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Project: M180

Report on the feasibility of large-scale actinium-225
production

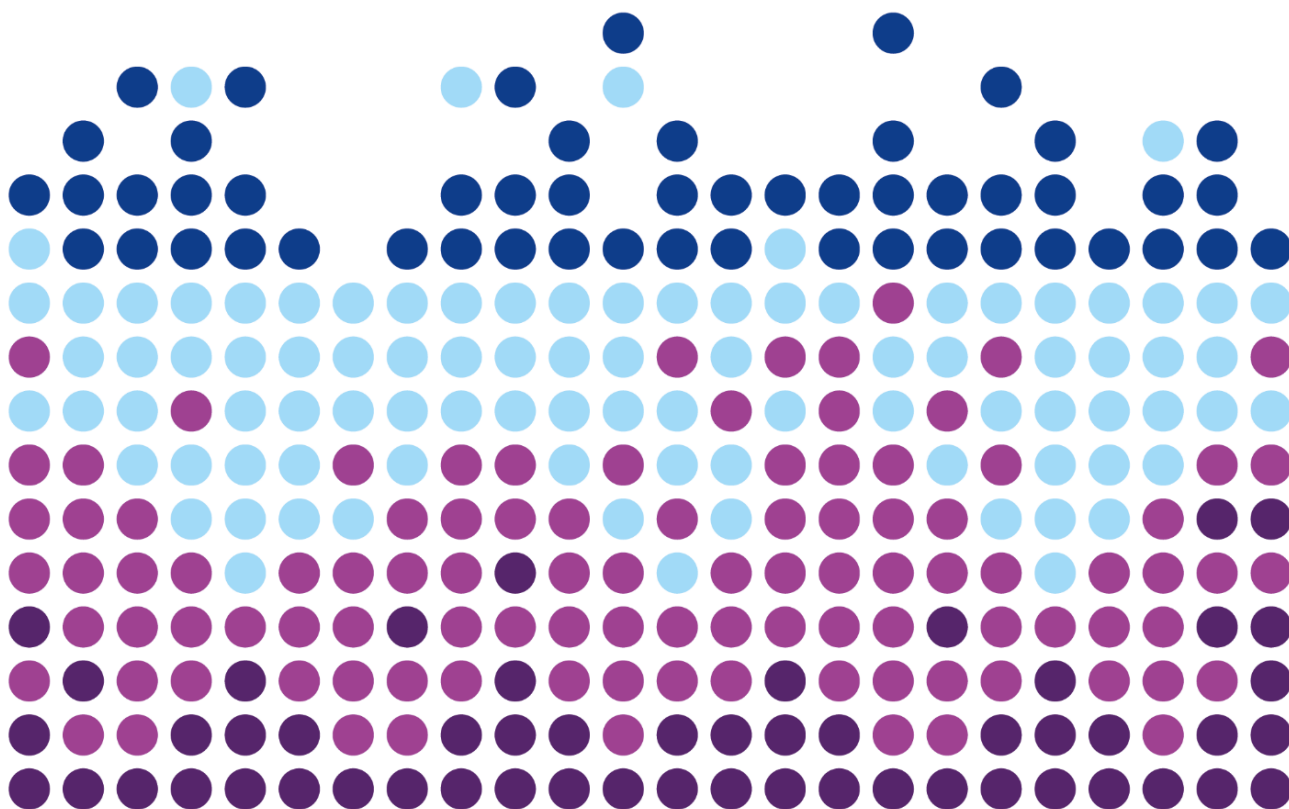
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Glossary of abbreviations

AHU	Air Handling Unit
BMS	Building Management System
BR2	Belgian Reactor 2
CDS	Centralized Decay Storage facility
Ci	Curie (radioactivity unit)
CRF	Centralized Radiochemistry Facility – radioisotope facility
CTS	Central Technical Services at SCK CEN
DGA	Diglycolamide resin
DOTATATE	DOTA-(Tyr ³)-octreotate (radiopharmaceutical peptide)
EOB	End of bombardment
FAGG	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
FANC	Federaal Agentschap voor Nucleaire Controle
GBq	Gigabecquerel (radioactivity unit)
GMP	Good Manufacturing Practice
HDEHP	Bis(2-ethylhexyl) phosphoric acid (extraction agent)
HEPA	High-Efficiency Particulate Air (filter)
HVAC	Heating, Ventilation and Air Conditioning
IBA	Ion Beam Applications (Belgian medical technology company)
IDPBW	Interne Dienst voor Preventie en Bescherming op het Werk
IRE	Institut National des Radioéléments
LET	Linear Energy Transfer
LINAC	Linear Accelerator
LN resin	Extraction resin (LN type)
LRM	Low-level Radioactivity Measurements group at SCK CEN
mb	Milli-barn – cross section unit
MBq	Megabecquerel (radioactivity unit)
MeV	Mega-electronvolt (energy unit)
nDGA	normal Diglycolamide resin
NURA	Nuclear Medicine program at SCK CEN
P&ID	Piping and Instrumentation Diagram
PET	Positron Emission Tomography
PFD	Process Flow Diagram
PLC	Programmable Logic Controller
PPE	Personal Protective Equipment
PSAR	Pre-Safety Assessment Report
PSMA	Prostate-Specific Membrane Antigen
QA	Quality Assurance (Person)
QP	Qualified Person
QC	Quality Control
R&D	Research & Development
RCS	Radio-Chemical System
RDS	Radon Delay System
RRF	Recovery and Resilience Funds
RTS	Radon Trapping System

SAT	Site Acceptance Test
SAR	Safety Assessment Report
SBS	System Breakdown Structure
SCK CEN	Belgian Nuclear Research Centre
SPECT	Single Photon Emission Computed Tomography
SUP	Facility Process and Support
TAT	Targeted Alpha Therapy
TLR	Top Level Requirements
TRT	Targeted Radionuclide Therapy
TSS	Target Station System
UPS	Uninterruptible Power Supply
URS	User Requirement Specifications
WP	Work Package
XC	Extraction Chromatography
bDGA	branched Diglycolamide resin

Executive summary

This feasibility study, funded through the EU Recovery and Resilience Facility (RRF) under project I-5.08 (M180 – Nuclear Medicine), delivers a comprehensive assessment of the technological package required to enable the large-scale production of actinium-225 (^{225}Ac) from radium-226 (^{226}Ra).

The study confirms that Belgium is uniquely positioned to play a leading role in securing European and global supply of this critical radioisotope for targeted alpha therapy (TAT), based on its exclusive legacy stock of ^{226}Ra and the successful development of key enabling technologies across the full production chain.

The project has delivered the following key elements:

1) Operational hot cell installation to handle ^{226}Ra

Development and demonstration of a prototype radon capture system (radon trap) enabling the safe handling of ^{226}Ra ready for implementation at SCK CEN. This radon trapping system allows controlled manipulation of ^{226}Ra sources within existing hot cell facilities and represents a critical enabling step for any large-scale production approach based on radium. The underlying technology has been consolidated through a dedicated European patent, review by authorities and described in a peer reviewed publication.

2) Electron-to-gamma converter design for large-scale production

A high-efficiency electron-to-gamma converter has been designed as part of the preferred photonuclear production route. This technology enables the generation of high-intensity gamma radiation required for the (γ, n) reaction on ^{226}Ra and constitutes a key building block for scalable ^{225}Ac production. The innovation is protected through a dedicated European patent.

3) Target and irradiation module design for large-scale production

The study delivers a design of the ^{226}Ra target and irradiation module, including systems tailored to the selected liquid-gamma irradiation approach. The proposed designs address key challenges such as heat management, radiation safety, and process efficiency, and are supported by experimental validation and patented technological developments.

4) Fully scaled-up radiochemical separation method and ^{226}Ra recycling process

A radiochemical separation process for $^{226}\text{Ra}/^{225}\text{Ac}$ has been developed, validated, and brought to a level compatible with large-scale implementation. The process includes provisions for automation, pharmaceutical-grade production, and efficient recycling of ^{226}Ra , ensuring sustainability and optimal use of the scarce target material. This development is also protected through intellectual property.

5) Conceptual design of a ^{225}Ac production facility

A conceptual design of a dedicated ^{225}Ac production facility has been established. The design integrates all key process steps including irradiation, radiochemical processing, target recycling, and product handling, while incorporating GMP requirements and radiation protection. This provides a clear pathway towards industrial implementation.

Furthermore, the project has generated significant innovation outputs, including four European patent applications covering radon trapping, irradiation technology, gamma conversion, and radiochemical processing. Key outcomes of the feasibility study therefore include:

- **Infrastructure** that will ensure the safe handling of ^{226}Ra within hot cell facilities.
- **Scientific publication** – A peer-reviewed article detailing the experimental methodology, resin selection, and performance results of the prototype radon trap.
- **Four key technologies developed and protected** through European patents.
- **Validated technological building blocks** covering the full ^{225}Ac production chain.
- **Conceptual design delivered** for a dedicated large-scale ^{225}Ac production facility.
- **Significant reduction of the technological gap** between current capabilities and industrial-scale implementation.

Together, these results demonstrate that all critical technological components required for large-scale ^{225}Ac production from ^{226}Ra have been successfully developed at feasibility level, with multiple components already advancing beyond a conventional feasibility stage. The integration of these components into a coherent production concept confirms the technical viability and strategic relevance of establishing such a facility in Belgium.

The study concludes that the realization of ^{225}Ac production capacity based on ^{226}Ra is both realistic and strategically important. Its implementation will secure European patients' access to life-saving isotopes while reinforcing Europe's leadership and sovereignty in nuclear medicine.

Introduction

This report presents the findings of the EU Recovery and Resilience Facility (RRF) project I-5.08 – Nuclear Medicine, project number M180, titled “ ^{225}Ac Feasibility Study,” conducted at the Belgian Nuclear Research Center, SCK CEN, Belgium.

The project has received funding through the EU Recovery and Resilience Facility to evaluate the feasibility of establishing large-scale production of ^{225}Ac . This involves developing technologies, providing scientific solutions, and proposing various infrastructures required for an efficient production.

^{225}Ac is considered one of the most promising medical therapeutic radioisotopes due to its application in targeted alpha therapy (TAT), which offers high precision in treating various cancers. However, scaling up the production of ^{225}Ac poses significant challenges across multiple domains, including technological limitations, complex logistical requirements, stringent safety standards, and unresolved scientific hurdles. These scientific challenges include the development of novel radiochemical solutions and addressing gaps in existing technologies. Overcoming these obstacles is essential to meet the surging demand for this critical radioisotope, ensuring its availability for clinical trials and routine hospital use.

Achieving a stable and sufficient supply of pharmaceutical-grade ^{225}Ac is a pivotal step in advancing its application in nuclear medicine. SCK CEN is uniquely positioned to contribute to the large-scale production of ^{225}Ac , thanks to its exclusive stock of ^{226}Ra . This rare resource can serve as an efficient target material for the production of ^{225}Ac , thereby addressing a key bottleneck in the supply chain. The feasibility study under project M180 aimed to bridge the gap between existing production technologies and the advanced requirements needed for scaling up ^{225}Ac production.

The findings and recommendations presented in this report will serve as a foundation for future initiatives aimed at ensuring the reliable and sustainable supply of ^{225}Ac for therapeutic radiopharmaceuticals. By addressing the identified challenges and opportunities, SCK CEN seeks to advance nuclear medicine and contribute to the development of future innovative cancer treatments.

Applications of radioisotopes in nuclear medicine

Cancer treatment has evolved and improved significantly over the years, offering a variety of approaches tailored to the type and progression of the disease. The primary treatment methods include surgery, which removes tumors physically; external radiation therapy, which targets cancerous cells with high-energy beams; chemotherapy, which uses cytotoxic drugs to eliminate rapidly dividing cells; hormonal therapy, which blocks or alters hormone production to slow hormone-sensitive cancers; and immunotherapy, which enhances the body's immune system to recognize and attack cancer cells [1].

A more recent and promising advancement is targeted radionuclide therapy (TRT). This approach delivers radioactive isotopes directly to cancer cells, minimizing damage to surrounding healthy tissue. Unlike traditional external radiation, which affects a broader area, TRT provides a more selective and precise treatment. TRT can be used as a standalone therapy or in combination with other treatments, enhancing their effectiveness while potentially reducing side effects. By integrating TRT into cancer treatment strategies, clinicians can improve therapeutic outcomes, particularly in cases where conventional therapies have limitations [2].



Figure 1: TRT has the potential to enhance the overall effectiveness of multimodal treatment strategies.

Radioisotopes play a vital role in both the diagnosis and treatment of various diseases, especially in the context of cancer and other serious medical conditions. In diagnostic imaging, radioisotopes are used to generate high-quality images that allow clinicians to observe the functioning of organs and tissues, detect abnormalities, and plan treatment strategies. In therapeutics, radioisotopes serve as powerful tools to treat diseases, particularly cancers, by delivering targeted radiation to affected areas.

Diagnostics

Radioisotopes like fluorine-18 (^{18}F) and technetium-99m ($^{99\text{m}}\text{Tc}$) are commonly used in Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) scans. These isotopes emit radiation detectable by specialized imaging devices, allowing healthcare providers to view inside the body in real-time. For example, ^{18}F is frequently used in PET scans to locate and evaluate the extent of cancer, while $^{99\text{m}}\text{Tc}$ is used in SPECT scans to monitor heart function, bone disorders and more [3, 4].

Therapeutics - Targeted Radionuclide Therapy (TRT)

Targeted Radionuclide Therapy is an exciting and rapidly advancing field within nuclear medicine, offering a highly precise and personalized method for cancer treatment. In TRT, radioisotopes are linked to targeting agents such as antibodies, peptides, or small molecules that recognize and bind to unique markers expressed on the surface of cancer cells (as shown in Figure 2). This selective targeting ensures that the radioactive payload is delivered directly to the tumor, sparing normal tissues, and thereby minimizing side effects often associated with other forms of radiation therapy.

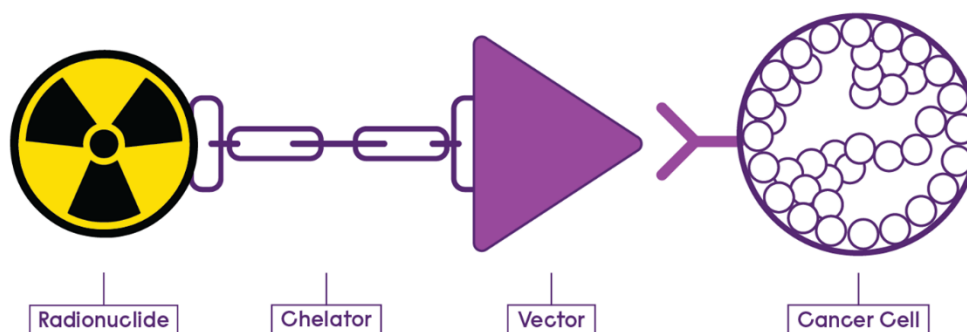


Figure 2: Mechanism of action of TRT showing therapeutic radioisotope linked with molecule (vector) targeting specific receptors on the surface of cancer cells.

Once the targeting molecule carrying the radioisotope (an example is illustrated in Figure 3) binds to cancer-specific receptors, such as those present in neuroendocrine tumors, prostate cancer, or lymphomas, the radioisotope emits therapeutic radiation in the form of alpha or beta particles. These high-energy particles cause irreparable DNA damage and disrupt vital cellular processes, ultimately leading to the destruction of the cancer cells. The precise delivery and powerful therapeutic effect of TRT make it a promising option for treating a wide range of malignancies, including those that may be resistant to traditional therapies [5].

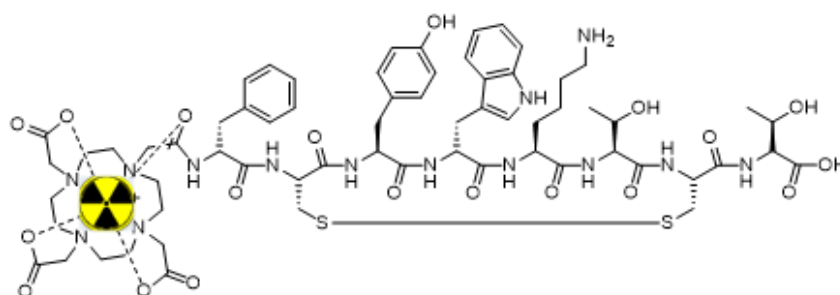


Figure 3: DOTATATE molecule radiolabeled with a therapeutic radioisotope for the treatment of neuroendocrine tumors.

By combining advanced molecular targeting techniques with the potent therapeutic effects of radiation, TRT not only enhances treatment outcomes but also represents a paradigm shift in the way we approach cancer therapy. This approach continues to evolve, driven by ongoing research into novel targeting molecules and radioisotopes, further expanding its potential to improve patient care.

Actinium and its increasing importance in nuclear medicine

^{225}Ac is gaining significant attention in nuclear medicine due to its unique properties and its potential for use in TRT.

Properties of ^{225}Ac

^{225}Ac is an alpha-emitting radioisotope with a half-life of 10 days. During its decay several radioactive daughter isotopes are created (see Figure 4 for the decay scheme of ^{225}Ac) before reaching stable bismuth-209 (^{209}Bi).

During the decay of ^{225}Ac high-energy alpha particles are created with a very short range, meaning they are highly effective in killing cancer cells without significantly affecting surrounding healthy tissue. This makes ^{225}Ac an excellent candidate for precision medicine and targeted cancer therapies.

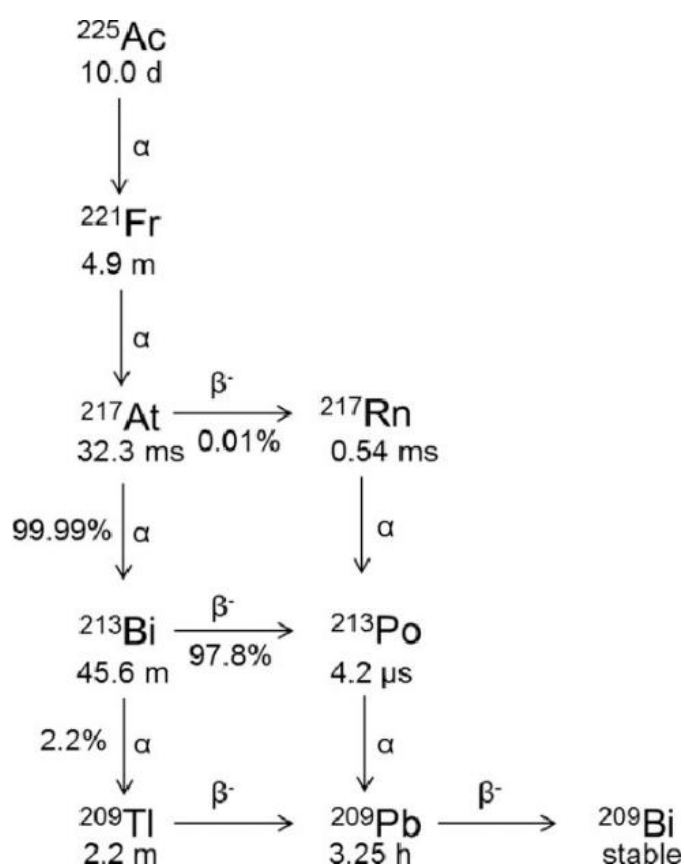


Figure 4: Decay scheme of ^{225}Ac .

Clinical potential of ^{225}Ac

^{225}Ac has demonstrated considerable promise in early clinical trials for treating various cancers, including prostate cancer, leukemia, and glioblastoma. Research highlights its potential particularly in hematological malignancies (blood cancers) and solid tumors that are resistant to conventional treatments. The unique characteristics of ^{225}Ac make it a powerful tool for tackling challenging cases where other therapies fall short [6].

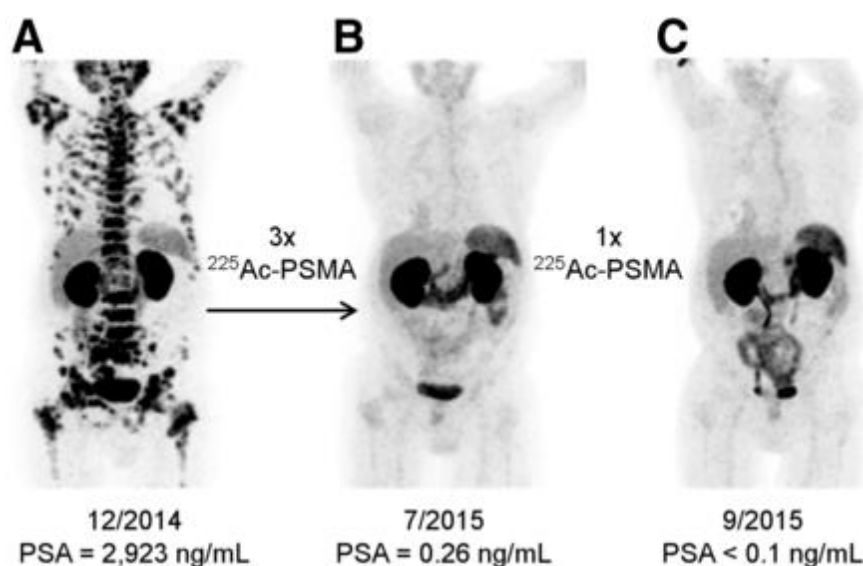


Figure 5: ^{68}Ga -PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 months after third cycle of ^{225}Ac -PSMA-617 (B), and restaging 2 months after one additional consolidation therapy (C) [6].

In certain clinical scenarios, ^{225}Ac has shown superior efficacy compared to lutetium-177 (^{177}Lu), particularly in cases where ^{177}Lu -based therapies have limited success. Studies indicate that tumors with low expression of targeted receptors or poor vascularization may not respond effectively to ^{177}Lu . This limitation arises because ^{177}Lu emits beta particles with a longer range, which can dilute the radiation dose delivered to the tumor under suboptimal receptor density or perfusion conditions. Consequently, ^{177}Lu therapy may fail to deliver sufficient therapeutic impact in such cases [7].

In contrast, ^{225}Ac emits high-energy alpha particles, characterized by their short range and high linear energy transfer (LET). This unique property enables ^{225}Ac to deliver highly localized radiation, making it particularly effective at eradicating poorly vascularized or receptor-low tumor cells. For instance, in prostate-specific membrane antigen (PSMA)-targeted therapies for metastatic prostate cancer, patients who showed resistance or minimal response to ^{177}Lu -PSMA therapy experienced significant therapeutic benefits with ^{225}Ac -PSMA [8]. Alpha particles emitted by ^{225}Ac can cause double-strand DNA breaks, which are far more lethal to cancer cells than the single-strand breaks typically induced by beta particles. This mechanism of action underscores the clinical potential of ^{225}Ac as a potent alternative for patients with tumors that do not respond to conventional or beta-emitting radionuclide therapies.

As research continues to explore ^{225}Ac -based therapies, their ability to target resistant cancers with precision and potency positions them as a promising innovation in the field of nuclear medicine.

Principles of production of radioisotopes for nuclear medicine

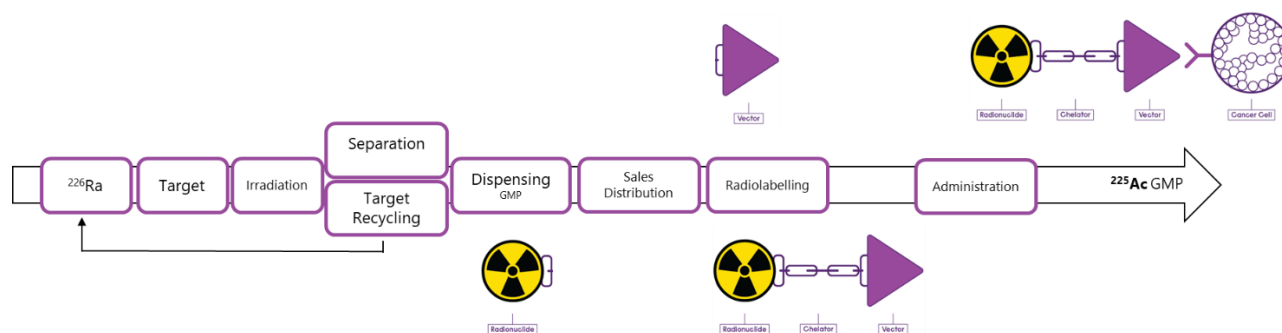


Figure 6: Key stages of radiopharmaceutical production.

The production of radiopharmaceuticals for nuclear medicine is a complex, multi-step process that involves specialized materials, technologies, and strict regulations to ensure safety, quality, and efficiency. These steps include radioisotope production, separation and purification, radiolabeling, and final administration as shown in Figure 6 [9].

Below, the key stages of radioisotope production are outlined.

Enriched target material

The process begins with the selection of (enriched) target materials, which can be isotopically enhanced forms of elements needed to produce specific radioisotopes. These materials are critical for achieving efficient nuclear reactions and ensuring high yields of the desired radioisotope. As an example, ytterbium-176 (^{176}Yb) is used to produce ^{177}Lu as well as ^{226}Ra can be used to produce ^{225}Ac depending on the type of irradiation applied.

Targets for irradiation

The enriched material is carefully prepared into a form suitable for irradiation, such as a solid pellet, liquid solution, metal or oxide forms of the material encapsulated in a quartz ampoule or gas-filled container. The design of the target depends on the specific nuclear reaction required and the type of irradiating device (e.g., a nuclear reactor or cyclotron). Targets must be robust enough to withstand the bombardment of neutrons, gamma-rays or charged particles during irradiation.

Chemical separation

After irradiation, the target undergoes a chemical separation process to isolate the desired radioisotope from the target material and any (radioactive) byproducts. Separation processes may involve dissolution, filtration, ion exchange, or precipitation, depending on the isotope.

Recycling of enriched target material

Given the high cost of enriched target materials, recycling is usually an essential step in the production process. Unreacted enriched material is recovered from the chemical separation process and purified for reuse in future irradiations. This results in reduced waste, lower costs, and ensures the sustainability of isotope production.

Dispensing into vials

The purified radioisotope is formulated into a stock solution and dispensed into individual vials under sterile, Good Manufacturing Practice (GMP) conditions. This ensures the product meets the required specifications for use in patients. Dosages are carefully calibrated to account for the decay rate of the radioisotope and ensure efficacy at the time of administration.

Quality control (QC)

Each batch of the radioisotope undergoes rigorous quality control testing to ensure it meets safety, purity, and efficacy standards. Key tests include radionuclidic purity, (radio)chemical purity and sterility. QC is critical to guarantee that the radiopharmaceutical is safe for clinical use [10].

Distribution

Once approved, the radioisotope is packaged in radiation-shielded containers and transported to medical facilities where typically the radiolabeling takes place. Radiolabeling is the process where the radioisotope is linked with the vector molecule. Because many isotopes have short half-lives, transport must be rapid and efficient to minimize decay during transit. Logistics must comply with strict regulations to ensure safety during handling and transportation.

Safety and radiation protection

Radiation exposure to personnel and the public should be minimized through advanced shielding, remote handling technologies, use of hot cell installations and strict protocols. Facilities must adhere to radiation safety standards set by regulatory bodies like the IAEA (International Atomic Energy Agency) and national authorities.

Good Manufacturing Practices (GMP)

All production steps must comply with GMP guidelines to ensure consistent quality and safety of the final product. This includes sterile manufacturing, validated processes, and thorough documentation.

Radioactive waste management

The production process generates radioactive waste, including spent targets, contaminated equipment, and byproducts. Waste is classified based on its activity level and managed through decay storage, conditioning, or disposal in approved facilities. Sustainable practices, such as recycling enriched materials and decay storage of shorter-lived radioactive waste, help reduce the volume of waste.

Focus points of the ^{225}Ac large-scale production feasibility study

SCK CEN has carried out a groundbreaking feasibility study, supported by the RRF funding, to address the technological challenges associated with the large-scale production of ^{225}Ac . Leveraging its unique stock of ^{226}Ra , SCK CEN has aimed to develop innovative solutions to close the gap between existing production methods and the requirements for efficient, scalable production of ^{225}Ac . This feasibility study focuses on critical technological decisions and developments that will ensure the success of this initiative and lay the groundwork for implementing a full-scale production facility.

