^{169}Er	Joint diseases		
^{90}Y	Lymphoma (radioimmunotherapy)		
^{90}Y	Primary/metastases of liver cancers		
^{131}I	Thyroid cancer		
^{131}I	Treatment with [^{131}I]I-mIBG		
^{90}Y, ^{177}Lu	Neuroendocrine tumours		

All other radiopharmaceuticals and indications are covered under EANM guidelines.

6. Future demand

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
[^{131}I]I-mIBG	Stable for majority of respondents	[4]
[^{131}I]-NaI	Stable for majority of respondents	[4]
[^{153}Sm]Sm-EDTMP	Stable for majority of respondents	[4]
^{169}Er-colloids	Stable for majority of respondents	[4]

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
[^{177}Lu]Lu-DOTATATE	Increase or strong increase for vast majority of respondents	[4]
^{177}Lu-peptides	Increase for vast majority of respondents	[4]
[^{177}Lu]Lu-PSMA	Strong increase for majority of respondents	[4]
^{186}Re-colloids	Stable for majority of respondents	[4]
[^{223}Ra]$RaCl_2$	Increase for majority of respondents	[4]
[^{225}Ac]Ac-PSMA	Increase or strong increase for vast majority of respondents (NOTE: currently in clinical trials)	[4]
[^{89}Sr]$SrCl_2$	Decrease for majority of respondents	[4]

7. Supply situation [1]

POLATOM is the manufacturer and distributor of isotopes used in medicine, science, industry and environmental protection in Poland. The construction of a large cyclotron at POLATOM for the production of radiopharmaceuticals is currently underway. Currently, production of certain radiopharmaceuticals is carried out as follows:

- LUTAPOL® or Lutetium (^{177}Lu) chloride [radiopharmaceutical precursor] is produced from Lutetium enriched with ^{176}Lu isotope which is irradiated with neutrons in a nuclear reactor
- MIBG and sodium iodide (^{131}I) is produced in a nuclear reactor from tellurium oxide irradiated with neutrons in the reactor or from uranium fission products
- Strontium (^{89}Sr) chloride is produced in the nuclear reactor
- ITRAPOL® - Yttrium (^{90}Y) chloride [radiopharmaceutical precursor] is produced from the decay of Strontium-90

8. Patient access to radionuclide therapy

1.2 centres per million inhabitants

- There are 45 practicing radionuclide therapy centres (according to the National Centre for Radiation Protection in Health, Poland). [1]

9. Sources of information / References

[1] Email exchange with Mr Dariusz Kluszczyński, Director of the National Centre for Radiation Protection in Health, Poland

[2] Lievens, Y., Borras, J. M., & Grau, C. (2020). Provision and use of radiotherapy in Europe. *Molecular Oncology*.

[3] Technopolis survey (Round 1), N = 11

[4] Technopolis survey (Round 2), N = 5

[5] Email exchange with Dr Rafał Czepczyński, Polish Society of Nuclear Medicine

[6] Email exchange with Dr Jolanta Kunikowska, Polish Society of Nuclear Medicine

C.22 Portugal – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use [1]: ^{131}I, ^{166}Ho, ^{177}Lu, ^{223}Ra, ^{90}Y, ^{32}P, ^{89}Sr, (but ^{32}P and ^{89}Sr is exceptional - roughly one patient every 5 years).

Radiopharmaceuticals in compassionate use: [^{177}Lu]Lu-DOTATATE (Lutathera®) to treat neuroendocrine tumours [2]

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use [2][3]:

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTATATE	Neuroendocrine tumours	NETTER-P and NETTER-2 trials to evaluate paediatric use and long term safety. Under pharmaco-economic evaluation by INFARMED for adult use.

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year (in all Nuclear Medicine Departments)		Average activity per procedure (MBq)		Total activity (GBq) (in all Nuclear Medicine Departments)
			Source		Source	
[^{131}I]I-mIBG (IOBENGUANE)	Adult neuroendocrine tumours	6	[4] [5]	7400	[4] [5]	44
[^{131}I]I-mIBG (IOBENGUANE)	Neuroblastoma	2	[4] [5]	7400	[4] [5]	15
[^{131}I]-NaI	Benign thyroid diseases	855	[4] [5]	464	[4] [5]	385
[^{131}I]-NaI	Thyroid cancer therapy for adults	201	[4] [5]	5541	[4] [5]	1114
[^{131}I]-NaI	Thyroid cancer therapy for children and young adults	9	[4] [5]	4812	[4] [5]	44
[^{131}I]-NaI	Thyroid remnant ablation of adults	721	[4] [5]	1425	[4] [5]	1127

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year (in all Nuclear Medicine Departments)		Average activity per procedure (MBq)		Total activity (GBq) (in all Nuclear Medicine Departments)
			Source		Source	
[^{131}I]-NaI	Thyroid remnant ablation of children and young adults	18	[4] [5]	1457	[4] [5]	23
^{166}Ho-microspheres	Intra-arterial treatment in the liver	9	[4] [5]	1833	[4] [5]	30
[^{177}Lu]Lu-DOTATATE	Gastroenteropancreatic neuroendocrine tumours	40	[4] [5]	7400	[4] [5]	296
[^{223}Ra]$RaCl_2$	Bone metastases	98	[4] [5]	3,9	[4] [5]	<1
^{90}Y-colloids	Radiation synovectomy	1	[4] [5]	185	[4] [5]	<1
^{90}Y-glass microspheres	Intra-arterial treatments in the liver	18	[4] [5]	1757	[4] [5]	11
^{90}Y-resin microspheres	Intra-arterial treatments in the liver	25	[4] [5]	1001	[4] [5]	44