Key focus points of the feasibility study

The structure of this feasibility study was specifically defined to ensure that each key technological element required for ^{225}Ac production from ^{226}Ra was systematically developed and assessed (an overview of the different elements of the study can be found in Figure 7).

Pre-phase analysis

A critical decision involves determining the optimal irradiation method of the target material: gamma irradiation versus proton irradiation which are the two main routes considered in this study. Each has unique implications for efficiency, scalability, and infrastructure requirements. Another focus is selecting between liquid and solid target technologies, balancing ease of handling, irradiation efficiency, and compatibility with the downstream separation processes. The pre-phase of the feasibility study will define the basis and give directions for the other focus points of the feasibility study.

Enabling handling of ^{226}Ra

Developing a radon capture system (radon trap) to safely manage radon emissions during the handling of ^{226}Ra to be implemented in an existing hot cell infrastructure. This part of the feasibility study aims at finalizing the actual design, in-house construction, testing including preparations for implementation of the installation in an existing hot cell facility at SCK CEN.

Target and converter technology

Proposing designs for essential components, including the ^{226}Ra target/irradiation module tailored for the chosen irradiation and target technologies.

Radiochemical separation methodology

Develop a radiochemical separation process for $^{226}\text{Ra}/^{225}\text{Ac}$ to meet the demands of large-scale production focusing on optimizing resource utilization, particularly the unique ^{226}Ra and propose the type and level of automation required to ensure operational efficiency and safety, particularly in handling radioactive materials and minimizing radioactive waste.

Facility design

Developing a conceptual design for the production facility, including the integration of all chosen technologies.

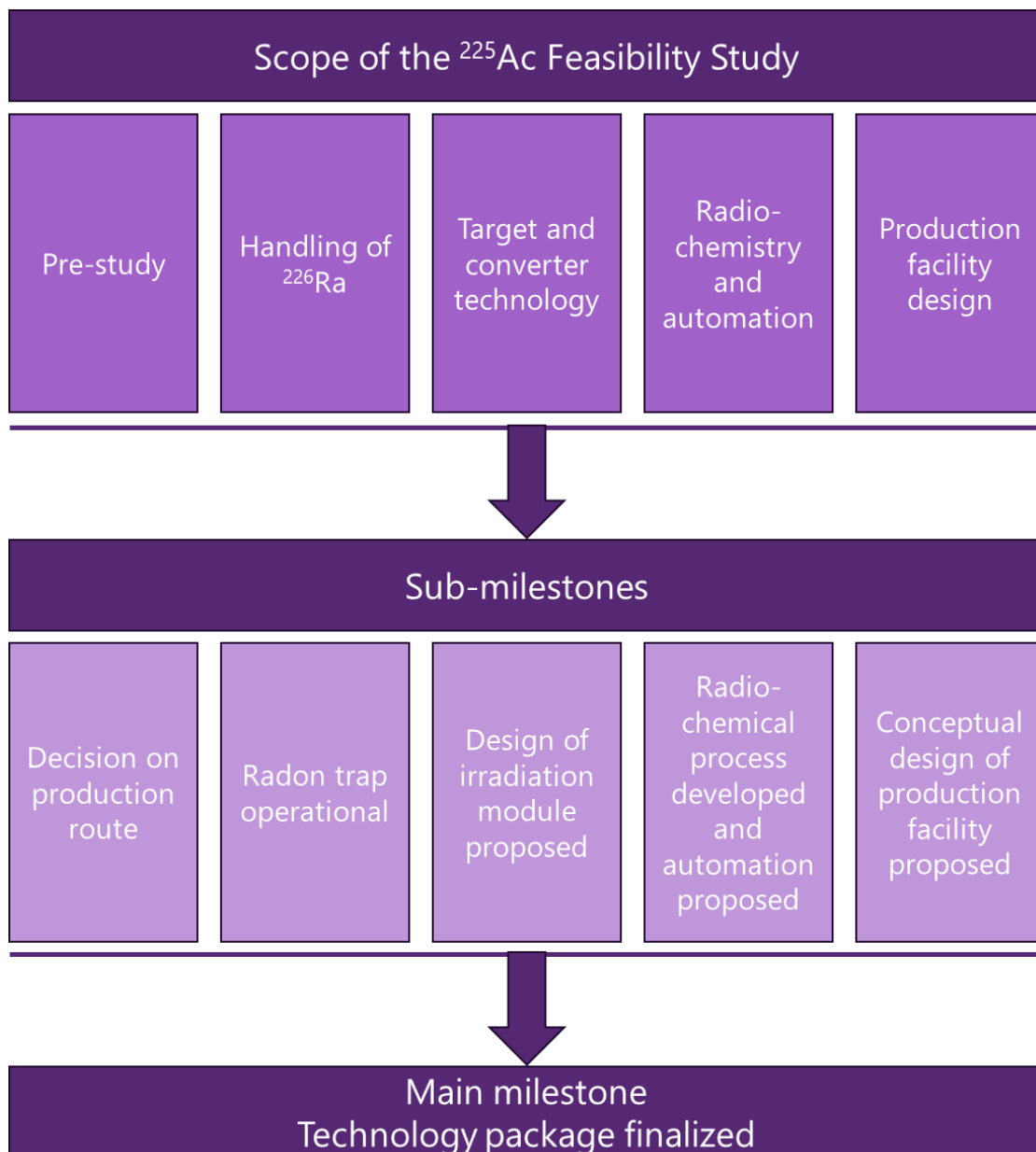


Figure 7: Scope, sub-milestones and main milestone of project M180, ^{225}Ac Feasibility Study.

Pre-study: Evaluation of different ^{225}Ac production routes from ^{226}Ra

As part of the feasibility study on large-scale ^{225}Ac production, this pre-study focused on evaluating production routes that use ^{226}Ra as the starting material. SCK CEN is uniquely positioned for this approach due to its access to pure radium stocks from previous activities [11, 12, 13].

While ^{226}Ra -based routes formed the core of the analysis, other potential production pathways for ^{225}Ac were also initially considered to provide the full picture of the current technical level. These included proton-induced reactions on thorium targets and spallation-based methods, among others. However, the focus was ultimately directed toward valorising ^{226}Ra , given its strategic availability at SCK CEN and the potential for developing a dedicated large-scale ^{225}Ac production facility.

Several production methods based on ^{226}Ra were explored in this context, including proton-induced and photonuclear reactions, as well as both liquid and solid target configurations. Each method presents distinct technological, radiochemical, and logistical challenges that must be assessed to determine their feasibility for large-scale implementation.

This pre-study serves as an initial evaluation of the various production routes for ^{225}Ac from ^{226}Ra , while acknowledging the broader landscape of alternative approaches. The findings will contribute to defining the most viable production strategies, ensuring a stable and sustainable supply of ^{225}Ac for future therapeutic applications.

Pre-study execution and methodology

This pre-study was conducted through a combination of internal expertise at SCK CEN and external benchmarking. The work builds on SCK CEN's existing knowledge and experience in radionuclide production, radiochemistry, and facility operation. A thorough review of scientific literature and public domain information was performed to assess the state of the art in ^{225}Ac production technologies.

The evaluation included a comparison of different production routes, notably those involving accelerator- and reactor-based methods, and considered their technical maturity, scalability, and safety implications (see overview Figure 8). Key elements were benchmarked against developments at other leading institutions worldwide, allowing for an informed assessment of the potential applicability and competitiveness of various technologies.

The insights gathered provided the foundation for identifying viable production strategies, needed technologies, associated infrastructure needs, and safety considerations, as well as outlining the next steps towards a full-scale feasibility assessment.

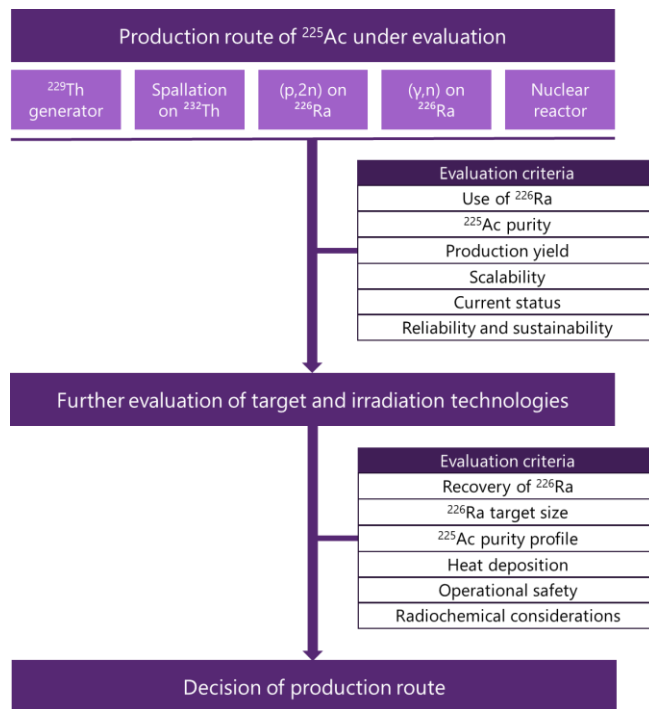


Figure 8: Methodology of the pre-study.

Introduction to the different ²²⁵Ac production routes

Several routes can be considered to produce ²²⁵Ac using different target materials. These routes involve different nuclear reactions and target configurations, each with specific operational, radiochemical, and infrastructure characteristics. Some of the current and potential future main production routes to ²²⁵Ac are considered below:

Thorium generator

The thorium generator route involves the use of thorium-229 (²²⁹Th) with a half-life of >7,400 years as a parent isotope, which decays to ²²⁵Ac through its natural decay chain. ²²⁹Th can for example be obtained from legacy uranium-233 (²³³U) sources. In this approach, ²²⁵Ac accumulates over time and can be periodically separated (milked) from the generator. The system functions similarly to other isotope generators used in nuclear medicine, with a long-lived parent isotope and a shorter-lived daughter [14, 15]. This route does not require particle irradiation but involves the long-term management and handling of alpha-emitting materials.

Thorium spallation

In this method, high-energy protons (typically above 100 MeV) are directed onto a thorium-232 (²³²Th) target, initiating a spallation reaction that produces a broad range of fission and fragmentation products, including ²²⁵Ac. The reaction occurs in thick solid or liquid thorium targets, and the irradiated material contains a complex mix of radionuclides [16, 17]. Post-irradiation radiochemical separation is required to isolate ²²⁵Ac. The process involves high-energy accelerator systems and must account for heat deposition, radiation damage, and radiological shielding.

Proton irradiation, (p,2n) on ^{226}Ra

This production route uses low- to medium-energy protons (in the range of ~15–30 MeV) to irradiate ^{226}Ra , resulting in nuclear reactions such as (p,2n) that produce ^{225}Ac [18]. The radium target can be in solid or liquid form, and the production yield is influenced by factors such as beam energy, current, and target thickness. Radiochemical processing involves separation of ^{225}Ac from ^{226}Ra and other reaction products, while managing the decay chain of ^{226}Ra and the potential presence of short-lived contaminants.

Radium gamma irradiation (γ ,n) on ^{226}Ra

In this emerging method, ^{226}Ra is irradiated using high-energy gamma rays, typically generated by bremsstrahlung radiation from an electron accelerator. The gamma-induced reaction (γ ,n) can produce radium-225 (^{225}Ra), which subsequently decays to ^{225}Ac . The target material remains relatively unaffected by direct particle bombardment, but photonuclear cross-sections are generally low [17], and the process requires a high-intensity gamma flux to achieve measurable production rates. This method may offer advantageous alternative target configurations and irradiation setups compared to charged-particle-based systems.

Nuclear reactor

Nuclear reactor-based production of ^{225}Ac typically involves neutron capture reactions on long-lived precursor isotopes. One example is the irradiation of ^{226}Ra with an intense source of high (>6.4 MeV) neutrons to produce ^{225}Ra via the (n,2n) reaction, followed by decay to ^{225}Ac . Another possible route is the production of ^{225}Ac through decay chains initiated by neutron-induced reactions on thorium or uranium targets [16].

Preliminary evaluation of production routes with emphasis on ^{226}Ra valorization

A central objective of this feasibility study is to identify and prioritize production routes for ^{225}Ac that allow for the strategic use and valorization of existing ^{226}Ra stocks at SCK CEN. Given the institution's unique access to high-purity ^{226}Ra , production pathways that incorporate this material are of particular interest.

This section presents a comparative evaluation of the main production routes under consideration, including both radium- and thorium-based approaches, as well as reactor and generator options to bring the full picture. Each pathway is assessed based on its compatibility with ^{226}Ra , expected product purity, scalability, production yield, current development status, and long-term sustainability.

Thorium generator

In the context of this feasibility study, the thorium generator route is considered a complementary long-term option for small-scale or backup ^{225}Ac production. It does not support the valorization of ^{226}Ra and is therefore not prioritized in the current evaluation, which focuses on radium-based production strategies. The thorium generator method relies on the long-lived alpha emitter ^{229}Th ($T_{1/2} = 7,340$ years), which decays via a well-characterized pathway to ^{225}Ac . Once chemically isolated, ^{229}Th can function as a generator parent, producing ^{225}Ac continuously over time. This isotope can then be periodically “milked” using established radiochemical techniques, in much the same way other radionuclide generators are employed in nuclear medicine.

^{229}Th is not naturally abundant and is typically recovered from the decay of ^{233}U ($T_{1/2} = 160,000$ years), a material originally produced through neutron irradiation of ^{232}Th during nuclear weapons and reactor programs in the mid-20th century. Legacy stocks of ^{233}U , mainly held in national laboratories, remain the primary source for ^{229}Th . Notable institutions such as Oak Ridge National Laboratory (ORNL), the Joint Research Centre (JRC) in Karlsruhe, and IPPE in Russia have maintained production of ^{225}Ac from these sources

for clinical and research purposes. More recently, new efforts have been made to recover ^{229}Th from historical waste, potentially expanding future availability.

Radiochemical separation of ^{225}Ac from ^{229}Th is relatively straightforward, utilizing ion exchange and extraction chromatography methods. This approach produces ^{225}Ac with high radionuclidic purity and minimal contamination from other actinium isotopes, a distinct advantage for therapeutic applications. However, the scalability of this production route is fundamentally limited by the finite global supply of ^{229}Th and the impracticality of producing new ^{233}U in the short to medium term.

While the thorium generator method avoids the need for irradiation infrastructure, it requires the secure handling and long-term storage of alpha-emitting materials with long half-lives. From a regulatory and safety standpoint, this adds complexity to its implementation and long-term sustainability.

In the context of this feasibility study, the ^{229}Th generator is considered a reliable but limited method, well-suited for small-scale or backup production of ^{225}Ac . It does not contribute to the valorization of ^{226}Ra and therefore remains outside the central focus of this evaluation, which emphasizes radium-based production strategies more amenable to scale-up.

Thorium spallation

The thorium spallation route involves the irradiation of ^{232}Th targets with high-energy protons, typically in the range of 100–500 MeV. When these protons interact with the thorium nuclei, they induce spallation reactions that produce a broad spectrum of radioisotopes, including ^{225}Ac . This method has been demonstrated at several large-scale research facilities with high-energy accelerator infrastructure, such as TRIUMF (Canada), LANL (USA), and CERN-ISOLDE (Europe).

The main advantage of this approach is the potential for relatively high ^{225}Ac production yields, particularly when operated at high beam intensities and optimized target configurations. However, the spallation process also generates a complex mix of radioactive reaction products. Among these are radionuclidic impurities, including actinium-227 (^{227}Ac), a long-lived isotope ($T_{1/2} = 21.8$ years) that poses challenges for both radiological safety and clinical applications. The co-production of ^{227}Ac can compromise the purity of the final product and requires careful radiochemical separation to ensure that the ^{225}Ac meets stringent pharmaceutical-grade standards. However, potential exists for current target processing methods to be modified to produce ^{225}Ac quantities that are free of ^{227}Ac by focusing on the isolation of radium instead [19].

In addition to radiopurity concerns, the process requires robust infrastructure for target irradiation, radiological shielding, heat dissipation, and post-irradiation chemical separation. Target systems must be engineered to withstand the high radiation doses and thermal stresses associated with spallation. Radiochemical processing is complex due to the presence of multiple actinides and fission products and must be performed in shielded hot cells under strict quality control conditions.

While this route offers scalability and has been successfully demonstrated at pilot scale, it entails high technical and operational demands and typically involves long processing times and costly infrastructure. Furthermore, since this method does not use ^{226}Ra , it does not contribute to the valorization of SCK CEN's available radium stocks, a central consideration in this study.

In summary, the thorium spallation route remains a technically mature and potentially high-yield option for ^{225}Ac production, but its applicability in the current context is limited by its reliance on external thorium sources and the challenge of controlling long-lived impurities such as ^{227}Ac .

Proton irradiation (p,2n on ^{226}Ra)

The radium proton route involves the direct irradiation of ^{226}Ra targets with low-energy protons, typically in the range of 15–30 MeV. The primary nuclear reaction is $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$, which enables the efficient production of ^{225}Ac . This method has been successfully demonstrated at multiple facilities and is well-suited to medium-sized medical cyclotrons operating below 20 MeV [18]. At optimized energies (15–16 MeV), the process offers high efficiency and favorable economics. For example, a 24-hour irradiation of 50 mg of ^{226}Ra at 100 μA can yield approximately 5 GBq of ^{225}Ac , sufficient for about 500 patient doses of 10 MBq each.

A key advantage of this route is the high isotopic purity of the final product. Careful selection of incident proton energy can minimize the co-production of unwanted short-lived isotopes such as actinium-226 (^{226}Ac , $T_{1/2} = 29$ h) and actinium-224 (^{224}Ac , $T_{1/2} = 2.9$ h), which decay further during target cooling and processing. Importantly, the long-lived impurity ^{227}Ac is barely formed, distinguishing this route from spallation-based methods and supporting its suitability for clinical use.

Solid targets are typically based on radium nitrate or carbonate, embedded in thermally stable matrices or coated onto inert, conductive backings. The highly radiotoxic nature of ^{226}Ra , and the generation of radioactive radon-222 (^{222}Rn , $T_{1/2} = 3.8$ days), necessitate strict safety protocols, including remote handling, shielding, and contamination control. Liquid targets can also be considered but require further development.

Engineering challenges stem from the limited penetration depth of low-energy protons, which restricts effective target mass to below 1 gram and results in high volumetric energy deposition. A 100 μA beam at 10 MeV, for instance, deposits about 1 kW of thermal power in the target. To mitigate thermal damage, advanced designs such as grazing angle irradiation are employed to reduce effective target thickness and enhance heat dissipation.

Post-irradiation, radiochemical separation techniques are used to isolate ^{225}Ac from co-produced radionuclides like ^{224}Ra and ^{225}Ra . These processes are well established and can achieve the purity levels required for medical applications. Although some co-production of ^{227}Ac may occur, levels are significantly lower than in spallation-based production. The overall production yield depends on factors such as beam energy, current, irradiation time, and target composition. Given the limited global supply of ^{226}Ra , recycling strategies are also essential for sustainable production.

From a feasibility perspective, this route is technically mature, scalable, and compatible with existing cyclotron infrastructure. It is particularly attractive for facilities seeking to valorize ^{226}Ra stocks, especially when paired with optimized targetry and remote processing capabilities.

In the context of this study, the radium proton route is considered a technically feasible and well-documented pathway that directly supports the strategic goal of ^{226}Ra valorization. It is therefore included in the more in-depth comparative assessment performed below.

Radium gamma irradiation (γ, n on ^{226}Ra)

The photonuclear route using ^{226}Ra relies on the (γ, n) reaction, in which high-energy photons induce the emission of a neutron from the ^{226}Ra nucleus, yielding ^{225}Ra . This intermediate isotope decays with a half-life of 14.9 days to produce ^{225}Ac , the desired therapeutic radionuclide.

The photons required for the (γ, n) reaction are typically generated via bremsstrahlung by directing an electron beam onto a high-Z converter material. When appropriately configured, this setup can deliver a high photon flux in the energy range suitable to induce the (γ, n) reaction on ^{226}Ra [20, 21].

Although the (γ, n) cross section is modest, high-intensity electron accelerators can compensate for the low reaction probability. Experiments at JRC Karlsruhe and other facilities (e.g., INR Dubna, Illawarra Cancer Centre) have validated the method's viability, with measured yields of up to 550 Bq/(mA·mg ^{226}Ra) at 24 MeV [22].

The photonuclear process does not produce a wide range of fission or spallation products, which simplifies subsequent radiochemical separation. Additionally, since the radium target material remains largely chemically intact during irradiation, recovery and reuse of ^{226}Ra may be possible, supporting long-term sustainability.

In terms of infrastructure, the approach is compatible with electron accelerator technology and does not require high-energy proton beams or nuclear reactor access. Shielding and safety measures must account for the handling of ^{226}Ra , as well as the management of gaseous by-products such as ^{222}Rn .

This method directly supports the valorization of existing ^{226}Ra stocks and has the distinct advantage of producing ^{225}Ac with minimal radionuclidic impurities. In particular, the risk of co-producing long-lived actinium isotopes such as ^{227}Ac is very low, which is favorable for achieving the high purity standards required in medical applications.

In conclusion, the (γ, n) route on ^{226}Ra offers a direct and radionuclidically clean pathway to ^{225}Ac production while enabling the efficient use of existing radium resources. This method is a central focus in the evaluation of production routes due to its alignment with strategic objectives and its potential for sustainable, high-purity isotope supply.

Nuclear reactor

The nuclear reactor route for ^{225}Ac production typically involves neutron irradiation of selected target materials to induce nuclear reactions that lead to the formation of ^{225}Ac . While several reaction pathways are theoretically possible, the most relevant options in the context of ^{226}Ra valorization include neutron-induced reactions such as ($n, 2n$) or (n, γ) on ^{226}Ra or related target materials [23].

One such route involves the ($n, 2n$) reaction on ^{226}Ra , which could yield ^{225}Ra and subsequently decay to ^{225}Ac . However, this reaction requires access to fast or epithermal neutron spectra, which are less common in conventional research reactors. Thermal neutron capture (n, γ) reactions are more accessible, but may lead instead to ^{227}Ra and undesired long-lived impurities unless carefully optimized. The feasibility and efficiency of these routes depend strongly on the specific neutron flux characteristics of the reactor and on detailed cross-section data, some of which remain experimentally uncertain.

The use of reactors offers advantages in terms of well-established infrastructure, high neutron flux, and large-volume target processing capabilities. Reactors are often equipped with hot cells and remote handling systems, which facilitate post-irradiation radiochemistry. However, for radium-based targets, additional

considerations include activation of the matrix material, gas evolution, and contamination risks due to ^{222}Rn release.

Radiochemical processing following reactor irradiation would be required to isolate ^{225}Ac from the target material, and to manage the potential co-production of other isotopes, particularly ^{227}Ac and ^{224}Ra . High-purity separation methods must be employed to ensure pharmaceutical-grade output, especially in a GMP setting.

In the current study, which prioritizes the valorization of ^{226}Ra , the nuclear reactor route is considered a theoretically interesting pathway, particularly if suitable high-energy neutron fields can be accessed. However, this approach remains less developed compared to proton or photonuclear options, and further investigation is needed to assess its reaction efficiency, impurity profile, and scalability. While not the immediate focus of development, the reactor route may provide a useful complement or backup strategy for future diversified production scenarios, especially within multipurpose nuclear research facilities.

Conclusion

Based on the initial evaluation, production routes that directly involve ^{226}Ra , specifically proton irradiation ((p,2n)) and photonuclear ((γ ,n)) reactions, emerge as the most relevant for further development. These approaches align with the strategic goal of valorizing existing radium stocks at SCK CEN, while offering promising prospects in terms of product quality, scalability, and infrastructure compatibility. In contrast, routes that do not make direct use of ^{226}Ra , such as thorium spallation, generator systems, or reactor-based production, are considered less aligned with this objective. While some may serve as complementary or long-term options, the primary focus of future efforts will be on advancing and optimizing radium-based accelerator-driven production strategies.

Conclusions are summarized in Table 1 below:

Production route	Use of ^{226}Ra	^{225}Ac purity	Production yield	Scalability	Current status	Reliability and sustainability
^{229}Th generator	No	High, the resulting ^{225}Ac is free of other actinium isotopes	Low	Limited by ^{229}Th supply	Established for small scale	Long-lived waste, limited availability of ^{229}Th
Spallation on ^{232}Th	No	Risk of ^{227}Ac	High	Technically scalable, however requires large-scale infra-structures	Demonstrated	Dependent on legacy Th stock, challenging to handle radioactive waste
(p,2n) on ^{226}Ra	Yes	Good (limited amount of ^{227}Ac)	High (proven yields)	Scalable with cyclotrons	Demonstrated at pilot scale	Reliable with radium handling expertise
(γ,n) on ^{226}Ra	Yes	High (low ^{227}Ac risk)	Moderate, but depends on target chosen target technology	Good with suited target technology	Emerging technology	Promising, needs infrastructure scale-up, accelerator technology exists
Nuclear reactor	Possible, but requires complex safety study for reactor irradiation	Variable (depends on route)	Low–Moderate	Potential if optimized	Conceptual/Early stage	Potential backup, needs further R&D

Table 1: Decision matrix – first evaluation of ^{225}Ac production routes.

Evaluation of irradiation technologies

The production of ^{225}Ac via charged particle irradiation and photonuclear reactions represents two distinct approaches in the context of large-scale production for clinical and industrial applications. Both methods rely on the utilization of radium as a target material but differ in the nature of the irradiation process and the resulting product characteristics.

Charged particle-induced reactions, where e.g. protons or deuterons directly interact with the target nuclei, offer a well-established pathway, benefiting from existing accelerator-based technologies. On the other hand, photonuclear reactions introduce a different set of dynamics, relying on gamma rays to induce nuclear reactions within the target, facilitating new advantageous production technologies.

This section will focus on key factors that differentiate proton and gamma irradiation routes, including the direct versus indirect production routes, the impurity profile of the resulting ^{225}Ac , heat deposition effects, the size requirements for the radium target, radiochemical considerations, and the technology starting points, i.e. the extent to which these methods are already validated and scalable for large-scale production. These factors will guide the subsequent evaluation of which method holds the most promise for development within the scope of this feasibility study.

It is important to note that the evaluation of irradiation type (proton vs. gamma) cannot be decoupled from the physical form of the target material (solid vs. liquid). These parameters are inherently interlinked and must be assessed in combination, as the feasibility, efficiency, heat dissipation, chemical processing, and operational complexity are strongly influenced by the chosen irradiation-target configuration. Therefore, a holistic comparison must consider gamma-liquid and proton-solid (or other combinations) as integrated technological options rather than treating each variable in isolation.

^{225}Ac production by low energy medical cyclotron

Irradiation of ^{226}Ra with charged low-energy particles (protons or deuterons) using a cyclotron or LINAC can directly produce ^{225}Ac through the (p,2n) and (d,3n) reaction. The feasibility of ^{225}Ac production starting from ^{226}Ra was demonstrated by ITU using low-energy protons and reported in 2005 [4]. The cross section for the $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$ reaction is very high, up to 700 mb at 16.8 MeV (see Figure 10). As it can be observed from the cross-section low energy cyclotrons (but also superconducting magnet cyclotrons, low energy LINACs, etc.) can be sufficient for ^{225}Ac production. Such accelerators are the most distributed and are commonly used in hospitals for in-house production of short-lived radionuclides such as ^{18}F (Figure 9) for diagnostic applications.

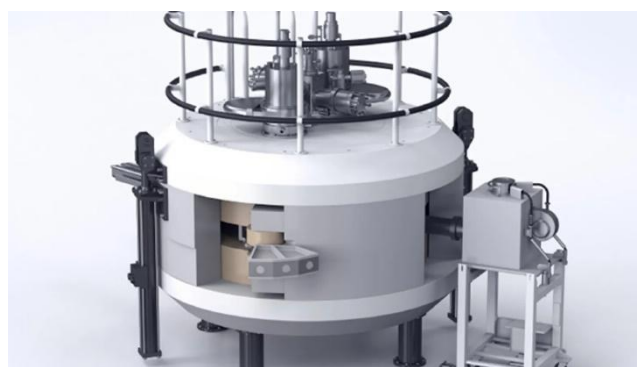


Figure 9: IBA Cyclone® 30 XP.

Co-production of $^{224}\text{Ac}/^{224}\text{Ra}$ can be significant depending on the chosen energy, see Figure 10 and Figure 11. Other possible contaminants are also illustrated. In case ^{224}Ra and ^{225}Ra are produced in significant quantities (see Figure 11), this can lead to additional production of lead-212 (^{212}Pb) and isotopically pure ^{225}Ac that can be chemically separated from ^{226}Ra (see also [5]).

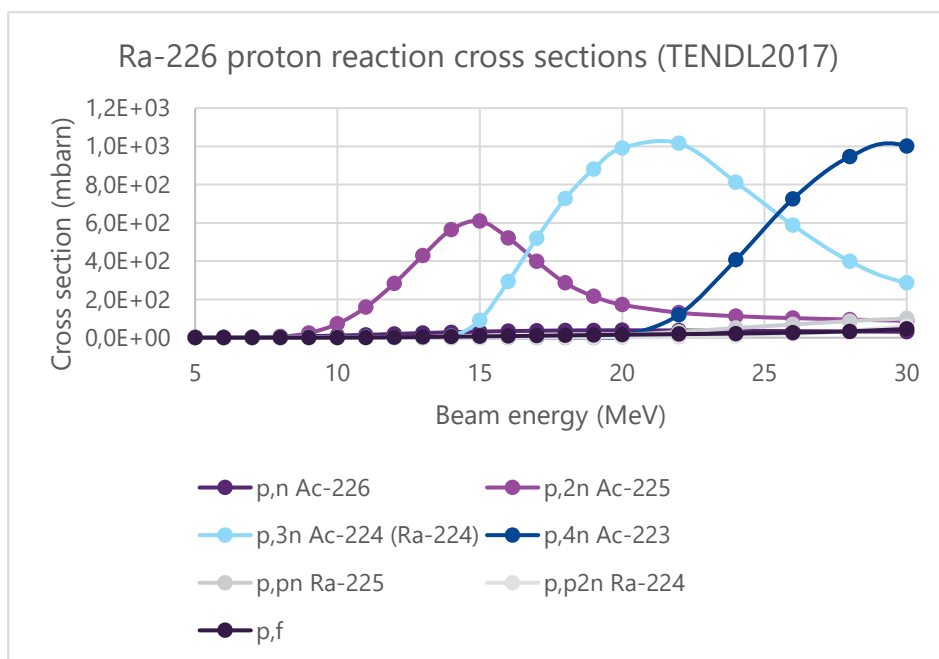


Figure 10: ^{226}Ra proton reaction cross sections (TENDL2017).

As in the case of the (p,2n) using (d,3n) nuclear reaction (see Figure 11), ^{225}Ac is also directly produced. It should be specified that no experimental data on the corresponding cross-sections exists. The ^{226}Ra target mass remains quite low (<1 g), allowing a separation fully based on extraction chromatography columns (DGA, HDEHP columns) with an optional ^{226}Ra precipitation pre-treatment.

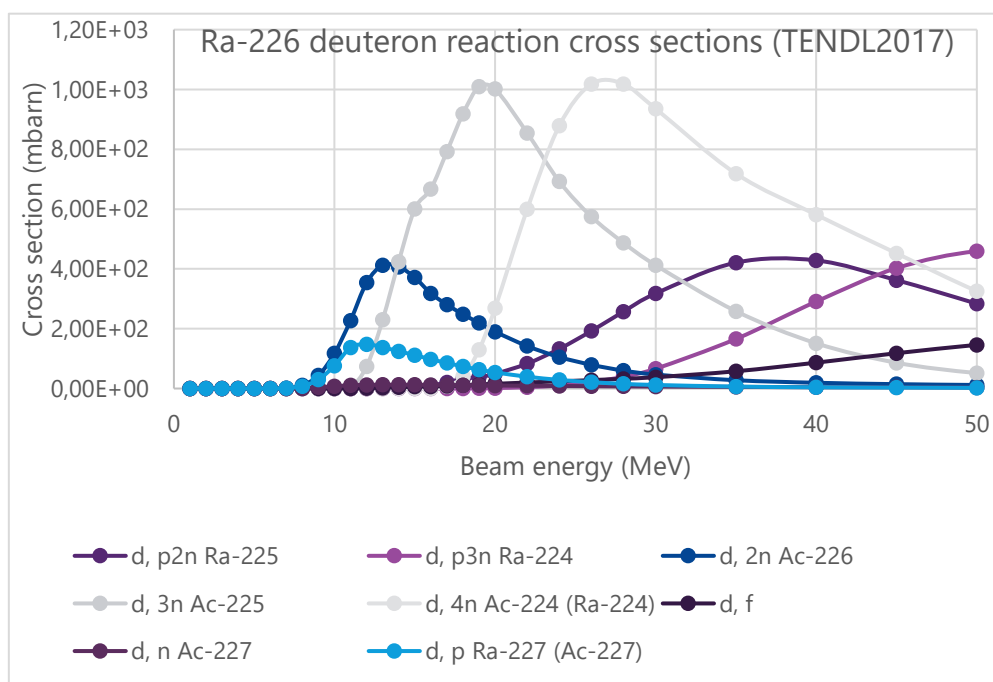


Figure 11: ^{226}Ra deuteron reaction cross sections (TENDL2017).

As charged low-energy particles are used for irradiation, the range in the radium target is limited, therefore the target mass and source term will remain relatively small, $<1 \text{ g/cm}^2$ (See Figure 12 for a schematic drawing of proton irradiation of solid targets).

Consequently, the energy deposition on the small target will be high and could be the limiting factor for ^{225}Ac production in a single target, as evidently target failure needs to be avoided. For a 10 MeV energy attenuation (20MeV..10MeV) and 100 μA current, the deposited power would be 1 kW. For standard medical cyclotrons with up to $\varnothing 1 \text{ cm}$ beam size and beam perpendicular to the target, it will correspond to about 300W/cm^2 heat power density. Using a grazing angle for irradiation increases the target area, reduces the required thickness of the target and therefore improves the cooling capacity.

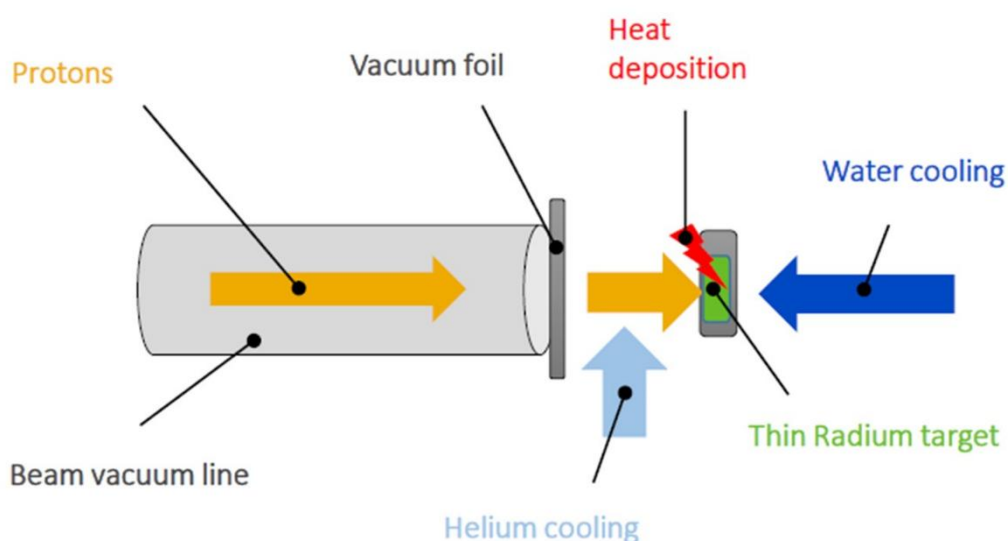


Figure 12: Schematic drawing of the setup for proton irradiation of solid targets.

For the (p,2n) and (d,3n) methods, the limiting factor for the production of ^{225}Ac is the maximum current on the ^{226}Ra target, guaranteeing that the target will survive irradiation. The limited thermal conductivity of the radium compound limits the total power deposition on the target. Although the cross section for these reactions is very high, the maximum current on a grazing angle target could remain limited to 50-100 μA proton current and two times less for deuteron correspondingly, and safety precautions could decrease this value. On the other hand, multiple small targets could be irradiated on a low current to achieve the necessary production yields of ^{225}Ac . The co-production of ^{224}Ac can be dealt with and can create opportunities for additional production of ^{212}Pb [5]. A recent estimation from TRIUMF [6] states a monthly yield of 107.65 Ci ^{225}Ac using 20 MeV protons and 500 μA current on a 1 g ^{226}Ra target. Consequently, a single irradiation of a thick target of ^{226}Ra for 20 h at a moderate proton current of 50 μA would result in the production of 18 GBq (486 mCi) ^{225}Ac .

Realistically, with a cyclotron/LINAC not running 24/7 and a proton current 50 μA on target as safety margin, this method would still yield monthly Ci amounts of ^{225}Ac and can still be scaled up when the demand for ^{225}Ac increases. However, the handling of cyclotron targets containing ^{226}Ra is technically demanding and will be discussed in further sections.

²²⁵Ac production by gamma route

²²⁵Ac production using gammas requires high energy photons (> 6.4 MeV) to convert ²²⁶Ra to ²²⁵Ra [10, 11]. It is theoretically the cleanest way to produce ²²⁵Ac as no actinium isotopes are produced, while production of ²²⁴Ra only becomes significant above 12 MeV, and photofission is hardly present.

The cross section of this reaction is, however, not so high, requiring a far higher current than a medical LINAC



Figure 13: IBA Rhodotron TT300 HE.

can provide in case Ci quantities of ²²⁵Ac are needed. A 20 – 40 MeV electron accelerator is needed in combination with a high-power (tungsten) electron converter target to produce the needed bremsstrahlung photons for this reaction and stopping all electrons. Target mass can be up to 10 g ²²⁶Ra or ever higher [10]. Cooling of the ²²⁶Ra target is not expected to be needed in case all electrons can be stopped by the tungsten converter. For 40 MeV electrons, the range in tungsten metal is ~ 0.65 cm (Range & Stopping Power++ nucleonica.com). Commercial high-power solutions exist, e.g. IBA Rhodotron TT300-HE (40 MeV, 3.125 mA) (Figure 13), or the Niowave superconducting electron LINAC.

All currently existing solutions to produce Ci quantities of ⁹⁹Mo through γ -irradiation of highly enriched ¹⁰⁰Mo (threshold energy 9 MeV) can be envisioned for ²²⁵Ac production. The electron energy of the accelerator might be lowered to suppress production of ²²⁴Ra.

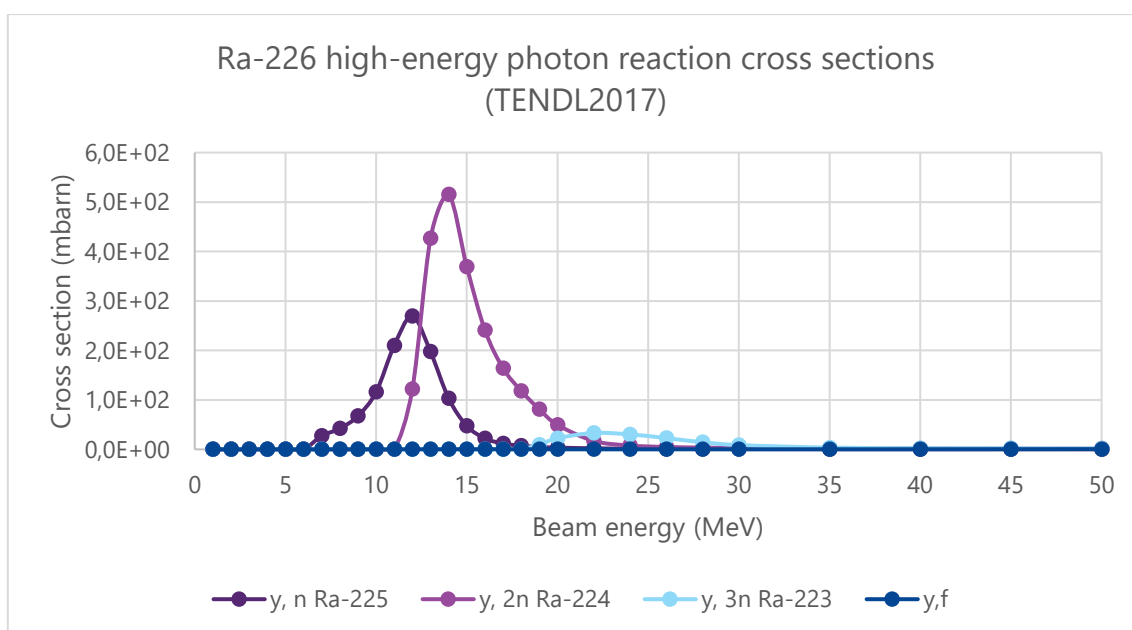


Figure 14: ²²⁶Ra high-energy photon reaction cross sections (TENDL2017).

In case of the (γ ,n) production method, ^{225}Ac is not directly produced and grows in from ^{225}Ra . The separation techniques are similar to the reactor based route, excluding the issues related to the presence of ^{227}Ac and ^{228}Th .

The reaction cross-section has never been experimentally verified, but cross sections in the range of 250 mb are expected at 12 MeV (Figure 14). An electron LINAC or cyclotron combined with a tungsten converter can produce a high quantity of bremsstrahlung photons, however most photons are in the energy range 0-5 MeV where no ^{225}Ra is being produced, as the threshold for the reaction is 6.4 MeV. If a sufficiently high flux of photons above 6.4 MeV can be produced, starting from a high electron current (0.1 - 1 mA), in combination with a high mass ^{226}Ra target, yields can also be very high. Possibly this method requires the circulation of several 10 gram (or higher) ^{226}Ra targets to allow a continuous production and milking of ^{225}Ac from the ^{225}Ra . As irradiation is performed by photons, the complexity of an irradiation target is expected to be very low, and moreover strong safety precautions can be taken that will not significantly influence the yields. For instance, the ^{226}Ra compound can be safely encapsulated in one or more welded stainless-steel capsules or liquid targets can be applied as shown in Figure 15. Also, off-site production (BE, EU, US) can be envisioned without influencing the ^{225}Ac yields, as ^{225}Ac still needs to grow in from the ^{225}Ra after irradiation. For example, 1 week between EOB and processing would seem acceptable. A recent yield estimation from TRIUMF [6] for a 50 MeV 10 μA LINAC gives a monthly production of 1.5 Ci ^{225}Ac per gram ^{226}Ra . When 1 mA is used instead, and multi gram ^{226}Ra targets are irradiated, hundreds of Ci ^{225}Ac can be produced on a monthly basis.

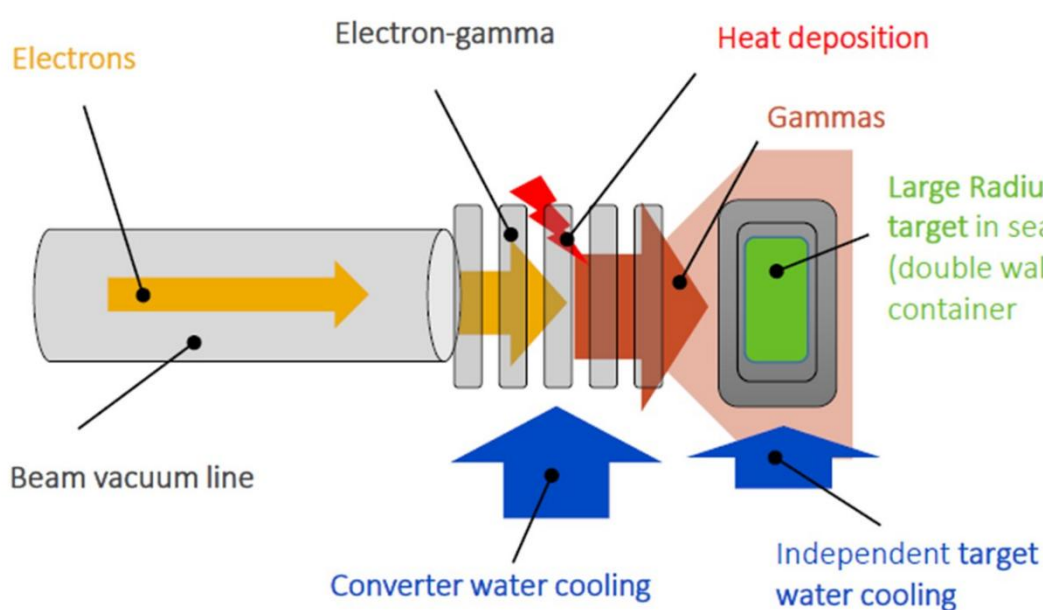


Figure 15: Schematic drawing of the setup for gamma irradiation of liquid targets.

Evaluation of target technologies suited for gamma-irradiation

In the production of radioisotopes, solid targets are commonly used because they can provide a high yield due to their high density of parent nuclides. Liquid targets are less common because many parent nuclide compounds, such as ^{226}Ra salts, have limited solubility in water at room temperature, which restricts their concentration.

Fortunately, the penetration depth of the generated bremsstrahlung is relatively large compared to that of charged particles such as protons. As a result, photonuclear reactions produce isotopes over a more

distributed region along the interaction path, rather than at a specific location and the target material can be distributed in a larger volume. This spatial distribution reduces only slightly the yield compared with positioning it just in front of the converter. Figure 16 illustrates this effect, in practice the yield loss is limited to about 20 % compared with a solid target. But liquid targets offer a huge advantage by eliminating the need for solid-to-liquid and liquid-to-solid conversions during the isotope separation process, reducing the risk of isotope loss and radioactive waste production.

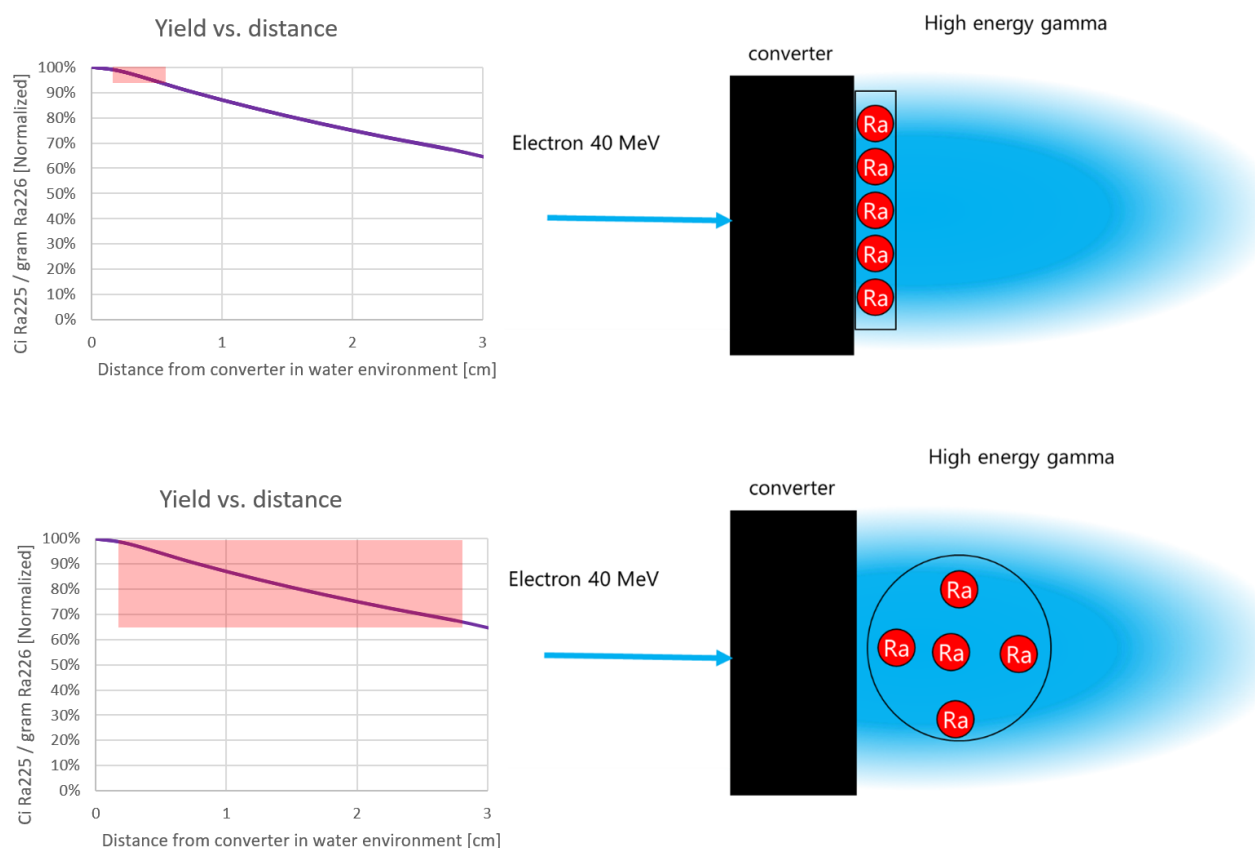


Figure 16: Illustration of the yield of a solid target on top in a liquid environment compared with a liquid target.

Comparative evaluation of irradiation modes and target types for ^{225}Ac production

In the context of large-scale ^{225}Ac production using ^{226}Ra as target material, a systematic evaluation was performed to assess the feasibility and desirability of different irradiation modes (gamma vs. proton) in combination with different target types (liquid vs. solid). Each combination was evaluated against six critical criteria relevant to safe and efficient production:

1. Recoverability of ^{226}Ra post-irradiation.
2. Maximum usable target size.
3. Expected purity profile of ^{225}Ac .
4. Heat deposition and thermal management.
5. Operational safety, including radioprotection.
6. Radiochemical complexity of target processing.

In the framework of large-scale production of ^{225}Ac from ^{226}Ra , a systematic assessment was conducted to determine the most promising combination of irradiation mode and target type, with particular attention to safe operation, efficient isotope recovery, and compatibility with radiochemical processing. The evaluation

focused on six key criteria, each relevant to the industrial feasibility and radiological safety of the process. Based on this assessment, the use of liquid ^{226}Ra targets irradiated via high-intensity gamma photons emerges as the most favourable approach.

Recoverability of ^{226}Ra post-irradiation

The recoverability of ^{226}Ra is critical due to its radiotoxicity and limited availability. Liquid targets allow for continuous or batchwise chemical processing that facilitates efficient recovery of unreacted ^{226}Ra under controlled conditions. In contrast, solid targets require complex post-irradiation dissolution steps that can be less efficient and more labour-intensive, increasing the risk of material loss.

Maximum usable target size

Liquid targets offer the flexibility to scale volume and adjust flow dynamics, supporting larger effective target masses and continuous operation schemes. This scalability is essential for achieving meaningful production yields of ^{225}Ac . Solid targets are inherently limited by mechanical and thermal constraints, particularly under prolonged or high-intensity irradiation conditions.

Expected purity profile of ^{225}Ac

Gamma-induced reactions on ^{226}Ra predominantly follow the (γ, n) pathway, resulting in a clean formation of ^{225}Ra , which decays to ^{225}Ac . This indirect route significantly reduces the formation of long-lived impurities compared to direct proton-induced reactions, which may activate other isotopes within the matrix or surrounding materials. The cleaner radionuclidic profile of the gamma route aligns better with regulatory expectations for waste treatment and clinical applications.

Heat deposition and thermal management

Photon irradiation deposits substantially less localized heat in the target material compared to charged particle irradiation, reducing the risk of hot spots and target degradation. In a liquid system, thermal dissipation can be managed through controlled flow and external cooling, further enhancing system stability and safety.

Operational safety, including radioprotection

The use of a liquid target in a closed, shielded system allows for automation and remote handling, minimizing operator exposure during loading, irradiation, and processing. Gamma irradiation systems, while requiring appropriate shielding for high-energy photon flux, offer more straightforward beam-target interaction geometries and potentially less activation of structural materials compared to proton accelerators.

Radiochemical complexity of target processing

Radiochemical processing of liquid targets benefits from established techniques in aqueous separation chemistry, including online extraction or resin-based purification. The chemical homogeneity of the liquid phase allows for reproducible and efficient separation protocols. Solid targets, by contrast, introduce significant radiochemical complexity due to heterogeneous matrices and dissolution steps, complicating GMP-compliant processing workflows.

Conclusion

Considering all six criteria, the combination of liquid ^{226}Ra targets with gamma irradiation offers the most balanced and forward-compatible approach for the reliable, safe, and scalable production of ^{225}Ac . This configuration minimizes technical and regulatory risks while supporting efficient radiochemical operations and

high-quality product output. As such, it constitutes the preferred technological pathway for further development within the scope of this feasibility study.

Parameter	(p,2n) on ^{226}Ra	(γ ,n) on ^{226}Ra
Recoverability of ^{226}Ra post-irradiation	Moderate – solid targets complicate full recovery	Favourable – liquid targets enable near-total recovery
Maximum usable target size	Limited – small mass due to low proton penetration	Scalable – gamma penetration allows larger or liquid targets
Expected purity profile of ^{225}Ac	Good – minor ^{227}Ac possible, short-lived impurities	High – minimal impurities due to cleaner reaction path
Heat deposition and thermal management	Challenging – ~ 1 kW for 100 μA beam, high thermal load	Low – minimal thermal stress, even at high photon flux
Operational safety & radioprotection	Demanding – ^{222}Rn release, remote handling of solid radium targets	Moderate – radioprotection still needed, but improved with liquid targets
Radiochemical complexity of processing	Established – but solid target dissolution, Ra/Ac separation needed	Simpler – liquid phase chemistry streamlines separation steps

Table 2: Decision matrix – Final evaluation of ^{225}Ac production routes.

In summary the (γ ,n) route combined with a liquid targets offers multiple technical advantages:

- **Higher recoverability of valuable ^{226}Ra .**
- **Scalable target designs.**
- **Superior thermal profile.**
- **Simplified processing workflows.**

Technological developments required for the preferred liquid–gamma irradiation route

Following the comparative evaluation of irradiation modes and target configurations, the combination of **liquid ^{226}Ra targets with high-intensity gamma irradiation** has been identified as the most promising pathway for the large-scale production of ^{225}Ac . This choice sets a clear direction for the next phase of technological development and infrastructure planning. The feasibility study outlines the following priority developments that are critical to enabling and supporting this production route:

Advanced liquid target system for ^{226}Ra

A core requirement is the design and construction of a robust and scalable liquid target module compatible with high-intensity gamma irradiation. This system must ensure homogeneous distribution of ^{226}Ra in a chemically stable and radiolytically resistant liquid form, capable of withstanding prolonged irradiation. Engineering efforts must focus on optimizing fluid dynamics, containment materials, heat dissipation, and online monitoring, all within the constraints of radiological safety and maintainability.

High-intensity gamma converter and irradiation infrastructure

The successful implementation of photonuclear production hinges on the availability of a reliable high-flux gamma source, typically generated via electron accelerators and bremsstrahlung converters. Development must focus on designing a converter system optimized for coupling with the liquid target, ensuring efficient

photon delivery while minimizing heat deposition and activation of structural components. Shielding, beam control, and target accessibility for maintenance will be integral to the system layout.

Radon capture and handling technologies

Safe manipulation of ^{226}Ra requires advanced radon mitigation solutions, particularly during target preparation and post-irradiation processing. The planned installation of a dedicated radon trapping system within the existing hot cell at SCK CEN will be an important asset for the whole future project. This system should enable continuous capture of ^{222}Rn , ensuring compliance with radioprotection standards and preventing environmental release during operations.

Radiochemical separation and recovery process

Efficient, high-yield separation of ^{225}Ac from the irradiated ^{226}Ra solution must be developed, with full integration of ^{226}Ra recovery and recycling protocols to ensure sustainability. The process should be compatible with liquid target chemistry and designed to meet GMP standards for clinical use. Key technological aspects include resin-based extraction or liquid–liquid separation, inline monitoring, and automation to minimize operator exposure and process variability. To ensure operational safety and scalability, the entire production chain from target loading through irradiation to separation and product collection must be automated or remotely operable.

Conceptual facility design

The integration of the above technologies into a fully functional production facility requires the development of a conceptual design, encompassing infrastructure layout, radiation shielding, ventilation, and waste handling. The conceptual building design must be prepared, addressing nuclear safety, radioprotection, pharmaceutical compliance, and radioactive waste management to satisfy national and European regulatory authorities.