4. Prices and reimbursement

Information based on survey

Radio-pharmaceutical	Price in € (mean, (min max))	Total budget spent per year	Calculation method	Other information / reflection on distributors
[^{131}I]-NaI	242.50 (85, 400)	-	-	-
[^{177}Lu]Lu-DOTATATE	22,500 (20,000, 25,000)	-	-	-
[^{223}Ra]$RaCl_2$	4,300 (4,300, 4,300)	-	-	-
^{90}Y-glass microspheres	12,500 (10,000, 15,000)	-	-	-

5. Medical guidelines

Portuguese survey respondents only reported using European clinical guidelines

6. Future demand

Radionuclide	Growth / Number of Patients Expected to receive therapy in future	Source of data
^{177}Lu-peptides	42.9% of Portuguese respondents expect there to be a **strong increase** (>15%) in demand. Another 28.6% expect there to be **weak increase** in demand (+1 to +15%)	[1]
[^{177}Lu]Lu-DOTATATE	28.6% of Portuguese respondents expect there to be a **strong increase** (>15%) in demand. Another 28.6% expect there to be **weak increase** in demand (+1 to +15%)	[1]
[^{177}Lu]Lu-PSMA	42.9% of Portuguese respondents expect there to be a **weak increase**(+1 to +15%) in demand. Another 28.6% expect there to be **strong increase** in demand (>15%)	[1]
[^{225}Ac]Ac-PSMA	28.6% of Portuguese respondents expect there to be a **weak increase**(+1 to +15%) in demand. Another 14.3% expect there to be **strong increase** in demand (>15%)	[1]
[^{153}Sm]Sm-EDTMP	28.6% of Portuguese respondents expect there to be a **strong decrease** (<-15%) in demand. Another 14.3% expect there to be **weaker decrease** in demand (-15% to -1%)	[1]
[^{89}Sr]$SrCl_2$	42.9% of Portuguese respondents expect there to be a **strong decrease** (<-15%) in demand	[1]

7. Supply situation

- [^{131}I]-NaI – 16.7% of relevant respondents suggested that [^{131}I]-NaI had been in shortage often (>4 times) over the last 5 years whilst 50% of relevant respondents suggested that [^{131}I]-NaI had been shortage rarely (1-2 times) over the last 5 years. A variety of reasons were suggested for these shortages occurring: during external production and during transport. These shortages were reported to have had a disruptive effect to some extent on the treatment of patients.
- [^{131}I]I-mIBG **(IOBENGUANE)** - Relevant respondents suggested that [^{131}I]-NaI had been in shortage often (>4 times) over the last 5 years. It was suggested that the reason for these shortages occurring was due to external production. These shortages were reported to have had a large disruptive effect on the treatment of patients.

8. Patient access to radionuclide therapy (e.g. regional differences)

There are 34 Nuclear Medicine Departments in Portugal. All are authorised to give therapy, however, only 7 of have the facilities to do inpatient procedures [2]. Twelve have a significant number of therapeutic procedures and the other twenty-two have only a residual therapeutic activity. There is a strong concentration of Nuclear Medicine Departments in the 3 main Portuguese cities (Lisbon, Porto and Coimbra), where 26 of the 34 departments are located. The remaining 8 departments are located in other high population density areas.

9. Other information

Lutathera® is imported from Spain, Iodine based radionuclides from France, Radium from the US and Yttrium from The Netherlands.

10. Sources of information / References

[1] Technopolis survey (survey respondents N = 14)

[2] Interview with Dr Gracinda Costa, Portuguese Nuclear Medicine Society - SPMN

[3] Technopolis clinical trials analysis

[4] SPMN survey to the twelve Nuclear Medicine Departments that are more representative in the therapeutic area (survey respondents N = 8)

[5] SPMN estimation based on reliable historical data (N = 26)

C.23 Romania – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu, ^{188}Re

2. Emerging radionuclides

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{131}I	Lenvatinib (E7080)	Differentiated Thyroid Cancer	Y

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Number of procedures per year	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I, e.g. [^{131}I]-Thyrotop	Thyroid cancer	2600	[2]	4000	1040

With regard to the remaining radiopharmaceuticals, we only know that they are used in Romania, but not in what amount – no data was provided in the survey.

4. Prices and reimbursement

Radiopharmaceutical	Price (€)	Total budget spent per year	Calculation method
^{131}I	>520€	If the patient is not insured, the payment goes up from 2500 RON (520 EURO), depending on the associated procedures performed and the days of hospitalisation.	Patients x price = € 1.352 million

5. Medical guidelines

Radio-pharmaceutical	Indication	Recommended dosage	Guideline making organisation	Title of/link to guideline
^{131}I	thyroid malignancies, hyperthyroidism	Patients with hyperthyroidism - receive doses between 10-20 mCi, on average 15 mCi. Usually, a single administration is sufficient. Patients with thyroid cancer - receive doses of 30-50 mCi for the low-risk category, 100 mCi for the other categories, > 100 mCi for patients with metastases.	EANM, ATA, NCCN	National Guide to the diagnosis and treatment of differentiated thyroid cancer derived from follicular epithelium (2010) National Guide to the diagnosis and treatment of clinical hyperthyroidism EANM guidelines on I-131 therapy of Differentiated Thyroid Cancer (2008) ATA Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis (2016) ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (2015) NCCN Clinical Practice Guidelines in Oncology 2019

Note: EANM = European Association for Nuclear Medicine, ATA = American Thyroid Association, NCCN = National Comprehensive Cancer Network (USA)

6. Future demand

The Romanian survey respondents did not provide any data on future demand.