Development of a radon capture system (radon trap) enabling handling of ^{226}Ra

Introduction

The successful large-scale production of ^{225}Ac critically depends on the availability of substantial quantities of ^{226}Ra , which serves as the target material in the irradiation process. SCK CEN possesses historical stocks of ^{226}Ra in quantities sufficient to support ^{225}Ac production on a long-term, sustainable basis.

To enable its use, the highly radioactive ^{226}Ra must first be retrieved from its current storage at SCK CEN and safely transferred to a shielded hot cell facility. Within this controlled environment, the sealed capsules containing the ^{226}Ra will be mechanically opened using remote manipulators. This operation allows the radium to be subdivided into smaller, more manageable aliquots, suitable for experimental use such as chemical purification and formulation for target preparation.

However, one of the critical challenges in handling ^{226}Ra is the continuous generation of ^{222}Rn , a radioactive noble gas and decay product. To prevent any release of ^{222}Rn into the working environment or beyond, an effective radon capture system must be in place – a so-called radon trap. The current hot cell infrastructure lacks a dedicated system capable of capturing and containing this specific isotope of radon. Therefore, the installation of a specialized radon trap is a prerequisite before any operations involving ^{226}Ra can commence. This system will ensure safe manipulation of the material and compliance with radiological protection standards.

Importantly, the radon trap to be installed in the existing hot cell will serve as a prototype for the final production facility. Building and operating this system in a later phase will allow SCK CEN to test and optimize the technical concept under realistic conditions, generate operational experience, and validate its performance before implementing a scaled-up version in the future production infrastructure.

Radon trap project phases

This part of the ^{225}Ac feasibility study addresses the development of demonstrated solution (prototype) for the safe handling of ^{226}Ra in hot cell environments. It focuses on the design, realization, and validation of a radon trapping system and its later integration into existing hot cell infrastructure.

The development of the radon trapping system for ^{225}Ac production comprised a coordinated set of activities, including R&D to identify suitable adsorption materials, engineering from conceptual to detailed design, and functional testing in a non-radioactive full-scale mock-up configuration. In parallel, integration into the hot cell environment was prepared, defining the necessary interfaces and operational conditions. Together, these activities establish a solid basis for implementation within SCK CEN's hot cell facility at a later phase.

Scope of the radon trap project and project phases

The project reaches its endpoint with the successful validation of the radon trapping system in a non-radioactive full-scale mock-up configuration and the submission of the supporting results for regulatory review by BelV/FANC.

Within the context of this feasibility study, the operational level of the radon trapping system is considered to be achieved based on the successful outcome of comprehensive testing performed under representative conditions. The prototype tested in the mock-up configuration is directly transferable to the hot cell environment without modification, ensuring that the validated performance is representative of the intended operational setup.

The obtained results provide the technical basis for authorization by FANC to proceed with the implementation of the system in an existing hot cell facility at SCK CEN.

Radioactive testing and operation with ^{226}Ra are considered beyond the scope of the present feasibility study. Such activities require additional regulatory approvals, access to dedicated radioactive materials, and extended implementation timelines. These steps are therefore positioned as part of the subsequent deployment phase.

In this context, the implementation of the radon trapping system in the hot cell environment is to be considered in conjunction with the detailed planning of the subsequent phase. This ensures alignment with the overall facility design, operational strategy, need for additional mechanical tooling and licensing approach, and avoids constraining key technical and regulatory decisions to be taken in the next stages of development.

It is noted that final commissioning, including authorization for operation with gram-scale quantities of ^{226}Ra , represents a distinct step beyond prototype validation and will require a dedicated follow-up project. This subsequent phase will address the specific requirements associated with large-scale radioactive operation and full system deployment.

In-scope radon trap project phases:

R&D: Identification of adsorption resin

- Establish a first small-scale prototype for adsorption material testing.
- Experimental testing of candidate resins under simulated radon gas conditions.
- Selection of optimal adsorption material based on adsorption capacity, retention time, regeneration potential, and radiation resistance.

Design phase

- Conceptual layout of radon trap system (dimensions, components, interface points).
- Safety and radioprotection considerations integrated into the design basis.
- Complete engineering drawings and 3D models.
- Detailed specification of all components (adsorption columns, pipework, detectors, etc.).
- Definition of control logic, instrumentation, and materials compatibility.
- Finalized procurement list and installation instructions.

Functional testing (Non-radioactive/Mock-up)

- In-house construction of a full-scale mock-up of the radon trap
- Functional testing to verify flow rates, leak tightness, pressure drops, and monitoring instrumentation

Submission of documentation to BelV/FANC – end-point feasibility study

- Documentation compiled and submitted to BelV/FANC for approval to perform the installation of the radon trap in an existing hot cell facility at SCK CEN including:
 - Full technical description of the radon trap and safety aspects.
 - Description of changes made to current installations.

Radon trap project verification documentation of performed work

As part of the radon trap project, a set of formal deliverables was produced to document the work completed and verify the performance of the system.

These deliverables include:

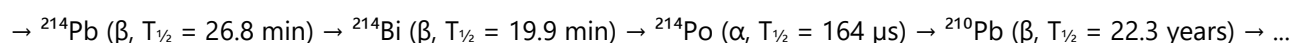
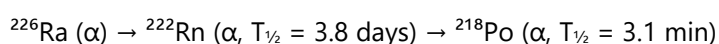
- **Designs** – Complete engineering documentation covering basic and detailed designs of the radon trap, including PFDs, P&IDs, equipment specifications, and integration drawings.
- **Scientific publication** – A peer-reviewed article detailing the experimental methodology, resin selection, and performance results of the prototype radon trap under simulated and real operating conditions.
- **Patent application** – Submission of a patent titled *"Method and apparatus for removing a radioactive noble gas from a gas volume,"* capturing the novel technical solutions developed during the project.
- **Validation and regulatory submission dossier** – Based on the first designs of the radon trap BelV granted permission to proceed with the development and implementation of the setup into the existing hot cell facility at SCK CEN in 2022. A comprehensive set of technical documentation demonstrating the successful validation of the radon trap prototype in a non-radioactive full-scale configuration, including functional test results and safety assessments, has during the feasibility study been obtained. This documentation has been submitted for final regulatory review by BelV/FANC and forms the basis for authorization to proceed with implementation in a hot cell environment. The successful validation of the system supports the conclusion that the operational performance of the radon trap has been demonstrated at prototype level.

Confidentiality and security restrictions

Due to the high-security nature of the radioactive facility at SCK CEN, certain technical details and visual materials related to the radon trap installation cannot be disclosed in this report. The sensitive nature of the infrastructure, combined with strict regulatory and safety requirements, necessitates limiting the distribution of photographs, detailed engineering drawings, and other proprietary information. This restriction ensures compliance with security protocols while safeguarding the integrity and safety of ongoing operations.

Decay properties of ^{226}Ra and rationale for radon trapping

The production of ^{225}Ac requires as earlier mentioned handling its precursor, ^{226}Ra . ^{226}Ra is a long-lived alpha emitter with a **half-life of 1,600 years** that decays via the following simplified chain:



Among these, ^{222}Rn is the key concern. It is a radioactive noble gas that can easily escape containment, accumulate in closed spaces, and introduce significant radiological hazards through its radioactive progeny. Its relatively short half-life (~ 3.8 days) means it emits intense alpha radiation, and its short-lived daughters contribute additional alpha and beta emissions, creating substantial inhalation and contamination risks. For these reasons, a radon trap is essential to capture and contain ^{222}Rn before it can enter the facility environment. This not only prevents unintended emissions but also minimizes radiation dose to personnel and ensures that all operations comply with strict radiological safety requirements.

R&D: Identification of adsorption resin

As part of the feasibility study for large-scale ^{225}Ac production, we undertook a series of adsorption experiments to identify and validate efficient ^{222}Rn retention materials under hot-cell-relevant conditions. The results of this investigation subsequently led to the peer-reviewed publication by Jasper Mermans and co-workers at SCK CEN [24], which provides a detailed account of the findings.

In these experiments, commercial activated carbons and silver-exchanged zeolites including Ag-ETS-10, Ag-ZSM-5, and Ag-13X were evaluated for their radon retention capacity, breakthrough behavior, and sensitivity to carrier-gas composition and humidity. Below a summary of the experimental part can be found:

Materials

A range of adsorbents was tested for radon retention capacity:

- Ag-ETS-10 (granular, binderless, 16x30 mesh), from Extraordinary Adsorbents, Canada.
- Ag-13X (spherical, +20 mesh), from Sigma-Aldrich.
- NuclearCarb 207C (granular, 6x12 mesh), from Chemviron Carbon.
- CarboAct (fragmented, 0.01–0.4 cm), from Carbo-act International.
- Ag-ZSM-5 (spherical, 0.2–0.5 mm), prepared at CEA, France, by silver exchange of Na-PZ-2/25.
- 13X APG molecular sieve as moisture adsorbent.
- Radon-222 was sourced from a 3.77 MBq ^{226}Ra generator (PYLON RN-1025), flushed with carrier gas (dry nitrogen (N_2), dry air, or argon (Ar)).

Results are summarized in Table 3:

Material	Packing density [kg/m ³]	Mass [g]	Mean retention time [min]	Adsorption coefficient <i>K</i> [m ³ /kg]	Injected ²²² Rn activity [kBq]	Released ²²² Rn activity [kBq]
NuclearCarb 207C	450	7.65	21	5.6	11.7	12.4
CarboAct	250	4.20	15	7.2	16.3	16.0
Ag-13X	970	16.50	240	29	16.3	20.8
Ag-ZSM-5	520	8.85	1.54·10 ⁴	3,500	1,030	132
Ag-ETS-10	950	16.30	2.76·10 ⁴	3,400	1,070	34.2

Table 3: Material and results from experimental studies.

Experimental setup

In order to be able to test the various materials, a first small-scale prototype of the radon capture system was made. The radon adsorption setup (see Figure 17) consisted of:

- Two moisture traps containing 13X APG to control water vapor.
- Two radon adsorption columns (17 cm³ each), housed in stainless steel.
- Flow control using mass flow controllers and a calibrated pump.
- In-line radon monitor (AlphaGUARD DF2000) for real-time breakthrough detection.
- Vacuum and pressure sensors to ensure leak-tight operation.
- Temperature-controlled regeneration was possible in situ using heated columns under nitrogen at 150–250°C.

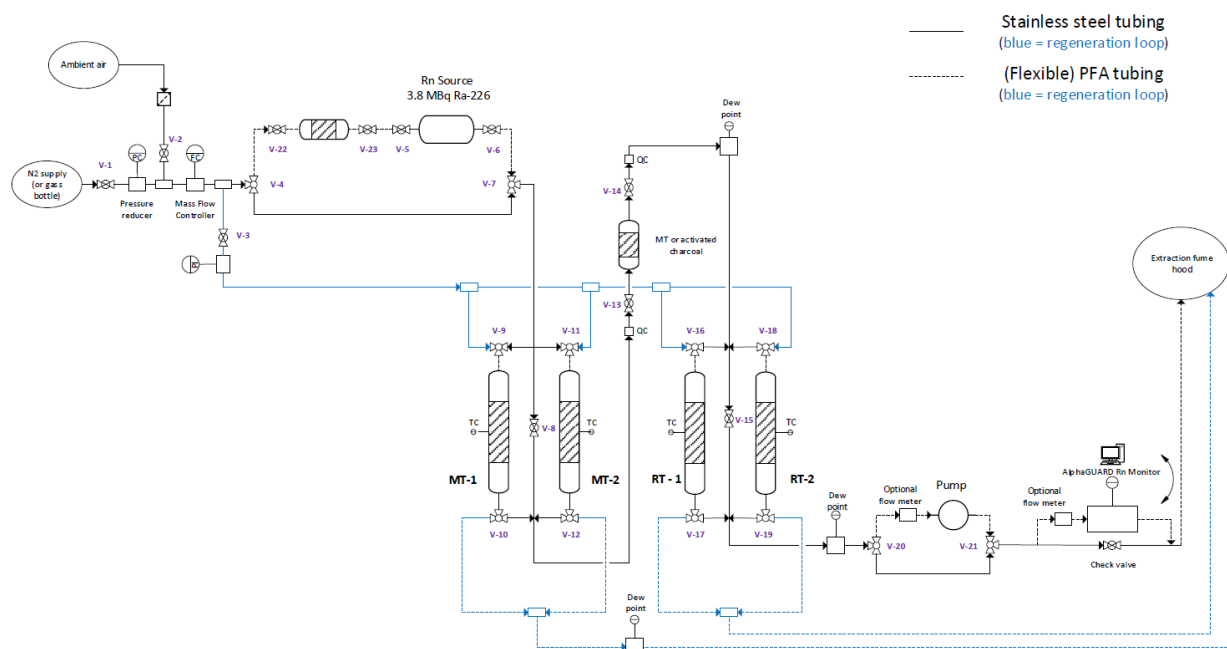


Figure 17: Schematic representation of the setup used for ²²²Rn adsorption experiments.

Experimental procedure

1. Source degassing: Radon was degassed for 1 hour with N₂, ensuring repeatable activity.
2. Adsorbent regeneration: Prior to each run, columns were regenerated at elevated temperature under dry N₂.
3. Breakthrough experiments: Radon was allowed to accumulate in the source, then flushed into the columns at 0.5–5 L/min carrier gas. Breakthrough was measured as radon activity at the column outlet vs. time.
4. Data analysis: Retention time was determined as the mid-point of breakthrough; adsorption coefficients (*K*) calculated as

$$K = (t_r * f) / m$$

where t_r is the mean retention time in [h], m the mass of adsorbent in [kg] and f the volumetric flow rate in [m³/h].

An example of measured breakthrough curves is shown in Figure 18.

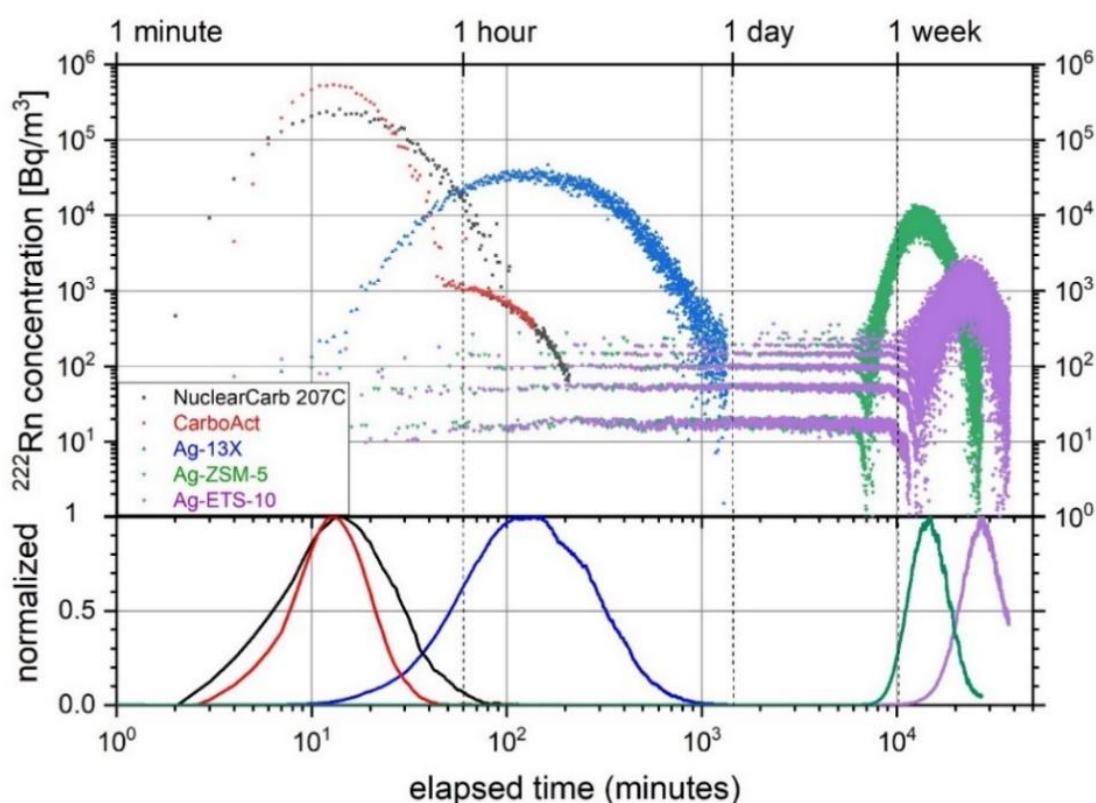


Figure 18: a) Measured breakthrough curves of ²²²Rn on NuclearCarb 207C, CarboAct, Ag-13X, Ag-ZSM-5 and Ag-ETS-10 for an adsorbent bed volume 17 cm³; temperature 293 K; flow rate 2 L/min; N₂ carrier gas; b) normalized, decay-corrected and adjacent-averaged representation of data in a).

Results and discussion

Key observations included:

- Silver-exchanged ETS-10 and ZSM-5 exhibited exceptionally high radon adsorption coefficients ($> 3 \times 10^3 \text{ m}^3/\text{kg}$), markedly outperforming traditional activated carbons under dry gas conditions.
- Carrier-gas effects revealed better retention under N_2 than air or Ar, attributed to differences in competitive sorption and thermal conductivity.
- Even modest water vapor concentrations drastically reduced retention capacity, underscoring the need for careful moisture control and regeneration protocols.

The experimental setup and selected results, shown in the figures, document this work. These data not only supported the design of the radon trapping prototype but also formed the core of the Mermans et al. article [24], thereby validating the technical feasibility of silver-exchanged zeolites as radon traps for hot-cell implementation.

Description of the patent: EP 4 288 183

Detailed information on the patent can be found via this link:

<https://register.epo.org/application?number=EP22704899&lng=en&tab=doclist>

Based on the experimental investigations carried out within this feasibility study, a patent application was submitted to protect the novel method and apparatus for the removal of radioactive noble gases.

Below is a summary of patent **EP 4 288 183**.

Title: Removing a Radioactive Noble Gas from a Gas Volume

Technical Field: The invention focuses on removing radioactive noble gases, particularly radon (^{222}Rn), from gas volumes using adsorption techniques. It is especially relevant for applications in nuclear environments, such as the production of ^{225}Ac for medical purposes.

Background: Radioactive noble gases like radon are challenging to trap due to their chemical inertness. Traditional methods, such as cryogenically cooled activated charcoal beds, face issues like moisture condensation, large bed sizes, and fire hazards. This invention addresses these limitations by using microporous molecular sieves with transition metals.

Key features of the invention:

1. Method:
 - Step (a): Ensure the gas volume has a dew point of -20°C or lower (preferably -45°C or lower).
 - Step (b): Pass the gas volume over a microporous molecular sieve with a transition metal (e.g., silver) to adsorb the radioactive noble gas.
2. Apparatus:
 - Includes moisture adsorbent beds and noble gas adsorbent beds.
 - Can operate at room temperature, avoiding the need for cryogenic cooling.
 - Compact design allows installation near radioactive gas sources.

3. Advantages:

- Effective adsorption at room temperature.
- Reduced water adsorption improves efficiency.
- Compact and economical design.
- Beds can be regenerated easily.
- Suitable for short-lived and long-lived radioactive noble gases.

Experimental results:

- Adsorbents Tested:
 - Activated carbon (NuclearCarb 207C).
 - Silver-exchanged zeolites (Ag-13X, Ag-ZSM-5, Ag-ETS-10).
 - Ag-ETS-10 (16-30 mesh granules) showed the highest adsorption coefficient (320,000 ml/g), outperforming other materials.
- Moisture Impact:
 - Moisture reduces adsorption efficiency. Controlling humidity is critical for maintaining bed performance.
- Thermal Stability:
 - Ag-ETS-10 starts degrading at 400°C and loses adsorption properties at 500°C.
- Gas Contaminants:
 - Contaminants like nitrogen oxides can poison the adsorbent bed, reducing efficiency.

Applications:

- Removal of radioactive noble gases in nuclear environments (e.g., hot cells, glove boxes).
- Safe handling of radon during ^{225}Ac production.
- Industrial and medical applications requiring noble gas removal.

Claims: The invention claims methods, apparatuses, and systems for removing radioactive noble gases using microporous molecular sieves with transition metals. It emphasizes efficiency, compactness, and adaptability to nuclear environments.

Conclusion: This invention provides a novel, efficient, and compact solution for removing radioactive noble gases, addressing challenges in adsorption technology and enabling safer operations in nuclear and medical applications.

Design phase of the radon trap project

The design of the radon purification and adsorption system, intended for the safe handling of radioactive noble gases, was developed through a structured two-phase approach: a basic design followed by a detailed design phase. This methodical process ensured that all technical, safety, and operational requirements were fully addressed.

Basic design

The basic design phase established the overall system architecture, defining key functional units and their interconnections. It integrated critical operational parameters such as gas flow rates, dew point conditions, and selection criteria for adsorption media based on experimental data. The conceptual layout was devised to ensure safe and efficient integration within the existing hot cell environment, while respecting spatial constraints.

Detailed design

The detailed design phase further developed the system specifications with comprehensive engineering detail.

This included:

- Selection and specification of high-efficiency adsorption materials as validated by experimental research.
- Design of gas flow paths, moisture control units, and adsorption beds optimized for radon removal at ambient temperatures, avoiding cryogenic systems.
- Choice of radiation-resistant materials and components to ensure thermal and mechanical stability under nuclear conditions.
- Incorporation of instrumentation for real-time monitoring and control, supporting operational safety and system performance.

Throughout the design, nuclear safety standards, risk assessments, and failure mode analyses were rigorously applied to ensure regulatory compliance and operational reliability.

Confidentiality and security

Due to the sensitive nature of the technology and nuclear safety implications, detailed design drawings, schematics, and proprietary technical data are subject to strict confidentiality and security restrictions. These materials are protected and only accessible to authorized personnel under appropriate nondisclosure agreements. Consequently, this public report provides a high-level overview while safeguarding critical information.

Detailed design documentation supporting this work is available upon request to authorized parties; however, due to the sensitive nature of the information, it will be provided under confidentiality agreements to ensure security and compliance with regulatory requirements.

Design validation and collaboration

The design development involved close collaboration among multidisciplinary teams spanning engineering, radiochemistry, and safety disciplines. Iterative validation through calculations, simulations, and small-scale experiments supported design decisions and component selection. This collaborative approach ensured that the final design met stringent performance and safety requirements.

Basis for construction

The finalized design package, including detailed technical specifications and process descriptions, was formally documented in internal reports. These confidential documents serve as the authoritative basis for procurement, fabrication, and assembly of the radon trapping system, as well as for its subsequent implementation in a controlled hot cell environment, ensuring compliance with all applicable standards.

Summary

In summary, the design effort represents a thorough and systematic engineering process transforming experimental findings into a practical, secure, and reliable system for radon removal in nuclear applications. While detailed design documentation remains confidential to protect proprietary and safety-sensitive information, the design phases are fully documented and provide a robust foundation for subsequent system deployment.

Conclusion, validation and regulatory approval of the radon trap

Following the comprehensive design and realization phases, the radon trapping system has undergone extensive validation in a non-radioactive full-scale configuration. This validation included functional testing under representative conditions, demonstrating that the system meets the required performance, safety, and operational criteria.

The results of these validation activities have been compiled into a comprehensive technical dossier and submitted for review by SCK CEN to BelV/FANC. A first positive assessment was already given by BelV in 2022. The positive assessment of this additional documentation constitutes a key milestone of the feasibility study, confirming that the system meets the necessary requirements to proceed to implementation in a hot cell environment.

This outcome demonstrates that an operational radon trapping solution has been achieved at prototype level, providing SCK CEN with a validated technological capability for the safe management of radon in the context of ^{226}Ra handling. The transition to radioactive operation and full deployment in the hot cell environment is addressed as part of the subsequent project phase, given the need for additional licensing and the scale-up to gram-level ^{226}Ra handling.

Detailed validation and supporting documentation are available upon request to authorized parties, subject to confidentiality agreements and applicable security protocols.

Development of the ^{226}Ra irradiation module

Introduction

Based on the pre-study findings, the production of ^{225}Ac via irradiation of ^{226}Ra is optimally achieved using a liquid target system combined with gamma irradiation. Liquid targets offer significant advantages, including improved heat dissipation, ease of handling, and better control over irradiation parameters.

Gamma irradiation provides a non-destructive, uniform energy input that facilitates efficient nuclear reactions within the liquid radium solution, maximizing isotope yield while minimizing target damage. This method also reduces the risks associated with handling solid radium targets, which are highly radioactive and chemically reactive.

Developing a dedicated radium irradiation module tailored for liquid targets and gamma irradiation is therefore essential. The module must ensure safe containment, adequate shielding against gamma emissions, and precise control of irradiation conditions. This approach enables scalable, reproducible production of ^{225}Ac , supporting its application in medical therapies.

Radiation module verification documentation of performed work

This phase of the project focused on conducting a feasibility study to establish and validate the core principles of using a liquid radium target combined with gamma irradiation for the production of ^{225}Ac . The work included both theoretical analysis and experimental investigations to optimize irradiation parameters, ensure material compatibility, and guarantee radiological safety.

Key activities encompassed the design of the irradiation and target containment modules demonstrated in patent applications, alongside experimental validation of critical process steps. Throughout this development, special attention was given to protecting and managing the intellectual property generated.

The main deliverables from this phase are therefore two patents that secure the innovative solutions arising from the study (and partly in collaboration with external parties):

- **Patent application:** EP 4 285 390, which covers the liquid target system,

and

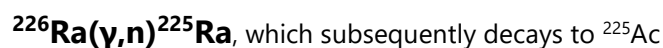
- **Patent application:** EP 4 243 036, which describes the converter technology.

These patents form the technical and legal foundation for further engineering, scale-up, and implementation steps.

Basics of gamma irradiation

The production of ^{225}Ac via gamma irradiation is based on photonuclear reactions, where high-energy photons (typically in the 12–20 MeV range, see Figure 19) interact with the nucleus of ^{226}Ra . Unlike charged-particle reactions, gamma rays penetrate deeply into the target material without significant scattering losses, allowing uniform exposure of the entire target volume.

The reaction of interest is



Target and converter design

The gamma irradiation module consists of two key components:

1. **The Target** – a liquid-phase radium-containing medium designed to maximize interaction with the photon flux. Liquid targets offer advantages in heat removal and chemistry flexibility, allowing continuous removal of produced ^{225}Ac if desired. The target system is enclosed in a corrosion-resistant, gamma-transparent vessel that can withstand high radiation doses and elevated temperatures.
2. **The Converter** – a high-Z material (typically tungsten or tantalum) placed upstream of the target. The converter absorbs the incident electron beam from the accelerator and efficiently produces a broad-spectrum bremsstrahlung photon field. The converter is thermally managed with active cooling to dissipate the significant heat load generated under continuous operation.

Physics of gamma irradiation

Bremsstrahlung photons are produced when high-energy electrons impinge upon the dense converter material. The resulting photon spectrum spans a broad energy range, including the threshold energies required for (γ, n) reactions on ^{226}Ra . By adjusting the converter thickness and electron energy, the photon spectrum can be optimized to enhance ^{225}Ra formation rates while minimizing undesirable by-products and heat deposition in the target (illustrated in Figure 20).

This integrated design, target and converter, ensures a robust and flexible gamma irradiation setup. It allows careful control of reaction rates, straightforward scalability, and compatibility with the thermal and radiological safety requirements of ^{225}Ac production.

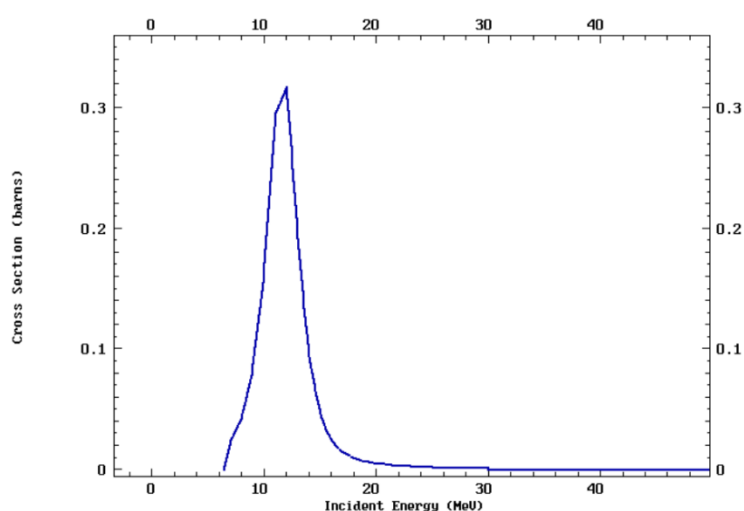


Figure 19: Cross section (barns) as a function of the incident energy of the gamma-rays.

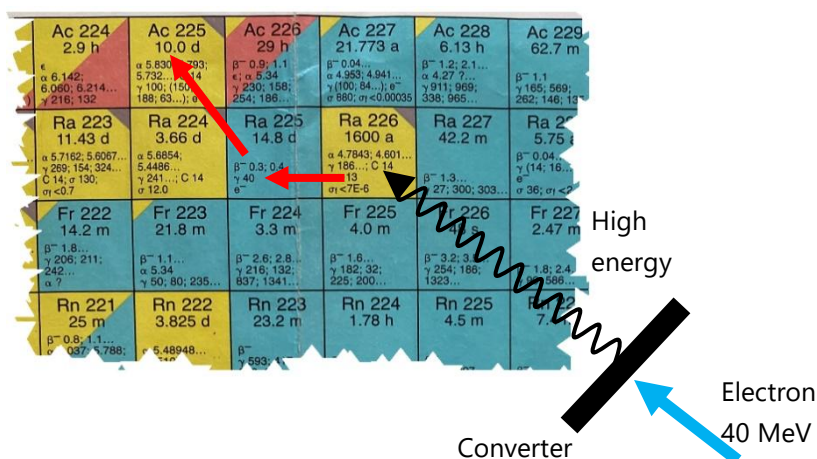


Figure 20: Section of the chart of the nuclides illustrating the principle of the nuclear reaction used for production of ^{225}Ac by gamma irradiation of ^{226}Ra .

Target design development

The design of the liquid-phase irradiation target and its associated systems was a central part of the feasibility study. This work involved a comprehensive investigation into material selection, heat removal strategies, and geometry optimization to achieve stable, uniform gamma exposure at relevant photon energies.

In the production of radioisotopes, solid targets are commonly used because they can provide a high yield due to their high density of the parent nuclides. Liquid targets are less common because many parent nuclide compounds, such as ^{226}Ra , have limited solubility in water at room temperature, which restricts their concentration.

However, liquid targets offer an advantage by eliminating the need for solid-to-liquid and liquid-to-solid conversions during the isotope separation process, reducing the risk of isotope loss and radioactive waste production. Although liquid targets generally have a lower concentration of parent nuclides, this limitation can be mitigated depending on the design of the converter and target, as well as the electron beam characteristics. In the production of ^{225}Ra from ^{226}Ra via photonuclear reactions, factors like electron beam current, energy, and the configuration of the converter and target play a significant role. The converter, designed to produce high-energy Bremsstrahlung photons, is essential for maximizing ^{225}Ra production, but high energy deposition in the converter can reduce the photon yield, limiting production capacity.

One way to address this is by using multiple thin converter slices separated by cooling systems and rastering the electron beam over a larger surface area. However, spreading the electron beam across a larger area can reduce production efficiency, as the radium solution distribution must also expand across this area, weakening the density benefits of solid targets.

While solid targets have some limitations, they are still preferred in current practices due to the generally low efficiency and yield of liquid targets. This highlights an ongoing need for improved methods and devices to enhance the efficiency and yield of liquid target systems for radioisotope production.

The fundamental physical principle used in the proposed design of the ^{226}Ra target can be referred to as a so-called heat pipe, which is a solid metal pipe, filled with a working fluid, closed on both ends, whose walls are covered in a wick material.

One end of the heat pipe is held in a hot environment and acts as an evaporator, and the other end is held in a cold environment and acts as a condenser. Between the evaporator and condenser exist the adiabatic section. Heat pipe operates by circulating the working fluid between evaporator and condenser, using evaporation and condensation principle. Working fluid evaporates in the hot end of the heat pipe and rises towards the cold end, where the heat is rejected through condensation, and the condensate is returned to the evaporator via the capillary action in the wick material. A schematic of a heat pipe is shown in the Figure 21 below.

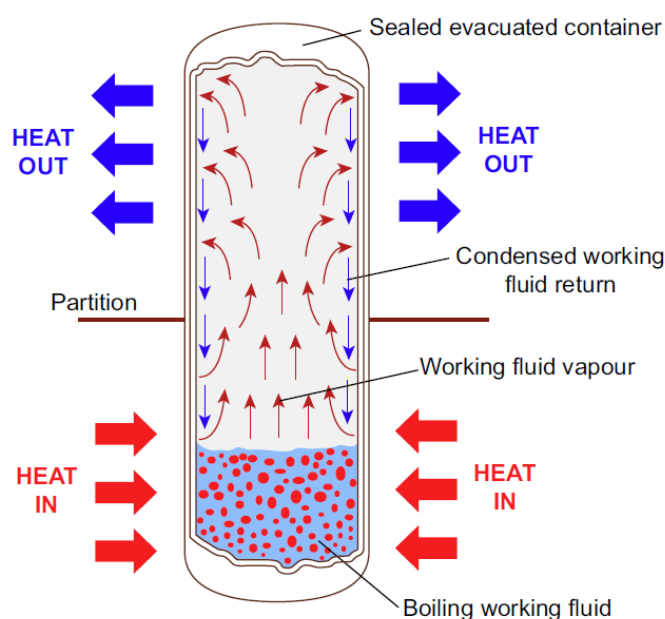


Figure 21: Schematic representation of the heat pipe (figure 1.15 in [25]).

The heat pipe is a very efficient heat transfer device, because it utilizes evaporation-condensation cycle, capable of transferring large heat load due to the high heat of vaporization of working fluid. The heat transfer can only exist when there is a temperature difference between the evaporator and condenser. In addition, heat pipe is reliable because it doesn't require any moving parts for its operation. Besides, it is a flexible device that can be utilized in various configurations (inclination, shape, length).

The movement of the working fluid in heat pipe is possible in vertical and horizontal plane, as well as at different angles of declination due to the return of the condensate via the wick. If the heat pipe is oriented vertically, with the evaporator located under the condenser, the return of the condensate is gravity-assisted, and it is possible for a pipe to operate without a wick. Such gravity-assisted, wickless heat pipe is called a thermosiphon.

The core concept of the patented design involves a liquid capsule (containing a radium nitrate solution) designed with a volume larger than its fill level, creating a headspace for the condensing part and the lower part that holds the radium nitrate solution, Figure 22. During irradiation, the capsule is cooled through conduction, convection and boiling mechanisms. Pressure control ensures stable and safe capsule operation. The capsule solution can also be concentrated by venting part of the condensate or via water vapor extraction

which makes on-line concentrating possible. This design has therefore the ability to fill the capsule with excess water, which allows the feed capillary to be rinsed and fill the capsule with sufficient margin from the solubility limit. This prevents the risk of radium precipitation. During filling the liquid remains cold, and upon operation, the temperature increases (due to the gamma-beam) and allows higher concentration which allows to increase the yield.

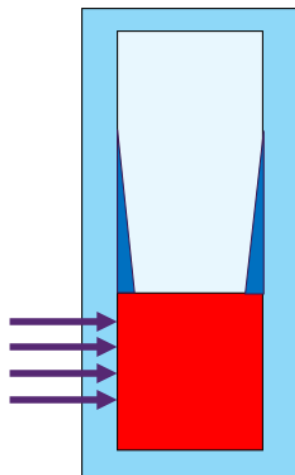


Figure 22: Illustration of the capsule principle, red radium nitrate solution, dark blue condensate, blue cooling water, arrows the x-rays.

Experimental validation of the target design

For testing the fundamental working principles of the target capsule and thereby validate the design an experimental setup was developed, Figure 23. In essence it is a pressurized stainless-steel heat-pipe filled with barium nitrate solution with an aluminum heatsink at the bottom and a condenser bath at the top. The pipe is heated via 8 cartridge heaters of 300 W, planted in the aluminum sink in the lower part of that tube which forms the evaporator section of the heat-pipe. The heat is only applied on the walls of the tube instead of volumetric heating. This test setup is sufficient to support the development of the capsule's operation strategy. The upper part of the pipe is enclosed in the external, open condenser tube, filled with water, that receives the heat of condensation from the vapor. The main mechanism of the heat transfer inside the pipe is via boiling of the water in the lower part, vapor circulation and its condensation on the pipe's walls in the upper part. The boiling process would be regulated via the applied power of the cartridges, the pressurization of the pipe with non-condensable gas and the height of the water in the condenser. The lower end of the pipe is closed by a flange with a viewport which allows visual feedback on the boiling process and bubble formation. This experiment setup will help better understand the boiling process /control of barium salt solution. It also allows to explore the safety margins, pressure control, as well as gain experience with filling, draining, rising, online measuring of the solution height of the capsule and gain experience with potential deposition of salts in the process.

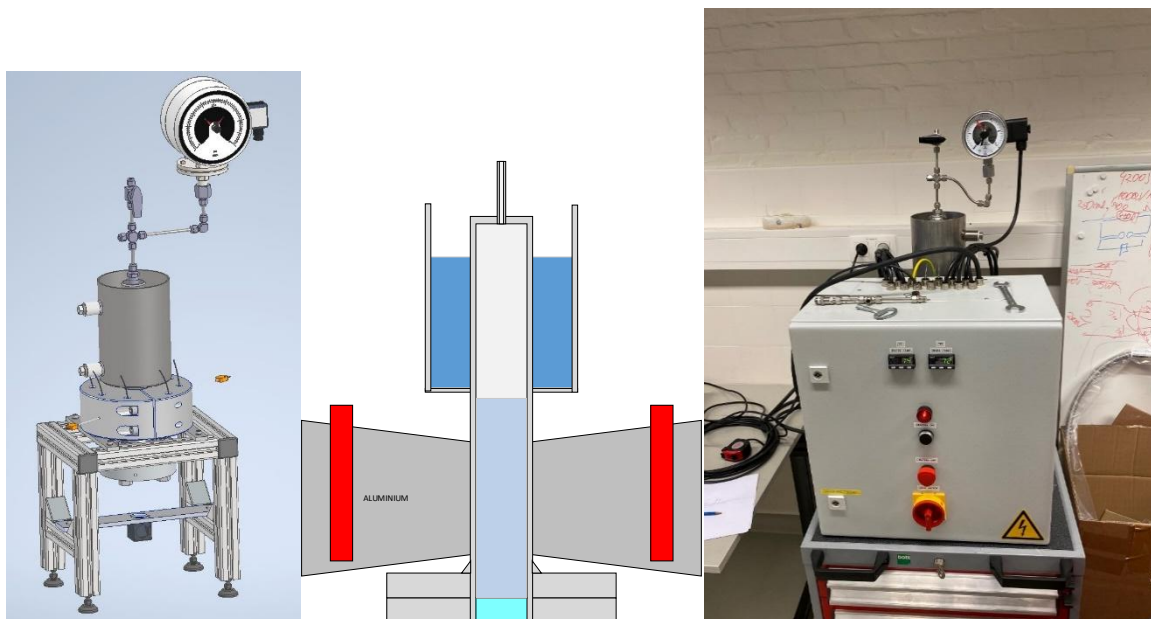


Figure 23: Capsule experimental setup, left 3D model, middle the cross-section, right the actual setup with control box.

Figure 24 below two photos from videos taken via the viewport flange are shown. The picture on the left shows a steady state boiling in a pressurized capsule. On the right is the photo of the boiling process when the pressure valve is opened, and pressure gradually decreases. Boiling becomes bulk boiling and bubble size increases. This will be similar boiling regime as volumetric heating resembling a situation with beam on the real target.

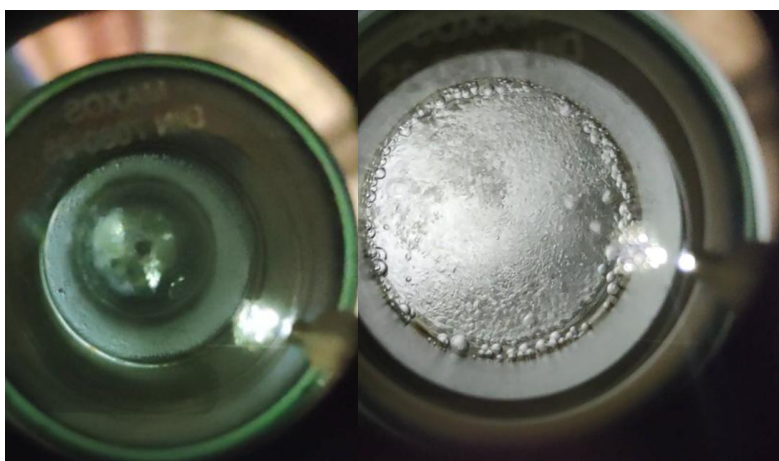


Figure 24: Screenshots from the recordings of the boiling process taken through the viewport flange. On the left: boiling process at the quasi-steady state case, with pressurization. On the right: boiling during depressurization.

The experimental setup successfully demonstrated the fundamental working principles of the irradiation target capsule as outlined in patent EP 4 285 390. The heat-pipe behavior under controlled heating, the stable boiling regime under pressure, and the observed transition to bulk boiling under pressure decrease all support the design concepts and claims described in the patent. Furthermore, the setup provided valuable operational data on safety margins, pressure control, solution level monitoring, and salt deposition tendencies. Taken together, these findings strongly substantiate the validity of the patent claims and provide a robust experimental basis for the target design.

Description of the patent: EP 4 285 390

A key outcome of this development is the successful filing of a dedicated patent, which summarizes the technical advances and innovations embodied in the target design. Details of the target concept, including its liquid-handling architecture and compatibility with high-radiation environments, are protected under EP 4 285 390. This patent underlines the novelty of the design and secures the intellectual property resulting from the feasibility-phase work.

Detailed information on the patent can be found via this link:

<https://register.epo.org/application?number=EP22840228>

Title: Liquid target system

Technical field: The invention relates to the production of radioisotopes using a liquid target system, which offers advantages over solid targets, such as reduced radioactive waste and simplified chemical processes.

Background: Solid targets are commonly used for radio-isotope production due to their high yield, but they have drawbacks such as complex chemical processes and limitations in converter design. Liquid targets, while less efficient, avoid these issues and reduce radioactive waste. However, their efficiency and yield need improvement.

Invention summary: The invention provides a liquid target system and method for producing radioisotopes.

Key features include:

1. **Boiling Chamber:** Contains liquid and basic chemicals irradiated to produce radioisotopes. Overheating is controlled by the thermodynamics of evaporation.
2. **Condensation Area:** Positioned above the boiling chamber to condense vapor into liquid condensate, which is systematically returned to the boiling chamber.
3. **Communicating Vessels:** Condensate collecting areas are interconnected with the boiling chamber to maintain liquid flow and prevent overheating.
4. **Up-Concentration:** During operation, the concentration of basic chemicals increases due to evaporation, enhancing production efficiency.
5. **Cooling System:** Eliminates the need for large heat exchangers and cooling circuits by relying on evaporation and condensation processes.

Advantages:

- Comparable yield to solid targets.
- Reduced radioactive waste generation.
- Continuous cooling prevents overheating.
- Safe operation with accurate monitoring of temperature and pressure.
- Increased solubility of basic chemicals at higher temperatures and pressures.

Applications: The system is designed for producing various radioisotopes, including ^{225}Ac , ^{47}Sc , ^{67}Cu , ^{131}Cs , and ^{155}Tb .

Claims: The patent claims include the design of the boiling chamber, condensation area, condensate collecting areas, and methods for controlling overheating, up-concentration, and efficient isotope production.

Figures: The patent includes schematic diagrams illustrating the liquid target system, solubility data, and operational mechanisms.

Conclusion: This invention addresses the limitations of liquid targets by improving efficiency, yield, and safety, making it a viable alternative to solid targets for radio-isotope production.

Electron-to-gamma converter development

To enable efficient production of high-energy gamma rays for the irradiation of radium targets, a specialized electron-to-photon converter was developed as a critical component of the irradiation module. The converter's function is to transform 40 MeV electron beams into bremsstrahlung radiation with sufficient intensity and directionality to ensure optimal photon yield at the target site.

Tantalum was selected as the converter material due to its high atomic number – enhancing bremsstrahlung production – as well as its excellent thermal and mechanical stability under irradiation. However, the dissipation of beam power, up to 125 kW, presents a significant design challenge. If a single tantalum sheet were used with conventional water cooling on one side, the beam would need to be spread over a large area (e.g., 0.0205 m^2) to maintain the maximum heat flux below 5 MW/m^2 . This would result in a large and potentially inefficient converter setup.

To overcome this, the design evolved toward a multi-layered converter concept (Figure 25), where thin tantalum sheets are cooled on both sides. This approach not only maintains the heat flux within acceptable limits but also increases the total gamma flux, as multiple sheets contribute to bremsstrahlung generation. The geometry of the converter can be tailored to match the size and positioning of the target, ensuring efficient energy deposition. Further optimization was achieved through the development of a novel curved converter geometry, now protected under patent EP4 243 036. This design leverages the forward-peaked nature of bremsstrahlung at 40 MeV: electrons are scanned across a broad converter area, but their emission is focused towards a single spatial point – precisely where the target is located (the principle is illustrated in Figure 26, Figure 27, Figure 28). This configuration maximizes gamma flux at the target while spreading heat deposition over a wide surface area, allowing for efficient cooling and increased power-handling capability.

This patented converter design is central to the feasibility of using high-power electron beams for isotope production and marks a key innovation in this project.

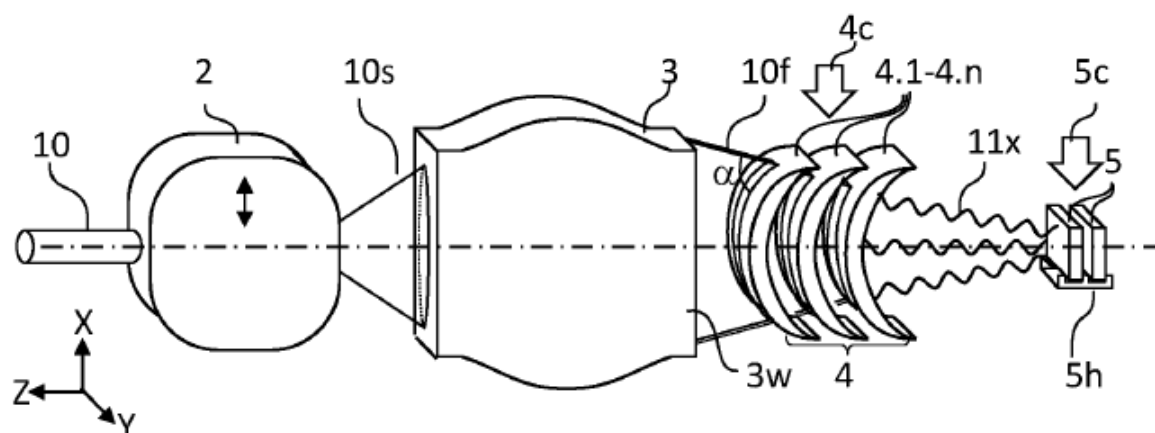


Figure 25: Curved bremsstrahlung converter (drawing from patent).

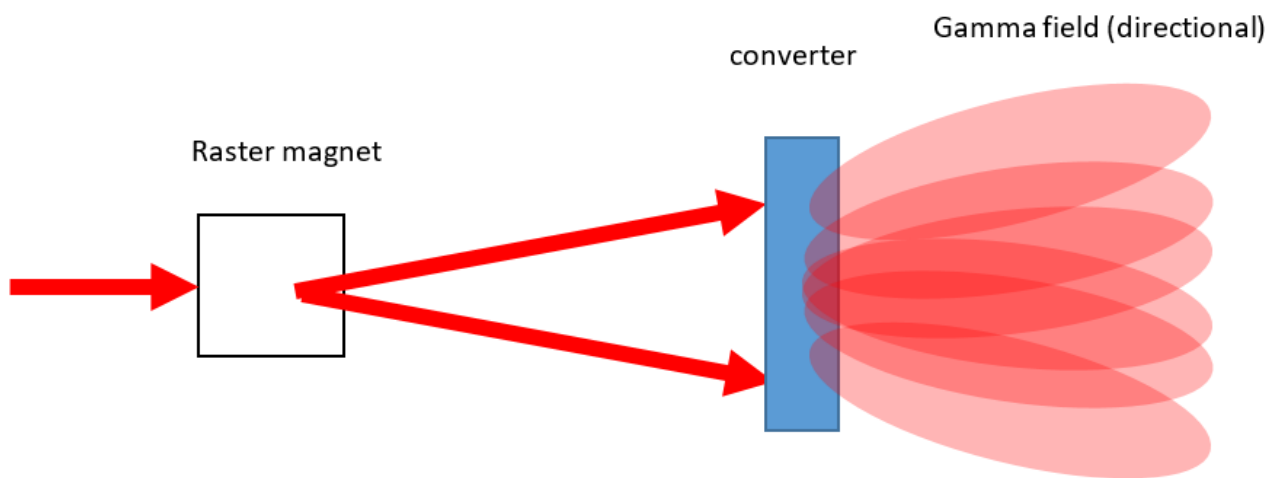


Figure 26: Intended set-up of ^{225}Ac irradiation area.

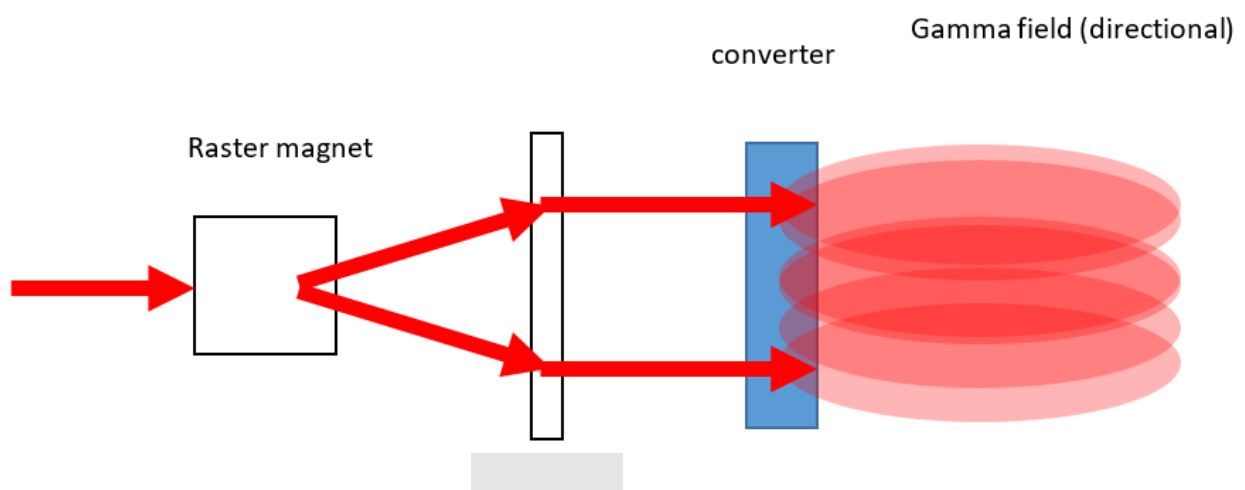


Figure 27: Bending magnet positioned after raster magnet.

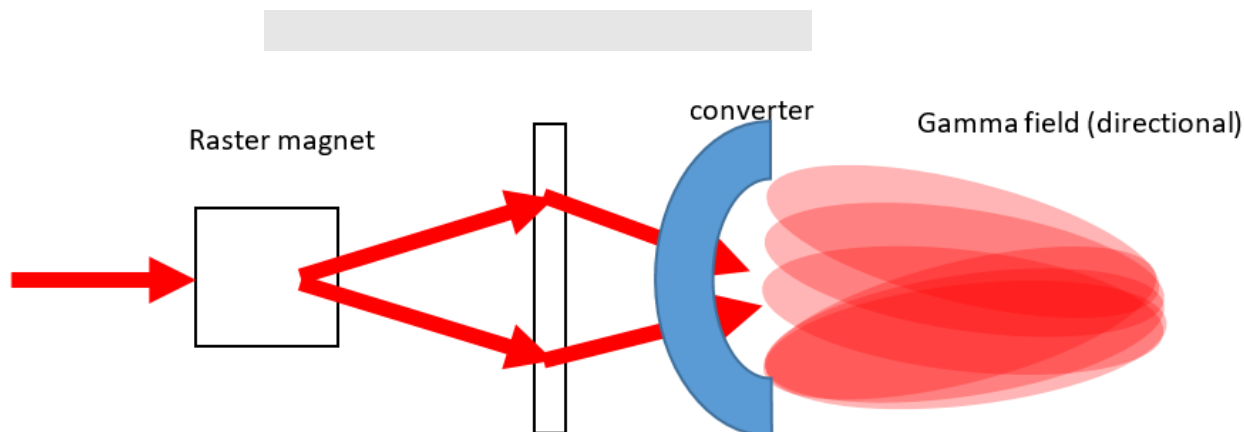


Figure 28: Bending magnet positioned after raster magnet - strong field to focus gamma beam.

Description of the patent: EP 4243 036

Detailed information on the patent can be found via this link:

<https://register.epo.org/application?number=EP22161257>

Title: System for production of radioisotopes by Bremsstrahlung comprising a curved converter.

Technical field: The invention relates to a system for producing radioisotopes by irradiating a target with X-rays generated through Bremsstrahlung. It introduces a curved converter geometry to reduce heat generation and enable conventional cooling systems.

Background: Radioisotopes are produced using photonuclear reactions, where X-rays interact with a target material. Bremsstrahlung converters, typically made of high-Z metals like tantalum (Ta), tungsten (W), or titanium (Ti), convert electron beam energy into X-rays. However, heat generation during this process poses challenges for cooling and durability.

Invention highlights:

1. System Components:
 - Electron Accelerator: Generates an electron beam with energy between 10-40 MeV.
 - Scanning Unit: Deviates the electron beam along predefined patterns to distribute heat.
 - Focusing Unit: Focuses the scanned beam onto a specific point to form a focused beam.
 - Converting Unit: Contains curved Bremsstrahlung converters to convert the focused beam into X-rays.
 - Target Holder: Holds the target material for irradiation.
2. Curved Bremsstrahlung Converters:
 - Curved geometry ensures the electron beam intersects at angles between 65° and 115°, preferably 90°, reducing heat concentration and improving cooling efficiency.
 - Larger scanned areas distribute energy more evenly, minimizing thermal degradation.

3. Cooling System:

- Conventional cooling systems (gas or liquid) are used to maintain the temperature of the converters and target.

4. Applications:

- Produces radioisotopes like ^{225}Ac , $^{99\text{m}}\text{Tc}$, ^{187}Re , ^{131}I , and ^{67}Cu for medical imaging and diagnostics.

Advantages:

- Homogeneous heat distribution across the converter.
- Larger scanned areas reduce energy concentration.
- Enables the use of conventional cooling systems.
- Suitable for small targets, improving efficiency in isotope production.

Claims: The invention claims a system with curved Bremsstrahlung converters, focusing units, and cooling systems, along with a process for producing radioisotopes by X-ray irradiation.

Key features:

- Curved converters (spherical or cylindrical) optimize heat management.
- Scanning and focusing units ensure precise beam control.
- Supports small and large targets with efficient cooling mechanisms.

This system addresses the dual challenge of thermal management and high-intensity X-ray production, making it ideal for medical isotope generation.

Conclusion

The target and electron-to-gamma converter system has been successfully demonstrated at feasibility level and validated experimentally. The results as described in two patents demonstrate that the proposed technological solutions can meet the functional and performance requirements for large-scale ^{225}Ac production from ^{226}Ra .

The outcomes achieved confirm that a robust and implementable design is available, providing a solid basis for integration into a future production facility where a detailed design will be the next step. The transition to full-scale realization, including irradiation under operational conditions, is addressed in the subsequent project phase, taking into account the associated technical, regulatory, and infrastructure requirements.