7. Patient access to radionuclide therapy (e.g. regional differences)

5 hospitals: two private and three public [2]. This would mean access of 0.3 centres per million inhabitants.

8. Sources of information / References

[1] Survey respondents (N = 4)

[2] Email exchange with Olga Girjoaba, National Institute of Public Health

[3] IAEA DIRAC (Directory of radiotherapy centres)

C.24 Slovakia – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{223}Ra, ^{177}Lu, ^{89}Sr, ^{90}Y

2. Therapies and procedures

Information based on data received from the national contact point:

Radio-pharmaceutical	Indication and type of procedure	Number of Patients receiving therapy per year (dose)	Source of data
^{131}I-NaI	thyroid cancer	656 (1.1-4.1 GBq)	[1]
^{131}I-NaI	adjuvant therapy/therapy of metastatic diseases	307 (3.7-7.4 GBq)	[1]
^{131}I-NaI	orbitopathy	41 patients (2.4-3.7 GBq)	[1]
^{131}I-NaI	thyreotoxicosis	135 patients, about 10% of them need second therapy (185-925 MBq)	[1]
^{223}Ra		circa 180 applications	[1]

Information based on data received from Technopolis survey:

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	1133	Survey	500	567
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	4095	Survey	5500	22523
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	98	Survey	1942	190

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	1095	Survey	3000	3285
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	38	Survey	1942	74
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	135	Survey	7400	999
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	1058	Survey	3.85	4
^{89}Sr	[^{89}Sr]$SrCl_2$ used in bone metastases (EMA authorised)	8	Survey	150	1
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	8	Survey	3133	25

3. Prices and reimbursement

Radionuclides and radiopharmaceuticals for therapy are bought from qualified and certified distributors: ^{131}I - GE (company MGP) prices as in EU, ^{223}Ra– Bayer, prices as in EU, ^{177}Lu – in-house preparing. Source: [1]

4. Medical guidelines

Overall, EANM guidelines are used.

5. Future demand

Radionuclide	Number of Patients expected to receive therapy in future	Source of data
[^{177}Lu]Lu-DOTATATE	Strong increase (more than +15%)	Survey data
^{177}Lu-peptides	Strong increase (more than +15%)	Survey data
[^{177}Lu]Lu-PSMA	Strong increase (more than +15%)	Survey data

6. Supply situation

According to data from national contacts, ^{89}Sr stopped after Brexit.

7. Patient access to radionuclide therapy (e.g. regional differences)

Reported problems with insurance for the radionuclide therapy: diagnosis-related groups (DRG) system in place leading to very low price for inpatient therapy. If expensive radiopharmaceuticals (such as [^{177}Lu]Lu-PSMA) are

needed, patients have to be treated on outpatient basis. In some patients with neuroendocrine tumour this can be risky, at the moment they are treated abroad. Source: [1]

- Number of radiotherapy practicing centres:

  There are 3 centres for therapy (12, 10, 10 beds) in Slovakia, according to our data request [1]. However, national statistics mention 15 centres for nuclear medicine in the country. [3]

8. Sources of information / References

[1] Information received from Dr Pavol Povinec

[2] Technopolis survey data (N = 3)

[3] Cinnost_nuklearnej_mediciny_klinickej_a_radiacnej_onkologie_v_SR_2018c

[4] Gleisner et al. (2017)

C.25 Slovenia – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: **^{131}I, ^{177}Lu, ^{90}Y,** ^{223}Ra, **^{186}Re**, ^{64}Cu

Radionuclides in bold have been listed by URSJV and were confirmed by the survey. Underlined RNs have been indicated in the survey but are likely only rare RNs in experimental use.

2. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 1360 therapeutic treatments in nuclear medicine are performed in Slovenia. More recent (2019) and specific data is obtained from the URSJV and provided in the table below.

Radiopharmaceutical	Number of Patients Receiving therapy per year	Number of procedures per year	Activity	Source of data
^{131}I	700 (average 2017-2019	700 (average 2017-2019)	1027.4 GBq	URSJV, 2019
^{177}Lu	17 (average 2017-2019)	17 (average 2017-2019)	111.5 GBq	URSJV, 2019
^{90}Y	2 (average 2017-2019	2 (average 2017-2019)	12.0 GBq	URSJV, 2019
^{223}Ra	31 (average 2017-2019)	186 (average 2017-2019)	1.4 GBq	URSJV, 2019
^{186}Re	3 (average 2017-2019	3 (average 2017-2019)	<1 GBq	URSJV, 2019

3. Prices and reimbursement

Radiopharmaceuticals are fully reimbursed in Slovenia from the “Public Insurance Budget”. Some proce data have been obtained from this Public Insuramce Budget on the radiopharmaceuticals listed below, obtained from

the Slovenian Government. These concern the highest prices that have been paid. Based on these max prices a total max budget spent per year has been calculated using the numbers on procedures and total annual activity.

No information was obtained on distributors/producers in Slovenia.