Development of a $^{226}\text{Ra}/^{225}\text{Ac}$ radiochemical separation method and automation

Introduction

In this part of the ^{225}Ac feasibility study, the radiochemical process required for the fully scaled-up GMP production of ^{225}Ac from ^{226}Ra was developed. Furthermore, the principles for an automated processing system have been worked out to ensure safe, reproducible, and GMP-compliant operation.

The development of the chemical process focused on minimizing the generation of radioactive waste, recycling process liquids, and recovering the valuable ^{226}Ra for reuse. Throughout the optimization work, particular attention was given to producing a high-purity end-product that meets all requirements for GMP-grade ^{225}Ac suitable for clinical and commercial use. Together with the automation strategy, this work forms a robust foundation for future fully scaled-up GMP production.

Radiochemical separation verification documentation of performed work

The key outcome from this part of the ^{225}Ac feasibility study is a patent that secures the innovative solutions arising from the study:

- **Patent application:** EP 4 352 754, which covers the radiochemical separation process – suitable for automation

This patent forms the technical and legal foundation for further engineering and implementation steps.

Description of separation principles

The main reason to choose a liquid target over a more traditional solid target is to avoid the solid-to-liquid and liquid-to-solid conversions, as the chemical separations are always performed with radium and actinium in a dissolved form. While RaCO_3 , $\text{Ra}(\text{NO}_3)_2$ and RaSO_4 precipitation reactions are well known and understood [26, 27], the filtration processes are typically difficult to perform, and the filtrates are never completely free from radium and would need further treatment. Feedback from the former actinium projects at SCK CEN in the 1970s revealed that sintering could occur of the RaCO_3 target material, making it more difficult to dissolve. This is due to the low heat conductivity of the RaCO_3 target. An added advantage of a liquid target is that the target can be transferred by capillary and does not require the use of a heavily shielded container.

The main principle for purification of Ac relies on the use of extraction chromatography resins [28]. Most notably, the TODGA (N,N,N,N-tetraoctyl diglycolamide) and TEHDGA (N,N,N,N-tetra-di-2-ethyl-hexyl diglycolamide) solvating extractants are well known for their capability of extracting Ac from 1 – 5 M HNO_3 , and are commercially available from Triskem and Eichrom as normal-DGA (nDGA) and branched-DGA (bDGA), both given in Figure 29 and Figure 30, respectively [29].

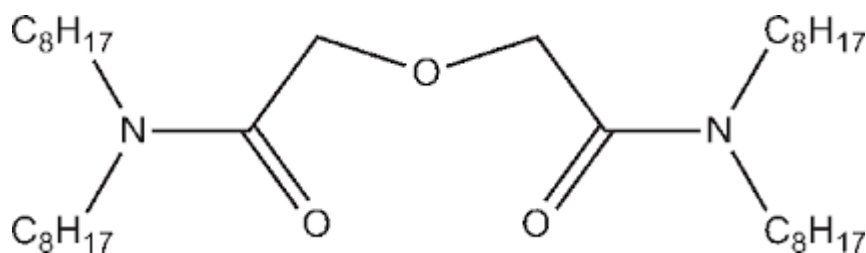


Figure 29: Chemical structure of the normal-DGA extraction chromatographic agent.

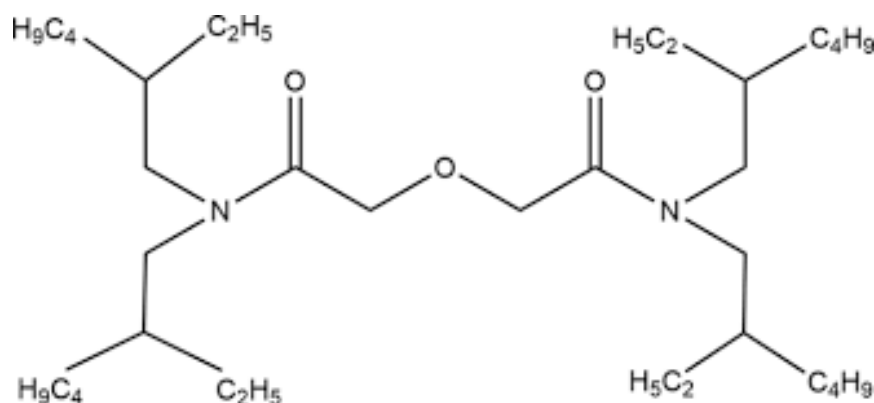


Figure 30: Chemical structure of the branched-DGA extraction chromatographic agent.

The commercially available Lanthanide resin (LN resin), composed of the D2EHPA or HDEHP (di-2-ethyl-hexyl phosphoric acid) acidic extractant, is known to extract Ac in the dilute HNO_3 concentration range of 0.1 – 0.01 M (pH 1-2). The chemical structure of the active component of the LN resin is depicted in Figure 31.

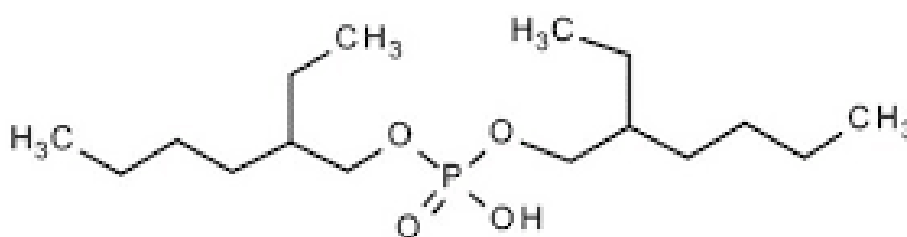


Figure 31: Chemical structure of the HDEHP extraction chromatographic agent.

None of these extractants exhibit affinity towards radium at $\text{pH} \leq 2$. The significant advantage of using these extractants in combination is the ability to separate Ac from Ra in consecutive stages by changing the nitric acid molarity of the mobile phase. A mixture of Ra and Ac in dilute nitric acid, for example at 0.01 M HNO_3 , would undergo the first Ra/Ac separation by passing the mixture over a column containing the LN resin. A second stage purification is performed when the Ac is eluted from the LN resin using 1 - 5 M HNO_3 and directly bound to a second column containing the DGA resin. The distribution coefficients for Ac on DGA and LN as function of acid molarity are given in Figure 32, where the opposite nature of affinity for both extractant types is clearly visible.

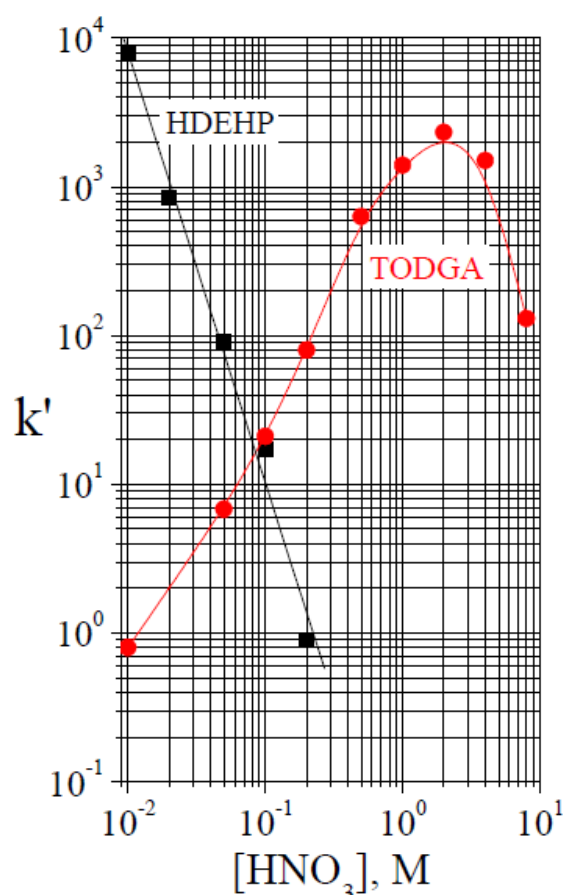


Figure 32: Distribution coefficients for actinium on the LN and nDGA resin as function of nitric acid concentration.

Process development and validation of radiochemical methods

Based on these extraction chromatographic properties, the principle of the separation performance was experimentally verified using representative model experiments, as described below. These experiments demonstrate the key separation mechanisms, including the selective retention and elution behavior of ²²⁵Ac and ²²⁶Ra on different resins under controlled conditions.

The results obtained confirm that the separation process is robust, reproducible, and consistent with the expected behavior derived from chromatographic theory. Importantly, the experiments are designed to be directly scalable, as they capture the governing physicochemical interactions and process parameters relevant for larger-scale operation. As such, the experimental validation provides sufficient evidence that the proposed radiochemical separation method is suitable for implementation, thereby fulfilling the requirements of a fully scaled-up separation process at feasibility level.

In 2018, the development of a commercially applicable separation process was initiated. ²²⁵Ac and ²²⁵Ra were made available from a 6 MBq ²²⁹Th source and in 2019, a patent application was filed by SCK CEN on this method. The fully scaled-up process presented here in this report as a part of the ²²⁵Ac feasibility study was developed, building further on the experience and knowledge obtained through this early work. The method makes use of a combination of DGA and LN resin, where different routes can be followed, depending on if the radium solution is in high or low nitric acid concentrations. When the Ac is present in low nitric acid concentrations, it's selectivity for LN resin is apparent. If the Ac is present in higher concentrations of nitric acid, the use of DGA is preferable. A typical value for decontamination of Ra from Ac is around 10⁴, while the

required purity for the Ac needs to be many orders of magnitudes higher, which necessitates the use of multiple Ac selective columns. The early patent describes a method on how to purify Ac without taking intermediate fractions, that need to be reconcentrated and matrix adjusted. Therefore, it makes optimal use of the reverse selectivity on DGA and LN, where the desorption step is performed in the conditions that allow adsorption on the next. Part of the method also describes a pre-treatment step using concentrated HNO_3 to remove the bulk of Ra from the solution before the purification on column. When this step is chosen, it is straightforward to look at the method starting with high concentration of acid. The method also foresees the option of using the DGA with HCl in the presence of Fe^{3+} , but this method is not further explored due to the corrosiveness of HCl towards stainless steel.

While the method mainly focuses on the removal of Ra from Ac, also synergies were found between the main process steps, and in-line guard columns for specific elements like Pb, Bi, and Po. At specific parts of the process, the use of Sr or Pb specific resin (based on the 18-crown-6 ether) is also foreseen. Especially removal of Pb is important, due to the presence of ^{210}Pb as progeny of ^{226}Ra , and ^{212}Pb originating from the co-produced ^{224}Ra during irradiation.

It is important to mention that all the proposed routes allow a high level of automation, which is important in the case of an envisioned GMP process where reproducibility is very important. During the development phase, two different separation and purification routes were chosen, where both routes have advantages and disadvantages. Referenced to as "Route A" and "Route B", both methods will be further described.

Route A

Route A is best aligned with the composition of the liquid target, which is the radium solution dissolved in a dilute nitric acid matrix, as the first step in the process is to use a LN resin to remove Ac from the Ra. Therefore, it requires a pH check of the mother solution to make sure an optimal pH of approximately 2 is reached. The full inventory of the Ra is passed over the LN column and collected in similar pH conditions. After rinsing the LN, the Ac^{3+} can be transferred to a DGA column using approximately 1 M HNO_3 . This matrix allows for a PB resin in tandem to capture any Pb being eluted from the LN resin. The Ac is present on the DGA, and further washed to remove impurities. Finally, the purified Ac can be eluted in dilute HNO_3 or HCl. The largest advantage is that Ra is never present in high concentrations nitric acid.

Route B

Route B was developed based on the assumption that the loading step in Route A would be too problematic for the LN resin, and the risk of unrecoverable radium losses would outweigh its benefits [30]. Therefore, a method was developed where the bulk of Ra (> 99%) was removed by precipitation in concentrated nitric acid. A filtration method was needed to obtain the filtrate containing the Ac. After diluting a factor of 3 and homogenization, this solution would be the feed solution for a DGA based separation step. After the separation of $\text{Ra}(\text{NO}_3)_2$ crystals from the liquid phase containing the Ac, the Ra could be redissolved in water. After purification of Ac on the DGA, the column is eluted in dilute HNO_3 where the ^{225}Ac is adsorbed on a LN resin that is in tandem with the DGA at that point in the process. After further rinsing, the Ac is transferred back to a DGA column, and finally can be eluted in dilute HNO_3 or HCl.

It was clear that the precipitation step, as being part of the Route B, would still require further improvement, especially because of the filtration step needed, and the risks associated with working with concentrated nitric acid. Moreover, it became apparent that small quantities of ^{227}Ac would be co-produced in the liquid target, and co-precipitation of small quantities Ac in the $\text{Ra}(\text{NO}_3)_2$ would be problematic in case non-carrier added ^{225}Ac is desired. A method is therefore developed that gradually precipitates Ra while evaporating a mixture of

nitric acid and water. This is best performed under strong under pressure (e.g. 50 mbar), in this way the temperature of the boiling liquid can also be left low, and a secondary heater circuit based on water can be used. To maximize precipitation of $\text{Ra}(\text{NO}_3)_2$, in the final step this secondary circuit can be used to cool down the liquid to close to zero. The feasibility of this step was investigated, and besides the complexity of a filtered dip tube, the method works surprisingly well.

Separation of Ra/Ac using LN resin

The separation performance of the LN resin was tested using commercially available 2 mL (= 1 bed volume, BV) columns at a flow rate of 1 mL/min using a peristaltic pump. The resin material, 50 – 100 μm in particle size, pre-filled inside a Triskem column of 10 mm diameter and 25 mm bed height, was pre-equilibrated with 5 BV of 0.01 M HNO_3 . Subsequently, a model solution containing 1 gram of Ba dissolved in 20 mL H_2O as nitrate spiked with 20 kBq ^{225}Ac and 15 kBq ^{224}Ra was pumped over the column, followed by 20 mL of H_2O , 20 mL of 0.01 M HNO_3 and 20 mL of 0.1 M HNO_3 . Ultimately, the column was stripped using 20 mL of 4 M HNO_3 . The absence or presence of ^{225}Ac and/or ^{224}Ra was checked quantitatively using gamma spectrometry using the 218 keV peak of ^{221}Fr for ^{225}Ac and 238 keV peak of ^{212}Pb for ^{224}Ra . Sufficient in-growth time and decay correction was applied where necessary.

Separation of Ra/Ac using bDGA resin

Routine Ra/Ac separations are well-known to SCK CEN and already performed in the frame of the in-house supply of ^{225}Ac for various PhD projects. The branched DGA resin having a bed volume of 2 mL is pre-equilibrated with 20 mL of 4 M HNO_3 using a vacuum box supplied by Triskem, France. Afterwards, a 20 mL mixture of $^{225}\text{Ra}/^{225}\text{Ac}$ in 4 M HNO_3 is passed over the bDGA column at a flow rate of 1 mL/min. The column is subsequently rinsed with 20 mL HNO_3 by 4 consecutive additions of 5 mL. The final product ^{225}Ac is then eluted using 20 mL of 0.01 M HNO_3 and its purity assessed using gamma spectrometry. Quantitative analysis is done by using the 40 keV peak of ^{225}Ra and the 218 keV peak of ^{221}Fr for ^{225}Ac .

Separation of Ra/Ac using LN/bDGA in tandem (fully scaled-up route A)

The route A separation principle is tested using a full-scale target volume of 270 mL 0.01 M HNO_3 with 10 g of barium dissolved as nitrate. As tracers, 500 kBq of ^{225}Ac and 200 kBq of ^{225}Ra were added to resemble a real target configuration. The separation was performed using a two-stage approach using the LN and bDGA resins in consecutive order. For the separation run, 2 mL columns identical to the ones described in the sections above. Additionally, Sr resin as well as UTEVA resin was used for the adsorption of Pb and Bi ions, respectively. The layout of the separation columns is schematically depicted in Figure 33.

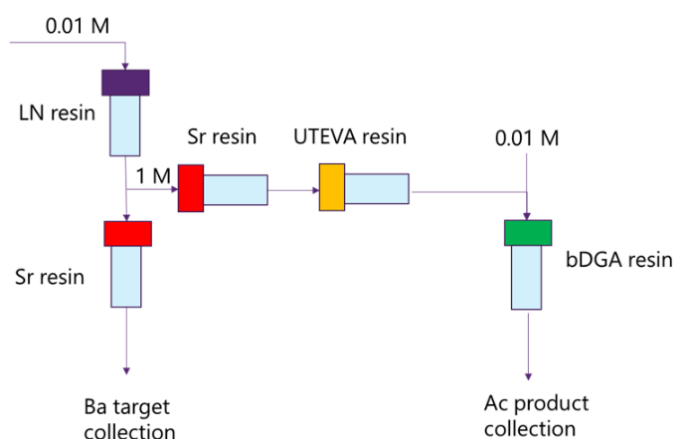


Figure 33: Schematic representation of the full-scale route A separation test.

At first, each column is pre-equilibrated using the same molarity of HNO_3 as it will later be exposed to by the working solution. In the second step, the entire 270 mL target volume is pumped over the LN and first Sr resin using a peristaltic pump at a flow rate of 2 mL /min. Afterwards, the LN and first Sr resin column are rinsed using 20 mL of 0.01 M HNO_3 . The ^{225}Ac on the LN is eluted using 20 mL 1 M HNO_3 , passed over the second Sr column and UTEVA column and is caught by the bDGA resin column in series. The bDGA column is subsequently rinsed with 20 mL 4 M HNO_3 and the ^{225}Ac then eluted using 20 mL 0.01 M HNO_3 , representing the final product.

Gamma spectrometry was then used to assess the purity of the final ^{225}Ac product by checking for the absence of the 40 keV peak of ^{225}Ra . Similarly, the purified liquid target is analyzed for residual activity of ^{225}Ac . Each column additionally undergoes checks for residual activity of ^{225}Ac and/or ^{225}Ra to assess process losses.

Results on the fully scaled-up route A radiochemical separation method

Based on the experimental data obtained from the separations described above, the following conclusions could be drawn:

- Each single separation step involving either the LN of the DGA column enables a Ra/Ac and Ac/Ra separation factor between 10^3 to 10^4 . Column design, accurate column packing, the absence of voids and air pockets, the flow rate etc. are few of important parameters in order to achieve a reliably and reproducibly high separation factor.
- A tandem separation involving the LN and DGA resin enables the purification of Ac from Ra to an extent exceeding 10^6 .
- The residual activity found in the columns was always found to be $< 0.02\%$ of the initial activity of ^{224}Ra , ^{225}Ra and ^{225}Ac , respectively.
- The Sr and UTEVA resin showed excellent retention for Pb and Bi, respectively, with $> 99\%$ retention efficiency.
- A 3% break-through is observed for ^{225}Ac on the final bDGA column during the 1 M rinsing procedure. Optimization is required to maximize the ^{225}Ac product recovery efficiency.

Although cation-exchangers can also be used to separate elements based on their charge difference, the use of compounds with sulfonic acid functional are not recommended. The degradation products from oxidation or radiolysis can form sulfate, that can cause in-situ precipitation of RaSO_4 , which is very difficult to dissolve and can lead to unrecoverable losses.

Radiolysis studies

To assess the influence of radiation towards the stability of the used organic resins, different additional experiments have been undertaken using internal SCK CEN facilities as well as external entities. The BRIGITTE facility of SCK CEN offered the possibility to expose different resins to gamma radiation from ^{60}Co to varying total accumulated doses between 100 kGy up to 10 MGy.

The following resins (Table 4) have been irradiated, each sample being exposed to gamma radiation under wet conditions using HNO₃ solution:

		100 kGy	1 MGy	10 MGy	
LN resin std	1	8	15	each time, 1 g resin and 5 mL of solution	
Pb resin std	2	9	16		
nDGA resin std	3	10	17		
bDGA resin std	4	11	18		
TK221 resin std	5	12	19		
UTEVA resin std	6	13	20		
Ag-MP-1 resin	7	14	21		
0.01 M HNO3			22		
4.0 M HNO3			23		

Table 4: List of resins irradiated in the BRIGITTE facility at SCK CEN.

The analysis of the performance of these resins is evaluated in experiments assessing their total capacity, elution profile etc. The results obtained indicate that all the studied resins suffer to a certain degree from degradation of the organic extractant. A measurable increase in the concentration of carbon and phosphorus has been observed for the LN and DGA resin at doses above 100 kGy, indicating radiolytic degradation. However, the measured ion capacity did not change significantly up to 1 MGy of dose. Higher doses are known to alter the properties of DGA-type resins, which are less radiation resistant than LN and Ag-MP-1 resin types. The results from this study will be used in further evaluations on process robustness towards radiolysis.

Description of the patent: EP 4 352 754

Detailed information on the patent can be found via this link:

<https://register.epo.org/application?number=EP23735282>

Title: Purification of Target Material for the Production of Radioisotopes

Technical Field: The invention relates to the field of radioisotopes, specifically methods and systems for purifying irradiated targets for re-use in the production of radioisotopes.

Background: Radioisotopes are typically produced using solid targets due to their high yield and density of parent nuclides. Liquid targets, while limited by solubility issues, have gained interest due to advancements in overcoming these limitations. Separating radioisotopes from targets is essential, often performed using solid-phase extraction methods. The global stock of certain parent nuclides, such as ²²⁶Ra, is limited, making the re-use of target materials critical. Existing methods, such as those described in WO 2020/260210 and WO 2020/148316, address aspects of target material re-use and purification but leave room for improvement in efficiency and reliability. This invention aims to provide better purification methods and systems to enable the re-use of irradiated targets for further radio-isotope production.

Invention highlights:

- Provides a method and system for purifying target materials (e.g. ^{226}Ra) after irradiation so they can be re-used in radioisotope production.
- Reduces losses of valuable target material.
- Uses acid addition, selective water removal, and cooling to precipitate target material without co-precipitation of radioisotopes and impurities.
- Applicable to both solid and liquid irradiation targets.
- Focus on minimizing contamination and maintaining high chemical purity.

Advantages:

- Efficient target recycling, enabling higher radioisotope yields with limited material.
- Avoids radioisotope co-precipitation (^{225}Ac), improving product purity.
- Reduces need for additional target material.
- Enables purification of targets containing ^{226}Ra with minimal losses.
- Simplifies radiochemical handling by using standard equipment like rotary evaporators and double-walled jackets.
- Reduces formation of corrosive NO_x fumes.
- Operable under reduced pressure and controlled temperature for safety and scalability.

Claims:

1. Method for purifying target material (e.g. ^{226}Ra) involving:
 - Dissolving irradiated material in acid.
 - Evaporating water under controlled conditions.
 - Precipitating target material selectively while keeping radioisotopes in solution.
 - Cooling, filtering, washing, and preparing the target material for re-irradiation.
2. Steps can be done under reduced pressure and with temperature control.
3. Use of stirring, rotary evaporators, and immersion filtration.
4. Claims also cover the system setup:
 - Reactor vessel with inlets for irradiated material and acid.
 - Evaporation and filtration apparatus.
 - Heating/cooling system, pressure control, and radon removal apparatus.
 - Controller for process automation.

Key Features:

- Temperature and pressure control (evaporation under vacuum at 50–200 mbar and heating with double-walled jackets).
- Selective removal of water leaving acid behind, concentrating solution until target material precipitates.
- Immersion filtration and washing of precipitated target.
- Designed to minimize contamination (e.g. organic, metallic, radioisotopic).
- Apparatus can integrate into existing radioisotope production setups.

Automation

All operations involving the handling of ^{226}Ra , its daughters and other radioactive products from the irradiation such as ^{224}Ra and ^{225}Ra require a hot-cell environment. The manipulations will be performed using robotic telemanipulators behind thick protective Pb walls. To enable all the operations that arise from the ^{225}Ac production process, a specific automation strategy needs to be put in place so that human interaction is reduced to a limited time and duration.

The following list gives examples of operations that might involve the use of semi-automatic or fully automated equipment, depending on their complexity:

- Transfer of liquids from one recipient into another including a quantitative rinsing procedure.
- Purification by peristaltic pumping over a set of columns including valve management (route A).
- Sub-boiling distillation and adjustment of feed solution (route B).
- Measurement and adjustment of process parameters (pH, volume, temperature etc.).
- Sample taking at appropriate process steps to assure product / educt quality.
- Extraction / Insertion of process consumables.

While specialized companies exist that offer customized solutions and process equipment that can cope with the listed tasks, the difficulty lies in the harsh radiation environment putting any electronic component under significant stress, increasing the failure rate. Additionally, the emanation of ^{222}Rn causes plastic material to become brittle significantly faster since radon tends to accumulate in organics. Thus, the proper design of the automation equipment will be crucial for a reliable and durable process that involves the handling of significant ^{226}Ra quantities.

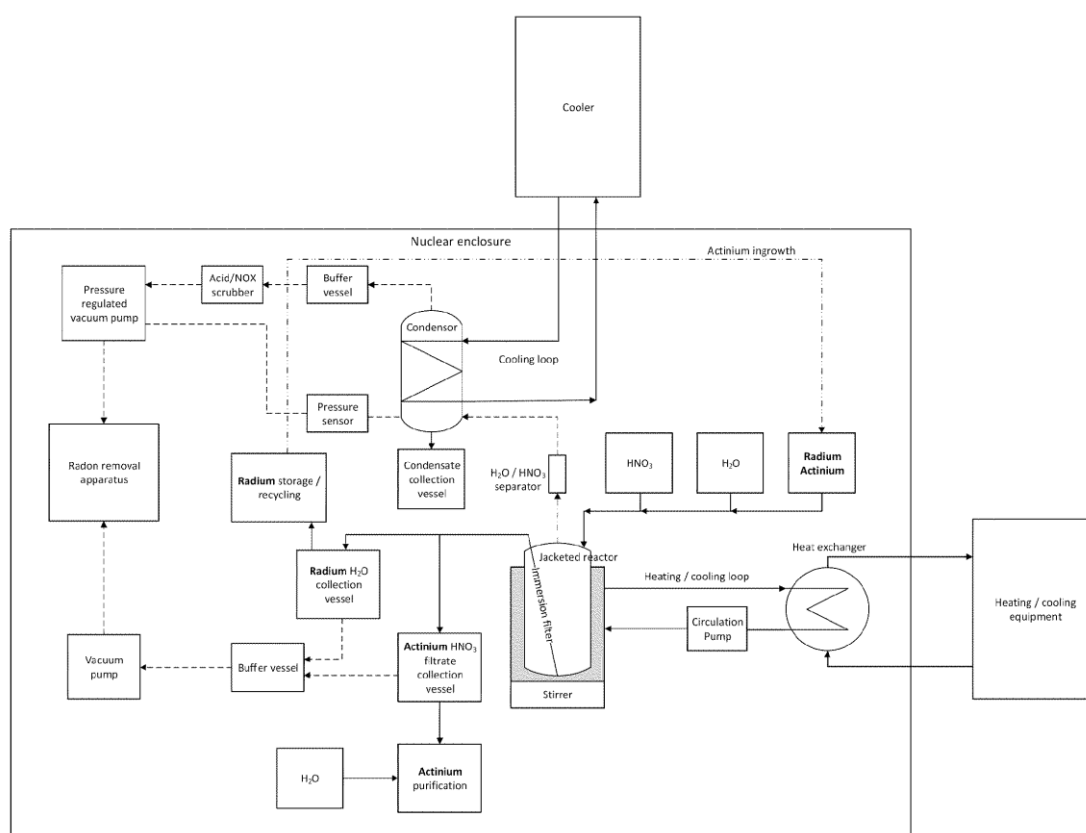


Figure 34: Flow-diagram of the upscaled radiochemical separation method (from patent).

To achieve that, a pre-selection of components is mandatory to ensure certain quality standards. Where possible, design must enable the exchange of electronic equipment with a telemanipulator without complex operations. Moreover, the equipment needs to be modular, so it can be assembled and dismantled in a hot cell without the need for an intervention (i.e. physical entry of personnel inside the hot cell). Electronics can either be shielded from the main sources of radiation or – even more desirable – completely detached from the mechanical parts of the equipment and placed outside of the hot cell. Either way, thorough testing and failure analysis of each component is mandatory to ensure a reliable automation process. In Figure 34 a flow-diagram is shown of the process described in patent EP 4 352 754. The flow is defined in such a way that the process is easy to automate taking all of the considerations mentioned above into account.

Reclaiming of ^{226}Ra

The ^{225}Ac production involves the usage of a relatively large quantity of ^{226}Ra that should be constantly reused and kept in circulation in the facility to assure a sustainable process. The reason for that is two-fold: on one hand, radium containing waste is one of the most expensive radioactive waste forms in Belgium, requiring significant investments. On the other hand, radium is not available for purchase in gram quantities on the market since there is currently no commercial supplier (anymore) existing. Thus, it is of crucial importance to reduce radium losses to a minimum and include, where losses are unavoidable, a ^{226}Ra reclaim strategy. Reducing the losses of ^{226}Ra is achieved by minimizing the number of conversions between liquid and solid state. Specifically, radium is preferably kept in solution and contained at all times, meaning that no operations with open radium sources are foreseen in the ^{225}Ac production process. Transfer of radium containing liquids is always accompanied by rinsing with sufficient volume of distilled water that is subsequently evaporated. Losses of ^{226}Ra are therefore minimized to locations inaccessible for rinsing (column voids, dead sections in piping etc.). Any consumable that is suspicious for containing residual radium will undergo a reclaim procedure that should enable recovery to reduce losses to waste as much as reasonably achievable. The chemistry of radium in solution closely resembles those of the alkaline earth elements. Being exclusively in its divalent state (Ra^{2+}), radium is readily soluble in dilute nitric and hydrochloric acid as well as in water. Thus, reclaim operations might include intense rinsing protocols with these media to recover residual fractions of ^{226}Ra on columns, in tubings etc.

To recover radium from a mixture of other metal ions, the use of a resin specific for radium offers the potential to achieve a fast and efficient purification. Such a resin does already exist commercially and is based on a crown ether for “molecular recognition” of ions with certain ionic radii. Little experimental evidence on the practical implementation for the recovery of radium has been published for such a resin type, but it offers potential in reclaiming radium from large effluent volumes containing metallic and radioactive impurities.

Radioactive waste

Unrecoverable quantities of ^{226}Ra in solid and liquid consumables will ultimately be considered as radium containing waste. These waste streams need to be evacuated according to Belgian radioactive waste legislation, which currently considers only solid radium containing waste. Aqueous, liquid waste requires a pre-treatment to reduce the ^{226}Ra content to a level below 1000 Bq/L to be accepted by NIRAS as a suitable waste form. This implies that effluents from the reclaim and/or the production process, that still contain radium above said limit, need to undergo an additional chemical conversion step.

The co-precipitation of radium as sulfate using barium as carrier has proven to be a viable approach to decontaminate Ra waste streams. An excess of $\text{Ba}(\text{NO}_3)_2$ is added to a liquid containing ^{226}Ra and subsequently Na_2SO_4 is added under stirring to initiate the precipitation of $\text{Ba}(\text{Ra})\text{SO}_4$. Since the solubility of both BaSO_4 and RaSO_4 is well below 10 mg/L, the concentration of radium in the treated liquid might be reduced by several orders of magnitude. The filtered $\text{Ba}(\text{Ra})$ sulfate is evacuated according to existing

protocols for solid alpha-containing waste. Alternatively, liquids might be evaporated to dryness under controlled conditions to avoid cumbersome chemical conversion operations.

Conclusion

A comprehensive radiochemical separation and purification process for the production of ^{225}Ac from ^{226}Ra has been successfully developed and validated at feasibility level. The combination of extraction chromatographic techniques, supported by representative experimental verification, demonstrates that the proposed method is robust, reproducible, and suitable for automation and scale-up to large-scale operation.

The process integrates efficient separation performance with strategies for minimization of radioactive waste, recycling of process streams, and recovery of ^{226}Ra , thereby ensuring both technical and operational sustainability. In parallel, a coherent automation concept has been established, enabling safe, controlled, and GMP-compliant implementation in a hot cell environment.

Together, these elements constitute a fully developed radiochemical process at feasibility level, providing a solid and implementable basis for large-scale ^{225}Ac production.

Development of a conceptual design of a ^{225}Ac production facility

Development of a conceptual design

As part of the ^{225}Ac feasibility study, a conceptual design of the ^{225}Ac production facility has been developed that reflects the functional requirements for producing a GMP-grade pharmaceutical product.

Scope

This section outlines the conceptual design for the ^{225}Ac production facility. The scope of this design is to establish the core requirements and layout of the facility, ensuring that all critical processes, from target irradiation and radioisotope extraction to final product dispensing, can be safely and efficiently performed under full compliance with GMP and radiological safety standards.

At this early stage, the focus is on defining the core functional areas and basic design principles rather than specifying detailed engineering solutions or equipment. The objective is to illustrate how the facility could be arranged to support safe handling of radioactive materials, comply with GMP production requirements, and facilitate future licensing. This conceptual approach highlights key zones, material and personnel flows, and general containment and cleanliness principles that will need to be refined in later design phases.

The design is developed drawing on the experience of SCK CEN staff and leveraging existing expertise from the Centralized Radiochemistry Facility (CRF) for which a detailed design was developed also as a RRF funded project. This includes contributions from SCK CEN's teams specialized in radiological safety, process engineering, quality assurance, and environmental monitoring.

While this conceptual design sets out the broad functional areas, material and personnel flows, zoning, and containment principles, it does not detail engineering solutions or equipment specifications. These will be developed at later project stages and are out-of-scope for this feasibility study.

Key requirements

The key requirements capture the high-level expectations that the ^{225}Ac production facility must fulfill. These requirements define the intended functions, safety and quality standards, and constraints that will guide both the conceptual and later detailed design stages. They also serve as a basis for evaluating alternative design solutions and will be further refined as the project progresses toward licensing, validation, and GMP qualification.

Key requirements for the facility design are:

- **Radiological safety and containment**
The facility shall ensure safe handling of radioactive materials and minimize exposure to personnel and the environment, in accordance with applicable regulations.
- **GMP compliance**
The facility shall support cGMP-compliant production processes, including appropriate cleanroom classifications, controlled material/personnel flows, and traceable documentation.

- **Functional zoning**
The design shall incorporate clearly defined functional areas – receiving, processing/purification, dispensing/QC, support/utilities, and personnel areas – with appropriate segregation and containment.
- **Process flexibility**
The facility shall be designed to accommodate the anticipated process scale, future upgrades, and new equipment without major structural modifications.
- **Environmental control**
The facility shall maintain appropriate temperature, humidity, cleanliness, and pressure differentials between clean and containment areas to prevent cross-contamination.
- **Material and personnel flows**
The design shall establish unidirectional material and personnel pathways with dedicated entry/exit routes, gowning areas, and pass-throughs to minimize contamination risk.
- **Shielding and waste management**
Shielding shall be sufficient to protect operators, and the design shall incorporate systems for safe radioactive waste handling, decay, and removal.
- **Monitoring and safety systems**
The facility shall provide continuous monitoring of airborne radioactivity, dose rates, and contamination, as well as alarms, interlocks, and emergency systems.
- **Compliance and documentation**
The design shall facilitate full traceability, batch recording, and easy access for inspections and audits as required by GMP and licensing bodies.

Regulatory references and licensing

The ^{225}Ac production facility shall be designed and constructed in compliance with all applicable GMP, radiological safety, and nuclear facility regulations. Upon completion, the facility will be subject to inspection and licensing by the following competent authorities:

- **Belgian Federal Agency for Medicines and Health Products (FAMHP, FAGG)**
To be recognized as a Pharmaceutical Manufacturing Site and authorized for the production of ^{225}Ac as a radiopharmaceutical for human use.
- **Federal Agency for Nuclear Control (AFCN / FANC)**
To be licensed as a **nuclear facility**, in accordance with Belgian regulations governing the safe handling of radioactive materials.

Key guidelines and standards

To support licensing and regulatory compliance, the design will align with the following standards and guidance documents:

- **Eudralex – Volume 4 (EU GMP):**
 - Part 1: Medicinal Products.
 - Part 2: Active Pharmaceutical Ingredients (API).
 - Annex 1: Manufacture of Sterile Medicinal Products.
 - Annex 3: Manufacture of Radiopharmaceuticals.
 - Annex 13: Manufacture of Investigational Medicinal Products.
- **ISO Standards:**
 - ISO 14644: Cleanrooms and Associated Controlled Environments.
 - ISO 17873: Nuclear facilities – Design and operation of ventilation systems for nuclear installations (other than reactors).
- **Belgian Radioprotection Legislation:**
 - AR 20 juillet 2001 portant règlement général de la protection de la population, des travailleurs et de l'environnement contre le danger des rayonnements ionisants.
- **AFCN/FANC Guidelines:**
 - Applicable to Class II establishments (<https://afcn.fgov.be/fr/professionnels/activites-industrielles/classe-ii-et-iii>).

Compliance with these regulatory references will ensure that the facility meets national and international standards for radiological safety, product quality, and traceability, supporting the successful authorization of the facility for its intended GMP radiopharmaceutical production purpose.

Production process of ^{225}Ac

The process to produce ^{225}Ac consists of the irradiation of ^{226}Ra targets followed by repeated cycles of chemical extraction and purification of ^{225}Ac from the irradiated target material as described in detail earlier in this report. Once purified, the residual ^{226}Ra is recycled for further irradiations.

In this design, a liquid ^{226}Ra target will be used, allowing a continuous or semi-continuous operation that simplifies handling, improves recovery rates, and reduces operator dose.

The process steps considered are:

Target preparation and irradiation

Performed in the target reception area and the accelerator irradiation vaults.

Liquid target filling and integrity check

The ^{226}Ra solution is prepared and loaded into a dedicated irradiation container (target) or loop system in a hot cell. Its integrity is verified prior to irradiation.

Irradiation in the accelerator irradiation vaults

The target is irradiated using gamma rays produced via bremsstrahlung from accelerated electrons. The electrons are generated by an electron accelerator and guided into the vault via a transfer beamline.

Isotopic transmutation and build-up

During irradiation, ^{226}Ra transmutes into a mixture of ^{225}Ra , ^{225}Ac (and, depending on photon energy, also ^{224}Ra), along with decay products.

Liquid target recovery

After irradiation, the liquid is transferred back to a hot cell in the target reception area and the liquid ^{226}Ra mixture is prepared for purification.

Chemical extraction of ^{225}Ac

Performed in the radiochemistry hot cell line.

Liquid target processing

The irradiated liquid is directly processed by passing it through dedicated columns or extraction units. (There is no capsule opening as in the solid-target process. This simplifies operations and minimizes the risk of ^{222}Rn release at this stage).

Liquid target conditioning and separation

The $^{226}\text{Ra}/^{225}\text{Ra}/^{225}\text{Ac}$ mixture is chemically treated to adjust its chemistry for chromatographic or solvent extraction. Risks of $^{220}\text{Rn}/^{222}\text{Rn}$ release and radiological contamination are controlled by containment, active exhaust systems and radon capture systems.

Chromatographic ^{225}Ac extraction and purification

^{225}Ac is selectively extracted using column chromatography. This cycle can be repeated multiple times, allowing interim decay of co-produced isotopes and removal of unwanted species. The $^{226}\text{Ra}/^{225}\text{Ra}$ can be recovered and returned to a target recycle tank.

Target recycling

Once all ^{225}Ac is extracted, the ^{226}Ra can be purified and recycled into the target loop for the next irradiation cycle.

Product processing and dispensing

Performed in the dispensing hot cells in classified cleanrooms.

Dispensing and sterilization

The purified ^{225}Ac is transferred to a grade C hot cell for final purification, formulation, dispensing into vials, and autoclave sterilization. Some post-sterilization aseptic operations may take place under grade A conditions.

Quality control (QC)

Product samples are taken and tested prior to batch release.

Packaging and dispatch

The ^{225}Ac product (as bulk or in vials) is packaged into shielded containers and transferred to the buffer or staging area for shipment.

Facility areas

The facility will be organized into several dedicated areas, each serving a specific function to support the safe, compliant, and efficient production of ^{225}Ac . The layout reflects the functional zoning principles described earlier, ensuring appropriate containment, cleanliness control, and radiological safety.

The areas are:

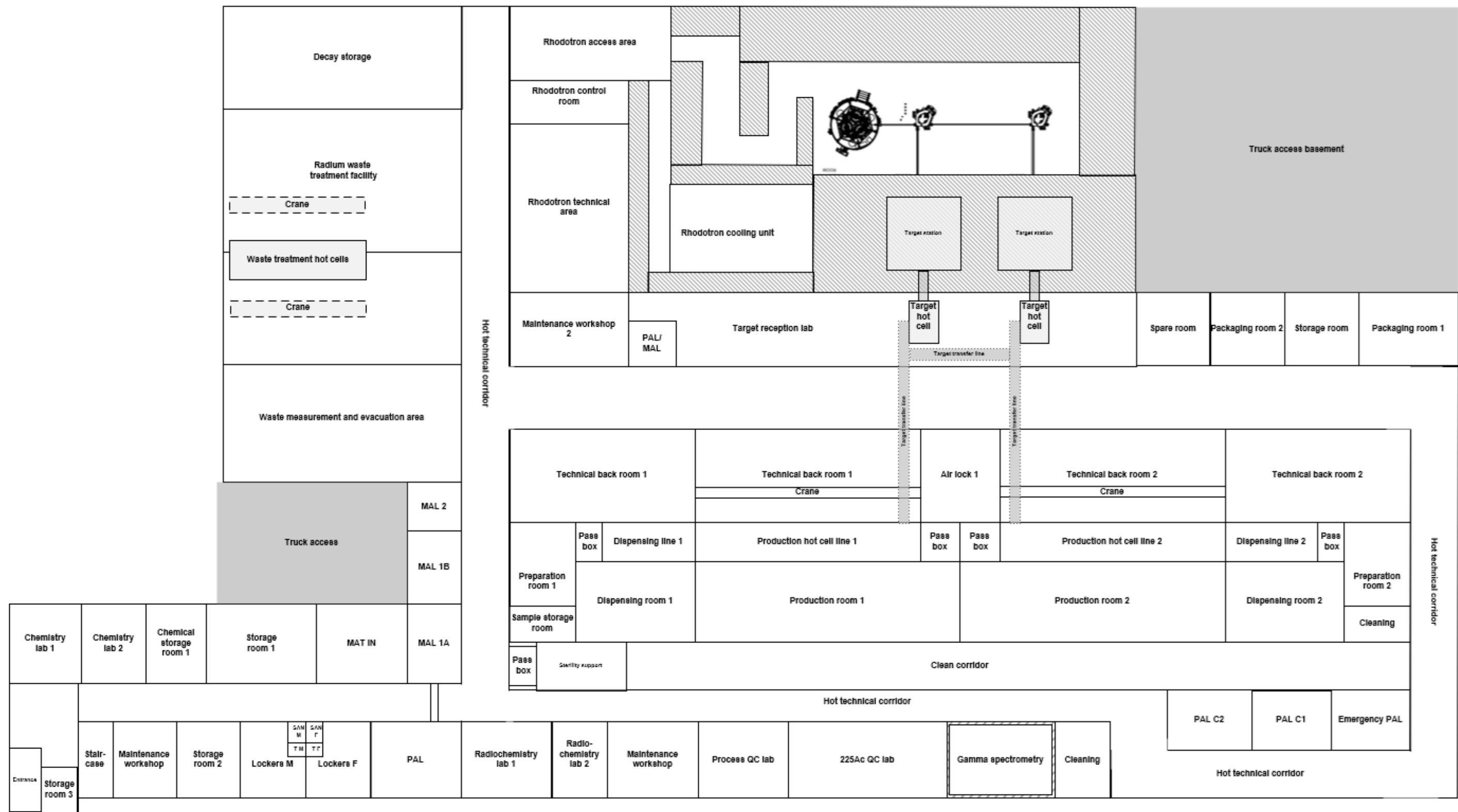
1. Irradiation and accelerator area – for target irradiation and electron beam handling.
2. Target handling zone – for receipt, inspection, and transfer of targets into the process.
3. Radiochemistry production area – for ^{225}Ac extraction, purification, and formulation under hot cell containment.
4. Non-radioactive support area – for cold-lab preparations, QC, R&D, and administrative support.
5. Radioactive support area – for QC, technical support, maintenance, and handling of radioactive materials and waste.
6. Non-radioactive and radioactive zone pathways – corridors and pass-throughs to support personnel and material movement in the different areas of the facility.
7. Storage and logistics area – for receiving and dispatching materials and products.
8. Technical and utility rooms – for HVAC, power, compressed gases, and other infrastructure.
9. Office and meeting area – for staff offices, meeting rooms, and administrative workspaces.

Each of these areas is designed in accordance with GMP and radiological safety requirements, including appropriate radiological zoning, environmental controls, shielding, and access restrictions. In the sections that follow, the design and purpose of each area will be described in greater detail.

Conceptual layout of the building

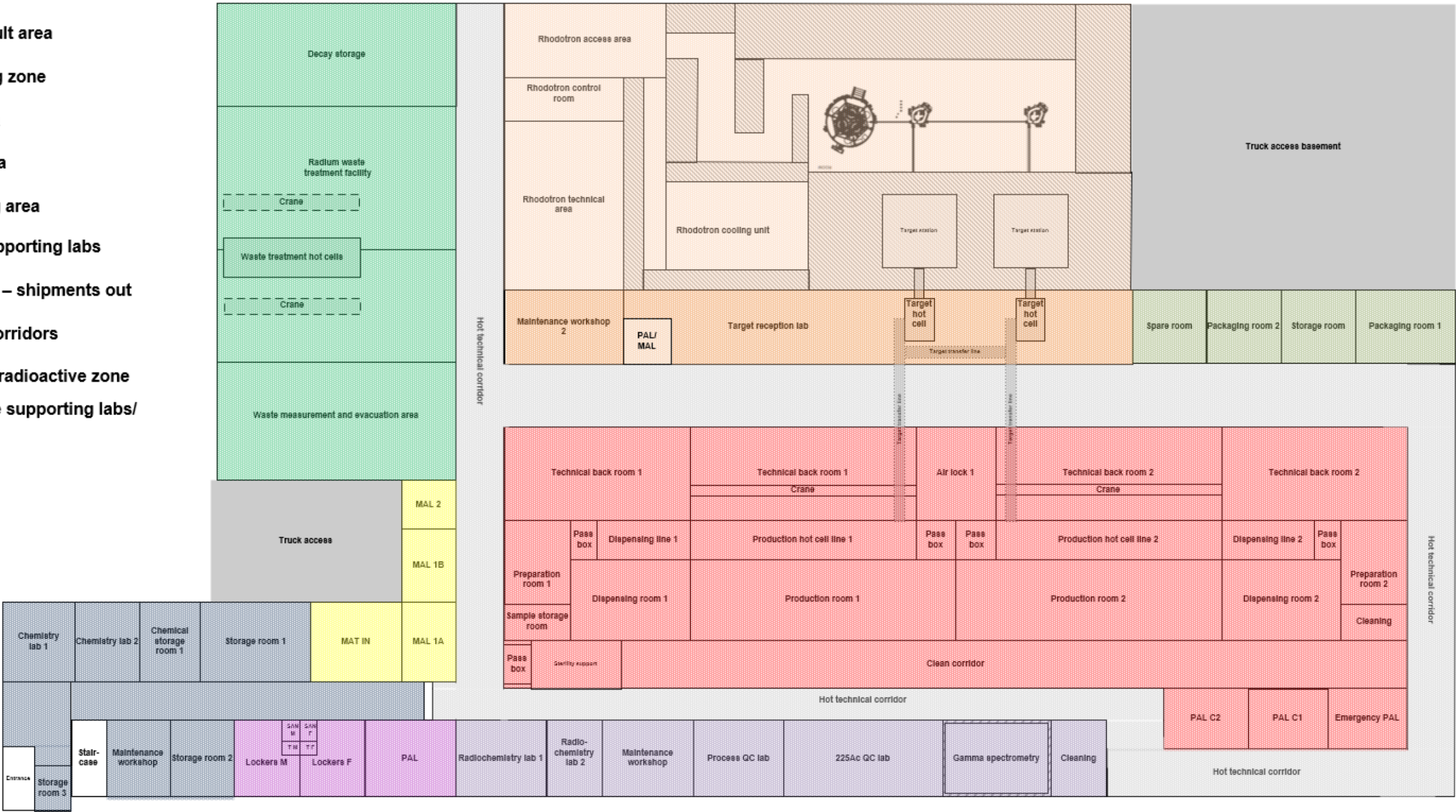
Schematic drawings of the conceptual design can be found below.

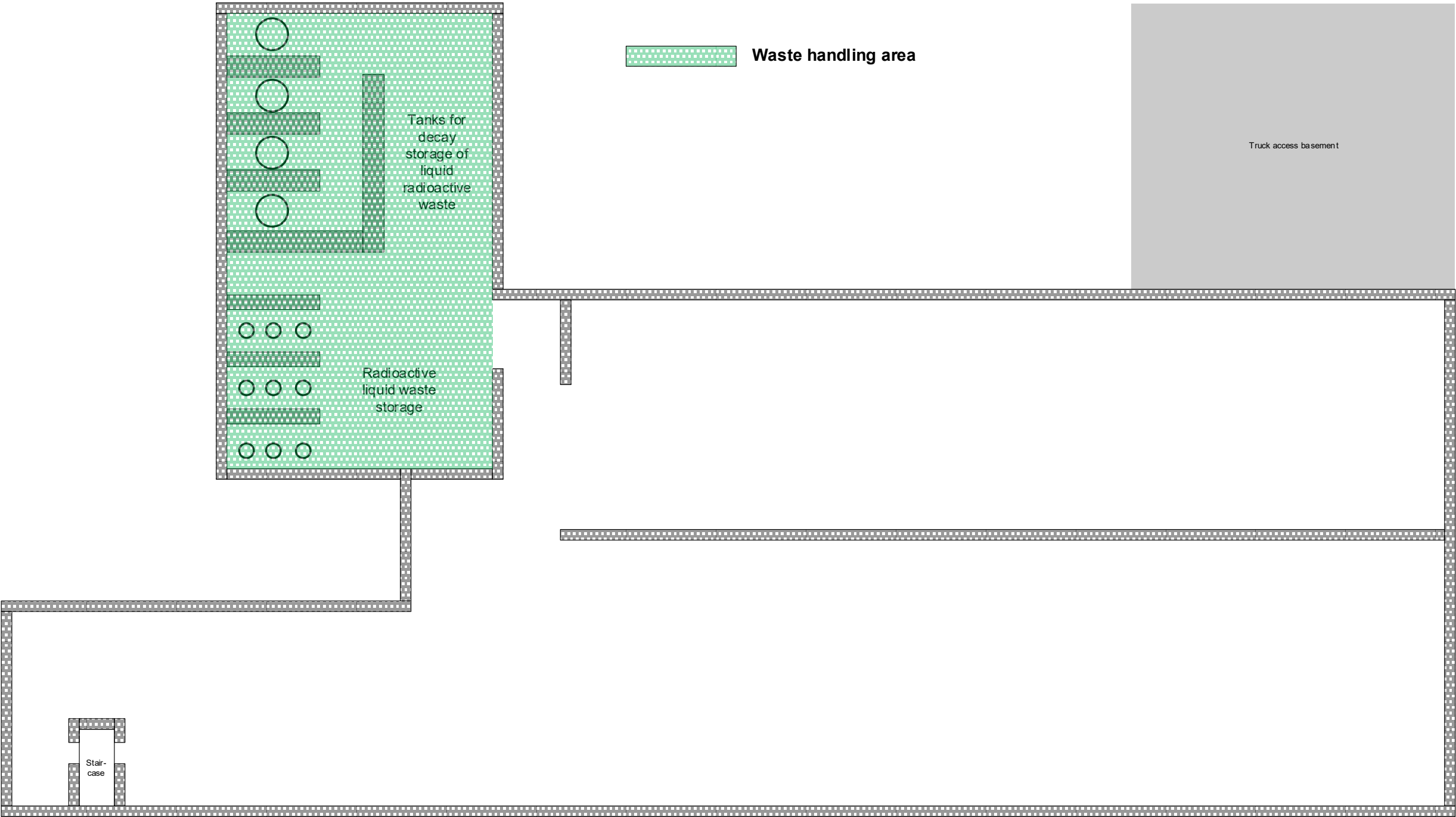
Ground floor

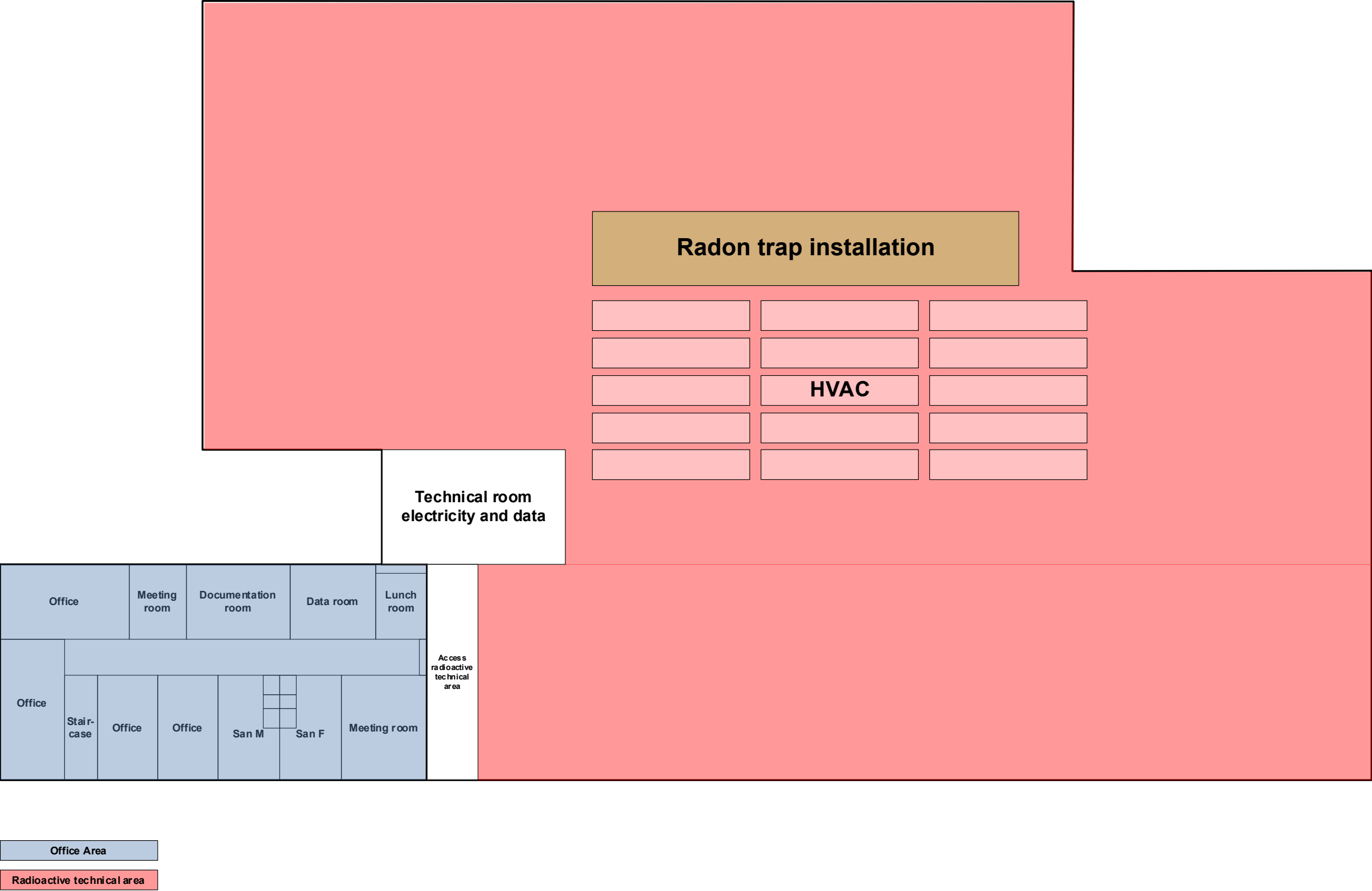


Ground floor

- Accelerator vault area
- Target handling zone
- Packaging area
- Processing area
- Waste handling area
- Radioactive supporting labs
- Materials in/out – shipments out
- Hot technical corridors
- Access area to radioactive zone
- Non-radioactive supporting labs/ storage







Area descriptions

Irradiation and accelerator area – for target irradiation and electron beam handling

Accelerator vault area

The accelerator room houses the electron accelerator (e.g. Rhodotron) used for the photonuclear production of ^{225}Ac . The accelerator generates high-energy electron beams that are converted into bremsstrahlung photons via a high-Z target (typically tungsten), which subsequently interact with ^{226}Ra targets to produce ^{225}Ac through (γ, n) reactions.