Radiopharmaceutical	Price (€, highest)	Total budget spent per year (€, max)	Calculation method	Other information / reflection on distributors
[^{131}I]-NaI	273.47	37,968- 75,936	(Average activity per year (in MBq) /7400 MBq) x price	POLATOM, 37-7400 MBq
[^{90}Y]Y-ibritumomab-tiuxetan	10,334.27	20,669	Average number of procedures per year x price	Zevalin® 1,6 mg/mL, [^{90}Y]Y-ibritumomab tiuxetan
[^{223}Ra]$RaCl_2$	4,434.27	824.774	Average number of procedures per year x price	Xofigo® 1,000 kBq/mL
^{177}Lu (precursor)	31,509.50	63,019	(Average activity per year / 40GBq/ML)	2 mL EndolucinBeta® 40GBq/mL
	59,054.50	59,055	(Average activity per year / 40GBq/ML)	10 mL EndolucinBeta® 40GBq/mL

4. Medical guidelines

In Slovenia guidelines and protocols are based on EANM guidelines.

5. Future demand

In Slovenia the demand of ^{177}Lu is growing quickly: from 6 patients in 2017, through 15 patients in 2018 to 30 patients in 2019. No other demand information for Slovenia was obtained in the survey or interviews.

6. Supply situation

No isotopes are produced within Slovenia. Radionuclides and radiopharmaceuticals are imported without any serious supply issues in the last years. No additional information was obtained in the survey regarding shortages.

7. Patient access to radionuclide therapy (e.g. regional differences)

- Number of radiopharmacies:

  Slovenia has six radiopharmacies related to radionuclide therapy, located at the six centres that practice radionuclide therapy.

- Number of radionuclide therapy practicing centres:

  Slovenia has six centres practicing radionuclide therapy: KNM, OI, UKC Maribor, SB Celje, SB Slovenj Gradec and SB Izola.

8. Sources of information / References

[1] Information based on written interview/e-mail exchange (2020) with Dr. Damijan Skrk from the Slovenian Radiation Protection Administration.

[2] The Slovenian Radiation Protection Administration (URSJV) (2019), *Razširjeno poročilo o varstvu pred ionizirajočimi sevanji in jedrski varnosti v Republiki Sloveniji leta 2018*, section 2.2.7.2.

[3] Technopolis survey (N = 1)

C.26 Spain – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{32}P, ^{89}Sr, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{169}Er, ^{177}Lu, ^{186}Re, ^{188}Re, ^{223}Ra

2. Emerging radionuclides

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTA0-Tyr3-Octreotate	Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours	Y
^{177}Lu	[^{177}Lu]Lu-edotreotide PRRT	GEP-Net patients	Y
^{177}Lu	Betalutin®	Relapsed Non-Hodgkin Lymphoma	Y
^{90}Y	^{90}Y SIRT	Unresectable Intrahepatic Cholangiocarcinoma	Y
^{90}Y		Transarterial Radioembolisation in Uveal Melanoma Liver Metastasis	Y
^{90}Y	^{90}Y SIRT	Advanced Stage Intrahepatic Biliary Tract Cancer	Y
^{90}Y	TheraSphere®	Inoperable Liver Cancer	Y
^{90}Y	TheraSphere®	Metastatic Colorectal Cancer	Y
^{90}Y	Nivolumab After SIRT	HCC	Y
^{131}I	^{131}I-omburtamab	Neuroblastoma Central Nervous System/Leptomeningeal Metastases	Y
^{131}I	Lenvatinib (E7080)	Differentiated Thyroid Cancer	Y

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{223}Ra	Radium-223 Dichloride	Castration-resistant Prostate Cancer Metastatic to the Bone	Y
^{223}Ra	Radium-223 Dichloride	Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases	Y
^{223}Ra	Radium-223 Dichloride	Bone Predominant HER2 (Human Epidermal Growth Factor Receptor 2) Negative Hormone Receptor Positive Metastatic Breast Cancer	Y
^{223}Ra	Radium-223 Dichloride	Stage IV Non-small Cell Lung Cancer With Bone Metastases	Y
^{223}Ra	Radium-223 Dichloride	Asymptomatic Patients With mCRPC	Y
^{223}Ra	Radium-223 Dichloride	Cancer of the Prostate	Y

3. Therapies and procedures

Radio-pharmaceutical	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{90}Y	^{90}Y-colloids used in radiation synovectomy	600	Survey	203	122
^{90}Y	^{90}Y-glass microspheres used in intra-arterial treatments in the liver	372	Survey	11500	4278
^{90}Y	[^{90}Y]Y-ibritumomab-tiuxetan used in b-cell lymphoma and non-hodgkin lymphoma (EMA authorised)	84	Survey	1000	84
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	540	Survey	3000	1620
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in adult neuroendocrine tumours (EMA authorised)	60	Survey	7450	447
^{131}I	[^{131}I]I-mIBG (IOBENGUANE) used in neuroblastoma (EMA authorised)	96	Survey	7450	715
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	5484	Survey	500	2742
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	3540	Survey	5550	19647
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	1056	Survey	1942	2051

Radio-pharmaceutical	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average activity per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	3084	Survey	3000	9252
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	396	Survey	1942	769
^{166}Ho	^{166}Ho-microspheres used in intra-arterial treatment in the liver (EMA authorised)	168	Survey	1890	318
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (EMA authorised)	336	Survey	6475	2176
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases (EMA authorised)	240	Survey	3.85	1
^{32}P	^{32}P-sodium-phosphate ($Na_3{}^{32}PO_4$) used in myeloproliferative disease	12	Survey	185	2
^{89}Sr	[^{89}Sr]$SrCl_2$ used in bone metastases (EMA authorised)	24	Survey	150	4
^{153}Sm	[^{153}Sm]Sm-EDTMP used in bone metastases (EMA authorised)	72	Survey	3133	226
^{169}Er	^{169}Er-colloids used in radiation synovectomy	84	Survey	25	2
^{186}Re	^{186}Re-colloids used in radiation synovectomy	132	Survey	111	15
^{188}Re	^{188}Re used in non-melanoma skin cancer	24	Survey	452	11
^{188}Re	[^{188}Re]Re-HEDP used in painful bone metastases	24	Survey	3079	74