- **Function:** This is the high-radiation zone where the accelerator is installed and operated. It houses the electron beam generator and associated beamline infrastructure.
- **Shielding:** Heavily shielded with thick concrete walls to contain prompt radiation from accelerator operation. Entry is strictly controlled.
- **Access:** Personnel access is restricted during beam operation; interlock and safety systems prevent accidental entry when radiation is present.

Rhodotron cooling unit room

- **Function:** Contains the thermal management system for the accelerator, including water cooling circuits and heat exchangers.
- **Safety:** Monitored for leaks and temperature control. Critical to maintain stable operation and protect sensitive components.

Rhodotron access area

- **Function:** Serves as a controlled entry zone for maintenance and inspections when the accelerator is shut down.
- **Features:** Includes shielding doors, radiation survey checkpoints, and safety interlocks.

Rhodotron technical area

- **Function:** Hosts support infrastructure such as RF (radiofrequency) generators, power supplies, and control electronics required for beam acceleration.
- **Environmental Control:** Temperature and humidity control systems are typically installed here to protect sensitive electronics.

Rhodotron control room

- **Function:** The operational hub for controlling the Rhodotron. Includes interfaces for beam settings, monitoring parameters, safety overrides, and logging.
- **Access:** Located outside the radiation zone; designed for safe 24/7 monitoring during operation.

Target station

- **Function:** The electron beam from the Rhodotron is directed to the converter and ^{226}Ra target assembly in this area, where photonuclear (γ, n) reactions produce ^{225}Ac .
- **Configuration:** May include shielding, remote handling tools, and target cooling systems.
- **Connection:** Positioned adjacent to the target hot cells and transfer lines for post-irradiation handling.

Target handling zone – for receipt, inspection, and transfer of targets into the process

Function

This area is dedicated to the controlled receipt, inspection, and preparation of ^{226}Ra targets for irradiation, as well as the initial handling of irradiated targets post-exposure. It serves as the logistical and operational interface between external target supply, the irradiation process, and downstream processing.

Location

The target handling zone is located adjacent to the irradiation area and includes the target reception lab, target hot cells, and the target transfer line.

Key equipment and spaces

- **Target reception lab:** Secure area for receipt and registration of targets, including contamination checks and dose rate measurements.
- **Inspection zone:** Shielded workspace for visual inspection, integrity verification, and possible non-destructive quality control.
- **Temporary storage:** Shielded cabinets or decay storage positions for holding targets prior to or after irradiation.
- **Target transfer line:** Mechanical or shielded system for safe and remote transfer of targets between the handling zone, the irradiation station, and the target hot cells.

Safety features

- Located within the controlled area with local shielding provisions.
- Material/personnel access via PAL/MAL area.
- Access restricted to trained personnel and subject to radiological control measures.
- Equipped with dose rate monitoring systems and provisions for contamination control.

Radiochemistry production area – for ^{225}Ac extraction, purification, and formulation under hot cell containment

Function

This area is a classified clean room facility dedicated to the radiochemical processing of irradiated targets for the extraction, purification, and formulation of ^{225}Ac . All operations are performed under hot cell containment to ensure both product sterility and radiological safety.

Location

The radiochemistry production area is located downstream of the irradiation and target handling zones. It is directly connected to the target hot cells and includes production hot cells, preparation rooms, dispensing lines, clean corridors, and technical back rooms.

Key equipment and spaces

- **Production hot cell lines:** Shielded and classified hot cells equipped for remote handling of irradiated targets, chemical separation processes, and product formulation in a controlled clean room environment.
- **Preparation rooms:** Classified areas for the preparation of reagents and materials, directly connected to the hot cell lines.

- **Dispensing lines and rooms:** Clean areas for the final sterile transfer and filling of the purified ^{225}Ac product into primary containers, potentially under laminar airflow or isolator systems.
- **Clean corridors and pass boxes:** Ensure controlled unidirectional flow of personnel and materials, with integrated systems for decontamination and pressure cascade management.
- **Technical back rooms:** Non-classified support zones for hot cell maintenance and utility access, separated from clean production areas.

Safety features

- The entire area is operated under clean room classification with defined air cleanliness grades.
- Equipped with shielded containment, HEPA-filtered HVAC systems, pressure differentials, and radiation monitoring.
- Personnel and material flows are strictly controlled via gowning areas, airlocks, and pass-throughs to prevent cross-contamination.

Operational considerations

- Designed in accordance with GMP standards for radiopharmaceutical production.
- Ensures the sterile and radiologically safe handling of $^{225}\text{Ac}/^{226}\text{Ra}$ during all stages from separation to final formulation.
- Environmental monitoring and routine qualification ensure compliance with cleanliness and safety specifications.

Non-radioactive support area – for cold-lab preparations, QC, R&D, and administrative support

Function

This area supports non-radiological activities essential to the operation of the ^{225}Ac facility. It includes laboratories for non-radioactive chemistry, quality control testing, and research and development, as well as spaces for documentation, data analysis, and administrative functions.

Location

The non-radioactive support area is located outside the controlled radioactive zone, with convenient access to both the main facility and the office areas. It includes chemistry labs, QC labs, documentation rooms, and offices.

Key equipment and spaces

- Cold chemistry labs equipped for the preparation and testing of reagents, process development work, and validation studies without radioactive material.
- Quality control labs for non-radioactive QC method development, reference testing, and analytical support.
- Research and development spaces for process optimization, alternative target studies, and new product development.
- Administrative and support rooms such as offices, documentation rooms, data analysis workspaces, and meeting rooms for operational coordination.

Safety features

- Operates under standard laboratory safety protocols.
- Physically separated from radioactive areas to prevent contamination.
- Includes ventilation, fume hoods, chemical storage, and spill response equipment.

Operational considerations

- Supports the overall ^{225}Ac production process through method development, planning, and recordkeeping.
- Serves as the interface for analytical services, documentation control, and interdepartmental coordination.
- Access is unrestricted with standard lab clearance, enabling collaboration across project teams.

Radioactive support area – for QC, technical support, maintenance, and quality control

Function

This area supports radiological operations through dedicated laboratories for target recycling, quality control of radiochemical processes, and maintenance of critical infrastructure. It enables compliant handling and analytical testing of radioactive materials within a controlled GMP environment.

Location

The radioactive support area is situated within the controlled zone, adjacent to production and processing areas. It includes radiochemical laboratories, shielded measurement rooms, technical corridors, and equipment workshops.

Key equipment and spaces

- Radiochemistry labs for target material recovery and recycling activities.
- GMP quality control labs equipped with instrumentation such as ICP-MS and radio-TLC for product and process testing – dedicated QC lab for ^{226}Ra handling and a dedicated QC for testing the purified ^{225}Ac product.
- Dedicated gamma spectrometry room with heavy shielding for low-background measurements, used for radionuclidic purity testing.
- Radiopharmaceutical QC zones for sterility testing, endotoxin control, and pH measurement.
- Maintenance workshops and hot technical corridors for equipment access and support without disturbing clean operations.

Safety features

- All laboratory and maintenance areas operate under strict radiological zoning.
- Shielding, air handling systems, and contamination monitoring are integrated throughout.
- Gamma measurement room is designed with enhanced shielding to minimise ambient background.

Operational considerations

- Supports compliant QC testing in line with GMP standards for radiopharmaceuticals.
- Ensures reliable recycling and reuse of valuable target materials.
- Facilitates maintenance and troubleshooting of active systems while maintaining process integrity.

Access areas to the radioactive zone

Function

The access area to the radioactive zone is a critical control point that regulates personnel entry into radiologically controlled areas. It is designed to protect both personnel and product by enforcing strict access procedures, contamination control, and compliance with radiological safety and GMP protocols.

Location

This area is strategically placed between the non-radioactive support zones (offices, labs, and logistics) and the controlled radioactive areas (target handling, radiochemistry production, waste treatment). It acts as a gateway for all personnel entering or exiting the radiological zones.

Key components

- Personnel Airlocks (PALs):
 - Multiple-stage changing and decontamination areas.
 - Controlled transitions from general to classified and radioactive zones.
 - Gowning sequences in accordance with cleanroom and radiological zoning requirements.
- Dosimetry and Access Control:
 - Electronic badge readers for access authorization.
 - Individual dosimetry monitoring points (entry and exit).
 - Radiation detection portals and hand-foot monitors for contamination checks.
- Locker and Sanitary Facilities:
 - Separate changing rooms for men and women (Lockers M/F).
 - Showers and handwashing facilities.
 - Sanitary zones (SAN M/SAN F) at the entrance to the controlled zone.
- Contamination Monitoring Station:
 - Continuous surface and airborne contamination monitoring.
 - Emergency eyewash and decontamination facilities.

Safety and operational considerations

- Access is limited to trained and authorized personnel only.
- Gowning protocols and PPE are defined based on the zone being accessed (e.g., radiochemistry vs. waste).
- Contamination control measures prevent backflow into clean or office areas.
- Radiation protection staff may monitor compliance and support incident response.

Integration with facility layout

- Positioned near gowning rooms, clean corridors, and the entry to critical production zones.
- Designed to support unidirectional personnel flow from clean to classified to radioactive zones, and back again via decontamination and exit control.
- Supports both GMP traceability and nuclear safety regulations.

Non-radioactive and radioactive zone pathways – corridors and pass-throughs to support personnel and material movement in the different areas of the facility

Function

This area facilitates the safe and controlled movement of personnel and materials between non-radioactive and radioactive zones. It maintains strict separation to minimize contamination and radiation exposure.

Design features

Dedicated corridors and pass-throughs clearly demarcate zone boundaries. Separate pathways for personnel and materials prevent cross-contamination. Pass-throughs include decontamination systems, airlocks, or

pressure cascades as needed. Shielding is integrated where pathways border radioactive zones to reduce radiation exposure.

Safety and access controls

Access is restricted using badge controls and training requirements depending on zone classification. Interlocks and radiation monitoring prevent unauthorized entry or transfer of materials. Clear signage and protocols ensure adherence to radiological safety measures. Routine contamination and dose rate monitoring is performed in transition areas.

Operational considerations

Pathways support efficient logistics for target materials, irradiated samples, and waste handling. Personnel transit is designed to minimize impact on clean and controlled environments. The layout complies with GMP and radiation safety standards to ensure smooth production flow.

Radioactive waste handling area

Function

The waste handling area ensures the safe, compliant, and efficient management of radioactive waste generated during ^{225}Ac production. This includes collection, segregation, decay storage, measurement, and preparation for final disposal. The design minimizes radiation exposure, supports environmental protection, and complies with national nuclear waste regulations.

Location

Located within the controlled radioactive zone, the waste handling area is physically separated from production and clean areas. It is situated adjacent to the radiochemistry and radiopharmaceutical production zones, with direct access to the hot technical corridors and truck access basement to facilitate shielded transport and waste logistics.

Key equipment and spaces

- Waste treatment hot cells
 - o Enclosed shielded cells for handling and processing of radioactive waste (liquid and solid).
 - o Equipped for sorting, containment, and decontamination tasks.
- Radium waste treatment facility
 - o Dedicated space for the safe management of long-lived ^{226}Ra waste, including conditioning and shielding.
- Decay storage
 - o Tanks or shielded enclosures for temporary storage of radioactive liquid and solid waste.
 - o Designed to allow sufficient time for decay of short-lived isotopes before disposal or further handling.
- Waste Measurement and Evacuation Area
 - o Monitored zone for radiological characterization, dose rate measurement, and labeling prior to transfer off-site.

- Sample storage room
 - Shielded location for storage of retained samples and QC waste under regulatory traceability protocol.

Safety and access controls

- Operates under strict radiological zoning, with shielding, ventilation, and contamination control.
- All areas monitored for airborne radioactivity, surface contamination, and dose rates.
- Access restricted to trained personnel, with protocols for protective equipment and waste handling.
- Integration with facility radiation monitoring and alarm systems.

Operational considerations

- Enables segregation of waste streams (e.g. active vs. non-active, long-lived vs. short-lived).
- Designed in compliance with Belgian radioprotection legislation and AFCN/FANC Class IIA facility guidelines.
- Minimizes operator dose and environmental release through containment and decay strategies.
- Supports efficient internal logistics with direct connection to technical corridors and truck access routes.

Storage and logistics area – for receiving and dispatching materials and products

Function

The storage and logistics area ensures the secure, efficient, and compliant handling of all incoming materials and outgoing radiopharmaceutical products. This zone acts as the operational interface between the production facility and external suppliers or recipients, supporting GMP traceability and radiological safety requirements.

Location

This area is strategically located with direct access to both the production zones and external transport routes, including a dedicated truck access basement. It serves as the entry and exit point for raw materials, consumables, intermediate goods, and final ^{225}Ac products.

Key equipment and spaces

- Receiving zone: For controlled intake of raw materials, chemicals, and packaging components.
 - Material airlocks (MALs).
 - Initial contamination monitoring.
 - Dose rate checks and registration.
- Storage rooms:
 - Non-radioactive storage: For consumables, chemicals, and packaging materials.
 - Radioactive storage: For irradiated targets and intermediate products under decay.
 - Decay storage tanks: For temporary holding of radioactive liquid waste prior to disposal.
- Packaging and dispatch rooms:
 - Final ^{225}Ac product is packaged in shielded containers.
 - Dedicated packaging rooms (Packaging Room 1 & 2) with dose monitoring.
 - Transfer to staging area or loading dock for regulated shipment.

Safety and access controls

- Segregated storage for radioactive and non-radioactive materials.
- Shielded storage and packaging zones to reduce operator dose.
- Controlled access with radiological monitoring at entry/exit points.
- Procedures in place for receiving inspection, inventory tracking, and material reconciliation.

Operational considerations

- Supports uninterrupted production through reliable inventory management.
- Ensures compliance with shipping and receiving regulations for radiopharmaceuticals.
- Interfaces with both non-radioactive and controlled radioactive zones via clean corridors and designated transfer routes.
- Contributes to full GMP traceability and documentation for all incoming and outgoing goods.

Technical and utility rooms – for HVAC, power, compressed gases, and other infrastructure

Function

The technical and utility rooms house the essential infrastructure required to support continuous, safe, and GMP-compliant operation of the ^{225}Ac production facility. These systems ensure environmental control, equipment functionality, and the reliable supply of utilities critical to radiopharmaceutical manufacturing.

Location

These rooms are located throughout the facility primarily on the first floor (technical space) and in the basement to provide efficient service access while being physically separated from clean and controlled production areas.

Key equipment and systems

- HVAC systems
 - o Supply and return air handling units (AHUs) with HEPA filtration.
 - o Pressure cascade systems for containment and cleanliness zoning.
 - o Temperature and humidity control to maintain environmental specifications in cleanrooms and hot cells.
- Electrical rooms
 - o Power distribution panels.
 - o Backup power systems (e.g., UPS or generator support).
 - o Monitoring systems for electrical load and fault detection.
- Compressed gases and vacuum supply
 - o Central gas distribution systems (e.g., nitrogen, argon, compressed air).
 - o Vacuum lines for process support and containment systems.
 - o Leak monitoring and emergency shutoff valves.
- Process utility systems
 - o Water purification and cooling systems for the Rhodotron and hot cells.
 - o Waste gas filtration and exhaust scrubbers.
 - o Control panels and PLCs for utility monitoring and automation.

Safety and access controls

- Restricted to trained technical personnel.
- Equipped with local monitoring systems for temperature, pressure, and alarms.
- Fire protection and emergency ventilation systems installed as required.
- Designed to allow maintenance without disrupting classified production areas.

Operational considerations

- Critical to maintaining GMP and radiological safety compliance.
- Designed for high reliability and redundancy to avoid production interruptions.
- Interfaces with Building Management System (BMS) for centralized monitoring and control.
- Supports scalability and integration with future equipment upgrades or expansions.

Office and meeting area – for staff offices, meeting rooms, and administrative workspaces

Function

The office and meeting area (1st floor) provides dedicated spaces for administrative work, project coordination, documentation control, and interdepartmental communication. It ensures that support functions essential to the operation, regulation, and oversight of the ²²⁵Ac production facility are carried out in a professional and secure environment.

Location

Located outside the controlled radioactive zone, this area is directly accessible from the main building entrance and is adjacent to the non-radioactive support areas. It is physically separated from GMP production zones to prevent any cross-contamination while remaining in proximity for efficient communication and oversight.

Key spaces

- Individual and shared offices.
- Workspaces for staff involved in quality assurance, production oversight, regulatory affairs, R&D coordination, and facility management.
- Meeting rooms
 - o Equipped for team meetings, regulatory inspections, project discussions, and teleconferences.
 - o Designed to support confidentiality, audiovisual needs, and documentation review.
- Documentation and data rooms (restricted access)
 - o Secure rooms for controlled document storage, data management, and GMP recordkeeping.
- Break and sanitary areas
 - o Staff restrooms, lockers (M/F), and lunchrooms to support daily operations.

Safety and access controls

- Access is unrestricted for authorized staff and visitors, with no special radiological training required.
- Located entirely within the non-radioactive zone.
- Fire safety, ventilation, and ergonomic considerations integrated into design.

Operational considerations

- Supports GMP-compliant documentation and administrative processes.
- Provides functional areas for training, inspections, and interdepartmental meetings.
- Enables efficient coordination between production teams, quality control, and management.
- Enhances staff well-being by providing a professional and comfortable working environment.

Pressure settings of the building

Function

The pressure setting of the ^{225}Ac production facility is engineered to meet the dual regulatory demands of **radiological containment** and **GMP-compliant sterile manufacturing**.

Pressure differentials between rooms and zones are used to:

- Protect sterile products from microbiological contamination.
- Contain radioactive materials within shielded zones.
- Ensure safe personnel and material flow throughout the facility.

The system design is based on principles outlined in:

- EU GMP Annex 1: Manufacture of sterile medicinal products.
- EU GMP Annex 3: Manufacture of radiopharmaceuticals.
- ISO 14644: Cleanroom classification and control.
- ISO 17873: Design and operation of ventilation systems in nuclear facilities.

Cleanroom classification requirements for radiopharmaceutical production

In line with EU GMP guidelines (Table 5), the following air cleanliness grades (based on particle counts in operation) are typically required for sterile radiopharmaceuticals such as ^{225}Ac :

Zone/Activity	Required Grade	Notes
Aseptic filling/dispensing	Grade A	Laminar airflow or isolator; sterile boundary
Background to Gr. A (e.g., hot cell room)	Grade B	Surrounding cleanroom to support aseptic area
Preparation of components, equipment	Grade C	For less critical but controlled operations
Storage and pre-cleaning of materials	Grade D or unclassified	Depends on contamination risk

Table 5: Air cleanliness grades according to EU GMP guidelines.

For ^{225}Ac production, this generally maps as follows but can depend on local interpretations:

- Dispensing hot cells: Grade A (isolator or LAF inside cell), with Grade B background.
- Preparation rooms: Grade C/D.
- Radiochemistry hot cells: Typically Grade C background with negative pressure (due to radioactivity).
- Clean corridors: Grade C or D, with pressure cascades toward critical areas.
- Waste and technical areas: Not classified for cleanliness but negatively pressurized for safety.

Pressure cascade strategy

The pressure cascade is used to direct air movement from clean to less-clean zones, while also ensuring that radioactive materials are not released from their containment areas.

This dual approach requires fine balancing:

- GMP-driven cascade (Clean → Less Clean) protects product sterility.
- Radioprotection-driven cascade (Ambient → Radioactive) contains radioactive material.

Typical pressure gradients in ²²⁵Ac production facility

Area	Cleanroom Grade	Pressure Relative to Adjacent Area	Purpose
Grade A hot cell (filling)	A (in isolator)	Positive to Grade B	Protect aseptic conditions
Dispensing room (background)	B	Positive to Grade C	Ensure sterile background
Preparation rooms	C	Positive to hot cell interior	Prevent contamination ingress
Production hot cells (radioactive)	C (or negative pressure enclosure)	Negative to preparation room	Radiological containment
Technical backrooms	Unclassified	Negative to production rooms	Prevent contamination from maintenance
Waste treatment and decay storage	Unclassified	Most negative	Isolate high-activity zones
Clean corridors	C or D	Neutral or slightly positive	Maintain general cleanliness
Administrative and office areas	N/A	Neutral	Outside controlled environment

Table 6: Typical pressure gradients in ²²⁵Ac production facility.

System implementation and monitoring

- Room pressure monitors (RPMs) and differential pressure gauges are installed at all critical zone interfaces.
- Alarm thresholds are configured per GMP and radiation protection requirements.
- Pressure differentials of 10–15 Pa are typical between adjoining rooms of different grades.
- HEPA filtration is provided at both supply and exhaust to meet ISO 14644 and radiological safety.
- HVAC interlocks and emergency protocols maintain negative pressure in radioactive zones during failures.

Operational and safety considerations

- Material airlocks (MALs) and personnel airlocks (PALs) are placed between zones to preserve pressure integrity.
- In isotope production, hot cells may prioritize negative pressure despite cleanroom requirements; therefore, aseptic operations are often conducted in Grade A isolators inside hot cells to resolve this conflict.
- Regular validation of pressure profiles and airflow patterns is required as part of GMP requalification.

Building flows

Function

Effective flow management within the ^{225}Ac production facility is essential to:

- Prevent cross-contamination between clean, radioactive, and non-radioactive zones.
- Ensure compliance with GMP and radiological safety regulations.
- Maintain operational efficiency while supporting traceability and inspection readiness.

The building design incorporates unidirectional and segregated flows for personnel, raw materials, radioactive substances, product, and waste - aligning with zoning, containment, and cleanliness requirements.

Personnel flow

Personnel flows are designed to:

- Prevent movement from "dirty" (lower-grade or radioactive) areas into "clean" (GMP-critical) zones.
- Segregate staff based on function (e.g., production, QC, maintenance).
- Use controlled access, gowning, and airlocks to maintain cleanliness and radiological safety.

Flow Path:

- Entry: Staff enter through designated entrance and proceed to changing areas (Lockers M/F, sanitary areas).
- Gowning: Personnel pass through PALs (Personnel Airlocks) and gown according to target zone (Grade D → C → B/A).
- Access:
 - o Administrative and support staff remain in non-controlled zones (offices, meeting rooms).
 - o Production/QC staff proceed to controlled and classified zones via clean corridors and airlocks.
 - o Maintenance staff access technical areas from back rooms or hot technical corridors without entering clean areas.
- Exit: Reverse flow through de-gowning areas, with contamination control and dosimetry checks.

Material flow (inbound and internal)

Principles:

- Materials enter through dedicated material airlocks (MALs) in a unidirectional manner.
- Segregation between radioactive and non-radioactive goods.
- Use of pass-throughs, pass boxes, and staging areas ensures containment integrity.

Flow Path:

- Non-radioactive materials (e.g. reagents, consumables) enter through MALs into Grade D/C areas, then progress to production zones (e.g., preparation rooms).
- Radioactive materials (e.g., ^{226}Ra targets) are delivered to the target reception lab, checked, and transferred through shielded routes to irradiation or hot cell zones.
- Movement within the facility uses:
 - o Shielded transfer lines for targets.
 - o Clean pass boxes for aseptic materials.
 - o Hot technical corridors for maintenance or waste containers.

Product flow (outbound)

Principles:

- Final ^{225}Ac product is handled aseptically, then securely packaged and dispatched under radiation protection guidelines.
- Flow must maintain sterility, traceability, and dose compliance.

Flow Path:

- Final product is dispensed in Grade A conditions, sealed in primary containers.
- Packaged in shielded secondary containers in dedicated packaging rooms.
- Transferred to the staging area or buffer zone, then out through the truck access.
- Documentation, labelling, and transport follow GMP and radiopharmaceutical distribution regulations.

Waste flow

Principles:

- Waste is segregated at source (radioactive, non-radioactive, solid, liquid).
- All active waste flows away from clean zones toward decay or treatment areas.
- Unidirectional flow prevents back-contamination.

Flow Path:

- Production waste: Routed via shielded internal paths to waste treatment hot cells.
- Liquid radioactive waste: Collected into dedicated basement decay tanks or intermediate storage (if reusable).
- Solid waste: Stored in shielded drums or decay boxes before measurement and evacuation.
- Final disposal: After decay and clearance, waste exits through dedicated logistic routes or via authorized external services.

Flow integrity and control measures

Flow Type	Controls implemented
Personnel	Gowning sequences, PALs, badge access, dosimetry
Materials	MALs, pass boxes, barcode tracking, quarantine storage
Radioactive material	Shielded transfer systems, airlocks, contamination checks
Product	GMP labelling, batch traceability, temperature control
Waste	GMP labelling, batch traceability, temperature control

Table 7: Flows and measures to be taken.

Operational considerations

- Facility layout ensures no crossing between incoming and outgoing materials.
- Visual zoning, signage, and colour coding are used to reinforce permitted flows.
- All flows are designed to support auditable traceability for GMP and radiological inspections.
- Automation and monitoring (e.g., badge-controlled access, smart pass-throughs) support compliance and reduce human error.

Summary – conceptual design ²²⁵Ac production facility

As part of the feasibility study for large-scale ²²⁵Ac production, a conceptual design of the dedicated facility has been developed. This design does not define engineering solutions or specify equipment, but instead establishes a firm architectural, functional, and regulatory foundation on which the detailed design will be built.

The conceptual design reflects the core requirements for producing a GMP-compliant radiopharmaceutical product, including functional zoning, personnel and material flows, containment principles, and regulatory alignment. It draws extensively on SCK CEN's in-house expertise and previous experience in designing complex radiochemical and nuclear medicine infrastructure, notably within the Centralized Radiochemistry Facility (CRF) and other RRF-supported projects.

The layout and zoning strategy are structured to support:

- Safe handling of radioactive materials.
- Compliance with EU GMP and Belgian radiological regulations.
- Efficient, traceable operations from target irradiation to product dispatch.
- Future scalability and process adaptability.

The conceptual facility design clearly defines critical areas such as irradiation and accelerator zones, target handling, radiochemistry processing, sterile dispensing, QC laboratories, waste treatment, and technical support systems. It also includes provisions for HVAC, utilities, environmental control, and differential pressure zoning, ensuring compatibility with both GMP cleanroom classifications and radiological containment needs. This conceptual phase sets the direction for subsequent engineering, licensing, and qualification activities. It serves as a structured, knowledge-based blueprint that translates regulatory expectations and operational experience into a practical, buildable facility concept ready for transformation into a fully engineered design.

Main conclusion of the ^{225}Ac feasibility study: M180

The feasibility study has confirmed that the establishment of a large-scale production capacity for ^{225}Ac in Belgium is both scientifically and strategically viable. By leveraging Belgium's exclusive stock of ^{226}Ra and advancing key enabling technologies (identified gaps), the study has delivered the essential foundations for future implementation.

One of the central achievements is the development and validation of a dedicated radon trapping system, supported by regulatory review. This system provides an operational solution enabling the safe handling of ^{226}Ra and represents a decisive step towards its practical use in radioisotope production.

The study also resulted in major technological innovations, protected through four European patents. These cover radon trapping, a liquid-target irradiation module, a high-efficiency electron-to-gamma converter, and a GMP-compatible full scale radiochemical separation process. Collectively, they establish a proprietary knowledge base and position Belgium at the forefront of technological innovation in ^{225}Ac production.

In addition, a validated radiochemistry route has been developed to ensure high-purity ^{225}Ac suitable for medical applications. This process not only safeguards pharmaceutical quality but also enables recycling of the valuable ^{226}Ra target material, supporting long-term sustainability.

Finally, the study produced a conceptual facility design that integrates the different technological components into a coherent production process. While not a final construction design, this conceptual framework provides a licensing-oriented roadmap and clarifies the requirements for GMP, radiation safety, and operational efficiency.

Taken together, these outcomes demonstrate that Belgium now possesses the critical scientific, technological, and regulatory building blocks for establishing a secure and large-scale supply of ^{225}Ac . Moving from feasibility to realization will ensure reliable access to this life-saving isotope for European patients, while reinforcing Europe's sovereignty and competitiveness in nuclear medicine.

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