4. Prices and reimbursement

In Spain, radiopharmaceuticals related medical procedures are classified as procedures “for hospital use”. For this category of procedures/products, the National Health System (NHS) funds 100% of cost as long as it is applied in a hospital/centre within the NHS (not in a private centre/hospital).[1]

There is a National Commission in charge of pricing policy to assess the price of the radiopharmaceutical.[1] Radionuclides are reimbursed at the price defined by the AEMPS (Spanish agency of Drugs and sanitary products).[2]

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
[^{131}I]-NaI	93-587	Survey
[^{131}I]I-mIBG	1031-3712	Survey

Radiopharmaceutical	Price (€)	Other information / reflection on distributors
[^{177}Lu]Lu-DOTATATE	13478	Survey
[^{223}Ra]$RaCl_2$	4596	Survey
^{153}Sm-EDTP	1716	Survey
^{186}Re-colloids	514-1249	Survey
[^{89}Sr]$SrCl_2$	1800-1900	Survey
[^{90}Y]Y-ibritumomab-tiuxetan	13518	Survey
^{90}Y-resin microspheres	8500-8600	Survey
^{90}Y-glass microspheres	8500-8600	Survey
^{90}Y-colloids	353-637	Survey

5. Medical guidelines

Radiopharmaceutical	Indication	Guideline making organisation
^{131}I		American Thyroid Association
^{177}Lu		ENETS guidelines
^{223}Ra	Prostate Cancer	European Urological Guideline for Prostate Cancer and NCCN
^{90}Y		Hepatocellular carcinoma guidelines and many digestive cancer guidelines for SIRT

6. Future demand

The most important advance in the near future could be the use of [^{177}Lu]Lu-PSMA and the most products with alpha emitter agents [2]

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
[^{177}Lu]Lu-DOTATATE ^{177}Lu-peptides	Strong increase expected by majority of respondents	Survey
[^{177}Lu]Lu-PSMA	Increase to strong increase expected by large majority of respondents	Survey
^{166}Ho-microspheres	Increase expected by majority of respondents	Survey

Radionuclide	Number of Patients Expected to receive therapy in future	Source of data
^{32}P-sodium-phosphate ($Na_3{}^{32}PO_4$)	Strong decrease expected by majority of respondents	Survey
[^{89}Sr]$SrCl_2$	Decrease expected by majority of respondents	Survey

7. Supply situation

The therapeutic products are manufactured outside Spain, with the exception of ^{177}Lu.[2] According to one interviewee, at this moment the supply is appropriate, even in a landscape with increased demand.[2] However, survey respondents report shortages with ^{131}I (mIBG and NaI), which they believe impacts patients to a certain extent. The shortages occur during external production and transport. To increase supply, licences would have to be increased (in the case of ^{131}I). [4]

8. Patient access to radionuclide therapy (e.g. regional differences)

Spain has approximately 60 centres (including public and private practice). The majority have radiopharmacies, however some rely on external radiopharmacies. [2]

9. Sources of information / References

[1] Correspondence with Yolanda Agra Varela, Ministry of Health, 22 April 2020

[2] Correspondence with Juan Antonio Vallejo (Hospital Universitarior Reina Sofía), 31 March 2020

[3] Gleisner et al. (2017)

[4] Technopolis survey (N = 6)

C.27 Sweden – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{131}I, ^{90}Y, ^{223}Ra, ^{153}Sm, ^{32}P, ^{177}Lu

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials):

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-PSMA	Metastatic Castrate-Resistant Prostate Cancer	Yes – Phase III

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTATATE	Relapsed Non-Hodgkin Lymphoma	Yes - Phase I and Phase II
^{225}Ac	[^{225}Ac]Ac-PSMA	Men With Cancer of the Prostate	Yes - Phase III

3. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 3496 therapeutic treatments in nuclear medicine are performed in Sweden. More recent data is presented below:

Radio-pharmaceutical	Indication and type of procedure	Number of Patients Receiving therapy per year	Number of procedures per year	Activity (MBq)	Source of data
[^{131}I]-NaI	Hyperthyroidism	n/a	1,502	660,880	SSM
[^{131}I]-NaI	Thyroid cancer	n/a	476	1,642,200	SSM
^{90}Y-colloids	Radiosynovectomy	n/a	1	209	SSM
[^{223}Ra]$RaCl_2$	Palliation of bone metastases	n/a	1,466	6,597	SSM
[^{153}Sm]Sm-EDTMP (Quadramet®)	Palliation of bone metastases	n/a	6	17,016	SSM
^{32}P–sodium-phosphate ($Na_3{}^{32}PO_4$)	Polycytemia vera	n/a	50	9,200	SSM
[^{131}I]I-mIBG (IOBENGUANE)	Neuroendocrine tumours	n/a	7	93,100	SSM
[^{177}Lu]Lu-DOTA-NOC (Octreotid)	Neuroendocrine tumours	n/a	444	3,210,120	SSM
^{90}Y- microspheres	Liver tumours	n/a	4	4,500	SSM

4. Prices and reimbursement

No price information was available.

5. Medical guidelines

There are no official Swedish national guidelines issued by authorities. There are however national care programmes issued by the care providers in which radionuclide therapy can be recommended with guidelines

on how to perform the treatments. In some cases, international guidelines, such as the EANM guidelines will be used [1].

6. Future demand

No survey information was reported on future demand for radionuclides in Sweden. However, an interviewee suggested that there has been a trend in Sweden towards more complex treatments with individualised treatment planning by using dosimetry based on SPECT-imaging. These developments add more demand on the radiotherapy sessions in terms of time as several SPECT CT sessions are needed to calculate dosimetry [1].

7. Supply situation

No issues have been raised regarding supply of radionuclides in Sweden. Radiopharmaceuticals are imported from other countries as ready to use capsules or injectable solutions. These countries include the Netherlands, Poland and Germany [1].

8. Patient access to radionuclide therapy (e.g. regional differences)

All radiotherapy is performed by public health care givers in 21 different regions at 23 different hospitals. There are more hospitals concentrated in Stockholm than other regions [2].

9. Sources of information / References

There were no complete responses from Sweden from the Technopolis survey

[1] Interview conducted in April 2020 with Lars Idestrom, Inspector at the Swedish Radiation Safety Authority (also known as the Strålsäkerhetsmyndigheten or SSM)

[2] SSM also provide public information on annual radiotherapy statistics in Sweden

C.28 UK – validated

1. Radiopharmaceuticals currently in use

Radionuclides in use: ^{90}Y, ^{131}I, ^{177}Lu, ^{223}Ra

Radiopharmaceuticals in compassionate use: may be used to fund Lu-177 PSMA in Scotland and Wales but unlikely in England and Wales but some privately funded treatment may occur

2. Emerging radionuclides / radiopharmaceuticals

Radiopharmaceuticals in experimental use (clinical trials):

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
^{177}Lu	[^{177}Lu]Lu-DOTATOC	rarer neuroendocrine tumours such as phaeochromocytoma	Used as part of research trials suspended for

Radionuclide	Radiopharmaceutical	Indication	In clinical trials?
			about 6 months restarting soon
^{177}Lu	[^{177}Lu]Lu-PSMA	Prostate cancer	Trial completed awaiting product authorisation and re-imbursement before roll-out
^{225}Ac	[^{225}Ac]Ac-PSMA	Prostate cancer	Not yet in clinical trials
^{32}P	^{32}P-silicon	Pancreatic cancer	Trails completed and now authorised awaiting decision on reimbursement

3. Therapies and procedures

According to the 2008 UNSCEAR Global Survey of Medical Radiation Usage and Exposure, 14500 therapeutic treatments in nuclear medicine are performed in the United Kingdom.

However, there is no central register of number of patients receiving radionuclide therapy or procedures. A new register for Lu-177 DOTATATE therapy has started and will be adapted for Lu-177 PSMA. The register is administered by the BNMS. In the meanwhile, a cross-section review of radionuclide usage was performed in July/August 2020.

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]-NaI used in benign thyroid diseases	5623	[3]	500	2811
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of adults	3931	[3]	3000	11794
^{131}I	[^{131}I]-NaI used in thyroid remnant ablation of children and young adults	155	[3]	1942.5	302
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for adults	1015	[3]	5500	5632
^{131}I	[^{131}I]-NaI used in thyroid cancer therapy for children and young adults	64	[3]	1942.5	124
^{131}I	[^{131}I]I-mIBG used in neuroblastoma	101	[3], BNMS	7450	749

Radionuclide	Indication and type of procedure	Average number of procedures per year nationally	Source of data	Average dose per procedure (MBq)	National annual demand (GBq)
^{131}I	[^{131}I]I-mIBG used in adult neuroendocrine tumours	357	[3], BNMS	7450	2656
^{177}Lu	^{177}Lu-antibodies used in non-hodgkin lymphoma	64	[3]	1062	68
^{177}Lu	[^{177}Lu]Lu-PSMA used in therapy of castration resistant prostate cancer and pc-metastases	1189	[3]	7400	8795
^{177}Lu	[^{177}Lu]Lu-DOTATATE used in gastroenteropancreatic neuroendocrine tumours (PRRT)	3438	[3], BNMS	6475	22259
^{166}Ho	^{166}Ho-microspheres used in intra-arterial treatment in the liver	18	[3]	1890	35
^{32}P	^{32}P-sodium-phosphate used in myeloproliferative disease	73	[3]	185	14
^{223}Ra	[^{223}Ra]$RaCl_2$ used in bone metastases	7077	[3]	3.85	27
^{186}Re	^{186}Re-colloids used in radiation synovectomy	82	[3]	111	9
^{90}Y	[^{90}Y]Y-ibritumomab-tiuxetan used in b-cell lymphoma and non-hodgkin lymphoma	9	[3]	1000	9
^{90}Y	^{90}Y-resin microspheres used in intra-arterial treatments in the liver	777	[3]	3000	2331
^{90}Y	^{90}Y-glass microspheres used in intra-arterial treatments in the liver	722	[3]	11500	8306
^{90}Y	^{90}Y-colloids used in radiation synovectomy	329	[3], BNMS	203.5	67

4. Prices and reimbursement

The table below is based on data from the Technopolis survey [4]

Radiopharmaceutical	Mean Price (€ per procedure)	Other information / reflection on distributors
[^{223}Ra]$RaCl_2$	1948.00	
[^{177}Lu]Lu-PSMA	14439.00	Price will increase after authorisation is obtained
[^{131}I]-NaI	178.50	According to BSNM, price is ~£500
[^{131}I]I-mIBG	4652.00	According to BSNM, price is ~£500
^{90}Y-resin microspheres	8853.00	
^{90}Y-glass microspheres	8853.00	

5. Medical guidelines

The National Institute of Health Excellence (NICE) publishes guidelines for radiotherapy in England. These allow for re-imbursement in England and may be adopted by the other UK nations as well.

For therapies not covered by NICE guidelines, the guidelines of the European Association of Nuclear Medicine are recommended.

Radio-pharmaceutical	Indication	Guideline making organisation	Title of/link to guideline
^{131}I	benign thyroid disease	NICE	https://www.nice.org.uk/guidance/ng145/documents/evidence-review-12
^{223}Ra	Prostate cancer with bone metastases	NICE	https://www.nice.org.uk/guidance/ta412/resources/radium223-dichloride-for-treating-hormonerelapsed-prostate-cancer-with-bone-metastases-pdf-82604599866565
^{177}Lu DOTATATE	neuroendocrine tumours	NICE	https://www.nice.org.uk/guidance/ta539/documents/committee-papers
^{90}Y (SIRT)	Liver cancer (HCC) and metastases	NICE	https://www.nice.org.uk/guidance/ipg460/chapter/2-The-procedure

6. Future demand

According to the BSNM, future demand will depend on funding and training. At present only about 50% of the eligible UK population receives radionuclide therapies they could benefit from as there is a lack of trained staff and ignorance among oncologists.

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
[^{131}I]-NaI	Stable for majority of respondents	[4]

Radiopharmaceutical	Number of Patients expected to receive therapy in future	Source of data
^{166}Ho-microspheres	Increase and strong increase for majority of respondents; will depend on results of clinical trials	[4]
[^{177}Lu]Lu-PSMA (or [^{225}Ac]Ac-PSMA in 5-10 years)	Strong increase for vast majority of respondents; this will take 10 years to achieve due to capacity issues	[4], BSNM
^{90}Y-glass microspheres	Stable for majority of respondents	[4]
^{90}Y-resin microspheres	Stable for majority of respondents	[4]
^{223}Ra	Growth expected until Lu-PSMA is authorised and reimbursed	BSNM
[^{177}Lu]Lu-DOTATATE (Lutathera®)	Growth expected to a plateau in about 5 years	BSNM

7. Supply situation

No radionuclide product used in the UK is made in the UK. They are mainly shipped from the EU, with some products being shipped directly from the US. Brexit has the potential to cause major change to supply chains – in the event of no EU-UK trade deal, radionuclide supply may have to come directly from the US and South Africa.

8. Patient access to radionuclide therapy (e.g. regional differences)

1 radiotherapy centres per million inhabitants (based on Gleisner et al. (2017))

Inhabitants in London, South East England, Manchester and Liverpool are offered a full range of services with highly trained staff. Elsewhere availability of services varies depending on the regional infrastructure and capacity. For instance, all the UK centres give ^{131}I for thyroid disease. The BSNM believes there are about 30 centres giving ^{223}Ra, 20 doing PRRT, and 10 doing SIRT in the UK. [^{131}I]I-mIBG is given in about 6 centres including 2 that treat children, while synovectomy is available in about 10 centres.

Regional differences seem to have a bigger impact on access to Lutathera® than other radiopharmaceuticals according to the BSNM. It also reports that almost no patient is eligible to receive SIRT in the UK.

- Number of radiopharmacies:

  There are about 30 radiopharmacies in England, 3 in Scotland, 2 in Northern Ireland and 3 in Wales run by the relevant National Health Service. Almost all of these are involved in providing some radionuclide therapy products even if just dispensing I-131. There are about 7 private radiopharmacies in the UK, but these only provide imaging products

- Number of radiotherapy practicing centres:

  The actual number of NHS hospitals providing radionuclide therapies is unknown. However, data from the British Institute of Radiology (2009) suggests that there are about 50 such centres in England including 2 which specialise in treating children. In Scotland, Wales and Northern Ireland, there are 5, 2 and 2 centres respectively. In England there are 5 private centres giving a range of radionuclide therapies. All these centres are in or near London and most of their patients come from outside the UK.

9. Sources of information / References

[1] Email exchange and interview with Dr John Buscombe, British Nuclear Medicine Society (BNMS)

[2] Gleisner, K. S., Spezi, E., Solny, P., et al. (2017). Variations in the practice of molecular radiotherapy and implementation of dosimetry: results from a European survey. EJNMMI physics, 4(1), 28.

[3] Technopolis survey (Round 1), N = 24

[4] Technopolis survey (Round 2), N = 4

Appendix D Glossary

Abbreviation	Full description
IAEA	International Atomic Energy Agency
EANM	European Association for Nuclear Medicine
Bq	Becquerel, unit of activity (disintegrations per second) (GBq = Giga Bq, MBq = Mega Bq)
CA	Carrier added
DCP	Decentralised procedure
DOE	Department of Energy (USA)
EC	European Commission
ECIS	European Cancer Information System
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
ESA	Euratom Supply Agency
ESS	European Spallation Source
HTA	Health Technology Assessment
JRC	Joint Research Centre
HALEU	High-assay low-enriched uranium
HLG-MR	High-level Group on the Security of Supply of Medical Radioisotopes
LEU	Low Enriched Uranium
LET	Linear energy transfer
MRI	Magnetic Resonance Imaging
MRP	Mutual recognition procedure
NCA	Non-carrier added
NET	Neuro endocrine tumour

Abbreviation	Full description
NHS	National Health Service
OECD-NEA	Organisation for Economic Cooperation and Development – Nuclear Energy Agency
PET	Positron emission tomography, a nuclear medicine imaging technique
PSMA	Prostate-specific membrane antigen, also known as PSMA617
RN	Radionuclide
RP	Radiopharmaceutical
RRDB	Research reactor database
SAMIRA	Strategic Agenda for Medical, Industrial and Research Applications of radionuclides
SHI	Social health insurance system
SPECT	Single-photon emission computed tomography, a nuclear medicine imaging technique
TOA	Time of administration
TRL	Technology Readiness Level

Notations for radionuclides and radiopharmaceuticals

Note that throughout the report the conventions for the notation of radiopharmaceuticals and radionuclides as promoted by the EANM[119] is followed as much as possible. In figures (for better readability) and sources (using different convention) notations may vary. For example, the notation [^{177}Lu]Lu-DOTATATE refers to the identical radiopharmaceutical (i.e. Lutathera®) in the 177Lu-DOTATATE notation. Similarly, [^{223}Ra]$RaCl_2$ denotes the same radiopharmaceutical (i.e. Xofigo®) as $^{223}RaCl_2$ or 223RaCl2 (as seen in some figures). For radionuclides similar differences between notations exist, where (for example) ^{90}Y is identical to 90Y and Y-90 (or Yttrium-90), albeit different notations are used.

[119] This notation is summarised in: EANM (2019). *Let's be precise!* Available at: https://www.eanm.org/content-eanm/uploads/2019/12/EANM_GUIDANCE-_TRACER_NOMENCLATURE-1.pdf.

Appendix E View of the EANM

The European Association of Nuclear Medicine has been supportive in promoting participation of and providing access to their members for the data collection and validation exercise performed in this study. Given the lack of accessible official data, their support has been important for the best-available insights provided in this report.

The EANM has been granted to opportunity to provide their view on the outcomes of this study. Therefore, their unedited commentary letter in the box below presents the sole view of the EANM Board and not the view of the authors nor the European Commission.

Comment by the European Association of Nuclear Medicine (EANM) on Study on sustainable and resilient supply of medical radioisotopes in the EU THERAPEUTIC RADIONUCLIDES

As prime umbrella organization for nuclear medicine, molecular and hybrid imaging in Europe, the EANM highly appreciates the focus that is given to the sustainability of supply of radionuclides for therapeutic purposes as examined in the SMER 2 project, based upon the learnings of SMER 1 for diagnostic radionuclides.

The EANM supports the general message given in the executive summary of the project, outlining the trends of current and future use of radionuclides. The general recommendations drawn will surely be a good basis for further decisions taken and actions put forward by the European Commission. Having said that, the devil is in the details i.e. data. While the general recommendations reflect the view of the EANM, the survey data as presented in Appendix B of this report needs to be put into perspective. Further, the methodological drawbacks of the survey at hand shall not stay unaddressed.

Firstly, the overall number of responses is considered to be very low, hence not representative and therefore also not suited to calculate demand of activities or number of procedures. Calculations as included in the report are considered to be unrealistic and are most certainly not reflecting the true demand.

Secondly, the report puts currently used and registered radiopharmaceuticals (e.g. [^{131}I]NaI, [^{131}I]mIBG, ^{90}Y-labeled colloids, [^{177}Lu]Lu-DOTATATE) onto the same level as radiopharmaceuticals there are not registered and only used in clinical trials or experimental therapies (e.g. ^{177}Lu-labeled antibodies; PSMA-ligands labeled with ^{177}Lu, ^{225}Ac, , and ^{227}Th; ^{227}Th –labeled conjugates). As a consequence of this clinical situation, the future demand of the two distinctively different types of radiopharmaceuticals should have been addressed and described separately in the report.

For the specific case of [^{177}Lu]Lu –PSMA-ligands, EANM supports the conclusion that demand will be increasing significantly in the near future compared to other radiopharmaceuticals. The authors very briefly investigate the main problem with the supply of ^{177}Lu which is the lack of sufficient target material for the irradiation process which is key when it comes to significantly increasing its production. Naturally, also other phases of the production and supply chain are important, but the availability of target materials in required quality and quantity seems to be the most important and pressing issue.

In summary, EANM is appreciative of the SMER 2 initiative and supports the statements of the main executive summary. The general parts of the report may surely serve as basis for further discussions and deeper evaluation but the European Commission shall stay away from taking actions based on the data presented in Appendix B, as this is not reliable and far from complete. A more reliable source of information could be the national health systems of the EU Member States, who, as a paymaster, should have the most reliable data. In other countries, national radiation protection authorities or producers and distributors could be addressed.

About EANM

The European Association of Nuclear Medicine (EANM) is the largest organisation dedicated to nuclear medicine in Europe. In this role, it has become the umbrella organisation which represents the whole sector towards the European Institutions and other international institutions.

The EANM's vision is to optimise and advance science and education in nuclear medicine for the benefit of public health and humanity within the concept of personalised healthcare.

The goal of the EANM is to be a platform for the dissemination and discussion of the latest results in the field of nuclear medicine including multimodality imaging and related subjects. It fosters and co-ordinates the mutual exchange of knowledge relating to the diagnosis, treatment and prevention of diseases through the use of unsealed radioactive substances and the properties of stable nuclides in medicine.

The EANM is a professional non-profit medical association, incorporated in Vienna/Austria. The EANM membership comprises physicians, scientists, technologists as well as other persons working in nuclear medicine or related fields. Currently, the EANM represents more than 9,000 specialists from 41 different countries within Europe and serves the interests of a community that goes far beyond these numbers and any geographical boundaries.

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KJ-NA-30690-EN-N

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doi:10.2760/642561

ISBN 978-92-76-37422-0